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Oral Presentations

Oral Session 1: TED (translational)

OP-01-01

Thrive-2 phase 3 trial of veligrotug in chronic thyroid eye disease (TED) : efficacy, safety, and quality of life at week 15

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Objectives
Veligrotug is an investigational full antagonist monoclonal antibody to IGF-1R. In the phase 3 trial THRIVE-2 in chronic TED (NCT06021054), we evaluated veligrotug's efficacy, safety, and disease-specific QoL at Week 15. In addition, we performed a post hoc analysis to further explore veligrotug's treatment effect across key clinical TED domains.
Methods
Adults with moderate-to-severe chronic TED (onset >15 months, proptosis ≥ 3 mm above normal, and any clinical activity score [CAS]) were randomized to 10 mg/kg veligrotug or placebo, each administered once every 3 weeks for a total of 5 IV infusions. Efficacy, safety, GO-QOL (exploratory endpoint), and a post hoc composite endpoint analysis of key domains including proptosis response by Hertel exopthalmometry, diplopia resolution, and disease inactivation (CAS 0/1) were assessed at Week 15. The primary efficacy endpoint in Europe was the overall responder rate (ORR; ≥ 2-mm proptosis reduction by MRI/CT and no worsening of CAS vs baseline).
Results
Overall, 188 patients received veligrotug ($n = 125$) or placebo ($n = 63$). At Week 15, greater improvements were observed in veligrotug vs placebo patients across all primary and secondary endpoints including ORR (48% vs 3%, $P < 0.0001$), PRR (56% vs 8%, $P < 0.0001$), diplopia resolution (32% vs 14%, $P = 0.0152$), and CAS 0/1 (54% vs 24%, nominal $P = 0.006$). In a composite endpoint analysis of patients with a response in key domains, 74% of veligrotug patients achieved at least one of the following: proptosis response, diplopia resolution, or CAS 0/1, compared with 26% for placebo. GO-QOL improvements were clinically meaningful for veligrotug vs placebo at Week 15 (mean change from baseline, overall: 12.5 vs 3.2, visual functioning subscale: 11.0 vs -1.4, appearance subscale: 13.8 vs 7.7; nominal $P < 0.01$ for all). The majority of AEs were mild, with one treatment-related serious AE occurring in each group.
Conclusion
In patients with chronic TED, a 12-week, 5-infusion regimen of 10 mg/kg veligrotug was generally well tolerated and led to statistically significant improvements in TED signs/symptoms. Most veligrotug-treated patients improved in at least one key domain of proptosis response, diplopia resolution, or disease inactivation, which translated into clinically meaningful improvements in QoL.

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OP-01-02

In-VITRO properties of regn24493, a novel TSHR-blocking monoclonal antibody for the treatment of graves' disease and thyroid eye disease

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Objectives
Graves' disease (GD) is a form of autoimmune hyperthyroidism with the major extrathyroidal manifestation of thyroid eye disease (TED). Thyroid-stimulating hormone receptor (TSHR)–stimulating autoantibodies (TSAbs) are produced and drive hormone production in the thyroid causing tissue expansion in the orbit. There are currently no approved TSHR antagonists, indicating an unmet clinical need. Here we introduce REGN24493, a novel monoclonal antibody that binds to TSHR and blocks downstream activation by TSAbs. We assessed binding and functional properties of REGN24493 in-vitro.
Methods
Flow cytometry was used to assess REGN24493 binding to HEK293 cells engineered to express human, monkey, mouse, and rat TSHR. To evaluate REGN24493's blocking efficacy of TSHR signaling, a bioassay was used with cells engineered to express a luciferase reporter responsive to cAMP (CRE-Luc) and TSHR. TSHR signaling was induced by its ligand TSH, patient derived monoclonal TSAb M22, or GD patient sera.
Results
REGN24493 displayed concentration-dependent specific binding to human, monkey, mouse, and rat TSHR engineered cells, with nanomolar half-maximal effective concentration (EC_{50}) values and no binding to parental cells that did not express TSHR. In functional assays, REGN24493 fully blocked activation of monkey, mouse, and rat TSHR expressed on HEK293/CRE-Luc cells by TSH and M22 in a concentration-dependent manner with picomolar to nanomolar half-maximal inhibitory concentration (IC_{50}) values. In CHO-K1/CRE-Luc cells expressing human TSHR, REGN24493 reduced basal activity and blocked activation induced by TSH, M22, and polyclonal GD human serum with IC_{50} values of 0.8 nM, 2.81 nM, and 0.935 nM, respectively.
Conclusions
In summary, REGN24493 demonstrated specific binding to cell-surface TSHR from human and tested non-human species. REGN24493 was able to block TSHR activation by its canonical ligand and TSAbs, a diagnostic hallmark and key drivers of GD and TED.

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OP-01-03

Scrnaseq of thyroid eye disease orbital fat demonstrates fibroblast thyroid hormone signaling and sparc production

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Objectives
To investigate the role of thyroid hormones in driving pathological processes in orbital fat fibroblasts, identify pro-inflammatory mediators secreted by these fibroblasts and discover serum biomarkers of thyroid eye disease (TED) activity.
Methods
Orbital fat samples were obtained from patients with TED undergoing surgical decompression and analysed using single-cell RNA sequencing (scRNAseq) to characterise cellular composition and gene expression profiles. Serum samples from multiple cohorts were assessed using ELISAs to quantify SPARC (osteonectin) and IGF-1. Immunofluorescent imaging of orbital fat tissue was also performed.
Results
scRNAseq revealed that orbital fibroblasts from orbital decompressions in people with TED express high levels of thyroid hormone receptors, growth factor receptors including IGF1R, and extracellular matrix proteins including SPARC. Orbital fat endothelial cells expressed thyroid peroxidase (TPO). SPARC was significantly raised in the serum of people with thyroid disease compared to healthy controls. Furthermore, those with moderate, severe and sight threatening TED had higher SPARC levels than those with thyroid disease but free of TED or mild TED. FT3

levels were positively correlated with SPARC in moderate-sight threatening TED. SPARC and IGF1 were positively correlated. Thyroid stimulating hormone (TSH) levels were negatively correlated with SPARC in moderate-sight threatening TED. When participants were followed longitudinally, SPARC decreased after the active phase of TED. At the protein level, immunohistochemistry indicated that SPARC was heterogeneously expressed by fibroblasts in both control and TED orbital fat.
Conclusions
SPARC is a key mediator of fibrosis and deposition of extracellular matrix, and is highly expressed at both RNA and protein level by orbital fat fibroblasts in TED. Serum SPARC levels were elevated across multiple independent cohorts in people TED, supporting its value as a biomarker. SPARC levels correlated with FT3 specifically in patients with moderate to sight-threatening TED, suggesting particular sensitivity of orbital fibroblasts to circulating thyroid hormone levels, and reinforcing the importance of achieving euthyroidism to prevent disease progression.

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OP-01-04

Serum mTOR: a potential associative marker of graves' orbitopathy

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Objectives
The mammalian target of rapamycin (mTOR) is involved in the pathogenesis of Graves' orbitopathy (GO) and sirolimus, a mTOR inhibitor, was found to improve GO. Because mTOR can be detected in the bloodstream, we considered the possibility that serum mTOR could be associated with GO. Thus, we conducted a cohort study to evaluate serum mTOR concentrations in patients with Graves' hyperthyroidism (GH), with or without GO, and in healthy subjects.
Methods
The study included 77 consecutive patients with GH, 57 of whom affected with GO, and 19 healthy subjects. GH patients underwent an ophthalmological assessment. Serum mTOR was measured by ELISA. Primary outcome: serum concentration of mTOR in GH patients with GO *vs* GH patients without GO. Secondary outcomes: (1) serum mTOR concentrations in GH patients with or without GO *vs* healthy subjects; (2) in patients with GO, relationship between serum mTOR and the clinical activity score (CAS); (3) in patients with GO, relationship between serum mTOR and GO severity; (4) relationship between serum mTOR and anti-TSH-receptor autoantibodies (TRAbs); (5) establishment of cut-off values of serum mTOR to distinguish. GH patients with GO from those without GO.
Results
Median concentrations of serum mTOR were 2440 pg/ml (1236-3053) in GO patients, 1236 pg/ml (388.5-1770) in GH patients without GO, and 247 pg/ml (0.9-705) in healthy subjects. mTOR levels were greater in GH patients than in healthy subjects, regardless of the presence of GO ($P = 0.00012$), and, within GH patients, in those with GO ($P = 0.0023$). Within GO patients, there was a significant, direct correlation between serum mTOR and CAS ($R = 0.377$; $P = 0.0038$). In addition, mTOR levels were higher in patients with moderate-to-severe than in those with mild GO [2741 (1945-4294) pg/ml vs 1890 (1035-2784) pg/ml; $P = 0.016$]. We established a cut-off value of 1,445.8 pg/ml of serum mTOR (97th percentile in healthy subjects) that distinguished GO patients within GH [positive predictive value (PPV): 79.2%; sensitivity: 73.6%; specificity: 55%].
Conclusion
Serum mTOR levels are associated with GH, and in particular with the presence, the activity and the severity of GO, suggesting that, provided additional studies are performed, it may be used as a biomarker in clinical practice.

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OP-01-05

Biomarker screening for disease progression in thyroid eye disease: a multicenter multi-omics study using multiple methodological approaches

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Objective
Thyroid eye disease (TED) is an autoimmune thyroid-associated disorder characterized by inflammation, fibrosis, adipogenesis, excessive hyaluronan production, and tissue remodeling. Its pathogenesis involves infiltration of multiple immune cell types, inflammatory cytokines, and receptor-mediated interactions among different cell populations. However, the underlying molecular mechanisms and reliable molecular biomarkers remain incompletely understood. High-throughput approaches, including proteomics, transcriptomics, and single-cell sequencing, provide powerful tools for identifying potential targets and are of great value for biomarker discovery and the development of novel targeted therapies for TED.
Methods
Multi-omics data, including proteomic, transcriptomic, and single-cell sequencing datasets, were integrated to identify key genes and differentially expressed proteins through cross-dataset intersection. Parallel reaction monitoring (PRM) was used to validate the top 20 differentially expressed proteins identified between active and inactive TED in high-throughput proteomic data, thereby further narrowing down key candidates. In addition, differentially expressed molecules from the raw data of the three datasets were intersected to identify molecules consistently upregulated across all three datasets or across at least two datasets. Eighteen molecules identified through multi-omics integration were further validated by immunohistochemistry in 40 orbital tissue samples, including 28 TED tissues and 12 normal controls. Immunostaining results were quantitatively analyzed using an automated and unbiased image analysis system. In addition, orbital fibroblasts were used to investigate the functional phenotypes of the two molecules showing the most prominent differences by quantitative immunohistochemical analysis.
Results
Through multi-omics integration and PRM validation, 18 molecules were repeatedly identified across high-throughput proteomic, transcriptomic, and single-cell sequencing data. These included BGN, LTBP2, EGR1, IGFBP5, C1R, CD44, HBB, FBLN1, FBLN2, FGFR2, ELN, LCP1, PLIN2, PCOLCE, VCAN, LUM, LMCD1, and ABI3BP. Quantitative immunohistochemical analysis showed that all 18 molecules were upregulated in TED tissues compared with normal controls. Furthermore, compared with inactive TED, BGN, LTBP2, EGR1, VCAN, LUM, LMCD1, IGFBP5, ELN, PCOLCE, and CD44 were further increased in active TED. Functional experiments in orbital fibroblasts showed that BGN promoted the secretion of inflammation-related cytokines, whereas LTBP2 induced a profibrotic phenotype.
Conclusion
By integrating cross-dataset multi-omics analysis, PRM, immunohistochemical validation, and functional experiments, this study identified a panel of recurrent TED-associated molecules closely related to inflammation and fibrosis. These findings may be valuable for biomarker screening and for the development of potential therapeutic targets in TED. Further validation in larger multicenter cohorts and animal models is warranted.

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OP-01-06

Characterization of proptosis response in the thrive phase 3 trial of veligrotug for active thyroid eye disease (TED)

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Objectives
Veligrotug, an investigational full antagonist monoclonal antibody to IGF-1R, demonstrated statistically significant improvement across key clinical domains in the phase 3 THRIVE trial in patients with active TED (NCT05176639). This analysis further characterizes the magnitude of proptosis response at the individual-patient level, enhancing understanding of veligrotug's treatment effect across the population.
Methods
Adults with moderate-to-severe active TED (onset $\leq$15 months, proptosis $\geq$3 mm above normal, and clinical activity score $\geq$3) were randomized to receive veligrotug (10 mg/kg) or placebo, each administered once every 3 weeks for a total of 5 IV infusions. Proptosis was assessed by Hertel exophthalmometry through Week 15. Proptosis responders were defined as patients who had a reduction of $\geq$2 mm in the study eye without a corresponding increase of $\geq$2 mm in the fellow eye.
Results
In the overall population, proptosis significantly improved in the veligrotug vs placebo group at Week 15 (mean reduction: 2.9 mm vs 0.5 mm, $P < 0.0001$; secondary endpoint). of the 107 patients (veligrotug, $n = 69$; placebo, $n = 38$) with both baseline and Week 15 proptosis measurements available, 71% vs 5% were proptosis responders for veligrotug vs placebo patients. Proptosis reduction of $\geq$3 mm was achieved in 55% vs 3% and reduction of $\geq$4 mm in 23% vs 0% of veligrotug vs placebo patients. Proptosis increased in 21% of placebo-treated but in none of the veligrotug-treated patients. Among veligrotug responders, proptosis reduction was observed as early as Week 3 (mean: 2.4 mm) and continued through Week 15 (mean: 3.7 mm). Individual-patient proptosis responses will be shown in the presentation. The majority of AEs were mild, with no serious treatment-related AEs, and a low treatment discontinuation rate.
Conclusion
A 12-week 5-infusion treatment regimen of 10 mg/kg veligrotug was generally well tolerated and led to significant improvement in proptosis among patients with active TED. In the veligrotug group, no increase in proptosis was observed, and among the 71% responders, a substantial proptosis reduction was observed at Week 15. Assessing proptosis response at the individual-patient level may provide deeper insight into veligrotug's effect and inform treatment expectations.

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OP-01-07

A novel TSHR-blocking antibody which effectively reduces hyperthyroidism and proptosis in a mouse model of graves' and thyroid eye disease

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Objectives
Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism driven by thyroid-stimulating hormone receptor (TSHR)–stimulating autoantibodies (TSAbs). Approximately 30% of patients with GD develop thyroid eye disease (TED), in which TSAbs activate aberrantly expressed orbital TSHR, causing tissue expansion and proptosis. M22 is a potent TSAb isolated from a GD patient. We establish an M22-induced mouse model reproducing key features of GD and TED and evaluated the *in vivo* efficacy of REGN23415, a potent TSHR-blocking monoclonal antibody, and its half-life extended version, REGN24493.
Methods
Female mice humanized for TSHR or FcRn received chronic M22 intraperitoneal (IP) injections (2 mg/kg twice weekly). After 1 or 3 doses of M22, mice received REGN23415, REGN24493 or isotype control IP injections (2 or 8 mg/kg twice weekly or 35 mg/kg single dose); controls received isotype only. T4 levels in serum were measured 24 hours post-injection. MRI scans assessed the percentage area of the eye protruding from the skull at baseline and Weeks 3 and 5 post-M22 initiation.
Results
M22 effectively increased T4 serum levels (from 55 ng/mL to 160 ng/mL after 1 dose), and continued dosing maintained elevated T4 over the studies. REGN23415 reduced hyperthyroidism, decreasing T4 to levels similar to controls. While no significant changes in percent eye protrusion were observed in animals that received isotype alone, in M22-treated mice protrusion increased from 46.3%$\pm$1.1% at baseline to 57.8%$\pm$6.1% at Week 3 and 55.5%$\pm$7.9% at Week 5. However, mice receiving M22 and REGN23415 showed no significant changes in eye protrusion throughout the study (Week 3, 48.7$\pm$7.7%; Week 5, 43.0$\pm$6.7%). We then evaluated the efficacy and durability of a single dose of REGN23415 and REGN24493 in the M22-induced GD model in FcRN-humanized mice. While all mice received M22 twice weekly, a subgroup received a single 35 mg/kg dose of TSHR blocker or isotype control 4 days after M22 initiation. Mice receiving M22 alone or M22 + isotype were hyperthyroid for the duration of the study (> 70 days); however, mice receiving TSHR blockers became hypothyroid within 24 hours. While mice receiving REGN23415 were protected from hyperthyroidism for 36 days, mice receiving REGN24493 were protected for 57 days.
Conclusions
These findings demonstrate that chronic M22 injections alone can induce both hyperthyroidism and proptosis in female mice. TSHR blockade effectively reduced hyperthyroidism and prevented TSAb-induced proptosis. These results suggest that REGN23415 and REGN24493 are potent TSHR blockers with therapeutic potential for GD and TED.

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Oral Session 2: Translating Thyroid Cancer Biology into Clinical Impact (cancer)

OP-02-01

Shorter telomeres and rare germline variants in familial papillary thyroid cancer

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Objectives
Papillary thyroid cancer (PTC) is the most common thyroid malignancy. Familial PTC (fPTC), defined by the occurrence of the disease in two or more first-degree relatives, accounts for less than 10% of cases. Despite its clinical relevance, the genetic basis of fPTC remains largely unknown. Telomere length is a key determinant of genomic stability and has been associated with cancer susceptibility. The aim of the study was to investigate relative telomere length (RTL) in individuals from families with fPTC and to explore potential predisposing germline variants through whole-exome sequencing (WES).
Methods
Eleven families with fPTC, each including at least three affected members, were recruited. Blood samples were collected from 25 affected individuals and 26 unaffected family members (UFM). In addition, 24 patients with sporadic PTC (sPTC) were included. DNA was isolated from peripheral leukocyte and RTL was measured using quantitative polymerase chain reaction (qPCR). WES was performed in six families (17 fPTC and 13 UFM), selected based on availability of sufficient high-quality DNA from at least three affected members.
Results
At study enrollment, mean age was 49.1$\pm$16.6 years for the fPTC, 44.3$\pm$18.8 years for the UFM group, and 48$\pm$15.9 years for the sPTC, with no difference between groups. An inverse association between RTL and age was observed in the entire cohort (r = -0.32, $P < 0.005$). RTL was significantly shorter in both fPTC and UFM compared with sPTC (0.88$\pm$0.35 vs 1.22$\pm$0.56; 0.74$\pm$0.21 vs 1.22$\pm$0.56, $P < 0.05$ respectively), whereas no difference was observed between fPTC and UFM. Among patients with aggressive tumor characteristics, fPTC showed shorter telomeres compared with sPTC cases with similar features (tumor invasiveness: $P < 0.05$; lymph node involvement: $P < 0.05$). WES analysis identified 32 rare segregating gene variants. Although most variants were family specific, variants in genes involved in key biological pathways, including DNA repair (ERCC gene) and cell proliferation (EGFR and FGFR genes), were detected in more than one family. Notably, two unrelated families shared the same previously undescribed variant in FBN3 gene.

Conclusions
Our findings indicate that individuals from families with fPTC, including unaffected members, exhibit shorter telomeres compared with patients with sporadic PTC, suggesting a possible inherited predisposition associated with telomere biology. Whole-exome sequencing identified rare segregating variants in genes involved in key biological pathways, providing further insight into the molecular background of familial PTC. Further studies are warranted to functionally validate the identified variants and to investigate the potential role of telomere length as a biomarker for cancer risk stratification in familial settings.

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OP-02-02

Dissecting somatic DICER1 hotspot alterations in the spectrum of DICER1-related disorders

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Introduction
DICER1 syndrome is a hereditary disorder, predisposing individuals to pleuropulmonary blastoma (PPB), thyroid follicular nodular disease (FND), thyroid cancer (TC), ovarian Sertoli-Leydig cell tumours (SLCT), and central nervous system (CNS) tumours. *DICER1*-associated tumours typically harbour a germline loss-of-function (LOF) variant, and a tumour-specific missense mutation affecting one of five hotspot codons in the RNase IIIb domain. Somatic amino acid changes within the *DICER1* hotspot region have not yet been clearly associated with specific clinical manifestations.
Objective
To characterize the spectrum of *DICER1* hotspot mutations and explore their potential relationship with clinical manifestations in families with DICER1 syndrome.
Methods
Twenty-two samples from eleven patients belonging to seven families, with a prior diagnosis of DICER1 syndrome were analysed, including samples from distinct neoplasms occurring in the same individual. These comprised SLCT ($n = 2$), CNS tumours ($n = 1$), PPB ($n = 1$), FND ($n = 8$), TC ($n = 6$), and normal tissues ($n = 4$). Germline *DICER1* variants were analysed by next-generation sequencing (NGS), and somatic hotspot mutations were assessed using Sanger sequencing.
Results
Germline *DICER1* variants were predominantly LOF. Additionally, 15 *DICER1* somatic hotspot mutations were detected in 9 patients' samples, mainly clustering in exon 24 (10/15; 67%), at codon 1709. The most common alteration was p.Asp1709Gly, detected in one PPB, two FND and three TC samples. Other alterations included p.Asp1709Val (one CNS tumour), p.Asp1709Glu (one FND), and p.Asp1709Asn (one TC and one FND). Moreover, 5/15 somatic mutations (33%) were detected in exon 25: p.Asp1810His and p.Glu1813Asp in two SLCT, and p.Asp1810His and p.Glu1813Lys in three FND tissues from the same patient. In two families, the index patients presented multiple TC and FND lesions with distinct *DICER1* somatic hotspot alterations, indicating independent second hit–driven evolution. *BRAF* $^{p.Val600Glu}$ mutation was absent in all samples.
Conclusions
DICER1 somatic hotspot mutations are frequently identified in PPB, SLCT, FND and TC, in patients with DICER1. Although some lesions are underrepresented in this study, these alterations do not show clear tumour-type specificity, supporting a shared molecular mechanism rather than phenotype-driven mutation patterns. The identification of two *DICER*1 hits in FND development, similarly observed in TC, suggests that histologically benign lesions may harbour malignant biological potential, further supported by the absence of *BRAF* mutations in TC arising in these patients. Nonetheless, additional cooperative alterations, affecting MAPK/other signalling pathways may influence tumour severity. Further investigation is warranted to clarify the mechanisms underlying *DICER1*-associated tumour behaviour and improve clinical management for affected families.

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OP-02-03

Longitudinal liquid BIOPSY detects tumor-derived alterations during surveillance of thyroid carcinoma

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Objectives
Although most thyroid carcinomas (TC) have an excellent prognosis, a subset of patients develops persistent or recurrent disease requiring long-term surveillance. Current follow-up strategies rely mainly on serum thyroglobulin (Tg), anti-thyroglobulin antibodies, and imaging studies. However, Tg interpretation may be limited by antibody interference, residual thyroid tissue, and low tumor burden. In addition, evolving management strategies, including selective use of radioactive iodine, lobectomy, and active surveillance, may further challenge postoperative monitoring, highlighting the need for complementary biomarkers. Liquid biopsy enables minimally invasive detection of circulating tumor DNA (ctDNA) and RNA (ctRNA), providing real-time molecular information on tumor burden and actionable alterations. This study aimed to evaluate the potential of longitudinal liquid biopsy analysis as a complementary tool for postoperative surveillance of TC.
Methods
We conducted a prospective longitudinal study including 70 patients with TC representing different American Thyroid Association (ATA) response-to-therapy categories. Patients were followed for up to five years, with plasma samples collected at three time points during surveillance. Cell-free DNA was analyzed for single-nucleotide variants and cell-free RNA for gene fusions using digital PCR (dPCR) assays targeting alterations previously identified in the primary tumor. For patients with active disease lacking available tumor tissue or prior molecular characterization, plasma samples were analyzed using targeted next-generation sequencing with a customized thyroid panel. Molecular findings were integrated with clinical and biochemical data and interpreted according to the ATA response-to-therapy categories at the time of sample collection.
Results and Conclusion
Serial liquid biopsy analysis revealed distinct ctDNA/ctRNA detection patterns that were strongly associated with the ATA response-to-therapy categories. All patients with structural incomplete response showed detectable tumor-derived alterations in plasma, several corresponding to potentially targetable variants. In contrast, ctDNA/ctRNA detection was less frequent among patients with biochemical incomplete or indeterminate response, who remained clinically stable without changes in ATA response classification during follow-up. Among patients with excellent response, most had negative liquid biopsy findings and maintained excellent response over time. Two patients classified as having an excellent response showed detectable *BRAFV600E* in plasma; both had a high risk of recurrence but remained clinically stable. Overall, these findings suggest that longitudinal liquid biopsy analysis may provide clinically relevant molecular information during postoperative surveillance of thyroid carcinoma. The consistent detection of tumor-derived alterations in patients with structural disease, including potentially actionable variants, highlights the potential clinical value of plasma-based monitoring to support molecularly guided therapeutic strategies while complementing conventional follow-up.

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OP-02-04

Thyroid cancer and environmental pollutants mixture: non persistent pollutants showed the strongest impact

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Objectives
Human activities release numerous chemicals into the environment, many of which significantly impact human health. Some of these chemicals can interfere

with endocrine systems (endocrine-disrupting chemicals, EDCs) and exhibit a carcinogenetic potential. Because the incidence of thyroid cancer (TC) has steadily increased over the past decades, a potential role for EDCs, possibly through a cocktail effect, can be hypothesized. The aim of this study was to evaluate the effect of a mixture of persistent and non-persistent pollutants on TC.
Methods
In this cross-sectional case-control study, 113 patients with TC and 119 control subjects were enrolled. Urine samples were analysed for non-persistent EDCs (4 phosphorus flame retardants, 7 bisphenols, triclosan, 4 parabens, 8 phthalate metabolites, and benzophenone-3), while serum samples were used to quantify persistent EDCs (11 PFAS, 12 PCBs, DDT, and DDE). Pollutants were quantified using gas or liquid chromatography coupled with mass spectrometry, depending on the specific analyte. Two statistical approaches, weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR), were employed to assess the impact of the pollutant mixture on TC risk.
Results
The mean age of participants was 51 years, and 76% were female. of the EDCs analyzed, 30 were detected in more than 40% of participants and were therefore included in the analyses. According to the WQS model, the mixture of pollutants was significantly and positively associated with TC (OR 10.7, 95%CI: 3.8–29.5). The EDCs with the highest impact were the phosphorus flame retardant DPP, bisphenols F and S, phthalate metabolites MBzP, MEP, and 5-OH-MEHP, PCB-180, PFDA, linear PFOS, and benzophenone-3. Results from BKMR analyses were roughly consistent with those from WQS.
Conclusions
This is the first study to evaluate the combined effect of persistent and non-persistent pollutants on TC, highlighting a significantly increased odds ratio. Notably, non-persistent EDCs appeared to have the greatest impact, emphasizing that their short half-life does not necessarily imply lower hazard. However, due to the cross-sectional design, causal direction could not be determined, and single spot measurements of short half-life EDCs may not fully reflect overall exposure.

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OP-02-05

Genetic heterogeneity exploration in matched primary and distant metastatic differentiated thyroid cancer

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Objective
Although genetic alterations in primary thyroid cancer have been extensively studied, investigations into the heterogeneity between primary and metastatic tumors remain limited. This study aimed to explore tumor genetic heterogeneity between primary and distant metastatic lesions in patients with differentiated thyroid cancer (DTC) and to assess its association with clinical prognosis.
Methods
This retrospective study included 30 paired primary and distant metastatic tumor samples obtained from patients with DTC. The variations in *BRAF*, *NRAS*, *HRAS*, *KRAS*, *TERT*, *PIK3CA*, *RET*, *PPARG*, *NTRK1* and *NTRK3* were detected using a multiplex PCR-based detection kit provided by Amoy Diagnostics. Patients were further divided into synchronous and metachronous metastases based on whether the time interval between primary and metastatic diagnosis exceeded 12 months. The concordance between primary and metastatic lesions was assessed and the relationship between genetic heterogeneity and progression-free survival (PFS) was analyzed using Kaplan-Meier survival analysis.
Results
Among the 30 paired primary and distant metastatic tumors, overall discordance of genetic mutations was observed in 36.7% (11/30) of cases. *TERT* mutations showed the highest heterogeneity with discordance rate of 30% (9/30) and were exclusively observed in metastatic lesions. Patients with heterogeneous mutations had more radiological progressive disease events and a significantly shorter median PFS than those with homogeneous mutations (11.0 vs 78.1 months; HR = 7.1, $P < 0.0001$). When stratified by metastatic timing, patients with metachronous metastases tended to show higher mutation discordance (52.9% vs. 15.4%, $P = 0.058$). Further comparison of PFS based on genetic heterogeneity and metastasis timing revealed that patients with homogeneous mutations and metachronous metastases had the longest mPFS of 42.2 months, while those with heterogeneous mutations and synchronous metastases had the shortest mPFS of 2.6 months.
Conclusion
Patients with heterogeneous molecular characteristics and synchronous distant metastases may have poor prognosis, updated genetic testing may provide guidance for clinical management. Young Investigator Session (Age < 35Yrs).

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Oral Session 3: Young Investigator (clinical + cancer)

OP-03-01

Development of a sensitive plasma lenvatinib quantification method and validation in thyroid cancer patients

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Background
Lenvatinib (LEN) is associated with frequent and potentially severe adverse events (AEs). The dose dependency of LEN-related toxicity remains unclear, as no data are currently available on this topic. In this study, we developed a novel method for quantifying LEN in plasma samples and investigated the relationship between LEN dose and plasma concentrations in real-life patients with advanced differentiated thyroid cancer (DTC).
Materials and Methods
A sensitive high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) assay for LEN quantification in plasma was developed, with a wide analytical range (0.7-500 ng/mL). Consecutive plasma samples ($n = 84$) from 19 patients with RAI-refractory DTC were analyzed. Linear mixed-effects model (LMM) analysis was used to evaluate the relationship between the administered LEN dose and the corresponding plasma concentrations (plasma LEN). The intraclass correlation coefficient (ICC) was calculated to assess the proportion of total variance attributable to inter-subject differences.
Results
A strong positive correlation between the administered LEN dose and plasma concentrations was observed. LMM analysis demonstrated significant inter-individual variability in plasma LEN concentrations, accounting for approximately one third of the total variance. After stratification by administered LEN dose, this variability was more pronounced at higher doses ($\geq$18 mg) than at lower doses (ICC 0.54 *vs* 0.24, respectively). Adjusting the LMMs for the occurrence of LEN-related toxicities (namely nausea, vomiting, diarrhea, and weight loss) led to a significant reduction in the ICC among patients receiving higher LEN doses (ICC 0.38 after adjustment), whereas it remained essentially unchanged (ICC 0.26) in patients treated with lower doses.
Conclusions
This is the first real-life evaluation of inter-individual LEN pharmacokinetic variability in patients with advanced DTC, obtained using a newly developed HPLC-MS/MS method. Our results suggest that the dose-response relationship of LEN in DTC is complex, with dose-dependent differences. The substantial inter-patient variability observed at high LEN doses is likely related to LEN-associated AEs, which occur heterogeneously in this subset of patients.

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OP-03-02

Liquid biopsy in BRAF-mutant anaplastic thyroid cancer: a tool for monitoring patients' response to dabrafenib and trametinib

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Objectives
Liquid biopsy enables minimally invasive monitoring of circulating tumour DNA (ctDNA), which reflects tumour-specific genetic alterations. In *BRAF* p.V600E mutant anaplastic thyroid cancer (ATC), combined therapy with Dabrafenib and Trametinib (DT) has significantly improved patients' survival. However, available imaging, such as CT and PET-FDG, often fails to detect minimal residual disease or early relapse, underscoring the potential of liquid biopsy for disease monitoring. The main aim of this study was to evaluate liquid biopsy-based cell-free DNA (cfDNA) analysis as a tool for monitoring response to DT in ATC patients harbouring the *BRAF* p.V600E mutation.
Methods
Eighty-six peripheral blood samples were collected from 21 patients with *BRAF* p.V600E ATC undergoing DT treatment, coincidently with imaging assessments. Fifteen patients had liquid biopsies performed prior to DT initiation (baseline), and 13 of these also during follow. In addition, 9/21 had samples collected at recurrence. Cell-free DNA levels were quantified in a Tapestation (Agilent) (100−300 bp size fragments) and the cfDNA integrity index (cfDNAii) was calculated (300−1000 bp size fragments/100−300 bp size fragments). Circulating tumour DNA with *BRAF* p.V600E (*ctBRAF+*) was assessed by digital droplet PCR (ddPCR, BioRad). Association analyses with imaging and clinical parameters, including overall survival (OS), progression-free survival (PFS) and duration of response (DOR), were conducted to determine whether liquid biopsy-based biomarkers correlated with therapeutic response and disease recurrence.
Results
Mean cfDNA levels decreased from baseline (167±49.5 ng/mL) to best response (112±44 ng/mL) and increased at recurrence (293±92 ng/mL; $P < 0.01$). cfDNAii did not significantly change, but there was a significant association of lower cfDNAii and higher tumour sizes ($P < 0.05$). Global baseline cfDNA levels and cfDNAii were not associated with clinical outcomes, although individual cfDNA trajectories reflected disease progression. *ctBRAF+* was detected in 13/15 patients at baseline and in all recurrences, being undetectable in the absence of ATC disease, thus mainly paralleling clinical and imaging assessment. *ctBRAF+* detection was associated with lower OS [48.5 *vs* 11 months; Hazard ratio (HR) = 2.9; $P < 0.05$], shorter PFS (46 *vs* 9 months; HR = 5.2; $P < 0.01$), and shorter DOR (22 *vs* 7 months; HR = 6.2; $P < 0.01$) at the end of follow-up. ddPCR demonstrated 79.8% sensitivity and 94.5% specificity, with a detection threshold of 1%.
Conclusions
Liquid biopsy analyses, particularly *ctBRAF+* and cfDNA monitoring, may provide a sensitive, non-invasive approach to follow treatment response, and identify ATC relapse, complementing imaging and potentially guiding therapeutic strategies.

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OP-03-03

Effect of age and histological subtype on mortality in differentiated thyroid carcinoma: an international multi-institutional individual participant data pooled analysis

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Background
Mortality risk in differentiated thyroid cancer (DTC) is postoperatively assessed by the American Joint Committee on Cancer (AJCC)/Tumor, Node, Metastasis (TNM) Staging system. This system applies a dichotomous age cutoff, does not distinguish between histological subtypes, and does not consider competing risks, which may not optimally reflect thyroid cancer biology.
Objective
To evaluate the prognostic value of age at diagnosis and histological subtype within the AJCC/ TNM Staging system on 10-year thyroid cancer-specific mortality risk in DTC, while accounting for competing risks.
Methods
We included adult DTC patients from the Thyroid Cancer Consortium, an international multi-institutional collaboration of clinician-collected data. We used a Fine-Gray model for thyroid cancer-specific mortality with age at diagnosis continuously, histological subtype and TNM-stage, including other causes of death as competing risk. We derived the subdistribution hazard ratios with 95% confidence intervals (sHR [95% CI]), and estimated 10-year absolute risks of thyroid cancer-specific mortality. Findings were externally validated using Surveillance, Epidemiology, and End Results Program data.
Results
We included 16,194 patients from 18 cohorts worldwide, of which 12 cohorts were from Europe, three from Asia, two from South America and one from North America. There was a positive, nearly linear association between age at diagnosis and thyroid cancer-specific mortality that attenuated in older patients. Higher age at diagnosis (sHR [95% CI]: 1·74 [1·62-1·86]), Follicular thyroid carcinoma (FTC) as histological subtype (sHR [95% CI]: 1·41 [1·12-1·76]), and higher TNM stages without age cutoff (sHR [95% CI] for stages II, III and IV respectively: 5·38 [3·33-8·19], 24·5 [14·7-40·3] and 45·6 [30·1-69·1]) were associated with higher risk of thyroid cancer-specific mortality. We found a subtype-dependent difference, with FTC showing higher risks at younger age and lower TNM-stage than papillary thyroid cancer (PTC). Findings were consistent in the external validation dataset ($n = 142{,}884$).
Conclusion
Our findings dispute using a dichotomous age cutoff, and show the importance of age at diagnosis as a continuous parameter and histological subtype when predicting thyroid cancer-specific mortality in DTC. Consequently, our results encourage attempts to develop a more accurate prediction model for DTC survival. Improving the prediction of DTC survival is essential for communication of patient outcomes, a personalized treatment approach, and optimalization of health care resources.

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OP-03-04

Pilot program of TT4 measurement in newborns with normal TSH uncovers rare thyroid disorders

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Objectives and methods
In Italy, neonatal screening for congenital hypothyroidism (CH) relies on TSH measurement, which may miss central hypothyroidism (CeH) or disorders affecting thyroid hormone action. As part of a pilot program in the Lombardy region (MR1-2022-12375726) to improve early detection of rare thyroid diseases, we measured total T4 (TT4) in newborns with TSH <10 mU/l on dry blood spot (DBS).
Results
Between October 2024 and October 2025, approximately 65,000 newborns underwent standard TSH-based screening. Infants with suspected CH were managed according to standard pathways. Additionally, the parents of 15,000 newborns with negative TSH screening accepted the extended TT4 screening. Among these, 154 had abnormal TT4, 85% of which were elevated. Nine males had low TT4 with normal fT4, compatible with possible TBG deficiency. of the remaining 145 newborns, 38 were sequenced for differential diagnosis, revealing no cases of resistance to thyroid hormone beta (RTHβ) or alpha (RTHα). An additional RTHβ case (p.R243W in *THRB*) was uncovered by elevated TSH (48 mU/l) during the project. Two cases of assay interference due to familial hyperthyroxinemia (p.G26S in *TTR*; p.R218H in *ALB*) and one case of TSH resistance (p.C41S in *TSHR*) were identified, along with one CeH case. This latter infant was referred after positive TT4 screening (TSH 2.25 mU/l, TT4 5.21 ng/dL on DBS; TSH 6.03 mU/l, fT4 8.6 pmol/l in serum; reference range 13.9-36.1). Clinically, the infant had respiratory distress requiring intubation, hypotonia managed with physiotherapy, constipation, and growth delay. Repeated tests confirmed low fT4 (TSH 4.8 mU/l, fT4 7.3 pmol/l), prompting levothyroxine 10 mg/kg/day. Genetic testing revealed a previously reported pathogenic *IRS4* variant (p.L592fs*12) inherited from the euthyroid mother. The grandmother had normal thyroid function, while the grandfather and older brother (age 4 years) showed biochemical CeH and are predicted to be carriers of the X-linked *IRS4* variant.
Conclusion
A combined TSH+TT4 measurement on DBS allowed the detection of 1 CeH case and 1 RTHβ case out of 15.000 newborns with negative TSH screening, two clinically significant thyroid disorders that would have otherwise remained undetected. The CeH case highlights the added value of TT4 screening.

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OP-03-05

Effects of tiratricol treatment withdrawal in monocarboxylate transporter 8 (MCT8) deficiency: the retriact trial

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Background
Monocarboxylate transporter 8 (MCT8) deficiency is a rare, X-linked, life-shortening neurodevelopmental and metabolic disorder due to mutations in the thyroid hormone transporter MCT8. Patients typically have profound neurocognitive impairment and persistent peripheral thyrotoxicosis. Tiratricol, a thyroid hormone receptor (THR) agonist that preferentially binds THR-β relative to T3, has been shown to normalize serum T3 concentrations and improve heart rate, blood pressure, body weight, and mortality.
Objective
To assess the effects of withdrawal of tiratricol vs continued treatment on serum total T3 concentrations.
Methods
ReTRIACt (NCT05579327) was a phase 3, multicenter, double-blind, randomized, placebo-controlled study. Male subjects ≥ 4 years of age on stable maintenance treatment with tiratricol were randomized 1:1 to receive placebo or tiratricol for 30 days (randomized treatment period, RTP) or until reaching the rescue criterion (serum total T3 above upper limit of normal, measured by LCMS/MS). Primary endpoints were the rate of change in serum total T3 and the proportion of subjects requiring rescue during the RTP.
Results
Fifteen subjects were enrolled and randomized [placebo ($n = 8$); tiratricol ($n = 7$)]. The rate of change in serum T3 showed a statistically significant difference between placebo and tiratricol (ratio = 1.494, 95%CI: 1.035–2.155, $P = 0.0341$), corresponding to an estimated 59% increase in serum T3 over the 30-day RTP for subjects in the placebo group vs 6% in the tiratricol group. The rescue criterion was reached by more subjects ($n = 4$; 50%) in the placebo group than in the tiratricol group ($n = 1$; 14.3%, imputed) ($P = 0.182$). One subject randomized to tiratricol discontinued during the RTP due to non-medical family reasons. All subjects randomized to placebo had an expected decrease in serum T3 upon reinitiation of tiratricol in the follow-up period. Tiratricol was well-tolerated: six serious adverse events were reported in four subjects; none were considered treatment-related. There was one death due to aspiration pneumonia and resultant respiratory failure.
Conclusions
In this placebo-controlled trial of tiratricol in subjects with MCT8 deficiency, we showed that withdrawal of tiratricol results in a significant increase in serum T3. These data corroborate existing evidence that tiratricol is well-tolerated and effectively normalizes serum T3, further indicating the potential for tiratricol in the treatment of MCT8 deficiency.

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OP-03-06

Clinical rationale for levothyroxine initiation in patients with normal or mildly elevated TSH levels: real-world insights from primary care practices

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Background
Levothyroxine (LT4) is among the most frequently prescribed medications in primary care. Although guidelines discourage LT4 therapy in euthyroid individuals or those with only mildly elevated thyroid-stimulating hormone (TSH) levels, registry studies suggest that 14–30% of initial prescriptions occur when TSH is within the normal range. The clinical rationale underlying these prescriptions remains poorly understood, representing a key knowledge gap that must be addressed to reduce unnecessary LT4 prescribing.
Objective
To examine documented reasons for initiating LT4 therapy in patients with normal or mildly elevated TSH levels in primary care.
Methods
We conducted a retrospective cohort study using electronic medical records from the Integrated Primary Care Information (IPCI) database in the Netherlands (2006–2024), including approximately 2.5 million patients. Adults with a first LT4 prescription and a TSH measurement within 90 days before treatment initiation were included. For patients with euthyroidism, mild subclinical hypothyroidism (TSH ≤ 6.0 mIU/l), or hypothyroxinemia at initiation, manual

chart review was performed to determine the rationale for thyroid function testing, treatment initiation, and documented symptom outcomes. This approach provided a unique opportunity to gain insight into the reasons for prescribing LT4 therapy among patients with (sub)normal thyroid hormone levels in primary care.
Results
Among 9,091 patients initiating LT4 therapy (mean age 55.3 years; 77.4% women), 14.7% started treatment for mild subclinical hypothyroidism and 4.9% despite normal TSH levels. Among patients with normal TSH or mild subclinical hypothyroidism (n = 1,740), common reasons for prescribing LT4 were interpretation of biochemical thyroid status as abnormal (37.4–72.7%), attribution of nonspecific symptoms to thyroid dysfunction (21.0–26.9%), and patient request (8.0–25.8%). Symptoms prompted initial thyroid function testing in 74.0% of cases, most frequently fatigue (55.2%), followed by weight gain (17.2%) and musculoskeletal pain (12.5%). At one-year follow-up, only 22.3% of patients with documented absence of symptom improvement discontinued LT4 therapy.
Conclusion
This study provides insights into reasons for LT4 initiation in patients with normal or only mildly elevated TSH levels, thereby identifying potential targets for interventions aimed at improving guideline adherence and reducing unnecessary LT4 use in primary care.

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Oral Session 4: Young Investigator (basic)

OP-04-01

A novel approach to inhibit TSH receptor signaling as a potential treatment for graves' disease

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Introduction
Graves' disease is an autoimmune disorder caused by stimulating autoantibodies targeting the Thyroid Stimulating Hormone Receptor (TSHR), leading to hyperthyroidism. Approximately 25%-40% of patients develop Graves' orbitopathy, an inflammatory eye disorder affecting the retro-orbital tissues. Current therapies do not target the root cause in Graves' disease or Graves' orbitopathy. The TSHR is a G protein-coupled receptor that can be activated by TSH, produced by the pituitary, or TSHR-stimulating antibodies (TSHR-Ab), with cyclic adenosine monophosphate (cAMP) as a key second messenger downstream of TSHR activation. We established a luciferase-based cAMP biosensor assay in human thyroid cells that retain endogenous TSHR signaling to screen for antisense oligonucleotides (ASOs) that target the *TSHR* mRNA for degradation.
Methods
The human differentiated oncocytic thyroid carcinoma cell line XTC.UC1, which endogenously expresses TSHR and thyroglobulin, was lentivirally transduced with the cAMP biosensor 22F. Cells were incubated with TSHR targeting or negative control Gapmer ASOs for 9 days and subsequently stimulated with bovine TSH, the TSHR-Ab M22, or the adenylyl cyclase activator forskolin as a positive control. Luminescence was measured and effect measures were calculated by first normalizing to solvent controls and calculating the fold change relative to the forskolin stimulated conditions. More than 80 different ASOs targeting the *TSHR* mRNA were screened with various backbone modifications.
Results
Intracellular cAMP production was activated by both TSH and M22 in a dose dependent manner, thus providing a method that allows for screening of *TSHR*-targeting ASOs. Initial screening with 14 different *TSHR* targeting sequences and 11 negative control sequences identified 3 lead sequences that showed the most significant reduction in cAMP signaling. Subsequent efforts to optimize the 3 sequences using ASOs of different sizes (16-20 nt), backbone and base modifications such as phosphorothioate, locked nucleic acid, 2'-methoxyethyl, 5-methylcytosine, and constrained ethyl modifications, yielded molecules that showed more than 80% reduction of TSHR signaling by TSH and M22 stimulation through unassisted uptake of these ASOs in the micromolar range.
Conclusion
We developed *TSHR* targeting ASOs that robustly inhibit TSHR signaling in the micromolar range in a human thyroid cell model via unassisted uptake. Our results represent a crucial first step in the development of an antisense therapy that targets a critical component in the pathophysiology of Graves' disease and Graves orbitopathy.

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OP-04-02

Molecular recognition of thyroglobulin by sortilin

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Thyroglobulin (TG) is the precursor of thyroid hormones and a central regulator of their storage and release. Following iodination and hormonogenesis within the follicular lumen, TG must be efficiently internalised by thyrocytes to undergo proteolytic processing and enable hormone secretion. Dysregulated TG processing has been implicated in hypothyroidism, goitre, thyroid cancer and autoimmune diseases. Despite the essential role of TG retrieval in maintaining thyroid hormone homeostasis, the molecular mechanisms governing its uptake remain poorly understood. Sortilin, a multifunctional endocytic receptor highly expressed in thyroid tissue, has been proposed to mediate TG internalisation, particularly of highly iodinated TG forms. However, the structural and mechanistic basis of this interaction remains unknown. Here, we integrate structural biology, biophysical analyses, and functional endocytosis assays in human thyroid cell lines to elucidate the mechanism of TG recognition by sortilin. We show that sortilin preferentially binds monomeric TG rather than its native dimeric form, revealing an unexpected conformational selectivity in TG uptake. Notably, *in vitro* iodination assays show that iodine incorporation does not significantly affect sortilin binding, indicating that recognition is independent of TG hormone content. Structural analysis of the sortilin–TG complex identifies a conserved C-terminal TG motif that docks into the β-propeller cavity of sortilin in a manner consistent with other known ligands. Computational modelling and sequence comparisons further reveal shared chemical features that may underlie sortilin's broad ligand repertoire. Based on these findings, we propose a model in which TG, secreted as a hormonogenic dimer, undergoes extracellular cathepsin-mediated proteolysis over time, leading to monomerisation and exposure of the C-terminal sortilin-binding motif. Independently of iodination, monomeric TG could then be recruited by sortilin for endocytic trafficking. This model aligns with the observation that both cathepsins and sortilin are upregulated by TSH stimulation, a key regulator of TG internalisation and thyroid hormone release, and suggests that sortilin-mediated trafficking may be linked to TG proteolysis rather than directly to iodination. By defining the structural basis of TG recognition, our study provides a molecular framework for future investigations of TG trafficking in more complex systems, including thyroid organoid models to evaluate the impact of sortilin on hormone production. Overall, these findings clarify the molecular principles governing TG–sortilin interaction and its role in TG processing and endocytic trafficking, while revealing a molecular interface that could be targeted to modulate thyroid hormone homeostasis.

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OP-04-03

Role of B-tubulin glutamylation in thyroid development and function

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Context
Discovery of mutations in a β-tubulin-encoding gene, *TUBB1*, in congenital hypothyroidism, has revealed an unexpected role of the microtubule cytoskeleton in thyroid development and hormone secretion. Microtubules are regulators of biological processes, including cell division, shaping, motility and intracellular

transport. Early studies have shown that a proper microtubules integrity in thyroid is required for follicular organization and thyroid hormone secretion. However, the specific roles of individual tubulin isotypes and their post-translational modifications (PTMs), such as polyglutamylation - collectively, known as the tubulin code - remain largely unexplored. The tubulin code programs microtubules for specific intracellular functions by changing their dynamics and stability in cells, or regulating the interaction with proteins. Consequently, microtubules-related mechanisms underlying thyroid development and physiology are still poorly understood.
Objective
To decipher the role of tubulin polyglutamylation in thyroid development and function.
Results
First, using immunoblotting, we confirmed that microtubules in thyroids of both developing and adult mice are indeed posttranslationally polyglutamylated. In order to study polyglutamylation developmental progression and to identify the enzymes responsible for this PTM in the thyroid, we cultured the thyroid gland tissue from E13.5 embryos using an ex vivo system, with and without TSH. *Ttll7*, encoding a β-tubulin-specific polyglutamylase was found to be the strongest polyglutamylation enzyme increased under TSH during thyroid culture. This prompted us to study the role of Ttll7 in thyroid differentiation and physiology. To do so, we took advantage of the *Ttll7* knockout (ko) mice, lacking tubulin glutamylation. These animals exhibit marked thyroid hypoplasia at E13.5 and E17,5, reduced T4 and thyroglobulin production at E17.5, and decreased T4 plasma level at adult stages, with statistically significant differences between ko and wild-type animals. In adult mice, a trend toward thyroid hypoplasia was observed but did not reach statistical significance, suggesting potential compensatory mechanisms. Interestingly, electron microscopy of adult *Ttll7* ko mouse thyroids show abnormally large vesicles, suggesting vesicular defects in thyrocytes. Surprisingly, transcriptomic profiling at E13,5 and E17.5 indicates broad downregulation of cytoskeleton-associated genes not well known to be expressed in thyrocytes. In parallel, pathways involved in proliferation, cell cycle regulation, DNA repair, inflammation and apoptosis are upregulated.
Conclusion
Our findings suggest that TTLL7-dependent tubulin modification is a critical regulator of microtubules with an impact on thyroid organogenesis and thyroid hormone secretion at the adult stage. Ongoing analyses aim to elucidate the cellular mechanisms underlying thyroid dysgenesis and impaired hormone secretion caused by *Ttll7* deficiency.

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OP-04-04

The emerging role of astrocytes in seizure susceptibility in murine Mct8/Oatp1c1 deficiency

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In humans, inactivating mutations of the thyroid hormone (TH) transporter MCT8 cause Allan–Herndon–Dudley syndrome (AHDS), a severe psychomotor retardation characterized by profound neurological impairments and frequent epileptic seizures of unknown etiology. These clinical manifestations are thought to derive from impaired TH transport across brain barriers and into neural cells. Mct8/Oatp1c1 double-knockout (M/O dKO) mice represent a well-established AHDS model, recapitulating key features of this pathology such as the increased seizure susceptibility and altered hippocampal neurotransmitter system development. Here, we aimed to elucidate further the mechanisms underlying the increased seizure susceptibility in M/O dKO mice, focusing on the hippocampus, a central region in seizure development. LC-MS/MS-based proteomic analysis on hippocampal homogenates from 4-month-old animals, followed by gene ontology enrichment analysis, identified synaptic modulation, ion transport, and glial cell differentiation as the most significantly affected biological processes in M/O dKO hippocampi. This highlights a central involvement of astrocytes. Consistently, several astrocyte-associated ion channels and transporters, including Kcnj10, Atp1a2, Atp1b2, and Slc22a2, were downregulated in these animals, as confirmed by qPCR and Western blot analyses, despite pronounced astrogliosis evidenced by increased astrocyte numbers. Given the critical role of Kcnj10 in potassium buffering, which is required for efficient glutamate clearance, we next assessed glutamate levels by LC-MS and observed elevated hippocampal glutamate concentrations in adult M/O dKO mice. Together, these findings indicate that deletion of Mct8/Oatp1c1, and the resulting TH deficiency, disrupts astrocytic ion and glutamate homeostasis, which may contribute to hippocampal hyperexcitability and increased seizure susceptibility.

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OP-04-05

Intrinsic IFN-I signaling drives dedifferentiation and PD-L1-mediated immune escape in anaplastic thyroid cancer

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Background
Anaplastic thyroid carcinoma (ATC) frequently arises through dedifferentiation of papillary thyroid cancer (PTC), yet the molecular mechanisms linking tumor dedifferentiation and immune escape remain incompletely understood.
Methods
We used a genetically engineered mouse model with thyrocyte-specific expression of mutant ALKF1174L combined with Trp53 deletion, which recapitulates the progression from PTC to ATC. A panel of thyroid cancer cell lines representing different stages of tumor evolution was established and characterized using transcriptomic profiling, *in vivo* tumor models, and functional immunologic experiments.
Results
PTC-like tumors were efficiently controlled *in vivo* by CD8? T cell–mediated anti-tumor responses, whereas ATC-like tumors demonstrated progressive growth and immune escape. Transcriptomic profiling revealed a marked enrichment of type I interferon (IFN-I) signaling in ATC-like cells, with progressive upregulation of interferon-stimulated genes including ISG15 and IRF7 during tumor evolution. Functionally, ATC-like cells responded to IFN stimulation with strong PD-L1 upregulation, promoting immune evasion. *In vivo* blockade of PD-L1 significantly suppressed tumor growth. Likewise, pharmacologic inhibition of JAK signaling using ruxolitinib reduced PD-L1 expression and limited tumor progression.
Conclusions
These findings identify a cell-intrinsic IFN-I–JAK–PD-L1 axis as a key mechanism linking thyroid cancer dedifferentiation to immune escape. Therapeutic targeting of this pathway may restore anti-tumor immunity and represents a potential strategy for the treatment of aggressive thyroid cancers.

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OP-04-06

DNA methylation biomarkers and pathways associated with lenvatinib resistance in differentiated thyroid cancer

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Patients with differentiated thyroid cancer (DTC) refractory to radioactive iodide (RAI-R) are usually treated with Lenvatinib (LEN) as a first line treatment. However, some patients do not respond, and most initial responders eventually develop resistance. Biomarkers predicting LEN response are limited, and the mechanisms underlying resistance remain poorly understood. DNA methylation, a key epigenetic mark involved in gene expression and chromatin structure, has emerged as a promising prognostic biomarker in thyroid cancer. In line with this, we previously identified a panel of DNA methylation biomarkers associated with the risk of distant metastases in DTC. Here, we aimed to use DNA methylation to identify biomarkers of response to LEN and elucidate the pathways associated with LEN resistance. We used Illumina's Infinium MethylationEPIC arrays to generate DNA methylation profiles from 21 DTC patients treated with LEN, as well as from a LEN-resistant cell model developed in our laboratory. We also analysed gene expression from the resistant cell model using bulk and single-cell RNA-seq, and integrated all data with clinicopathological and other molecular features. We identified over 32,000 CpGs whose methylation correlated with progression-free survival after LEN treatment, and over 69,000 CpGs differentially methylated between resistant and sensitive cells in the *in vitro* model. About 1,300 CpGs were common to both analyses, representing a robust set of candidate biomarkers for LEN response. Many of these CpGs were linked to thyroid-specific genes, LEN receptors and other genes involved in pathways that have been previously associated with LEN resistance in hepatocellular carcinoma, including RNA methylation and cytoskeleton organisation. Some of these genes were also differentially expressed in the resistance model and further validated by qPCR. Additionally, we performed a differentially methylated region analysis, identifying candidate genomic regions overlapping significant CpGs and genes from the previous analyses, further validating our findings. Our results suggest that DNA methylation plays a role in the resistance to LEN in DTC and highlight specific pathways involved in this process. Moreover, we provide potential candidate biomarkers associated with response to LEN, offering a step towards more personalised treatment strategies for RAI-R DTC patients.

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Oral Session 5: Clinical Updates in Thyroid Cancer (clinical/cancer)

OP-05-01

Mildly elevated CTN levels in patients with thyroid nodules: a conservative management strategy

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Background
Calcitonin (CTN) represents the most sensitive biomarker for the preoperative diagnosis of medullary thyroid carcinoma (MTC). Nevertheless, the routine use of CTN measurement remains debated, particularly to a slight extent. Our study aimed to assess the prevalence and the clinical significance of mildly elevated CTN levels.
Methods
A total of 13,315 consecutive patients evaluated for the first time at the Endocrinology Unit of the University of Pisa (2017-2024) for thyroid nodules were analyzed. All patients underwent the same-day clinical assessment, neck ultrasound, and CTN measurement. Serum CTN levels were determined using a CLIA assay (n.v. $<$11.5 ng/l in females and $<$18.2 ng/l in males).
Results
Elevated CTN levels were observed in 162/13,315 patients (1.2%). Among those, 46/162 (28.4%) underwent surgery for CTN (median 46.35 ng/l, IQR 22.4-143) $\pm$ FNAC, suggestive of MTC. In the remaining 116 (71.6%), in which CTN elevation was the only potential indication for surgery, active surveillance was performed. These cases had a median CTN value of 20.8 ng/l (IQR 14.7–25.5). Twenty-four patients (20.7%) (median CTN 21.1 ng/l; IQR 14.43–23.6) were lost during the follow-up and were excluded from further evaluation. The remaining 92 patients (79.3%) with a baseline median CTN value of 20.8 ng/l (IQR 14.7–25.5), were followed for a median of 15.9 months (IQR 4.7–38.8). In 48/92 patients (52.2%) (group 1) (baseline median CTN 17.8 ng/l - IQR 13.3–22), CTN concentrations normalized in a median follow-up of 13.6 months (IQR 2.8–28.2). However, 10/48 patients (20.8%) subsequently experienced a mild increase in CTN, but with levels not different from baseline. Conversely, in 44/92 patients (47.8%) (group 2), with a baseline median CTN value of 23.7 ng/l (IQR 19.8–32.5), CTN values persisted slightly elevated in a median follow-up of 19.4 months (IQR 6.5–37.1). Nevertheless, a reduction in median CTN levels was observed during follow-up (from 23.7 to 20.25 ng/l; $P = 0.007$), and these patients remained under clinical surveillance. A statistically significant difference between groups 1 and 2 was observed in baseline CTN levels ($P < 0.01$).
Conclusions
In this large cohort of patients with thyroid nodules, mildly elevated CTN levels were uncommon, with a prevalence of $<$1%. During follow-up, many patients showed either normalization or stable CTN concentrations. These findings suggest that a conservative management strategy may be appropriate in such cases, with surgical intervention reserved for patients presenting with progressively increasing CTN values.

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OP-05-02

Clinical presentation and outcomes of medullary thyroid cancer in two european countries: impact of diagnostic strategies

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Objective
To evaluate differences in clinical presentation, therapeutic modalities and outcomes in two cohorts of patients with sporadic medullary thyroid carcinoma (sMTC) from reference centres in Italy and the Netherlands, differing in the use of routine calcitonin (CT) measurement screening strategy. In the Netherlands, serum CT levels are determined only after cytological suspicion of MTC.
Methods
A total of 165 patients (106 Italian and 59 Dutch) were retrospectively included. Patients were diagnosed between 01/2000 and 01/2024 and had a follow-up of at least 6 months since primary treatment. The cohorts were compared overall and according to diagnostic modality. Logistic regression and multivariable Cox proportional hazards models were used to assess progression-free survival (PFS), disease-specific survival (DSS) and associated risk factors.
Results
The Dutch cohort presented a more advanced disease at diagnosis, as shown by larger tumour diameter (3.5 *vs* 1.2 cm), higher TNM (T3-T4 37 *vs* 19%, N1b 45% *vs* 19%, M1 25 *vs* 6%), more severe AJCC staging (Stage III-IVA/C 76 *vs* 28%) and significantly higher pre-operative CT levels [for all, $P < 0.001$]. Dutch patients received more second operations, radiotherapy, and systemic treatments. Outcome variables were worse in the Dutch cohort: 10-year PFS 68 *vs* 88%, P 0.001 and 10-year DSS 85 *vs* 96%, P 0.009. No differences were found in treatment and outcome after dividing patients per disease stage. The presence of

T4 tumours, N1b, distant metastasis at diagnosis and their progression during follow-up were independently associated with a shorter DSS (HR: 4.56, P 0.03; HR: 11.8, P 0.002; HR: 15.1, P 0.0002; HR: 7.5, $P = 0.013$, respectively). Patients diagnosed via FNAC presented a more advanced clinical presentation at diagnosis and more severe survival outcomes, independently of the centre: median tumour diameter (2.2 *vs* 1.1 cm, P 0.001), AJCC III–IV (54 *vs* 23%, $P < 0.001$), distant metastasis progression (27% *vs* 9%, $P = 0.01$) and death from MTC (11% vs 2%, P 0.06).

Conclusion

We compared for the first time two MTC cohorts from countries with different diagnostic and therapeutic approaches. Our data contribute to highlighting an association between routine CT measurement and MTC presentation and outcome.

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OP-05-03

Extranodal extension as a predictor of distant metastasis in papillary thyroid carcinoma

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Objective

Although papillary thyroid carcinoma (PTC) generally has a favorable prognosis, certain histopathological features may adversely affect disease course. Extrathyroidal extension (ETE) is a well-established risk factor for both locoregional metastasis (LRM) and distant metastasis (DiM). While ETE is incorporated into current staging systems, the clinical significance of extranodal extension (ENE) from metastatic LN remains unclear. Although ENE has been associated with aggressive disease behavior, its relationship with DiM has not been fully clarified. This study aimed to investigate the impact of ENE on the development of distant metastasis in patients with PTC.

Methods

In this single-center retrospective study, patients with PTC who underwent surgery between January 2010 and April 2023 were included. Clinicopathological data were obtained from medical records and pathology reports. ENE was defined as the extension of tumor cells beyond the LN capsule into the surrounding perinodal fibroadipose tissue. Evaluation of ENE was performed independently by two pathologists blinded to clinical information.

Results

A total of 228(64 with DiM and 164 with only LRM). Mean age was 47.9 ± 15.3 years, and $n = 16$(70.2%) of the patients were female. Mean follow-up duration was 66.8 ± 49 months. Patients with DiM were older(57 ± 17.2 vs 44.4 ± 12.9 years, $P < 0.01$) and had longer follow-up duration(82.9 ± 56.1 vs 60.6 ± 44.5 months, $P = 0.002$) than those with LRM. Primary tumor size was significantly larger in patients with DiM 27.9 ± 19.7 mm vs14.6 ± 9.2 mm, $P < 0.01$). Mean number of removed LN was similar between the distant DiM and LRM group(29.4 ± 21.6 vs 23.9 ± 20.0, $P = 0.06$), whereas the number of metastatic LN was significantly higher in the DiM group(7.9 ± 8.7 vs 4.7 ± 4.5, $P < 0.01$). Male sex was associated with a higher risk of distant metastasis($P = 0.026$). The presence of ETE was also significantly associated with DiM ($P = 0.001$). Similarly, DiM was significantly more frequent in patients with ENE compared with those without ENE [$n = 37$(57.8%) vs $n = 39$(23.8%), $P < 0.01$]. In multivariate logistic regression analysis, age(OR:1.069, $P < 0.01$), primary tumor size(OR: 1.086, $P < 0.01$), and presence of ENE(OR: 4.543, $P = 0.001$) were identified as independent risk factors for distant metastases.

Conclusion

ENE, older age, and larger primary tumor size are independent predictors of DiM in PTC. ENE may serve as an important marker of aggressive disease and should be carefully evaluated in metastatic LN to improve risk stratification and follow-up strategies.

Table 1. Clinicopathological Characteristics According to Presence of Distant Metastasis (DiM).

	Locoregional Met. (LRM) ($n = 164$)	Distant Metastases (DiM) ($n = 64$)	p value
Sex			0.026x
Female	122 (74.4%)	38 (59.4%)	
ETE	26 (15.9%)	23 (35.9%)	0.001[a]
ENE	39 (23.8%)	37 (57.8%)	<0.01[a]
Lymphovasc. Invasion	7 (4.3%)	5 (7.8%)	0.33[b]

[a]Chi-square. [b]Fisher's exact.

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OP-05-04

[^{68}Ga]Ga-CTR-FAPI versus [^{68}Ga]Ga-FAPI-04 PET/CT for patients evaluation in radioiodine-refractory differentiated thyroid cancer: a prospective comparative study

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Objective

Incorporating a sulfur (VI)-fluoride exchange (SuFEx) chemistry-based linker, FAPI-based covalent targeted radioligand (CTR) showed better tumor binding affinity and longer retention time than FAPI-04 in animal studies. This study for the first time compared the lesion detection efficacy of [^{68}Ga]Ga-CTR-FAPI PET/CT and [^{68}Ga]Ga-FAPI-04 PET/CT in a radioiodine-refractory differentiated thyroid cancer clinical cohort.

Methods

A single-center prospective comparative study was conducted, enrolling 40 RAIR-DTC patients with distant metastases. All patients underwent sequential [^{68}Ga]Ga-FAPI-04 PET/CT and [^{68}Ga]Ga-CTR-FAPI PET/CT examinations at a 24–48h interval. Two experienced nuclear medicine physicians performed blinded visual analysis of the images to assess lesion detection status. Semi-quantitative analysis included the measurement of maximum standardized uptake value (SUVmax) and tumor-to-background ratio (TBR) of lesions in different anatomical regions. The reference standard for lesion confirmation was a combination of conventional imaging, histopathological results (when feasible), and long-term clinico-radiological follow-up. The detection performances of the two imaging modalities ware compared in patient and lesion levels.

Results

Of the 40 enrolled patients, 37 had detectable metastatic lesions on both imaging modalities. Two patients had lesions exclusively detected by [^{68}Ga]Ga-CTR-FAPI PET/CT. [^{68}Ga]Ga-CTR-FAPI PET/CT achieved superior visual detection performance in 17.5% (7/40) of patients ($P = 0.016$) concerning lesion distribution areas. In total, 769 metastatic lesions were identified by the two tracers, with [^{68}Ga]Ga-CTR-FAPI PET/CT detecting 99.2% (763/769) and [^{68}Ga]Ga-FAPI-04 PET/CT detecting 62.4% (480/769) of lesions ($P < 0.001$). [^{68}Ga]Ga-CTR-FAPI PET/CT significantly improved detection rates in lung (99.4% vs 37.5%, $P < 0.001$), pleural/peritoneal (99.0% vs 76.4%, $P < 0.001$), lymph node (99.0% vs 81.7%, $P < 0.001$) and bone (100% vs 82.9%, $P = 0.031$) metastases. Semi-quantitative analysis showed that [^{68}Ga]Ga-CTR-FAPI PET/CT had significantly higher median SUVmax in lung (5.1 vs 3.8, $P < 0.001$) and bone (8.3 vs 3.4, $P = 0.013$) metastases, and significantly higher median TBR in local recurrence (11.2 vs 8.6, $P = 0.045$) and lymph node metastases (6.0 vs 5.1, $P = 0.026$) compared with [^{68}Ga]Ga-FAPI-04 PET/CT. Furthermore, [^{68}Ga]Ga-CTR-FAPI PET/CT exhibited additional cerebral and hepatic metastatic lesions as well as higher tracer uptake in shared lesions located at brain ($n = 1$), liver($n = 2$) and kidney ($n = 1$), while the only mediastinal soft tissue metastasis showed an SUVmax slightly higher in [^{68}Ga]Ga-FAPI-04 PET/CT.

Conclusion

[^{68}Ga]Ga-CTR-FAPI PET/CT exhibits superior lesion detection rate, higher tracer uptake and better tumor-to-background contrast compared with [^{68}Ga]Ga-FAPI-04 PET/CT in RAIR-DTC patients, thus enhances the comprehensive assessment of patients' tumor burden. These findings provide evidence for its potential as a novel and more effective molecular imaging and therapeutic agent.

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OP-05-05

Reshaping clinical practice: real-world evidence of surgical therapeutic de-escalation in differentiated thyroid cancer management in france from 2010 to 2022

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Objectives
Management of non-refractory radioiodine-differentiated thyroid cancer has progressively shifted toward therapeutic de-escalation. Pivotal randomized trials demonstrated the non-inferiority of low-activity radioiodine ablation (30 mCi vs 100 mCi; ESTIMABL, 2012; HiLo, 2012) and later supported omission of adjuvant radioiodine in selected patients (ESTIMABL2, 2022; IoN, 2025). Meanwhile international recommendations (ATA, ETA, ESMO) supported the use of lobectomy instead of total thyroidectomy for low-risk thyroid cancer. This study aimed to assess how these de-escalation process translated into clinical practice, by examining national trends in surgical management, using real-world data from the French National Healthcare System Database (SNDS), an administrative database covering health insurance claims for 99% of the French population.
Methods
Adult patients with incident non-refractory differentiated thyroid cancer were identified in 2010, 2014, 2018 and 2022 in the (SNDS), using ICD-10 codes C73 and D09.3. Only newly diagnosed cases were retained, excluding patients treated for thyroid cancer within two years prior to the index date. The index date corresponded to the date of thyroid surgery. To ensure a homogeneous cohort, patients with anaplastic or medullary cancer and metastatic or refractory disease were excluded, using procedure codes, drug reimbursement data (targeted therapies or immunotherapy), and repeated radioiodine treatments. Surgical procedures were categorized as lobectomy or total thyroidectomy (including completion surgery in one or more stage). Temporal trends in treatment patterns were assessed across the four study years.
Results
A total of 6,766, 7,870, 6,668, and 6,852 incident patients undergoing a thyroid surgery with a diagnostic of differentiated cancer were identified in 2010, 2014, 2018 and 2022, respectively. Over the study period, surgical management shifted toward less extensive procedures. The proportion of total thyroidectomies decreased from 85.3% in 2010 to 85.1% in 2014, 81% in 2018 and to 73.5% in 2022, while the proportion of lobectomies increased from 13.8% in 2010 to 25.8% in 2022. The proportion of patients requiring repeated surgeries within 18 months post-index date remained low and stable across the study period: 0.7–0.9% from 2010 to 2022.

Type of surgery	2010	2014	2018	2022	p-values
Total thyroidectomy	5772	6695	5399	5034	<0,0001
Lobectomy	935	1114	1221	1770	<0,0001
Repeated surgeries	59	61	48	48	0,26

Conclusion
These findings demonstrate a clear surgical de-escalation in the management of differentiated thyroid cancer, driven by an increasing use of lobectomy. Ongoing analyses of radioiodine use will further clarify the overall shift toward therapeutic de-escalation in routine clinical practice.

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OP-05-06

Disease progression with active surveillance versus immediate lobectomy in low-risk papillary thyroid microcarcinoma: the kompass prospective cohort study

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Objectives
Active surveillance (AS) and immediate lobectomy (IL) are established management strategies for low-risk papillary thyroid microcarcinoma (PTMC). This prospective nationwide multicenter cohort study aimed to compare clinical outcomes between AS and IL in patients with low-risk PTMC.
Methods
A KoMPASS study has been ongoing since 2020. A total of 1,226 patients were enrolled (616 in the AS and 610 in the IL group). After excluding those with insufficient follow-up, 1,063 patients (552 in the AS and 511 in the IL group) were included in the final analysis.
Results
Among 1,126 patients initially included, the mean age was 48 years, and 72% were female. More than 60% of patients were aware of AS at diagnosis, and prior awareness was associated with selecting AS. Patients undergoing IL were younger, more likely to reside in rural areas, and had larger tumors with more frequent capsular contact at diagnosis compared to those selecting AS. After a median follow-up of 32 months, 4 of 511 patients (0.8%) in the IL group experienced recurrence (two contralateral recurrences and two lymph node [LN] metastases). In contrast, 41 of 552 patients (7.4%) in the AS group showed disease progression (DP), including tumor enlargement ($n = 25$), LN metastasis ($n = 11$), intrathyroidal cancers ($n = 3$) , or both tumor enlargement and LN metastasis ($n = 2$). Overall, 114 patients (21%) in the AS group eventually underwent delayed surgery, including 33 patients with documented DP. Tumors that progressed were larger at baseline (7.8 $\pm$ 1.3 mm vs. 7.2 $\pm$ 1.1 mm, $P = 0.002$) and demonstrated significantly shorter tumor volume doubling times (2.4 years vs. not reached, $P < 0.001$) compared to stable tumors. IL was associated with a significantly lower risk of DP compared to AS (hazard ratio 0.07, 95% confidence interval 0.02–0.20, $P < 0.001$) after adjusting age, sex, and tumor size.
Conclusion
IL was associated with a markedly lower relative risk of DP compared with AS. However, the absolute progression rate under AS is modest, and manageable with timely intervention. These findings underscore that treatment strategy for low-risk PTMC should be individualized.

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OP-05-07

Determinants and center-level variation in radioactive iodine use for pediatric differentiated thyroid carcinoma: insights from the multi-center pedimap registry

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Objectives
In paediatric and young adult differentiated thyroid carcinoma (DTC), survival is excellent, making treatment burden and potential overtreatment major concerns. In paediatric and young adult DTC, postoperative RAI use is guided by risk stratification, yet real-world practice patterns remain heterogeneous across centres and diagnostic eras.
Methods
We analysed multi-institutional registry patients aged 0-25 years with DTC. of 3498 entries, 1130 had pathology-confirmed histology, including 718 malignant thyroid tumours. RAI data were available for 541 patients, who formed the analytic cohort. The primary outcome was RAI administration (yes/no). Use was assessed by AJCC T, N, and M stage, multifocality, bilaterality, diagnostic era, and continent. Determinants were analysed using mixed-effects logistic regression with centre as a random intercept.
Results
RAI was administered in 62% of patients. Use increased with disease extent, from 29% in T1 to 94% in T4 tumours, from 39% in N0 to 88% in N1b disease, and was nearly universal in distant metastases. RAI was more frequent in multifocal than unifocal tumours (71.1% vs 55.5%) and in bilateral than unilateral disease (76.8% vs 55.3%), but these associations weakened after adjustment for stage, suggesting mediation by disease extent. RAI use declined in more recent eras, consistent with risk-adapted de-escalation. Substantial between-centre heterogeneity remained after adjustment (MOR 4.34; ICC 0.42), with variation across continents (EU vs USA).
Conclusions
In paediatric and young adult DTC, RAI use is driven mainly by disease extent and has decreased over time. However, marked residual variation between centres persists after adjustment, indicating that similar patients may receive different treatment depending on the institution. These findings highlight an implementation gap and support benchmarking and harmonised treatment pathways.

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Oral Session 6: TED (clinical)

OP-06-01

Prospective, randomized eugogo study evaluating the efficacy of two intravenous methylprednisolone dosages for acute dysthyroid optic neuropathy: preliminary results

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Objectives
Dysthyroid optic neuropathy (DON) is a sight-threatening complication of thyroid eye disease requiring immediate treatment. Although high-dose intravenous methylprednisolone (IVMP) remains the first-line therapy, the optimal dosing regimen lacks universal consensus. This prospective, randomized, double-blind, non-inferiority trial aims to evaluate and compare the clinical efficacy of two distinct IVMP dosing protocols.
Methods
Twenty-three patients (30 orbits) diagnosed with acute DON were randomized into two treatment arms. Both groups received two cycles of IVMP administered over two consecutive weeks (three consecutive days per week). Group 1 (12 patients, 15 orbits) was treated with 500 mg/day (cumulative dose: 3.5 g), while Group 2 (11 patients, 15 orbits) received 1000 mg/day (cumulative dose: 6.0 g). The study was double-blinded for both patients and ophthalmologists. Clinical evaluations were performed at 1, 2, and 4 weeks. Treatment efficacy at the 4-week mark was determined based on the following criteria: Best Corrected Visual Acuity (BCVA) $>$ 0.7, Hardy-Rand-Rittler (HRR) color vision test $\leq$ 2 errors, Visual Field Mean Deviation (MD) $\geq$ -6 dB, and the complete resolution of optic disc edema.
Results
The study cohort had a mean age of 60.5 $\pm$ 11.4 years, comprising 11 males and 12 females. Baseline clinical parameters—including BCVA, color vision, visual field MD, exophthalmometry values, and the presence of papilledema—were statistically comparable between the two cohorts (P = ns). At the final 4-week follow-up, the clinical response rate was 53.3% (8 of 15 orbits) in the 500 mg cohort and 60.0% (9 of 15 orbits) in the 1000 mg cohort, revealing no statistically significant difference between the dosages ($P > 0.05$). Notably, 6 non-responding orbits in each group ultimately required surgical decompression.
Conclusions
These preliminary findings indicate that a 500 mg IVMP protocol is non-inferior to a 1000 mg regimen in the management of acute DON. Consequently, adopting a lower-dose IVMP strategy is supported, as it preserves clinical efficacy while maximizing patient safety through a reduced cumulative steroid burden.

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OP-06-02

Graves' disease in children and adolescents: clinical characteristics, management strategies, and thyroid eye disease profile

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Introduction
Graves' disease (GD) is the leading cause of hyperthyroidism worldwide. Although its clinical presentation is well characterized in adults, data on pediatric GD remain limited, particularly regarding Thyroid Eye Disease (TED).
Objectives
To evaluate the clinical presentation and treatment strategies in children diagnosed with GD.
Methods
This retrospective study included patients diagnosed with GD before the age of 18 years. Patients were evaluated for epidemiological characteristics, thyroid function biomarkers, clinical features of TED, therapeutic interventions, and GD treatment modalities.
Results
A total of 96 patients were included, of whom 78,13% were female. The mean age at diagnosis was 12 $\pm$ 4.2 years. Thyroid function assessment showed a mean TSH of 1.89 $\pm$ 3.42 µIU/mL and mean free T4 of 4.26 $\pm$ 2.61 ng/dL. TSH receptor antibodies (TRAb) were positive in 92% of patients, with a mean level of 28.02 $\pm$ 27.38 IU/l (reference $<$ 3.10 IU/l). At initial evaluation, the mean thyroid volume measured by ultrasound was 30.21$\pm$ 30.09 mL. TED evaluation demonstrated a mean proptosis of 20.83 $\pm$ 3.33 mm, mean palpebral fissure height of 12.04 $\pm$ 1.92 mm, and mean Clinical Activity Score (CAS) of 0.8 $\pm$ 1.17. According to EUGOGO classification, TED severity was mild in 50% of patients and moderate-to-severe in 23%, while no patients had sight-threatening disease. Notably, 26.92% of patients had no clinical signs of TED. The primary treatment for mild TED consisted of lubricating eye drops. Only one patient required intravenous glucocorticoid therapy, receiving a cumulative dose of 4.5 g of methylprednisolone over 12 weeks. The preferred initial treatment modality for GD was anti-thyroid drugs (ATD), used in 90.91% of patients, followed by radioiodine therapy (RAI) in 3.9% and thyroidectomy 5.19%. The mean initial methimazole dose was 21.75 $\pm$ 14.3 mg. After 12 months, 85.71% of patients remained on ATD therapy, 12.12% had received RAI, and 2% had achieved remission. At 24 months, 84.38% remained on ATD, 12.5% had received RAI, and 3.13% achieved remission. At 36 months, 71.43% remained on ATD, 14.29% had received RAI, and 14.29% achieved remission. At 48 months, 50% remained on ATD, 10% had received RAI, 30% achieved remission, and 10% thyroidectomy.
Conclusion
This study demonstrates a high prevalence of TED in pediatric patients with GD compared with adult; however, most cases presented with mild disease and a low frequency of severe or sight-threatening manifestations.

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OP-06-03

Mild thyroid eye disease (MTED) is more than "wait-and-see" – results of the european group on graves' orbitopathy (EUGOGO) survey

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Objectives
Mild thyroid eye disease (mTED) is the commonest presentation of TED, yet very few studies have included such patients. mTED is generally considered to be self-limiting, requiring only topical therapy, selenium supplementation and risk factor management.
Methods
An online survey of members of EUGOGO was conducted between 6 January-6 February 2026, to document current management practices for patients with mTED at experienced, multidisciplinary referral centres. The study was in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) recommendations, comprising 40 questions relating to the prevention, assessment, and treatment of mTED.
Results
Eighty-four of 122 EUGOGO members (69%) completed the survey: 51.2% endocrinologists and 46.4% ophthalmologists from 14 European and 1 Singaporean centre. Smoking, prolonged dysthyroidism, radioiodine treatment without steroid prophylaxis and high TSH-R autoantibodies levels were considered the most important risk factors for mTED development/progression. In patients with mTED, 45.6% of respondents would consider thyroid surgery as initial treatment for the Graves' hyperthyroidism; 91.1 % and 45.6% of respondents would use selenium or statins to prevent or treat mild TED. More than 70% of respondents used the 7-point CAS score, disease progression and measurement of TRAb levels to assess disease activity. Orbital imaging was chosen by 73.1% of respondents, with non-contrast-enhanced MRI being the commonest investigation (52.6%). The majority of endocrinologists would refer to ophthalmological examination for the assessment of ocular surface disease and eye motility dysfunction (96.1% and 78.0%, respectively).The most commonly prescribed additional local treatments were topical corticosteroids (26.9%), steroid sparing topical immunosuppression (16,7%) and botulinum injections for lid retraction (24.4%), apart from tear supplements. The same proportion of ophthalmologists and endocrinologists (comprising 45% of respondents) would prescribe systemic treatments: IVGC 4.5 g regimen (34.6%), IVGC 2.25 g regimen (17.9%), tocilizumab (12.8%), oral GC (7.7%) and mycophenolate (7.7%). Indications for systemic treatments included: soft tissue involvement (53.8%), proptosis (41.0%), transient diplopia (43.6%) and impaired QoL (53.8%). Surgical treatment was required in up to 25% of patients, with blepharoplasty (46.2%) and lid surgery (64.1%) being the most common procedures.
Conclusions
The high proportion of respondents who chose systemic treatments and surgery for mTED, is novel and may reflect a perception that a higher number of these patients could benefit from treatments other than those currently recommended. The significant functional burden and impact on QoL support the view that mTED should benefit more from experienced, multidisciplinary management.

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Abstract Withdrawn

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OP-06-05

Trends in thyroid eyes disease incidence and prevalence in france, 2019-23: a nationwide population study

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Objective
Thyroid eye disease (TED) is a rare, autoimmune disease occurring in up to 40% Graves' disease patients that affects orbital tissues and could lead to visual impairment. Despite the evolving therapeutic landscape, recent epidemiological data are scarce. This study aims to estimate the incidence and prevalence of TED patients treated in hospital settings, to characterize the patients' profiles, and to describe treatment use in France.
Method
A nationwide real-world retrospective study was conducted using hospital secondary data from the French hospital discharge database (PMSI) between 2019 and 2023. International classification of disease tenth revision (ICD-10) codes for dysthyroid exophthalmos, Graves' disease, systemic ophthalmic symptoms and intravenous (IV) treatment administration were used to defined two patient identification algorithms: one sensitive for upper bound (UB) and one specific for lower bound (LB). Baseline characteristics and ophthalmic symptoms were identified using a 4-year follow-back period. Patients were followed until in-hospital death or end of the study period to identify TED-related treatments, including systemic IV therapy, orbital radiotherapy, and eye surgery. Standardized incidence rates were estimated with exact 95% confidence intervals.
Results
Over the five-year study period, between 4,063 (LB) and 6,821 (UB) prevalent patients and 3,328 (LB) and 5,864 (UB) incident patients were identified. The annual incidence consistently increased, from 1.57 [1.48; 1.67] per 100,000 inhabitants in 2019 to 1.95 [1.84; 2.05] in 2023 (UB). Median age was 54.0 years old (Q1-Q3: 42.0-64.0) and around 75.0% were women in both prevalent and incident cohorts. Approximately 90.3% of patients had either proptosis and/or diplopia symptoms at diagnosis. Among patients identified with sensitive algorithm, almost 60% (prevalent cases: 59.2% and incident cases: 58.0%) received at least one TED-related treatment. Among the 4,422 incident patients with at least one year of follow-up (UB), 2,083 patients (47.1%) received infusion of intra-DRG (diagnosis related group) IV drugs (likely corresponding to intravenous corticosteroids) while tocilizumab, rituximab and teprotumumab (available through compassionate use program) were used in 214 patients (4.8%), 69 (1.6%) and 27 (0.6%) patients, respectively. Orbital radiotherapy was used in 233 patients (5.3%). A total of 976 patients (22.1%) underwent at least one eye surgery, of which 25% undergoing two or more. The most frequent procedures were orbital decompression (13.1%), followed by eyelid surgery (8.4%), and strabismus surgery (7.4%).
Conclusion
This study provides the first nationwide estimates of TED epidemiology in France and a general overview of patients hospitalized for TED in France between 2019 and 2023.

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OP-06-06

Baseline disease activity, rather than disease duration, predicts treatment response in graves' orbitopathy

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Objectives
In clinical trials on Graves' orbitopathy (GO), a disease duration of <9-12 months is commonly required as an inclusion criterion, based on the assumption that late disease stages respond less favorably to treatment, presumably due to progressive tissue fibrosis. The aim of this study was to evaluate whether disease duration truly influences treatment response or whether baseline disease activity, expressed as the Clinical Activity Score (CAS), is a more accurate predictor.
Methods
A total of 134 consecutive patients with moderate-to-severe, active GO referred to our center for first-line treatment with intravenous glucocorticoids (ivGCs) (methylprednisolone, 4.5 g) were included. All patients were evaluated at baseline and after 24 weeks. Treatment response was defined according to the European Group on Graves' Orbitopathy composite response index. Patients were stratified into three groups according to GO duration (<12 months, 12–18 months, >18 months).
Results
Overall, 72.4% of patients were female and the mean age was 52.9 yr. (11.4, range 23–82). Responders (47/134, 35.1%) and nonresponders did not differ significantly for age, sex, smoking status, baseline thyrotropin receptor antibody (TRAb) levels, or hyperthyroidism treatment. Disease duration was not associated with treatment response in both univariate ($P = 0.17$) and multivariate analysis ($P = 0.13$), the latter including sex, age, smoking status, TRAb levels, and hyperthyroidism treatment. None of the other variables showed significant associations with treatment response. Baseline CAS was significantly higher in responders than in non-responders [4.51 (1.23) vs 4.08 (1.04); $P = 0.035$]. Among all variables evaluated, baseline CAS emerged as the only predictor of treatment response at 24 weeks. In logistic regression analysis, CAS remained independently associated with response both in the univariate (OR = 1.40, 95% CI: 1.02-1.93; $P = 0.038$) and in the multivariate model (OR = 1.42, 95% CI: 1.02-1.98; $P = 0.037$). These results indicate a 40% and 42% increase in the odds of response, respectively, for each additional point in CAS, regardless of age, sex, smoking status, TRAb levels, and treatment of hyperthyroidism.
Conclusions
Our findings challenge the assumption commonly adopted in clinical trials that a disease duration longer than 9-12 months implies a lower likelihood of response to therapy. In this cohort, disease duration was not a significant predictor, whereas baseline CAS was confirmed as an independent marker of treatment response. These data suggest reconsideration of inclusion criteria in clinical trials, namely that patients with active GO, even with a disease duration longer than 12 months, may still benefit from treatment.

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OP-06-07

Evaporative dry eye syndrome with reflex hyperlacrimation defines the ocular surface profile of moderate-to-severe active graves' orbitopathy: results from a cross-sectional study

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Objective
DED is a known complication of GO, but its link to disease activity and severity, as well as objective ocular surface assessment, remain poorly defined. This study evaluates DED prevalence and features in GD patients, with and without GO, versus healthy controls.
Methods
A total of 160 consecutive GD patients (101 with GO, 59 without GO) and 67 matched healthy controls were enrolled. DED diagnosis required OSDI ≥13 plus abnormal non-invasive breakup time (NIBUT) and/or meniscus tear height (TMH). Primary endpoint: DED prevalence in GD patients, with and without GO, compared to healthy controls. Secondary endpoints:1) DED prevalence in moderate-to-severe active GO versus mild GO;2) comparison of OSDI and objective ocular surface parameters across disease groups;3) correlation between OSDI, objective ocular surface parameters and GO clinical features.
Results
DED was present in 102/160 GD patients, significantly more frequent than in healthy controls (OR 6.65,95%CI:3.35–13.1; $P < 0.0001$). Within GD patients, DED was more prevalent in those with GO than in those without (OR 2.82,95%CI:1.41–5.82; $P = 0.004$), with a significantly higher frequency in moderate-to-severe active GO compared to mild GO (OR 3.53,95%CI:1.28–9.55; $P = 0.01$). The OSDI score was significantly higher in moderate-to-severe active GO than in all other groups (all $P < 0.0001$), and higher in mild GO than in GD without GO ($P = 0.001$). A strong positive correlation was observed between OSDI and CAS ($r = 0.85$, 95%CI:0.79–0.90;$P < 0.0001$). Proptosis ≥22 mm and lagophthalmos were confirmed as independent risk factors for ocular surface disease (both $P = 0.001$). Among objective parameters, meiboscore was significantly higher across all GD subgroups compared to controls (all P≤0.01), and NIBUT showed a stepwise reduction across GD groups, with the lowest values observed in patients with moderate-to-severe active GO (all P≤0.01). Notably, TMH was paradoxically elevated across GD groups showing a graded increase that reached the highest values in moderate-to-severe active GO (all P≤0.01). Both TMH and bulbar redness correlated significantly with CAS (all $P < 0.0001$) and remained independent predictors of active GO on multivariate logistic regression ($P = 0.0009$).
Conclusions
Ocular surface disease burden increases along a severity gradient from GD without GO through moderate-to-severe active disease. The ocular surface profile of GO is characterized by a predominantly evaporative DED phenotype with paradoxical reflex hyperlacrimation, reflecting the interplay between meibomian gland dysfunction, corneal exposure and orbital inflammation. TMH and quantitative bulbar redness emerge as independent correlates of GO activity, supporting the routine integration of ocular surface assessment in the clinical evaluation of GO.

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Oral Session 7: Decoding Thyroid Cancer: New Insights from Basic Science (cancer)

OP-07-01

Polychlorinated biphenyls alter the molecular landscape of the thyroid normal and tumor cells differently

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Introduction
Our previous studies have shown that polychlorinated biphenyls (PCBs), persistent organic pollutants, alter thyroid differentiation markers in PCCL3 cells through epigenetic mechanisms and dysregulation of signaling pathways.
Objectives
To analyze the molecular alterations associated with PCB exposure in normal/malignant human thyrocytes.
Methods
Normal (Nthy-ori 3-1) and tumor (TPC1and BCPAP) thyrocytes were exposed, or not (control), for 24 h to Aroclor 1254, a PCB mixture, with doses 10^{-7} to 10^{-11} M. Gene expression was assessed by qPCR. Signaling pathways and histone methylation were evaluated by Western blotting. NIS function was evaluated by a non-radioactive iodide uptake assay. Cell viability was evaluated by MTT assay, oxidative stress by fluorescence assays, and cell migration by wound healing assays.
Results
PCB exposure reduced phospho-ERK levels in TPC1 and BCPAP cells, while increasing phospho-AKT in Nthyori cells and phospho-CREB in BCPAP cells. PCB exposure also altered the expression of enzymes involved in the epigenetic regulation of gene expression. In Nthyori and TPC1 cells, it reduced the expression of *DNMTs*, *HDACs, EP300*, and *KDM5c*, while increasing *HAT1* expression, a profile suggestive of enhanced transcriptional

activity. In contrast, BCPAP cells exhibited the opposite pattern. Consistent with these changes, Nthyori cells showed increased H3K4me3 and reduced H3K27me3 levels, whereas BCPAP cells displayed the reverse pattern. In TPC1 cells, both H3K4me3 and H3K27me3 levels were reduced. With respect to cell death, PCB exposure decreased the expression of the pro-apoptotic marker *BAX* and the necroptotic marker *RIPK1* in Nthyori and TPC1 cells, whereas both markers were increased in BCPAP cells. Cell viability was also differentially affected: it decreased in Nthyori cells, increased in TPC1 cells, and remained unchanged in BCPAP cells. Regarding epithelial–mesenchymal transition, PCB exposure increased migration in BCPAP cells, accompanied by higher expression of *VIM*, *SNAIL*, and *ZEB1* and lower expression of *E-CAD* and *TWIST*. In contrast, Nthyori cells showed reduced migration, associated with increased E-*CAD, TWIST,* and *ZEB1* expression and decreased *VIM* expression. In TPC1 cells, PCB exposure did not affect migration, although it increased the expression of *E-CAD, TWIST*, and *ZEB1*. Finally, PCB exposure increased iodide uptake and reduced ROS production in all three cell lines.

Conclusion

The PCB mixture modulates thyroid cell physiology in a manner that depends on whether thyrocytes are normal or malignant. Collectively, these findings indicate that PCBs differentially affect tumor-related phenotypes according to the molecular context of thyroid cells, reinforcing their potential contribution to thyroid dysfunction and tumor progression.

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OP-07-02

Combined exposure to BPA, nitrate, and perchlorate induces alterations in epigenetic and epithelial–mesenchymal transition pathways in thyroid cells

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Introduction

Endocrine disruptors (EDs), such as bisphenol A (BPA), nitrate, and perchlorate, are widely distributed in the environment and have been associated with adverse effects on thyroid function. At the same time, the increasing incidence of endocrine neoplasms, including thyroid carcinoma, has raised the hypothesis that environmental factors, such as ED exposure, may contribute to mechanisms of endocrine disruption and tumor progression.

Objectives

To evaluate the impact of exposure to a mixture of BPA, perchlorate, and nitrate on the expression of genes related to epigenetic regulation and epithelial–mesenchymal transition in normal and tumor thyroid cells.

Methods

BCPAP, TPC1, and Nthy-ori-3-1 cell lines were treated for 24 hours with a mixture of BPA, nitrate, and perchlorate at concentrations of 10^{-7}, 10^{-9}, and 10^{-11} M. Activation of the MAPK signaling pathway was evaluated by Western blotting, and gene expression was analyzed by qPCR.

Results

In Nthy-ori-3-1 cells, exposure to the mixture induced increased expression of mesenchymal markers, including *ZEB1, ZEB2, SNAI1*, and *SNAI2*, especially at the lowest tested dose. In addition, increased expression of *EZH2, HDAC3*, and *KDM5C* was observed in these cells. In BCPAP cells, only *ZEB2* expression was increased at all tested doses, along with increased expression of epigenetic markers associated with transcriptional repression, although only at the 10^{-9} M concentration. In TPC1 cells, increased *ZEB1* expression was observed, accompanied by reduced expression of genes involved in transcriptional repression, including *DNMT1, KDM5C*, and *HDAC3*. Regarding the MAPK pathway, exposure to the ED mixture increased pERK levels in Nthy-ori-3-1 and BCPAP cells, whereas no significant changes were observed in TPC1 cells.

Conclusion

The mixture of BPA, nitrate, and perchlorate induces alterations in genes related to epigenetic regulation and epithelial–mesenchymal transition in thyroid cells in a manner dependent on the genetic context. Taken together, these findings suggest that combined exposure to EDs may contribute to mechanisms associated with thyroid dysfunction and tumor progression.

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OP-07-03

From antibiotic to anticancer agent: antitumor effects of nifuroxazide in anaplastic thyroid carcinoma via JAK/STAT3 signaling modulation and oncogenic crosstalk

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Objective

To investigate the antitumor effects of nifuroxazide (NFZ) and three of its derivatives in anaplastic thyroid cancer (ATC) and to elucidate the mechanisms of action, focusing on the JAK/STAT pathway and its interaction with MAPK and PI3K pathways. Additionally, we assessed the impact of STAT3 knockout (STAT3-KO) on tumor properties of ATC cells and evaluated the effects of combining NFZ with BRAF or PI3K inhibitors.

Methods

ATC cells (HTH83 and KTC-2), STAT3-KO clones, and control cells were used. Cell viability and colony formation assays were performed to evaluate the effect of NFZ and its derivatives, as well as STAT3-KO. Modulation of the JAK/STAT3, MAPK, and PI3K pathways was assessed by Western blotting. Epithelial–mesenchymal transition (EMT) was analyzed by real-time PCR, and by migration and invasion assays. Cell death and reactive oxygen species (ROS) were determined by flow cytometry. Drug combination assays were conducted using BRAF and PI3K inhibitors.

Results

NFZ and its derivatives reduced colony formation, cell viability and induced apoptosis or necrosis in ATC cells, with ROS contributing to cell death in HTH83. Furthermore, NFZ decreased pSTAT3, pERK, and pAKT levels, suppressed migration and invasion, and increased E-cadherin expression. NFZ combined with BRAF or PI3K inhibitor reduced ATC cell viability, suggesting synergistic or additive effects. Notably, in STAT3-KO cells, NFZ reduced viability, colony formation, pERK and pAKT levels. In this cells basal levels of pERK and pAKT were increased, suggesting compensatory activation of the MAPK and PI3K pathways. STAT3-KO increased cell viability in KTC-2 but reduced proliferation in all cell lines. It also decreased vimentin expression in HTH83 while increasing it in KTC-2, without affecting colony formation.

Conclusion

NFZ reduced tumorigenic properties in ATC cells through modulation of the JAK/STAT3, MAPK and PI3K pathways. Our findings show that NFZ exerts broader signaling modulation beyond JAK/STAT3 and reveal bidirectional crosstalk within this oncogenic signaling network. These results highlight the therapeutic potential of NFZ repurposing, particularly in combination with targeted inhibitors, which may reduce adverse effects and delay drug resistance.

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OP-07-04

Targeting the interleukin-6 biology in anaplastic thyroid cancer to induce sodium iodide symporter (NIS)-mediated iodide uptake via engineered mesenchymal stem cells

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Objective

The sodium iodide symporter (NIS) provides the basis for the use of radioiodine (RAI) for diagnostic imaging and therapy of differentiated thyroid cancer (DTC). Anaplastic thyroid carcinoma (ATC) is unresponsive to radioiodine due to loss of NIS expression in the course of dedifferentiation. ATC is typically treated with a multimodal therapy approach, including surgery, targeted therapy ± immune therapy and radio chemotherapy with improved outcomes in the recent years,

however still poor prognosis in the absence of targetable mutations. The delivery of *NIS* as a transgene into the tumor microenvironment (TME) using mesenchymal stem cells (MSCs) has been demonstrated by our group as a promising strategy to restore NIS-mediated RAI uptake in RAI-refractory DTC. MSCs engineered to drive *NIS* transgene expression in response to IL-6-promoter activation may offer the possibility of a new tumor-targeted gene therapy approach of ATC. Therefore, MSCs were stably transfected with a NIS-expressing plasmid controlled by the human IL-6-promoter (IL-6-NIS-MSCs) to selectively drive *NIS*-transgene expression in the context of ATC with a strong inflammatory TME.
Methods
IL-6-NIS-MSCs were incubated with cytokines (IL-1 β, TNF-α and IFN-γ), strong activators of the IL-6 pathway, as well as with tumor cell conditioned medium (CM) derived from ATC cell lines SW1736 and 8505C, followed by analysis of the resulting functional NIS expression by ^{125}I uptake assay *in vitro*. Chemotactic behavior of IL-6-NIS-MSCs subjected to a gradient of CM of SW1736 and 8505C cells and growth medium was evaluated using 3D live-cell imaging migration assay over a period of 24 h. In a first *in vivo* imaging series, IL-6-NIS-MSCs were applied intravenously (i.v.) via the tail vein to mice harboring subcutaneous SW1736 and 8505C tumors and tumoral iodine uptake was monitored by ^{123}I-scintigraphy.
Results
IL-6-NIS-MSCs treated with IL-1 β, IFN-γ and TNF-α or SW1736- and 8505C-CM revealed significantly increased, perchlorate-sensitive ^{125}I uptake. IL-6-NIS-MSCs subjected to a gradient between tumor cell-CM and growth medium, showed stimulated migration towards tumor signals. *In vivo* biodistribution studies showed significant induction of tumor-selective iodine uptake in SW1736 and 8505C xenografts after i.v. injection of IL-6-NIS-MSCs with a maximum tumoral iodide accumulation of approximately $4.08 \pm 1.15\%$ (SW1736) and $4.19 \pm 0.82\%$ (8505C) of the injected dose per tumor.
Conclusion
In conclusion, the application of MSC-mediated NIS gene therapy focusing on IL-6 biology-induced NIS transgene expression represents a promising approach for the implementation of radioiodine therapy in ATC in a multimodal therapy approach.

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OP-07-05

Spatial profiling maps the transcription factor landscape driving the well-differentiated to anaplastic thyroid cancer transition

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Objectives
Anaplastic thyroid cancer (ATC) is a rare but highly aggressive malignancy characterized by a mortality rate exceeding 80%. While differentiated thyroid cancers (DTC) are often manageable, ATC is notoriously refractory to conventional therapies. Current evidence suggests that ATC frequently evolves from the dedifferentiation of pre-existing DTC, driven by a progressive accumulation of molecular alterations. The mechanisms driving this transition remain poorly understood, necessitating further investigation into the complex biological networks underlying the process. In this study, we aim to identify the key transcriptional drivers of ATC development to provide a comprehensive map of their interconnected roles in tumor progression.
Methods and Results
We took advantage of the GeoMx™ Digital Spatial Profiler to perform a high-resolution comparative transcriptomic analysis of ATC and DTC components within 7 biphasic thyroid cancer samples. We selected regions of interest based on PanCK and TTF1 expressions and sequenced the transcriptome using the Whole Transcriptome Atlas panel. Differential analysis identified a molecular signature subsequently validated by RNA-sequencing of an independent and larger cohort of pure DTC and ATC FFPE samples. This integrated approach provided insights into the biological processes underlying the DTC-ATC transition, highlighting five principal altered pathway clusters: epithelial-mesenchymal transition (EMT), cell cycle, thyroid hormone-related processes, immune system, and metabolism. To characterize the molecular drivers of this transition, we identified: (i) transcription factors (TFs) among the differentially expressed genes (DEGs), and (ii) TFs predicted to regulate these DEGs, through bioinformatic analyses. Using rigorous and unbiased prioritization, we refined a shortlist of candidate TFs that may orchestrate the ATC transcriptional program. Notably, most of these TFs are established regulators of the pathways most disrupted during the DTC-ATC transition and form a highly interconnected functional network. The biological significance of the most interesting candidates is assessed *in vitro* by measuring the impact of their knockdown in ATC cell lines. This validation encompasses the evaluation of proliferation and migration abilities to determine their potential involvement in sustaining key features of tumor aggressiveness.
Conclusions
Overall, this study seeks to provide a comprehensive molecular landscape of the DTC-ATC transition through a multi-layered characterization of the biological functions that drive the dedifferentiation process. By elucidating the synergy between interconnected signaling pathways and identifying the master transcriptional regulators, we provide a robust hierarchical regulatory framework that sustains ATC aggressive nature. These findings aim to bridge the gap in understanding thyroid cancer progression and highlight potential molecular vulnerabilities for targeted therapeutic intervention.

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OP-07-06

Enrageing fibroblasts by BRAF and TERT synergism affects thyroid cancer therapy response

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It is known that coexistence of BRAF and TERT promoter mutations induce Thyroid Cancer (TC) aggressiveness. While BRAF V600E has been associated with fibroblasts activation and extracellular matrix (ECM) remodeling, important in tumor progression, little is known on how TERT affects ECM. We aimed to study the effects of BRAF and TERT synergism on fibroblasts, ECM and the consequences on TC cells. We interrogated TCGA THCA thyroid cancer dataset, studied primary thyroid fibroblasts by direct and indirect co-cultures, proteome and cytokine array, western blot, confocal microscopy. In THCA dataset, expression of ECM-related genes was significantly higher in BRAF-mutated tumors with high TERT expression (B^+T^h) than in those with only BRAF or TERT alterations, with particular enhancement of Collagens and Proteoglycans. Primary fibroblasts conditioned by B^+T^h TC cells produced highly stable ECM with peculiar fibril organization. Consequentially, the B^+T^h induced ECM significantly increased cancer cell growth and resistance to Lenvatinib, remarking the significant role of ECM influence on TC cells response to therapy. Proteome array revealed significant variations in B^+T^h conditioned fibroblasts that could be reduced to two main clusters: one dominated by cytokine-cytokine receptor pathways and one enriched in HIF1, AGE-RAGE and PI3K/Akt pathways. Enrichment in EGFR and AGE-RAGE pathways in B^+T^h tumors was also confirmed in THCA dataset. Since the AGE-RAGE pathway plays a significant role in fibrosis and progression of other cancers, we further examined its role in TC biology. RAGE expression significantly correlated with fibroblasts reactivity, while its effectors differentially modulated ECM production and maturation. B^+T^h TC cells produce significant amounts of Advance Glycation End product (AGE), FGF, TGFb1, IGF1 and IFNg, all previously linked to RAGE pathway. These results were then validated in a cohort of TC tissues with different genetic backgrounds. We identified the RAGE pathway as one of the main actors in ECM alterations induced by the BRAF-TERT synergism. These alterations significantly influence TC cells response to therapy, and the specific pattern of cytokine secretion and AGE levels may be a valuable prognostic tool for patients follow up.

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OP-07-07

Identification of a senescent-like cell population with a low differentiation state in BRAFV600E-mutated follicular cell-derived thyroid carcinoma

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Introduction
The role of senescence in follicular cell-derived thyroid carcinoma (FCDTC) has been confirmed *in vitro* and *in vivo*. While senescence markers vary across tumor contexts, the role of thyroid senescent tumor cells has been confirmed in collective migration and invasion. Here we explore the spatial heterogeneity and the relationship between senescent markers and tumor differentiation to refine the characterization of senescent cells in BRAFV600E FCDTC.
Methods
Single-cell and Xenium spatial transcriptomic data were analyzed. Thyroid Differentiation Score (TDS) and senescence signatures were evaluated in clustered and spatially sequenced tumors. Differential gene expression analyses were conducted to identify novel markers of senescent tumor cells. Immunohistological validations were performed to assess senescence markers (SA-β-gal, p16, and p21) and validate a candidate marker (LAMC2, a known senescence-associated candidate gene).
Results
Single-cell transcriptomic analysis from 18 samples identified a FCDTC population with a lower TDS score enriched for CDKN2A expression and senescence signatures. Histological staining showed spatially heterogeneous p16 expression in FCDTC. Spatial transcriptomics identified two tumor clusters in BRAFV600E FCDTC with distinct TDS profiles. Senescence markers were enriched in TDS-Low cells, which were frequently located at the invasive front. Thyroglobulin (TG) immunohistochemistry confirmed a mutually exclusive distribution of p16- and TG-expressing cells. Differential expression analysis identified 74 candidate marker genes in TDS-Low senescent tumor cells, including LAMC2, for which histological expression and spatial distribution were confirmed in TDS-Low tumor regions.
Conclusion
Our analyses support that senescence markers are enriched in tumor cells located at the invasive front of BRAFV600E FCDTC, which also show reduced expression of thyroid differentiation markers. The identification of a gene signature associated with these TDS-Low senescent cells refines the biological characterization of intratumoral FCDTC heterogeneity. It further provides a foundation for exploring the prognostic value of TDS-Low senescent cells and their potential therapeutic interest in thyroid cancer.

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Oral Session 8: Evolving Therapies in Thyroid Cancer (cancer)

OP-08-01

Effects of LEVO-thyroxine titration in thyroid cancer patients with lenvatinib-induced TSH increase; a real-life study

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Background
In clinical practice, lenvatinib (LEN)-induced TSH increase is usually managed by increasing levo-thyroxine (LT4) dosage. Interestingly, pre-clinical studies suggest that thyroid hormones may promote tumour growth. The aim of this study was to investigate the impact of restoring TSH levels through LT4 dose titration on the outcomes of patients with DTC treated with LEN.
Materials and methods
We retrospectively evaluated 26 thyroidectomized patients treated with LEN for advanced iodine-refractory DTC. Thyroid function parameters – TSH, fT4 (n.r. 11.5-24.5 pmol/l), fT3 (n.r. 2.8-7.1 pmol/l) – and pro-kg daily dose of LT4 were recorded before starting LEN and systematically for 2 years. The daily LT4 dose was titrated to keep TSH below the target level (2.0 mU/l). Patients were stratified according to the magnitude of the LT4 increase and compared in terms of outcome, evaluated as progression free survival (PFS) and overall survival (OS).
Results
During the first 6 months of treatment, we observed a significant increase in mean TSH values (0.51 pre-LEN *vs* 4.49 mU/l, $P = 0.047$). Accordingly, we progressively increased the mean daily dose of LT4 (1.97 ?g/Kg/die pre-LEN *vs* 2.15 ?g/Kg/die after 6 months, $P = 0.033$). Over the following months, we stabilized serum TSH levels (4.49 mU/l after 6 months *vs* 4.38 mU/l after 2 years, $P = 0.97$) through a constant increase of the mean LT4 dose (2.15 ?g/Kg/die at 6 months *vs* 2.91 ?g/Kg/die after 2 years, $P = 0.0017$). Notably, mean fT4 concentrations remained within the normal range during the whole follow-up (22.5 pmol/l pre-LEN *vs* 21.4 pmol/l after 2 years, $P = 0.44$), whereas mean fT3 constantly decreased (4.5 pmol/l *vs* 3.5 pmol/l $P = 0.001$). After 2 years, the median LT4 dose increase was 50% of the starting dose. Patients requiring an increase in LT4 dose $> 50\%$ were comparable to those requiring a lower increase for all characteristics, but they had significantly shorter PFS (36 *vs* 56 months, $P = 0.0062$) and OS (38 *vs* 58 months, $P = 0.053$).
Conclusions
LEN induced a significant increase in TSH levels. Increasing doses of LT4 were required to stabilize TSH levels; however, they were not sufficient to maintain TSH below the target threshold or to restore fT3 levels. These findings, along with the increased risk of disease progression observed in patients requiring higher LT4 increase, suggest that restoring TSH levels through increasing LT4 doses may not be a cost-effective strategy in these patients.

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OP-08-02

Impact of neoadjuvant TKI therapy on tumor reduction and resectability in locally advanced thyroid carcinoma

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Introduction
Locally advanced thyroid cancer presents significant surgical challenges, particularly when tumors invade adjacent cervical structures. Tyrosine kinase inhibitors (TKIs) have demonstrated efficacy in advanced thyroid cancer and are increasingly explored in the neoadjuvant setting. However, the optimal use of neoadjuvant TKIs and factors influencing treatment response and surgical outcomes remain unclear.
Aim
To review our institutional experience with neoadjuvant TKI therapy in patients with locally advanced thyroid carcinoma.

Methods
Retrospective analysis of patients treated with neoadjuvant TKIs at a single tertiary referral center. Therapies included selective (dabrafenib/trametinib, entrectinib, larotrectinib, selpercatinib) and multikinase inhibitors (lenvatinib, cabozantinib, vandetanib). Patient and treatment characteristics, tumor response, and surgical outcomes were evaluated.
Results
Fifty-one patients were included (28 females, 54.9%), with mean age of 65.4 ± 13.8years at diagnosis and 66.6 ± 12.5years at treatment initiation. Tumor histology comprised 33(64.7%) differentiated and 18(35.3%) non-differentiated thyroid carcinomas (2 poorly-differentiated, 16 anaplastic). Patients with non-differentiated tumors were older (72.3 vs 66.3years), predominantly female (77.8% vs 42.4%), and had poorer performance status (PS ≥3; 16.7% vs 0.0%). Baseline tumor burden was higher in non-differentiated tumors (79.5 vs 52.0mm, $P = 0.014$). Neoadjuvant therapy was given for primary tumors in 39(76.5%) patients and recurrent disease in 12(23.5%). Overall, TKIs induced median tumor shrinkage of 28.2%, an objective response rate (ORR) of 45.1%, and disease control rate (DCR) of 90.2%. Selective TKIs achieved an ORR of 50.0% and DCR of 95.5%, while multikinase inhibitors achieved 41.4% and 86.2%, respectively. Median tumor volume reduction was similar (29.7% vs 26.7%). Nineteen patients (37.3%) underwent surgery post-neoadjuvant therapy (9[40.9%] selective, 10[34.5%] multikinase). Median therapy duration before surgery was shorter with selective TKIs (4.6months vs 11.5months, $P = 0.086$). Surgically treated patients had greater tumor reduction (36.7% vs 19.3%, $P = 0.008$), higher ORR (63.2% vs 34.4%, $P = 0.046$), and DCR (100.0% vs 84.4%, $P = 0.143$). Radiologic improvement of invasion of critical cervical structures was observed in esophageal involvement (38.7%), tracheal invasion (23.5%), and carotid encasement (33.3%). Among operated patients, 13(68.4%) achieved R0/R1 resection, more often in the selective group (88.9% vs 50.0%, $P = 0.141$). Median overall survival was substantially longer in patients with differentiated tumors compared with non-differentiated tumors (31.7 vs 7.7months; $P = 0.002$), reflecting the more aggressive biology of non-differentiated disease. Median overall survival was also longer among patients undergoing surgery compared with those managed non-surgically (31.7 vs 18.0months, $P = 0.451$).
Conclusion
Neoadjuvant TKI therapy demonstrated promising results in locally advanced thyroid carcinoma, achieving high disease control rates and enabling surgical resection in over one-third of cases. Outcomes were comparable between selective and multikinase TKIs, and meaningful responses were observed across histological subtypes, although survival remained significantly longer in differentiated tumors. These findings, representing one of the largest single-center cohorts, reinforce the growing role of neoadjuvant therapy in multi-disciplinary management of advanced thyroid cancer.

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OP-08-03

Lenvatinib vs dabrafenib and trametinib as first-line treatment for radioactive iodine-refractory differentiated thyroid carcinoma: a real-world study

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Backgroud
Sorafenib and Lenvatinib are the approved first-line (1L) treatments for radioactive iodine -refractory (RAIR) differentiated thyroid carcinoma (DTC). Newer single target drugs such as the BRAF/MEK inhibitor dabrafenib and trametinib (DT) have been more recently introduced, although not approved in Europe.
Objectives
To compare clinical, biochemical and imagiological outcomes in patients with advanced or metastatic RAIR DTC treated with first-line Lenvatinib or DT.
Methods
Retrospective analysis of 110 RAIR DTC cases at a single tertiary centre (84 in Lenvatinib group and 26 in DT group). Main outcomes were overall survival (OS), progression-free survival (PFS), best objective response rate (ORR) and best disease-control rate (DCR). Best biochemical response was also assessed. Patients with poorly differentiated or anaplastic thyroid carcinoma were excluded.
Results
Compared to the Lenvatinib cohort, the DT group had a significantly higher proportion of males (65.4% vs. 40.5%, $P = 0.026$), higher prevalence of the papillary histological carcinoma (92.3% vs. 69.1%, $P = 0.018$) and lymph node metastasis (96 vs 71%, $P = 0.009$). The median duration of therapy (16.5 vs. 11.0 months, $P = 0.041$), T and M staging, prior rates of radiotherapy (30.8% vs. 32.5%, $P = 0.867$) and radioactive iodine (RAI) (57.7% vs. 71.4%, $P = 0.189$) were similar. OS was similar between groups (59.1 vs 53.7 months, $P = 0.664$,) while PFS demonstrated a trend favoring the DT treatment (41.0 vs 26.3 months, $P = 0.059$). The best ORR was 80.2% in the Lenvatinib group and 70.8% in the DT group ($P = 0.327$) and the best DCR was 93.8% vs 91.7% ($P = 0.709$), respectively. Median time to best response showed a trend toward a faster response with the DT (81.0 vs. 99.0 days, $P = 0.055$). Lenvatinib demonstrated a greater reduction in thyroglobulin (median: -90.9% vs. -72.1%, $P = 0.015$). Toxicity was similar, with a median time to the first adverse event of 20.0 days for Lenvatinib and 18.0 days for DT, ($P = 0.347$). The incidence of severe adverse events (Grade ≥ 3) (80.8% vs. 83.3%, respectively, $P = 0.837$) and treatment discontinuation did not differ between groups (19.3% for Lenvatinib vs. 20.0% for DT, $P = 0.942$). However, 70.2% of patients in the Lenvatinib arm required at least one dose reduction, compared to 26.9% receiving DT ($P < 0.001$). A subgroup analysis comparing BRAF-mutated patients treated with Lenvatinib ($n = 19$) against the DT ($n = 26$) revealed similar efficacy outcomes: median PFS of 40 months, best ORR 94.4% vs. 70.8%, $P = 0.109$ or DCR 94.4% vs. 91.7%, $P = 1.000$. Lenvatinib remained associated with a significantly higher rate of dose reductions (68.4% vs. 26.9%, $P = 0.006$).
Conclusions
In this first series directly comparing 1L treatments for RAIR DTC, both therapies demonstrated comparable OS, DT showing a trend toward longer PFS, faster tumor response, and fewer dose adjustments. In the BRAF-mutated subgroup, efficacy outcomes were comparable while DT retained its safety advantage.

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OP-08-04

Abstract Withdrawn

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OP-08-05

Alkylating agent-based chemotherapy for the treatment of metastatic medullary thyroid cancer: the endocan-tuthyref experience.

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Objectives
Tyrosine kinase inhibitors (TKI) are the standard of care for first-line treatment of metastatic medullary thyroid cancer (mMTC). After disease progression, there is no established standard therapy. Although alkylating agent-based regimen (ALKY) are widely used for the treatment of neuroendocrine tumors of different primaries, their efficacy and safety in mMTC have not yet been formally evaluated. We report here the real-world ENDOCAN-TUTHYREF experience with ALKY regimen in this setting.
Methods
This is a retrospective study from the ENDOCAN-TUTHYREF, a national database of refractory thyroid cancers. Eligible patients had mMTC and received an alkylating agent temozolomide or dacarbazine administered alone or in combination with 5-FU or capecitabine. Endpoints included objective response rate, disease control rate, progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Exact 95% confidence intervals (95%CIs) were calculated for binary outcomes, and medians of time-to-event endpoints were computed using the Kaplan–Meier estimator.
Results
Eighty-six mMTC patients received an ALKY regimen. Table summarizes patient's characteristics. Most had been previously treated with multikinase inhibitors (MKIs; 62 patients, 72%) or RET inhibitors (RETIs, 10 patients, 12%). Fifty-four patients (63%) received temozolomide and 32 (37%) dacarbazine; 78 patients (91%) received a combination with antimetabolite; as first-line in 19 patients (22%), second-line in 27 (31%), third-line in 22 (26%) and fourth-line or later in 18 (21%). Median follow-up was 36.8 months (95%CI [23–70.2]). Five patients achieved an objective response (6%, 95%CI [2–13]), and 50 disease control (58%, 95%CI [47–69]). Median PFS was 5.5 months (95%CI [3.6–7.3]) and median OS was 21.7 months (95%CI [12.7–51.7]). Treatment discontinuation most frequently resulted from progression or death (51 patients, 63%). Twelve patients (16%) experienced serious AEs, including four (6%) treatment-related. In RETIs-pretreated patients, one achieved objective response (10%, 95%CI [0%-45%]) and five disease control (50%, 95%CI [19%-81%]); median PFS was 10.1 months (95%CI [7.3–NE]), and median OS was 12.3 months (95%CI [10.1-NE]).

Characteristics at baseline	Value (n = 86)
Age (years, median [Q1;Q3])	60.9 [49.7;66.9]
Gender (N, male)	64 (74%)
Year of diagnosis (median [min;max])	2010 [2003;2024]
Previous lines (N, median [min;max])	1 [0;6]
RET-mutant status (11 NA)	37 (49%)
Confirmed progression	72 (84%)
Metastatic sites (N median [Q1;Q3])	4 [3;4]

Conclusions
In mMTC patients, ALKY regimen showed modest efficacy but acceptable safety. Comparisons with MKIs, which may also be used in this context, are warranted.
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OP-08-06

Lenvatinib outcomes across histologic subtypes of differentiated thyroid cancer

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Background
Lenvatinib is the first-line therapy for advanced/metastatic differentiated thyroid cancer (DTC) requiring systemic treatment, particularly in radioactive iodine-refractory disease. However, evidence on lenvatinib in DTC is mainly derived from histologically heterogeneous cohorts, while potential differences in response across distinct histologic subtypes remain insufficiently characterized.
Objectives
To evaluate whether lenvatinib outcomes differ by histology in advanced/metastatic DTC.
Methods
Retrospective analysis of DTC patients treated with lenvatinib at a tertiary center. Included histology groups (WHO 4th edition) were classical variant papillary thyroid carcinoma (cvPTC), follicular variant PTC (fvPTC), follicular thyroid carcinoma (FTC) and oncocytic thyroid carcinoma (OTC). Mixed PTC variants and other rare variants were excluded.
Results
77 patients were included: 41 (53.2%) cvPTC, 13 (16.9%) fvPTC, 13 (16.9%) FTC and 10 (13%) OTC. Mean age at diagnosis was 60.1±13.5y and mean age at lenvatinib start was 67.9±11.2y; 55.8% were female. Median treatment duration was 13 (1-68) months. At lenvatinib start, 71.4% of patients had N1 disease and 85.7% were M1. N1 status was more frequent in cvPTC patients (cvPTC: 82.1%, fvPTC: 31%, FTC: 53.8%, OTC: 50%, $P = 0.029$); sex, age at diagnosis, age at lenvatinib start, T stage, M stage, prior radioactive iodine and lenvatinib treatment duration did not differ across histology groups. Best objective response rate (ORR) differed significantly between groups (cvPTC: 52.6%, fvPTC: 22.2%, FTC: 75%, OTC: 10%, $P = 0.007$), and progressive disease events during follow-up were more frequent in OTC (cvPTC: 39%, fvPTC: 31%, FTC: 15.4%, OTC: 70%, $P = 0.049$). Best disease control rate (DCR), median estimate progression-free survival (PFS), disease-specific survival (DSS) and overall survival (OS) did not differ across histology groups. In multivariable analyses adjusting for age, T, N and M status at lenvatinib start, OTC was associated with lower odds of objective response (OR 0.1, 95% CI 0.01-0.61, $P = 0.018$). Histology was not independently associated with DCR, PFS, DSS or OS.
Conclusions
In this real-world advanced/metastatic DTC cohort, structural response with lenvatinib therapy differed across histologic subtypes, while survival outcomes did not. After adjustment for age and T, N and M status at treatment start, OTC was independently associated with lower odds of achieving objective response with lenvatinib, likely reflecting its distinct genetic profile. These findings suggest histology-related heterogeneity in lenvatinib response.
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Oral Session 9: Thyroid Hormone signalling Mechanism (basic)

OP-09-01

Theo Visser Prize 2026: Molecular mechanism of thyroid hormone transport by monocarboxylate transporters

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Thyroid hormones (THs), specifically the prohormone thyroxine (T4) and the active form triiodothyronine (T3), are essential for vertebrate development and metabolic homeostasis. Their cellular uptake is primarily mediated by Monocarboxylate Transporter 8 (MCT8), which is recognized as the most specific TH transporter in humans. Unlike the closely related MCT10, which also transports aromatic amino acids, MCT8 is evolutionarily refined for the exclusive transport of THs. Mutations in the SLC16A2 gene encoding MCT8 cause Allan-Herndon-Dudley syndrome (AHDS), a severe X-linked neurodevelopmental disorder. Despite its clinical importance, the molecular basis for MCT8's high specificity and its transport mechanism remained unknown. Using cryogenic electron microscopy (cryo-EM), we determined high-resolution structures of human MCT8 in ligand-free and T4-bound outward-open states, and human MCT10 in a T4-bound inward-open state. Our results reveal that the MCT8 binding pocket is uniquely tailored to the iodinated thyronine backbone. We identified a critical network of residues, including Arg371 and Asp424, that coordinates the T4 carboxyl and amino groups, while a hydrophobic pocket accommodates the iodine atoms. Comparison with MCT10 shows that MCT8's specificity arises from a constrained binding environment that precludes substrates different from THs. Structural analysis of the pathogenic D424N mutation reveals that while the protein folds correctly, the mutation disrupts the salt bridge required for the "rocker-switch" transition between conformational states, effectively halting TH delivery. We also resolved the structure of MCT8 bound to the inhibitor silychristin, which locks the transporter in an outward-facing state. This study provides the first structural blueprint of the most specific

TH transporter, explaining how MCT8 selectively captures T4 and T3. These insights clarify the molecular basis of AHDS and provide a framework for the rational design of targeted therapies.

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OP-09-02

A unique rna G-quadruplex in THRA regulates TRα alternative splicing

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Objectives
In humans, *THRA* encodes for two major thyroid hormone receptor α (TRα) isoforms, TRα1 and TRα2. TRα2 cannot bind T3 and is considered to be non-functional. Thus, the cellular response to thyroid hormone is tightly controlled by the intracellular TRα1:TRα2 ratio. The isoforms are generated by alternative splicing and the ratio of TRα1 to TRα2 differs between tissues (heart TRα1 > TRα2 vs. brain TRα1 < TRα2). However, the underlying regulatory mechanisms are largely unknown. RNA guanine-quadruplexes (rG4s) are secondary RNA structures and may act as *cis*-regulatory elements to control alternative splicing. We hypothesize, that a G-rich sequence (G39) in exon 10 of *THRA* forms an rG4 and plays an essential role in regulating TRα1/α2 alternative splicing. Furthermore, *trans*-factors binding to this sequence may determine tissue-specific expression of TRα isoforms.
Methods and Results
Using CRISPR/Cas9, we introduced defined nucleotide substitutions that were predicted to either stabilize or disrupt rG4 formation. Remarkably, stabilizing substitutions led to a shift in alternative splicing towards TRα1 while destabilizing mutations resulted in increased TRα2. This was quantified by both isoform-specific RT-qPCR and western blot analysis. Biophysical characterization by circular dichroism spectroscopy and thermal difference spectra confirmed rG4 formation of the wild-type G39 sequence and further showed that the defined nucleotide substitutions indeed led to either stabilization or disruption of the rG4. Unlike canonical rG4s, the G39-rG4 contains a 21nt loop between the first two G-clusters. ^{1}H NMR spectroscopy revealed that this loop forms a hairpin. A G4-affinity pull-down of nuclear lysates from mouse heart and brain with subsequent HPLC-MS/MS verified a tissue specific pattern of *trans*-factors binding to the G39-rG4.
Conclusion
Our studies showed that the *THRA* G39 sequence forms a unique non-canonical rG4 stabilized by an internal hairpin structure. Targeting the stability of this rG4 alters the TRα1:TRα2 ratio. Furthermore, *trans*-factors binding to the rG4 likely modulate the tissue-specific expression of TRα isoforms. Together, these data provide novel evidence that the G39-rG4 acts as a structural modulator of TRα alternative splicing, thus regulating the TRα1:TRα2 ratio.

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OP-09-03

Thyroid hormone acts independently of the thyroid hormone receptor BETA in hepatocytes to improve systemic insulin sensitivity

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Background
Insulin resistance is central to type 2 diabetes. Thyroid hormone (TH) regulates glucose homeostasis, and both hyper- and hypothyroidism are associated with insulin resistance. The mechanisms behind this remain unclear, though the liver is thought to play a key role. Selective thyroid hormone receptor beta (THRβ) agonists, recently approved for treatment of liver fibrosis, are in phase 2–3 clinical trials for metabolic dysfunction–associated fatty liver disease. Given the close link between this disease and insulin resistance, understanding hepatic THRβ1 in glucose homeostasis is critical. We hypothesized that TH, acting via the THRβ1, is a key regulator of hepatic glucose metabolism and insulin signaling.
Methods
In mice that lack *Thrb1* expression in hepatocytes (L-TRBKO mice) and controls we analyzed changes in thyroid status, glucose tolerance (intraperitoneal glucose tolerance test), hepatic insulin signaling (western blot), liver histology, energy expenditure and skeletal muscle metabolism (qPCR and western blot). In both genotypes we assessed euthyroid chow fed mice, hypothyroid mice on a propylthiouracil/low iodine diet with and without T3 treatment, and finally in euthyroid mice fed a high fat diet (HFD). Finally we studied insulin signaling in human induced pluripotent stem cells differentiated to hepatocytes (iHeps) both with and without *Thrb1* expression.
Results
In contrast to our hypothesis, we found that insulin signaling was not impacted by the selective deletion of THRβ1 in hepatocytes. Both control and L-TRBKO mice have similar glucose homeostasis under basal conditions. Hypothyroidism impaired systemic insulin sensitivity to a similar degree in both genotypes and was rescued by T3 treatment. Both control and L-TRBKO developed insulin resistance and hyperglycemia on a HFD. In these HFD-fed mice, a single dose of T3 improved systemic insulin sensitivity to the levels of control chow fed mice in both control and L-TRBKO male mice. This single dose of T3 also increased glucose transporter expression in skeletal muscle. In iHeps, THRβ1 was not required to activate insulin signaling, and T3 treatment did not affect insulin signaling.
Conclusion
T3 signaling impacts systemic glucose homeostasis independently of its actions through the THRβ1 in hepatocytes.

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OP-09-04

Chip sequencing reveals binding sites of the thyroid hormone receptor α in murine bone marrow derived macrophages

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Macrophages are versatile immune cells, regulating both pro-and anti-inflammatory processes. They are also thyroid hormone (TH) target cells, possessing TH transporters, type 2 deiodinase and the nuclear TH receptor alpha (TRα). Here, we investigated which genes expressed in macrophages are directly regulated by the TRα. We generated bone marrow derived macrophages (BMDMs) from transgenic mice with a GS-TRα tag, enabling detection of the TRα. BMDMs were polarized into a pro- or anti-inflammatory phenotype, using endotoxin lipopolysaccharide (LPS) and interferon-γ or interleukin-4, respectively, or were left unpolarized. After polarization, cells were harvested and used for chromatin immunoprecipitation sequencing (ChIPseq). In an additional experiment, BMDMs were generated from wild type mice. One day before the polarization into a pro- or anti-inflammatory phenotype, the BMDMs were cultured on charcoal stripped culture medium (without hormones). Different concentrations of T3 (0 nM, 0,1 nM, 1 nM or 10 nM) were added subsequently during polarization. After 24 hours the cells were lysed and RNA was isolated for qPCR. In total, 333 genes are found near TRα binding sites in at least one type of BMDM. While some genes were found in all three BMDM types, others revealed TRα binding sites exclusively in unpolarized, pro-inflammatory, or anti-inflammatory BMDMs. Further analysis will aim on finding overlap of the TRα with known DR4 elements on the mouse genome to further confirm the identified genes. Besides genes known to be bound by TRs in different cell types, such as *Klf9* and *Dbp*, a number of genes with immune functions are found, including *Cd38*, *Il4i1, Cc5l* and *Ccl28*. mRNA expression of *Klf9* and *Cd38* increases upon T3 in wild type BMDMs, although for *Klf9* only after adding 10 nM T3. The remaining genes will be tested in BMDMs and in addition in resident macrophages such as microglia and Kupffer cells to establish if T3, likely via the TRα, also regulates gene expression in other types of macrophages. Our study demonstrates that the TRα binds near different genes in BMDMs, suggesting a regulatory role for the TRα in these cells. These findings

provide insight into the function of the TRα in macrophages and contribute to a broader understanding of the regulation of THs in the immune system.

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OP-09-05

Zebrafish models of thyroid hormone signalling reveal a biphasic response to maternal thyroid hormone developmental action

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Maternal thyroid hormone (MTH) is a key maternal determinant of human neurodevelopment. Disruption of MTH transport, as in Allan–Herndon–Dudley syndrome (AHDS), or impairment of thyroid hormone receptor (TR) function, as in thyroid hormone resistance syndromes (TRS), causes neurodevelopmental deficits and cognitive impairment. Notably, AHDS is typically more severe than TRS, suggesting that defective hormone transport and defective receptor function disrupt neurodevelopment through distinct mechanisms. To address this question, we used zebrafish CRISPR/Cas9 models of impaired MTH transport (*slc16a2* knockout) and impaired TR signaling (*thraa* knockout). Transcriptomic analyses indicate that loss of MTH transport leaves TRs in an aporeceptor state, imposing a repressive transcriptional program on thyroid hormone target genes and resulting in a more severe neurodevelopmental phenotype. In contrast, loss of *thraa*, the major transcriptionally active TR during zebrafish embryogenesis, produces a comparatively milder phenotype. Both models identify *pax6a*+ neural progenitors as key targets of MTH action during neurodevelopment and suggest that altered progenitor behavior contributes to the resulting neurological phenotypes through reduced NOTCH signaling. In both conditions, neurodevelopment converges on decreased neuronal diversity, likely driven by early depletion of the neural progenitor pool. This depletion appears to result from premature symmetric terminal divisions that transiently increase neuronal output at early stages, followed by a marked reduction in neurons at later stages relative to controls. Although the developmental-genetic mechanisms underlying these changes remain incompletely resolved, both zebrafish models recapitulate core features observed in AHDS and TRS. These findings establish zebrafish as a powerful model for defining the developmental genetics and cellular basis of MTH-dependent neurodevelopmental disorders.

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Oral Session 10: Thyroid Disease in Pregnancy (clincal)

OP-10-01

Structural thyroid abnormalities in women with recent pregnancy loss: a prospective danish cohort study of regional variation and association with fetal chromosomal abnormalities

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Objective
Pregnancy loss affects 10-30% of pregnancies – half are due to fetal chromosomal abnormalities, whereas the remainder may involve maternal factors such as thyroid dysfunction. Thyroid abnormalities are mainly assessed biochemically, but ultrasound can detect abnormalities not reflected in laboratory tests. Denmark was historically mildly to moderately iodine deficient, with regional differences. Despite national iodine fortification, pregnant women still have insufficient intake with possible regional variation. Whether structural thyroid abnormalities vary regionally among Danish women following pregnancy loss has not been investigated. We aimed to evaluate thyroid structural ultrasound characteristics in women with recent pregnancy loss, assess regional variation, and investigate associations with fetal chromosomal abnormalities.
Methods
A prospective cohort study, Copenhagen Pregnancy Loss (COPL), conducted at Hvidovre and Odense University Hospitals (October 2023-October 2025). Women aged $\geq$18 years with ultrasound-confirmed intrauterine pregnancy loss $<$22 gestational weeks were included. At inclusion, blood samples and pregnancy tissue were collected. Approximately 8-10 weeks post-pregnancy loss, thyroid ultrasound examinations were performed according to standardized protocols and afterwards reviewed by one blinded assessor. Regression models were adjusted for age, BMI, prior losses, live births, gestational age, and weeks to follow-up. P-values were Bonferroni corrected (reported as q-values).
Results
We included 819 women (639 from Hvidovre and 126 from Odense). Median age was 34 years (IQR 30.6–37.5), BMI 23.4 kg/m^2 (IQR 21.3–26.6), and gestational age 9.9 weeks (IQR 8.6-11.7). Women in Odense were younger than in Hvidovre (31.1 vs 34.5 years) with otherwise similar characteristics. Mean thyroid volume was 11.4$\pm$4.6 mL and did not differ between regions (q$=$0.11). Echogenicity was normal in 69.8%, borderline reduced in 19.3%, moderately to markedly hypoechoic in 7.3%, and pseudonodular in 3.5%. Moderately to markedly hypoechoic echogenicity was more frequent in Odense than Hvidovre (12.7% vs 6.3%), although not significant after Bonferroni correction (adjusted OR 2.09, 95%CI 1.05–4.00, q$=$0.13). Nodules $>$5 mm were similarly prevalent across regions (20.6% vs. 20.3%) with comparable EUTIRADS distributions. Among women with nodules, most were classified as low-risk (EUTIRADS 2: 42.2%; EUTIRADS 3: 28.9%, all q$>$0.9). Among 680 genetically characterized pregnancy losses, 305 (44.9%) had no chromosomal abnormalities, which was not associated with thyroid volume, echogenicity, or nodule prevalence (all q$>$0.9).
Conclusion
In this prospective cohort of women with recent pregnancy loss, structural thyroid abnormalities were common and predominantly benign. No statistically significant regional differences in thyroid structure were observed, and structural thyroid findings were not associated with fetal chromosomal abnormalities.

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OP-10-02

Maternal thyroid disease and the risk of excessive bleeding in pregnancy: a danish nationwide and regional cohort study

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Thyroid hormones are involved in regulation of haemostasis. It has been hypothesised that abnormal levels of thyroid hormones are associated with increased risk of bleeding. However, this association is yet to be investigated in pregnancy. This was a nationwide cohort study of Danish pregnant women from 1999-2015. Information on maternal hyper- and hypothyroidism and outcomes of bleeding, was collected via nationwide registers on hospital diagnoses and drug prescriptions. Women from the North Denmark Region Pregnancy Cohort, 2011-2015, were studied in a regional cohort including measurements of maternal thyroid stimulating hormone (TSH), thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab) in pregnancy along volume of postpartum bleeding for definition of postpartum haemorrhage (PPH). Maternal hyper- and hypothyroidism were defined by pregnancy- and method-specific reference intervals for TSH and thyroid autoantibody positivity as TPO-Ab or Tg-Ab above

the method-specific cut-offs. Multivariate logistic regression was used to calculate adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for the association between maternal thyroid disease and bleeding outcomes. In the nationwide cohort (n = 1,149,871), maternal hyperthyroidism (n = 17,702) diagnosed before/ during (aOR 1.11 95% CI 1.02;1.21) or after pregnancy (aOR 1.11 95% CI 1.01;1.22) and hypothyroidism (n = 27,674) diagnosed before/during (aOR 1.11 95% CI 1.03;1.19) or after pregnancy (aOR 1.10 95% CI 1.02;1.18) were associated with increased risk of bleeding in early pregnancy. For bleeding in late pregnancy, an association was found for maternal hypothyroidism diagnosed after pregnancy (aOR 1.22 95% CI 1.07;1.40). In the regional cohort (n = 13,584), PPH was found in 10.8% of euthyroid women, 9.5% of hyperthyroid women (aOR 0.86 95% CI 0.63;1.18), and 11.0% of hypothyroid women (aOR 1.00 95% CI 0.80;1.26). Furthermore, PPH was found in 11.1% (aOR 1.03 95% CI: 0.86;1.24) and 10.5% (aOR 0.96 95% CI 0.81;1.13) of TPO-Ab and Tg-Ab positive women. In these cohorts, maternal thyroid disease was associated with bleeding in pregnancy. Results provide clues on a possible role of undiagnosed maternal hypothyroidism in the risk of bleeding in pregnancy and do not suggest a major role of thyroid autoantibodies.

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OP-10-03

Abnormal thyroid-stimulating hormone levels are more frequent in late than early pregnancy loss: a prospective cohort study

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Objectives

Chromosomal abnormalities account for approximately half of pregnancy losses, while the remaining cases are thought to involve fetal, placental, or maternal factors. Thyroid dysfunction and autoimmunity are among maternal factors associated with pregnancy loss. However, most studies neither investigate fetal genetics nor distinguish late from early pregnancy loss. Because fetal development depends on maternal thyroid hormone supply and maternal thyroid hormone production increases during pregnancy, we hypothesized that inadequate maternal thyroid adaptation would be more prevalent in late than in early pregnancy loss.

Methods

We conducted a study within the prospective cohort Copenhagen Pregnancy Loss Study (COPL). Women $\geq$18 years with a confirmed intrauterine pregnancy were included. Late pregnancy loss was defined as a viable pregnancy at nuchal translucency screening (11-14 weeks' gestation) followed by pregnancy loss before 22 weeks' gestation. Data included reproductive history, comorbidities, prenatal risk assessment, and fetal genetic analyses. Thyroid dysfunction was defined as thyroid stimulating hormone (TSH) $<$0.4 mU/l or $>$3.5 mU/l at inclusion, and thyroid peroxidase antibody (TPOAb) positivity as $>$60 kIU/l. Groups were compared using chi-square tests with $P < 0.05$ considered statistically significant.

Results

Among 2,820 women included in COPL, 112 (4%) experienced late pregnancy loss. Genetic analyses demonstrated normal chromosomal findings in 95% of these cases; only six chromosomal abnormalities were identified, three despite normal risk assessment at the nuchal translucency screening. Late pregnancy loss more frequently presented as spontaneous abortion compared to early pregnancy loss (40.0% vs 9.8%, $P < 0.001$). Abnormal TSH was observed in 18 of 107 (16.8%) women with late pregnancy loss compared with 226 of 2654 (8.5%) in early pregnancy loss (p =0.003). Only two late pregnancy losses with abnormal TSH had chromosomally abnormal fetuses. TSH concentrations normalized in nearly all patients at follow-up 6–8 weeks after the loss. TPOAb positivity was present in 18 of 106 (17.0%) late pregnancy losses and in 340 of 2633 (12.9%) early pregnancy losses (p =0.20).

Conclusions

Maternal thyroid dysfunction was present in approximately one in six women with late pregnancy loss and occurred significantly more often than in early pregnancy loss. Chromosomal abnormalities were rare in late pregnancy loss. Although thyroid abnormalities at the time of loss were frequently transient, they may reflect insufficient maternal thyroid adaptation during pregnancy. Assessment of thyroid function following late pregnancy loss may be relevant in clinical evaluation of affected women and warrants further investigation of endocrine mechanisms contributing to late pregnancy loss.

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OP-10-04

TSH and thyroglobulin antibody positivity decline after an increase in iodine fortification: a cohort study of 25,253 danish pregnant women

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Objectives

The association between iodine intake and thyroid disease underlines the importance of population monitoring. In Denmark, iodine fortification (IF) of salt was implemented in 2000 with an increase in the level of iodine added from 2019. This study aimed to evaluate thyroid function and thyroid autoantibodies in Danish pregnant women before and after an increase in IF.

Methods

Retrospective comparison of TSH, TPO- and Tg-antibodies (Ab) among pregnant women in the North Denmark Region who had a blood sample drawn for non-thyroidal indication from 2011-2015 (cohort I, n = 14,851) or 2022-2024 (cohort II, n = 9,975). Furthermore, 427 pregnant women had a sample drawn in both cohorts. Samples were analyzed on Advia Centaur, Siemens Healthineers (Cohort I) or Alinity, Abbott Laboratories and Kryptor, ThermoFisher Scientific (Cohort II). A conversion factor of 1.11 was applied to TSH for assay alignment. For the antibodies, method- and pregnancy-specific cut-offs were established in reference cohorts (TPO-Ab; 60 kU/l, Tg-Ab; 33 kU/l in Cohort I and TPO-Ab; 77 kU/l, Tg-Ab; 66 kU/l in Cohort II).

Results

In both cohorts, samples were drawn in median week 10, and the women were median 30 years. The median TSH was 1.11 mIU/l (1.10-1.13 mIU/l) in Cohort I and 1.05 mIU/l (1.04-1.08 mIU/l) in Cohort II. The prevalence of TPO-Ab was 11.0% (cohort I) and 11.6% (cohort II) ($P = 0.1$), while the prevalence of Tg-Ab was 13% in cohort I and 8% in cohort II ($P < 0.001$). Among the 427 women assessed in both cohorts, a decrease in TSH from cohort I to II was found (mean difference; -0.25 mIU/l (-0.14; -0.36 mIU/l). Altogether 28 of 37 (76%) women were consistently TPO-Ab positive and 20 of 45 (44%) Tg-Ab positive across cohorts.

Conclusions

In a large study of Danish pregnant women, maternal TSH and the prevalence of Tg-Ab, but not TPO-Ab, had declined after an increase in iodine fortification levels when assessed across independent cohorts and with individual follow-up.

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OP-10-05

Analytical evidence of a dose-dependent moderator effect of human chorionic gonadotrophin (HCG) on the effect of thyrotrophin (TSH) on thyroid hormone (TH, FT4) throughout pregnancy

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Background
The beta-subunit of hCG binds to the TSH receptor increasing FT4 during early gestation with downsizing of TSH. Thus, it is a matter of speculation whether high FT4 levels during early gestation are related to low TSH levels, high hCG levels or both. The current study investigated whether there is analytical evidence that: (i) hCG has a moderator effect on the effect of TSH on FT4; (ii) this possible moderator effect is hCG 'dose dependent'.
Method
2433 singleton pregnant women (without thyroid hormone suppletion) participated in the Brabant Study with assessments of TSH, FT4, and hCG (adjusted for TPO-Ab) at 12, 20 and 28 weeks of gestation. Multivariate regression analysis evaluated the independent effect of TSH on FT4 with hCG as possible moderator and a potential dose dependent effect of the hCG concentration on moderation using Hayes Process statistics.
Results
The regression model at 12 weeks gestation (FT4, TSH, hCG and TPO-Ab) was highly significant ($F = 166$, $P < 0.001$), explaining 22% of the variance of the FT4 concentration (medium to high effect size). There was a highly significant negative interaction effect of hCG (standardize beta: - 2.19, $P < 0.001$) on the prediction of TSH on FT4 concentration: the higher the hCG concentration, the lower the effect of TSH on FT4. Johnson-Neyman analysis showed, that at low hCG concentrations ($<$ 20.000 IU/l), there was no interaction ($P > 0.05$) while the interaction became highly significant at hCG concentrations $\geq$ 40.000 IU/l (which was the 14th percentile hCG). At 20 and 28 weeks gestation, there was still a significant interaction effect of hCG on the association between TSH and FT4 but with only modest explained total variance of FT4 (5% and 6%, respectively, low effect size). Also, the hCG percentile concentration at which the interaction became significant was much higher compared to that of 12 weeks gestation: 40th and 20th percentile, respectively.
Conclusion
The predictive effect of TSH on FT4 is moderated by hCG levels at all trimesters, but especially at 12 weeks gestation and this moderator effect is dependent on the hCG concentration. This outcome is clinically relevant and should be considered when interpreting TSH and FT4 values of women with hypothyroidism who are treated with thyroid hormone during pregnancy.

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Oral Session 11: Clinical Aspects of Hyperthyroidism (clincal)

OP-11-01

Theo Visser Prize 2026: Effectiveness of early treatment with thyroid hormone analogue TRIAC on neurocognitive outcomes in young paediatric male patients with MCT8 deficiency: an international single ARM trial

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Background
Monocarboxylate transporter (MCT)8 deficiency is a rare, X-linked, genetic disorder characterized by severe motor and intellectual disability, combined with chronic T3-mediated thyrotoxicosis in peripheral tissues. Treatment with the T3 analogue Triac can effectively and safely alleviate features of thyrotoxicosis in paediatric and adult male patients with MCT8 deficiency. Early postnatal administration of Triac to mice modelling MCT8 deficiency fully rescues the brain phenotype in these animals. The effects of early treatment on motor and cognitive outcomes in patients with MCT8 deficiency are unknown.
Methods
We performed a phase II, open-label, multicentre, clinical trial (NCT02396459), which investigated the effect of Triac treatment on the motor and cognitive development of male patients with MCT8 deficiency, aged 0-30 months at baseline. Exclusion criteria included previous treatment with Triac or other (anti-) thyroid medication. Patients were treated for 96 weeks with Triac doses up to 200 mg/kg/day, targeting T3 concentrations between 10% of the lower limit of normal (LLN) and the LLN. Primary outcomes were neurodevelopmental changes as measured by the Gross Motor Function Measure (GMFM)-88 and the Bayley Scales of Infant Development (BSID)-III gross motor domain, compared to untreated historical cohort patients aged 0-9 years. Post-hoc analyses focused on other neurodevelopmental domains. Secondary outcomes included the effect of Triac on clinical and biochemical features related to thyrotoxicosis, and safety outcomes.
Results
Between Dec 3, 2020, and Jun 22, 2022, we screened 23 male patients. One patient was excluded due to previous levothyroxine treatment and another discontinued treatment because of personal circumstances. A total of 21 patients (median age 16 months at baseline) completed the 96-week treatment period. Compared to untreated historical cohort patients, there was no improvement in GMFM-88 total score (mean difference -2.42, 95%CI -4.36 to -0.48, $P = 0.02$) or BSID-III gross motor domain (mean difference 0.21, 90%CI -0.19 to 0.61, $P = 0.38$) after 96 weeks of treatment. Post-hoc analyses suggested small, significant, improvements in expressive language, fine motor, and cognition compared to untreated historical cohort patients. A decrease in serum T3 concentrations was observed during Triac treatment (mean difference -3.24 nmol/l). No patients discontinued due to severe adverse events.
Conclusions
In this phase II, open-label, multicentre, clinical trial, we found no significant treatment effect of Triac on gross motor outcomes in young paediatric male patients with MCT8 deficiency. Post-hoc analyses suggested small improvements in expressive language, fine motor, and cognition. Our findings validate the safety of Triac on outcomes related to peripheral thyrotoxicosis.

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OP-11-02

Bone mineral density in adults with resistance to thyroid hormone beta

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Objectives
Conventional thyrotoxicosis is associated with reduced bone mineral density (BMD) and increased bone turnover. Resistance to Thyroid Hormone β (RTH β) is characterised by lifelong elevation of thyroid hormones (TH), but data characterising its effect on skeletal health are limited. We have, therefore, (i) measured BMD in a large cohort ($n = 101$) of adults with RTH β, (ii) assessed its association with patient characteristics, and (iii) used established predictive models to estimate fracture risk.
Methods
BMD was measured in genetically proven RTH β patients (≥18 years; 37 males; 64 females; mean age 39.8 (range 18.2-74.9) years) using Lunar dual-energy X-ray absorptiometry at the lumbar spine (L1-L4; LS), total hip (TH) and neck of femur (FN). Standard deviations (SD) of bone mass compared to young (T-score) or age-matched (Z-score) healthy adults were correlated with height, body mass index, gender, menopausal status and TRb mutation. FRAX and QFracture algorithms were used to calculate probabilities of hip and osteoporotic fracture. Markers of bone turnover were measured in a subset of RTHb adults ($n = 30$) and compared to cases of conventional thyrotoxicosis ($n = 25$). Indices of bone formation and resorption were measured by histomorphometry in bone biopsies from two RTHb patients with markedly reduced BMD.
Results
BMD in the RTH β patients was reduced, with mean ± SD Z-scores of -0.442 ± 1.256, -0.361 ± 1.131 and -0.397 ± 1.091 at LS, TH and FN, respectively. In those ≥25 years old ($n = 80$), 34% (LS) and 39% (FN) of patients were osteopaenic, with osteoporosis in 3.8% at LS and 7.5% at FN. There was no significant correlation between BMD at these sites and age, sex, menopausal status or TRb mutation. In a subset of patients ($n = 24$) with longitudinal measurements (mean follow-up 4.6 years, range 2.3-9.6 years), there was no significant temporal change in BMD. Despite comparably elevated TH levels, mean bone turnover marker concentrations were normal, and lower in RTH β than conventional thyrotoxicosis. Bone histomorphometry showed normal resorption cavity characteristics in two and reduced formation in one case. Using published risk algorithms for those ≥40 years (the valid FRAX lower age limit) the median [interquartile range] 10-year risks of major osteoporotic fracture (FRAX, 4.4 [3.2-7.2]%; QFracture, 2.3 [1.1-5.1]%) and hip fracture (FRAX, 0.6 [0.1-1.4]%; QFracture 0.6 [0.1-1.3]%) were not elevated.
Conclusions
RTH β patients exhibit significantly reduced bone mineral density at LS, TH and FN. Unlike conventional thyrotoxicosis, this is not associated with increased bone turnover, suggesting that low BMD in this disorder is mediated by reduced attainment of peak bone mass.

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OP-11-03

Selenium supplementation in individuals with newly diagnosed graves' hyperthyroidism: a double-blind, multi-centre RCT

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Purpose
We examined the effect of selenium vs placebo on remission rate and quality of life (QoL) in the Graves' selenium supplementation (GRASS) trial.
Methods
Double-blinded, placebo-controlled, multi-centre trial in individuals with newly diagnosed Graves' hyperthyroidism randomised to daily supplementation with 200 µg selenium or placebo tablets during 24–30 months, depending on the timing of antithyroid drug (ATD) withdrawal. The primary outcome was the proportion of participants with non-remission, defined as receiving ATD or remaining hyperthyroid (thyroid stimulating hormone <0.1 mIU/l) during the last 12 months of the intervention period or referral to ablative therapy (radioactive iodine or surgery). QoL was serially assessed by the thyroid-related patient-reported outcome ThyPRO and compared with previously collected norm data.
Results
Between Dec 7th 2012 and Dec 3rd 2018, 430 participants with Graves' hyperthyroidism were recruited. Non-remission was observed in 114 (53.3%) participants in the placebo group and 118 (54.6%) in the selenium group (OR = 1.0 (95% CI: 0.7–1.5); $P = 0.98$). There was no beneficial effect of selenium, as compared with placebo, on any ThyPRO scale. The participants' QoL at the end of the study was comparable to that of the general population sample. Thyrotropin receptor antibody levels were similar in the groups at the 18-month and end-of-study follow-up visits.
Conclusion
In individuals with newly diagnosed Graves' hyperthyroidism, daily supplementation with selenium did not have any effects compared with placebo as add-on to standard antithyroid drugs. The GRASS trial findings do not support the use of selenium supplementation in Graves' hyperthyroidism.

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OP-11-04

ETHY-001, a half-life–extended tshr monoclonal antibody antagonist, potently inhibits M22-induced T4 production in an *in vivo* model

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Introduction
Graves' disease is a common autoimmune disorder affecting approximately 1–2% of the adult population. The primary contributors to disease burden are Graves' hyperthyroidism and thyroid eye disease (TED), which frequently coexist in the same individuals. Pathogenic stimulating autoantibodies (TSAbs) drive both hyperthyroidism and TED through inappropriate activation of the thyroid-stimulating hormone receptor (TSHR), which is expressed in thyroid and orbital tissues. Currently, no pharmacologic therapies for Graves' hyperthyroidism or TED directly target the underlying disease mechanism. ETHY-001 is a half-life–extended human monoclonal antibody antagonist of TSHR designed to directly block disease-causing TSAbs. It is being developed as a novel therapeutic candidate for the treatment of both Graves' disease and TED. Here, we characterize the *in vivo* potency of ETHY-001.

Methods
The pharmacokinetics and pharmacodynamics of ETHY-001 were evaluated in rats following subcutaneous administration. To further characterize the pharmacodynamic activity of ETHY-001, T3-suppressed rats were administered the stimulatory agonist mAb M22 via subcutaneous injection. The ability of ETHY-001 to inhibit M22-induced T4 elevation was assessed.
Results
ETHY-001 demonstrated pharmacokinetic properties in rats consistent with those expected for a monoclonal antibody. Administration of ETHY-001 resulted in rapid reduction in circulating T3 and T4 levels, which returned to baseline as the drug was cleared. Correspondingly, TSH levels increased before normalizing to baseline. ETHY-001 also exhibited dose-dependent inhibition of M22-induced T4 elevation.
Conclusion
ETHY-001 potently inhibits autoantibody-induced alterations in thyroid hormone levels *in vivo*. These findings support the potential of ETHY-001 as a best-in-class therapeutic option for patients across the full spectrum of Graves' disease and thyroid eye disease.

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OP-11-05

Liver, portal and systemic thyroid hormone concentrations in end-stage MASH reveal distinct roles for T3/RT3 ratio and T4

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Background
The liver is a central organ in thyroid hormone (TH) metabolism, mediating the conversion of thyroxine (T4) to bioactive triiodothyronine (T3) via type 1 deiodinase (DIO1) and the clearance of reverse T3 (rT3). Selective thyromimetics targeting the thyroid hormone receptor β (TRβ) in the liver are in development, and recently FDA-approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). To unravel the TH metabolism during MASH in patients, we aim to determine specific alterations in TH concentrations in both liver and circulation in patients with end-stage MASH.
Methods
Liver tissue, portal plasma, and systemic plasma were collected intraoperatively from 12 patients with MASH cirrhosis undergoing liver transplantation and 12 living liver donors serving as healthy controls (fibrosis stage F0-F1). Total T4, T3, and rT3 were quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results
Patients with MASH cirrhosis exhibited substantially lower total T3 and T4 across all three compartments, with elevated rT3 in portal and systemic plasma. The T3/rT3 ratio, a functional index of deiodinase-mediated TH metabolism, was markedly suppressed (-65% to -83%). For disease discrimination, hepatic T3 demonstrated the strongest capacity (BMI-adjusted OR $= 0.009$, 95% CI 0.001–0.190; $P < 0.001$) , followed by the systemic T3/rT3 ratio (BMI-adjusted OR $= 0.045$, 95% CI 0.001–0.328; $P < 0.001$). Within the MASH cohort, systemic T4 correlated inversely with Model for End-Stage Liver Disease (MELD) score ($r = -0.867$, adjusted $P = 0.005$) and Child-Pugh score ($r = -0.760$, adjusted $P = 0.033$), confirmed as the predominant severity correlate by multivariable regression independent of BMI (standardized $\beta = -0.744$, adjusted $P = 0.004$).
Conclusions
This study characterized the TH metabolism in human end-stage MASH, which provides direct tissue-level evidence supporting intrahepatic hypothyroidism. The systemic T3/rT3 ratio and hepatic T3 potently discriminate MASH from healthy liver, while total systemic T4 tracks disease severity within established cirrhosis. Our findings suggest that distinct TH parameters serve complementary roles as diagnostic and prognostic biomarkers, having implications for patient stratification and monitoring in the era of TRβ agonist therapy.

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Oral Session 12: TH effects in the Brain (basic)

OP-12-01

Modeling selenoprotein dysfunction in the human brain: insights from SBP2 deficiency

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Introduction
Selenocysteine insertion sequence-binding protein 2 (SBP2) plays a key role in the biosynthesis of selenoproteins. These proteins are essential for several physiological processes including antioxidant defense, thyroid hormone metabolism, and maintenance of cellular homeostasis. SBP2 deficiency is associated with heterogeneous features including abnormal thyroid hormone metabolism, growth delay and aortopathy. However, clinical manifestations and molecular mechanisms underlying the consequences of SBP2 deficiency for the human brain are not clear.
Objectives
To document the clinical features and investigate molecular mechanisms of SBP2 deficiency in the human brain.
Methods
Two adult patients with SBP2 deficiency underwent clinical and neurological examinations and repeated brain MRI-scans. Primary cells from patients and unaffected family members were reprogrammed to human induced pluripotent stem cells (hiPSCs). Patient and control hiPSCs were differentiated into neural progenitor cells (NPCs) and NGN2-neurons (iNeurons), co-cultured with wild-type astrocytes to model the human brain in the presence or absence of antioxidants. Immunocytochemistry, flow-cytometry based assays, selenoprotein expression (Western blot), deiodinase assays and multi-electrode arrays for neuronal function were employed.
Results
Both patients had compound heterozygous SBP2 mutations and exhibited a range of features compatible with SBP2 deficiency. In addition, both patients presented neurodevelopmental delay and varyingly features of neurodegeneration. Patient-derived NPCs showed absent DIO3 activity. They presented a ~50% reduction in culture density compared to control NPCs, which may partly be associated with ~2x elevated levels of cell death. Patient-derived iNeurons displayed 98% cell death in the absence of antioxidants, a phenotype which was fully rescued with antioxidants. They also showed no DIO3 activity and ~4x reduction in GPX4 expression levels compared to control cells. Although antioxidants restored cell survival, patient iNeurons exhibited significantly reduced electrophysiological activity. In contrast, control neurons showed a time-dependent increase in their mean firing rate, number of spikes and bursts.
Conclusions
SBP2 deficiency impairs selenoprotein expression and antioxidant defense in hiPSC-derived neural cells which results in elevated cell death, possibly mediated by ferroptosis, and decreased neuronal function. These mechanisms may contribute to neurodevelopmental and neurodegenerative features in patients. Antioxidants fully rescued these cellular defects, suggesting a promising and accessible therapeutic approach for selenoprotein-deficiency disorders.

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OP-12-02

Thyroxine action and metabolism in human cerebral organoids

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Thyroid hormones (TH) are essential regulators of human central nervous system development, but the specific neurodevelopmental processes controlled by fetal TH function remain poorly understood. Differentiation of human induced pluripotent stem cells (hiPSC) into neurons permits the study of TH-regulated processes during human neurogenesis. Here, we adopted hiPSC-derived cerebral organoids (hCOs) as a complex 3D model to investigate TH action during first trimester human corticogenesis. While our previous studies demonstrated pleiotropic effects of T3 on gene expression and neuronal development in hCOs, the effects of T4 on early cortical development are less well characterized. Analyzing T4 effects during early human cortex development is of particular interest since neither fetal cortex tissue (first trimester) nor *in vitro*-derived hCOs contain astrocytes, a glial cell type commonly believed to mediate T3 generation from T4 via type II deiodinase (DIO2). In this study, we cultured hCOs in the presence of T3 (2 nM), T4 (2 nM) or in TH-depleted media ($<$0.002 nM TH) for up to 10 weeks. Morphological analyses of cortical tissue showed that media supplementation with either T3 or T4 rescues the delayed corticogenesis observed in TH-depleted cultures. Surprisingly, we found that spent media from T4-treated hCOs did not accumulate detectable levels of T4-derived T3 (but high amounts of rT3) suggesting low DIO2 activity in hCOs. Single cell RNA-seq, qPCR measurements and RNAscope analyses consistently showed very low *DIO2* mRNA expression in developing hCOs. In fetal human cortex, *DIO2* expression increases after midgestation in glioblasts and astrocytes. We therefore treated hCOs with 1 ng/mL LIF to induce a precocious glioblast differentiation in hCOs. LIF treatment indeed caused a strong increase in the abundance of GFAP+ glioblasts and qPCR analyses of LIF-treated hCOs demonstrated strong up-regulation of several glial markers (*AQP4, S100B*) and a T4 transporter (*SLCO1C1*). In contrast, LIF treatment barely increased *DIO2* mRNA expression or DIO2 activity. We next performed scRNA-seq to compare T4 and T3 effects on gene expression in hCOs and observed similar transcriptional signatures for hCOs chronically treated with T3 or T4 from 3 to 10 weeks of culture. Similar observations were made following acute 48 h treatment of 7-week-old hCOs with T3 and T4. Collectively, our studies showed that T4 elicits T3-like effects on neuronal differentiation and neuronal gene expression following both chronic or acute treatment paradigms despite barely detectable levels of *DIO2* mRNA expression and DIO2 enzymatic activity.

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OP-12-03

The thyroid hormone-deactivating enzyme deiodinase type 3 affects neuronal identity acquisition and maturation

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Thyroid hormone (T3) promotes neurogenesis, and this study aims to determine T3 effects on neuronal identity acquisition and maturation. We developed a live/fixed correlative imaging method to directly map progenitor division and the generation of newborn neurons in human iPSC-derived cultures. Through live analysis, we identified hundreds of dividing progenitor cells (SOX2+) and intermediate progenitors (EOMES+) during the first nine days in culture (D9). Using a neuronal-specific probe (NeuO), we observed peak neurogenesis on D10, when newborn neurons began expressing the type 3 deiodinase (*DIO3*) as early as 10 hours after birth. However, newborn progenitors did not express *DIO3*. Preliminary studies of progenitors with a non-functional MCT8 T3 transporter showed that newborn MCT8-deficient neurons are more likely to undergo apoptosis than controls. To understand how DIO3 expression changes during neuronal maturation, we used RT-qPCR and observed a steady increase in *DIO3* mRNA levels in neuronal cultures at D10, D20, and D40. Consistently, DIO3 enzymatic activity progressively increased, reaching in D40 neurons extremely high values (200 pmol/h/mg; ~100 times higher than in mouse primary neurons). Notably, these D40 neurons exhibited spontaneous electrical activity and calcium signals. Since DIO3's function is to reduce T3 levels, we cultured differentiating progenitors in a medium containing B26, a homemade supplement lacking T3. Remarkably, progenitors differentiated into neurons and showed a steady increase in *DIO3* mRNA levels at D10, D20, and D40. Notably, neurons differentiated in B26 + T3 (60nM) exhibited similar levels of DIO3 expression. Notwithstanding, D40 neurons on B26 + T3 exhibited reduced mRNA levels of *GluN2A* and the postsynaptic protein *PSD95*, suggesting a maturation delay. These findings indicate that *DIO3* expression is a critical component of the developmental program of newborn neurons, likely associated with the expression of genes within the epigenetically regulated *DLK1-DIO3* imprinted domain, including *DLK1, MEG3, MEG8, and RTL1*, all of which increased their expression to a peak in D40 neurons. Targeted bisulfite sequencing of this domain identified 25 hypermethylated CpG sites in D40 neurons compared with progenitors, 3 of them in *MEG3* and *MEG8*, 1 in the *DIO3* promoter, and the remaining 21 in the *RTL1* gene body. Considering DIO3's function in reducing T3 availability in newborn and maturing neurons, a corollary of these findings is that T3's role in neurogenesis may be mediated by its epigenetically regulated action on neural progenitors rather than as a critical gatekeeper of neuronal identity acquisition and maturation.

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OP-12-04

The thyroid hormone-deactivating enzyme deiodinase type 3 affects microglial-dependent clearance of apoptotic neural cells during cerebral cortex formation

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Our objective was to define the effects of thyroid hormone (T3) on microglia function during cerebral cortex formation. We observed that the deiodinase type 3 (DIO3), an enzyme that reduces intracellular T3 levels, is expressed in amoeboid microglia near the ventricular neurogenic niches of postnatal day 5 (P5) mice pups. However, ramified microglia in the cerebral cortex no longer express DIO3. Primary microglia isolated from P3 pups exhibited high DIO3 enzymatic activity (~375 $\pm$ 302.11 fmol/h/mg). Moreover, treatment of primary microglia with ATP (10 μM), a pro-migratory and phagocytic stimulus, reduced the ramifications of these cells and reduced the expression of T3-responsive genes (*Hr, Aldh1a1,* and *Klf9*) by 50%. Next, treatment of neonatal mice from P1 to P5 with either high doses of T3 (0.13 μg/g b.w.) or the deiodinase inhibitor xanthohumol (0.30 μg/g b.w.) reduced microglial density at the ventricular neurogenic niche, which presented a more ramified morphology than untreated controls. To better understand the effects of these two treatments on microglia, we used anti-CD11b microbeads and magnetic-activated cell sorting to isolate microglia from the ventricular neurogenic niche and process them for bulk RNA sequencing. We identified 409 differentially expressed genes (fold change $\pm$ 2; FDR $<$ 0.25; P $<$ 0.05) common to microglia isolated from T3- and xanthohumol-treated groups (305 up- and 104 down-regulated), including 25 genes critical for microglial function (e.g., *Spp1* and *Csf1)*. Gene ontology and KEGG pathway analyses using Partek Flow revealed enrichment scores of more than 60 in genes associated with "regulation of neuron apoptotic process". Immunofluorescence studies of P5 brains of mice with global *Dio3* deficiency (*Dio3*KO mice) showed a significant reduction in the density of IBA1+ microglia (~73.1 vs.182.5/mm^2) near the ventricular neurogenic niches compared to controls. Similarly, the number of *Dio3*KO microglia immunolabeled for the lysosomal protease cathepsin B was lower than in controls. As cathepsin B is essential for microglial phagocytosis, we treated human microglia with apoptotic neurons, which made microglia phagocytic, as evidenced by an increase in the number and mean intensity of pHrodo fluorescent signal in microglia. A remarkable finding is that this increase in phagocytosis was paralleled by a ~360% increase in the number of microglia expressing DIO3 compared with untreated controls. Considering microglia's modulatory function of neuronal number during development, our results conclude a previously unappreciated role of DIO3 in these cells and add T3 signaling in microglia as a critical pathway regulating cortical formation.

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OP-12-05

Sobetirome improves psychomotor and neurological deficits in a mouse model of allan herndon-dudley syndrome

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Thyroid hormones (THs) are crucial for normal brain development, and their deficiency leads to severe neurological impairment. Allan–Herndon–Dudley syndrome (AHDS) is caused by mutations in the thyroid hormone transporter monocarboxylate transporter 8 (MCT8), a key transporter at brain barriers. The disorder results in systemic hyperthyroidism together with cerebral hypothyroidism and is associated with profound neurological deficits for which there are currently no effective treatments. Here, we investigated the effects of sobetirome, a TH receptor-β–selective analogue capable of entering the brain independently of MCT8, in an established model of AHDS (*Mct8/Dio2* double-knockout mice), as a potential therapeutic strategy for AHDS. Long-term post-weaning administration of sobetirome in the diet improved motor coordination and gait and produced an anxiolytic effect, partially alleviating psychomotor deficits. Transcriptomic analyses revealed that sobetirome reversed approximately two-thirds of the cortical gene expression alterations induced by MCT8 deficiency, restoring TH-responsive genes associated with myelination, synaptic signalling and neuronal structure. These molecular changes were accompanied by improved myelination, enhanced neuronal integrity and reduced astrogliosis. In addition, metabolite profiling indicated partial recovery of glial-associated metabolic pathways and membrane turnover processes. However, sobetirome also induced peripheral thyromimetic effects, underscoring the need for CNS-targeted delivery strategies to minimise systemic hyperthyroidism. Overall, sobetirome ameliorated key neurological and molecular abnormalities in MCT8 deficiency, supporting its potential as a repurposable therapeutic approach for AHDS. The development of CNS-selective analogues or prodrugs may further improve safety and efficacy, offering a promising strategy for this currently untreatable neurodevelopmental disorder.

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OP-12-06

A transcription-translation uncoupling of TTR in the murine postnatal subventricular zone uncovers functional convergence of thyroid hormones and transthyretin

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In the CNS, Transthyretin (TTR) is a thyroid hormone-binding protein that plays a central role by distributing thyroid hormones (THs) through the cerebrospinal fluid to neural cells. Beyond this classical transport function, increasing evidence suggests that TTR may exert additional cell-autonomous roles. However, its dynamic expression and functional significance in postnatal neural stem cell niches remain poorly understood. Here, we investigated the expression and function of *Ttr* in the murine postnatal subventricular zone (SVZ), the largest neurogenic niche in the postnatal mammalian brain. To characterize *Ttr* expression across the neurogliogenic lineage, we re-analyzed publicly available single-cell RNA-sequencing datasets from the postnatal SVZ. Spatial validation was carried out using RNAscope and immunohistochemistry to assess *Ttr* mRNA and TTR protein localization, respectively. To explore the functional impact of TTR, neurospheres derived from the SVZ of postnatal day 7 (P7) mice were exposed to exogenous TTR and analyzed using single-cell RNA sequencing combined with *in vitro* proliferation and differentiation assays. Re-analysis of single-cell RNA-Seq datasets revealed a transcriptional peak of *Ttr* at P7 across multiple SVZ neurogliogenic populations. RNAscope confirmed broad, but relatively weak, *Ttr* expression within the SVZ. Strikingly, immunohistochemistry failed to detect TTR protein within the SVZ, despite robust staining in the choroid plexus, revealing a pronounced transcription-translation uncoupling during the developmental stage. Functional experiments demonstrated that exposure of P7 SVZ-derived neurospheres to exogenous TTR induced significant changes in progenitor cell states. TTR promoted a pronounced shift toward more differentiated populations, including neuroblasts and oligodendrocyte precursor cells, while reducing the proportion and proliferative activity of uncommitted progenitor cells. Along with these results, transcriptomic analyses also revealed overexpression of mitochondrial and metabolic programs alongside repression of stemness and proliferation-associated pathways. However, transcriptomic analysis revealed minimal endogenous TH signaling changes in this context. Interestingly, lower, closer to detection threshold doses of TTR reproduced the anti-proliferative effects. In general, TTR partially recapitulated transcriptional and cellular outcomes induced by triiodothyronine (T3), suggesting functional convergence with thyroid hormone signaling pathways. Together, these findings uncover a previously unrecognized developmental window characterized by high *Ttr* transcription without detectable protein production in the SVZ. Our data further demonstrate that exogenous TTR is sufficient to modulate neural progenitor behavior and promote differentiation through mechanisms that converge, at least in part, with thyroid hormone signaling. This work expands the functional landscape of TTR in the brain and highlights its potential relevance for neurodevelopmental processes and disorders associated with thyroid hormone signaling.

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OP-12-07

The role of type 3 deiodinase in a human model for early brain development

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Background
Thyroid hormones (THs) are critical signaling molecules in neurodevelopment, acting on differentiation of neural cells, migration, and synaptogenesis, with deiodinases governing intracellular TH concentrations in a spatiotemporal manner. It is remarkable that fetal neural cells, while being key target cells of TH, exhibit strong activity of the TH inactivating enzyme DIO3. Currently, the molecular mechanisms underlying TH action and metabolism in brain are mainly derived from animal models and the role and timing of TH action and metabolism in neural differentiation in humans remains largely unclear.
Objectives
To investigate the role of DIO3 in a human model for early brain development utilizing human induced pluripotent stem cells (hiPSCs).
Methods
We generated a complete *DIO3* knock-out (KO) using the CRISPR/Cas9 technology in hiPSCs. hiPSC were differentiated to neurons by *NGN2* overexpression as a model for fetal human neurons. In parallel, we inhibited DIO3 in neural cells using iopanoic acid (IOP). Cells were cultured with different T3 concentrations (0-3-10 nM). We used immunocytochemistry, qPCR and RNA-seq, DIO3 and metabolism assays and multi-electrode assays as readouts for TH action.
Results
CRISPR/Cas9-generated *DIO3* KO neurons presented a complete absence of DIO3 activity. Upon T3 addition, there was an enhanced response in gene expression of T3-dependent genes such as *KLF9* and *HR* in *DIO3* KO vs wild-type *NGN2* neurons. Reduced DIO3 activity accompanied by an enhanced KLF9 induction were validated in IOP-treated neurons. Our RNA-seq results, however, showed a completely different gene expression profile of *DIO3* KO cells compared to WT, even in absence of T3. From these differentially expressed genes in *DIO3* KO, 80% were downregulated. Electrophysiology data also indicated aberrant neuronal activity in the *DIO3* KO cells irrespective of T3.
Conclusion
Our results suggest that complete deletion of the *DIO3* gene compromises the general function of neurons regardless of TH, possibly due to disruptions of gene regulatory elements. We are currently working on modifying the *DIO3* gene with CRISPR/Cas9 prime editing to introduce inactivating mutations to the *DIO3* gene without compromising its integrity.

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Oral Session 13: Clinical Aspects of AITD (clinical)

OP-13-01

Association of subclinical hypothyroidism duration with health-related quality of life (HR-QOL): a prospective cohort study with 18 years of follow-up

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Objective
This study prospectively evaluated the long-term impact of subclinical hypothyroidism (SCH) on health-related quality of life (HRQoL) using data from the Tehran Thyroid Study, one of the longest-running population-based thyroid cohorts with 18 years of follow-up. Given the ongoing uncertainty in deciding when to start treating SCH, any alterations in HRQoL can assist in overcoming the challenge of starting treatment in SCH. We assessed the association of SCH with HRQoL as a clinically applicable tool.
Methods
A total of 2272 participants from the Tehran Thyroid Study were included. SCH was defined as elevated TSH with normal FT4 and was categorized based on duration of diagnosis for each individual into two groups. Individuals with SCH diagnosis for 1–50% of follow-up period ($n = 136$), and those with $>50\%$ of the follow-up period spent in SCH status ($n = 127$). Always euthyroid participants were designated as reference ($n = 2009$). HRQoL was assessed at multiple time points using the SF-12v2 questionnaire. Multivariable regression models examined associations between SCH exposure and HRQoL, adjusted for age, sex, body mass index, fasting blood sugar, systolic blood pressure, and triglycerides.
Results
Higher exposure to subclinical hypothyroidism was associated with lower HRQoL. Each standard deviation increase in SCH exposure corresponded to reductions in the physical and mental component scores (PCS β -0.70 95% CI -1.07 to -0.34 MCS β -0.59 95% CI -1.05 to -0.14). Compared with always euthyroid participants, those with SCH for 1–50% and $>50\%$ of the follow-up period had progressively lower PCS scores, with all physical subdomains, including physical function, role limitation, bodily pain, and general health, significantly affected. Mental domains, including vitality, social functioning, emotional role, and mental health, were also reduced, with the largest impairments observed among participants with SCH $>50\%$ of follow-up.
Conclusion
Long-term subclinical hypothyroidism is associated with modest but consistent reductions in both physical and mental HRQoL. These findings suggest that given the ease of applicability of short HRQoL questionnaires, HRQoL may serve as a complementary clinical measure for evaluating the efficacy of therapy or deciding treatment initiation alongside laboratory measures.

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OP-13-02

Development of the TIR3 prediction score (TIR3-PS): a multimodal clinical-ultrasound tool to refine malignancy risk in indeterminate thyroid nodules

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Objectives
The management of indeterminate thyroid cytology (TIR3a/3b) remains a clinical challenge, resulting in high rates of unnecessary thyroidectomies. While standard ultrasound (US) risk stratification systems (EU-TIRADS) offer high sensitivity, they frequently lack the specificity required to manage this "gray zone" effectively. This study aimed to develop a multimodal scoring system—the TIR3 Prediction Score (TIR3-PS)—integrating US and clinical parameters to optimize malignancy risk assessment in indeterminate nodules.
Methods
A retrospective observational study was conducted on 315 nodules with definitive clinical-pathological outcomes. Features were analyzed using univariable and multivariable logistic regression. Regression coefficients were converted into an integer-based 13-point scale. The TIR3-PS assigns points as follows: marked hypoechogenicity (+3), taller-than-wide morphology (+3), irregular margins (+2), male sex (+2), microcalcifications (+1), mild hypoechogenicity (+1), and intranodular vascularization (+1). The score's performance was validated in the indeterminate sub-cohort ($n = 26$) and compared against the EU-TIRADS framework.
Results
In the indeterminate subgroup, the TIR3-PS demonstrated superior overall discrimination compared to EU-TIRADS (AUC 0.738 vs. 0.612). TIR3-PS scores were significantly higher in malignant nodules ($P = 0.022$). TIR3-PS ≥ 4 points, improved diagnostic specificity (80.0% vs. 40.0%) and Positive Predictive Value (PPV) (84.6% vs. 68.4%) relative to EU-TIRADS ≥ 4. Diagnostic accuracy increased from 65.4% (EU-TIRADS) to 73.1% (TIR3-PS). Risk stratification identified three distinct classes with significant trend for malignancy ($P = 0.019$): low risk (0-1 points, 25.0% malignancy rate), moderate risk (2-3 points, 50.0%), and high risk (≥ 4 points, 84.6%). Patients scoring ≥ 4 harbored an 8.8-fold higher odds of cancer.
Conclusions
Our findings suggest that TIR3-PS may offer a more specific approach than standard US-only frameworks for the risk-stratification of indeterminate nodules. While the score demonstrates a 84.6% PPV, the limited sample size of this study necessitates further large-scale validation to confirm its diagnostic reliability and its role in reducing unnecessary diagnostic thyroidectomies.

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OP-13-03

Timing of levothyroxine intake in hypothyroid patients: a randomized cross-over trial evaluating TSH levels, quality of life, and adherence

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Introduction
Although hypothyroidism is a common condition with a once-daily treatment, the need for an empty stomach to ensure levothyroxine absorption can be a burden for hypothyroid patients. In current guidelines, levothyroxine must be taken 60 minutes before breakfast to ensure optimal absorption, with a bedtime intake as an alternative. The aim of our study was to determine whether levothyroxine intake three hours after breakfast is comparable to fasting levothyroxine intake in maintaining stable TSH levels.
Methods
We conducted a randomized open-label cross-over trial on hypothyroid patients with stable TSH levels for at least six months with the same levothyroxine dosage, aged 18-65 years. Patients were randomly assigned to either taking levothyroxine three hours after breakfast for six weeks followed by fasting intake for six weeks or the reverse sequence. TSH levels were measured at the end of each six-week period. Treatment adherence and quality of life were assessed after each sequence. The primary outcome was the difference in serum TSH levels between the two intake conditions.
Results
We included 77 patients, including 8% men. Mean age was 53 $\pm$ 8.4 years old, with mean baseline TSH level at 2.25 ± 1.13µUI/mL. Hypothyroidism was secondary to Hashimoto thyroiditis in 71.4%, secondary to iodine therapy and surgery in 14.3% and 14.3% of patients, respectively. Age and baseline TSH levels were comparable between the two sequence order. Fifty-six percent of patients started with fasting intake and 44% with the three-hours-after-breakfast intake. TSH measurements at the end of each sequence are currently ongoing. Mean SF12 physical component summary was similar between the two intake conditions. The SF12 mental component summary and the Girerd medication adherence score were significantly better for the three-hours-after-breakfast intake ($P = 0.006$ and <0.001, respectively). At the end of the study, 56% of patients preferred fasting intake, 9% preferred intake three hours after breakfast, and the remaining patients reported no preference.
Conclusion
Levothyroxine intake three hours after breakfast was associated with better treatment adherence and improved mental quality of life scores compared with fasting intake. Final results regarding TSH stability are currently ongoing and will determine whether this alternative timing represents an interesting option for hypothyroid patients.

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OP-13-04

Sex and ethnicity are predictors for antitpo positivity in a multi-ethnic general population: the helius study

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Introduction
Antibodies against thyroid peroxidase (antiTPO) are common in autoimmune thyroid disease but are also present in 10-15% of the healthy population. AntiTPO positivity in euthyroid individuals is a risk factor for developing hypothyroidism.
Aim
To identify predictors for antiTPO positivity in a multi-ethnic cohort in the Netherlands.
Methods
We included baseline data (2011-2015) from the Healthy Life in an Urban Setting (HELIUS) study, a multi-ethnic prospective cohort in Amsterdam. An ethnicity and sex stratified random sample of 5737 Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan individuals was included. Serum antiTPO was measured using a chemiluminescent immunoassay (Alinity, Abbott). A cut-off value for positivity of 5.61 IU/mL, as specified by the manufacturer, was used. Univariate logistic regression analyses were done for a wide range of possible predictors, including socio-demographic factors, anthropometric measurements, laboratory measurements, and migration related factors. Subsequently, a multivariate logistic regression analysis with significant predictors from the univariate analyses ($P < 0.05$) was performed.
Results
The overall prevalence of antiTPO positivity was 12.1% (confidence interval (CI) 11.2, 13.0). In univariate analyses, significant predictors were sex, age, BMI, waist-to-hip ratio, fat percentage, HbA1c, LDL, triglyceride, ethnicity and duration of stay in the Netherlands. In multivariate analysis, female sex was a significant predictor for antiTPO positivity (OR 1.90, 95% CI 1.25, 2.87). Ethnicity was also a significant predictor for antiTPO positivity: South-Asian Surinamese individuals had increased odds compared to the Dutch (OR 1.69, 95% CI 1.14, 2.49) whereas Ghanaians had decreased odds compared to the Dutch (OR 0.52, 95% CI 0.30, 0.90). The prevalence of antiTPO positivity was 14.9% (CI 13.6, 14.9) in females and 7.6% (CI 6.3, 8.6) in males. Highest prevalence was observed in South-Asian Surinamese females (22.1%, CI 18.1, 26.1) and lowest prevalence was seen in Ghanaian males (3.7%, CI 1.6, 5.9).
Conclusion
Sex and ethnicity are predictors for antiTPO positivity. As antiTPO positivity is a risk factor for developing hypothyroidism, these insights help identify subpopulations at risk.

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OP-13-05

Negative impact of the DIO2 THR92ALA variant on quality of life in individuals on levothyroxine; data across 3 large cohorts

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Importance
Up to 15% of patients treated with levothyroxine report persistent symptoms despite biochemical euthyroidism. The Thr92Ala substitution in DIO2 (rs225014) may impair intracellular T3 generation, but evidence for its clinical relevance has been inconsistent.
Objective
To examine whether the Thr92Ala substitution modifies the relationship between levothyroxine therapy and quality of life.
Design, Setting, and Participants
Cross-cohort genetic association study combining the HUNT Study (Norway; 50,901 adults including 1,480 levothyroxine users), the GENTHYR Study (UK; 2,071 adults receiving levothyroxine monotherapy), and the WATTS Trial (UK; 552 participants receiving levothyroxine monotherapy). Additional analyses were performed in WATTS and GENTHYR cohorts using mixed-effects regression models and inverse-variance meta-analysis.
Main Outcomes and Measures
Psychological well-being assessed using the Hospital Anxiety and Depression Scale (HADS) and the General Health Questionnaire (GHQ-12). Models were adjusted for age, sex, thyroid-stimulating hormone (TSH), and other relevant covariates.
Results
In HUNT, individuals homozygous for Thr92Ala (CC) receiving levothyroxine had higher total HADS scores ($\beta = 1.83$ [95% CI 0.93–2.73]) and greater odds of anxiety caseness (OR = 2.08 [1.44–3.01]) compared with nonusers, whereas no association was observed in individuals not treated with levothyroxine. In GENTHYR, the CC genotype was associated with worse GHQ scores ($\beta = 1.11$ [0.48–1.73]) and higher odds of depression caseness (OR = 1.20 [1.06–1.35]), with stronger associations at levothyroxine doses ≥ 100 µg/day. Similar effects were seen in the higher dose WATTS cohort. In complementary cross-cohort analyses of WATTS and GENTHYR, additive Thr92Ala allele dosage was associated with higher psychological symptom scores. Meta-analysis demonstrated significant associations with GHQ scores ($\beta = 0.53$ [95% CI 0.30–0.77], $P = 8.98\times10^{-6}$) and HADS depression scores ($\beta = 0.24$ [0.12–0.35], $P = 7.97\times10^{-5}$), with a smaller association observed for HADS anxiety scores ($\beta = 0.15$ [0.004–0.30], $P = 0.043$).
Conclusions and Relevance
The Thr92Ala substitution in DIO2 is associated with poorer psychological well-being among individuals treated with levothyroxine. Consistent associations across cohorts, including meta-analytic evidence linking additive genotype dosage to higher depression-related and general distress scores, support a biological mechanism underlying persistent symptoms during levothyroxine monotherapy and highlight the potential for more personalized approaches to thyroid hormone replacement.

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OP-13-06

Undiagnosed sleep apnea is prevalent among hypothyroid patients with impaired quality of life

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Background
Compared to healthy controls, around 10-15% of the levothyroxine-treated patients complain of impaired quality of life (QoL) despite biochemical euthyroidism. Comorbidities have been proposed as a reason for persistent symptoms and reduced QoL. In this study, we screened a cohort of hypothyroid patients with reduced QoL for a predefined list of comorbidities and evaluated QoL before and after the screening program.
Methods
Adult hypothyroid patients with self-reported reduced QoL and stable plasma thyrotropin levels underwent a screening program for sleep apnea and several other predefined comorbidities (e.g. diabetes, adrenal insufficiency, hypo-D-vitaminosis, hypo-B12-vitaminosis). QoL was assessed using the ThyPRO-39 and SF-36 at baseline and at 3 months. To evaluate changes in QoL during the study, we used the minimal important change (MIC), defined as the smallest change patients perceive as important.

Results
One hundred and thirty patients were included, with 113 completing the 3-month follow-up questionnaires. Most participants were women; the mean age was 57 years; the mean body mass index was 28.8 kg/m^2; and they had significantly lower QoL across all scales measured with both ThyPRO and SF-36, compared with the general population. Overall, one or more undiagnosed comorbidities were found in 110 patients (85%). Seventy-two patients (55.4%) met the criteria for sleep apnea; nine (6.9%) were already diagnosed, while 63 (48.5%) had undiagnosed sleep apnea. of those with undiagnosed sleep apnea, 26 (20%) fulfilled the criteria for continuous positive airway pressure treatment. Patients with sleep apnea had a significantly higher BMI (mean 30.9 $\pm$ 6.1 kg/m^2) than those without (26.2 $\pm$ 4.4 kg/m^2; $p < 0.001$). QoL improved for the entire group 3 months after the screening program, surpassing the MIC on the ThyPRO scales for cognitive complaints, cosmetic concerns, and overall QoL. Participants with sleep apnea reported poorer QoL than those without, both at baseline and after 3 months.
Conclusions
A systematic and broad screening for unrecognized comorbidity significantly improves QoL among patients treated with levothyroxine. Nearly half of patients have undiagnosed sleep apnea. Thus, screening for sleep apnea should be considered in hypothyroid patients with impaired QoL.

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OP-13-07

Who needs levothyroxine after withdrawal? clinical and ultrasonographic predictors from a prospective study

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Background
Levothyroxine (LT4) is widely prescribed for hypothyroidism, although lifelong therapy may not be necessary for all patients. LT4 is often initiated for mild biochemical abnormalities or nonspecific symptoms, and the indication for continued treatment may not always be reassessed. This prospective study aimed to identify clinical and ultrasonographic predictors of hypothyroidism requiring LT4 reinitiation after LT4 withdrawal.
Methods
Patients receiving $\leq$100 μg/day LT4 for $\geq$1 year with stable, normal thyroid-stimulating hormone (TSH) levels during the preceding year were eligible for discontinuation. Follow-up visits were performed at 2, 6, and 12 months. Severe subclinical or overt hypothyroidism (TSH $\geq$10 mIU/l or elevated TSH with low free thyroxine) was considered an indication for LT4 reinitiation. of 327 patients who discontinued LT4, 32 restarted treatment outside the study protocol without meeting these criteria and were excluded. The final cohort included 295 patients.
Results
Mean age was 51.3 $\pm$ 14.8 years and 91.7% were female. At 12 months, 156 patients (52.9%) remained euthyroid, 67 (22.7%) developed mild subclinical hypothyroidism, and 72 (24.4%) developed severe subclinical or overt hypothyroidism requiring LT4 reinitiation. Among those requiring treatment, 84.7% developed hypothyroidism within the first two months after discontinuation. Patients who developed hypothyroidism had higher LT4 dose/kg, longer treatment duration, smaller thyroid volume, and greater thyroid echogenic heterogeneity at baseline (all $P < 0.001$). In multivariable analysis, higher LT4 dose/kg (OR 20.72, 95% CI 7.87–54.54), smaller thyroid volume (OR 0.92, 95% CI 0.86–0.99), and moderate-to-severe thyroid heterogeneity (OR 3.86, 95% CI 1.89–7.90) independently predicted hypothyroidism.
Conclusions
More than half of patients maintained euthyroidism after LT4 withdrawal, whereas about one-quarter required LT4 reinitiation within one year, most within two months. Higher LT4 dose/kg, smaller thyroid volume, and thyroid heterogeneity may help identify patients requiring closer monitoring after LT4 discontinuation.

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Oral Session 14: Insights in thyroid cell physiology (basic)

OP-14-01

Toward personalized regenerative medicine: generation of functional human thyroid follicles from non-genetically modified patient IPSCS

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Background
Thyroid hormone deficiency, particularly congenital hypothyroidism, which affects approximately 1 in 3,000 newborns, often results from thyroid dysgenesis, where the gland is absent, hypoplastic, or ectopic. While lifelong synthetic hormone replacement is the current standard of care, it frequently fails to adapt to fluctuating physiological requirements during life stages such as puberty or pregnancy. A definitive cure through the replacement of diseased tissue with healthy, patient-derived functional organs remains a primary goal of regenerative medicine.
Innovation and Methodology
While previous proof-of-concept studies successfully generated functional human thyroid tissue *in vitro*, these achievements relied exclusively on genetically modified human embryonic stem cells (ESCs). Such approaches carry significant ethical and safety concerns, severely limiting their clinical translation. In this study, we present a breakthrough protocol: the first efficient generation of functional thyroid follicles in the total absence of genetic modification. Furthermore, this represents the first successful protocol to generate hormone-producing thyroid follicles from induced pluripotent stem cells (iPSCs), offering a highly efficient production of thyroid hormones that mirrors physiological function.
Proof-of-Concept and Clinical Relevance
To demonstrate the therapeutic potential of this platform for patients with no functional thyroid tissue, we generated iPSCs from a patient diagnosed with complete athyreosis. This proband presented at birth with a severe congenital hypothyrodism with no detectable thyroid tissue, TSH > 500 mU/l and no detectable serum fT4 and thyroglobulin. By applying our differentiation protocol, we successfully transformed these patient fibroblasts-derived iPSCs into functional thyroid follicles capable of hormone synthesis. This achievement serves as a critical proof-of-concept for personalized regenerative therapies, suggesting that even patients with severe congenital defects can benefit from autologous tissue engineering.
Conclusion
This study marks a significant achievement in the thyroid field by providing a realistic perspective on curative, cell-based interventions. By bypassing the need for genetic manipulation and utilizing iPSCs, this strategy paves the way for autologous transplantations that could liberate patients from suboptimal, lifelong pharmacological replacement and restore dynamic physiological hormonal control.

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OP-14-02

GLIS3 shapes pituitary patterning and TSH set-point in zebrafish, modelling GLIS3-associated congenital hypothyroidism

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Objectives
Biallelic *GLIS3* mutations cause congenital hypothyroidism with heterogeneous biochemical phenotypes, including difficult TSH suppression during levothyroxine therapy. *GLIS3* polymorphisms were also linked with circulating TSH levels. We hypothesized that *GLIS3* deficiency alters adenohypophyseal lineage differentiation, shifting the thyroid-axis set-point. Using zebrafish, we tested whether *glis3* knockdown (glis3KD) affects pituitary patterning and TSH sensitivity to thyroid hormone (TH) feedback.
Methods and Results
Zebrafish glis3KDembryos were generated by morpholino silencing and validated by *glis3* mRNA rescue. TSH feedback regulation was assessed in glis3KD larvae versus uninjected controls, PTU-induced hypothyroid larvae (hypo-PTU), and a resistance to thyroid hormone β (RTHβ) model. Analyses included whole-mount and fluorescent in situ hybridization, qRT-PCR, immunofluorescence, and ELISA. HPT feedback was challenged with levothyroxine (LT4), triiodothyronine (T3), the TRβ agonist TRIAC, or the RXR agonist bexarotene. During pituitary development, glis3KD larvae showed increased *shha* in the ventral diencephalon and expansion of

Pit1 domain, resulting in the over-differentiation of lactotropes (+93%) and thyrotropes (+66%). Functionally, glis3KD larvae showed primary hypothyroidism with low TH levels and elevated *tsh*. In controls and hypo-PTU larvae, TH and TRIAC efficiently suppressed tsh. In contrast, glis3KD larvae showed partial tsh resistance (~2-fold IC50 increase). Bexarotene, which suppresses TSH independently of TH–TR signaling, also produced blunted *tsh* suppression in glis3KD larvae. RTHβ larvae were resistant to TH and TRIAC but retained near-normal suppression by bexarotene, indicating receptor-specific resistance rather than disruption of pituitary feedback architecture.
Conclusions
glis3 contributes to adenohypophyseal patterning and Pit1 lineage allocation during zebrafish organogenesis. Its deficiency expands thyrotrope and lactotrope populations, likely shifting the TSH set-point upward and reducing sensitivity to hormonal feedback and RXR-pathway modulation. These findings identify *glis3* as a modulator of the central TH feedback set-point.

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OP-14-03

Thyroid hormones and DNA methylation during post-embryonic development

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Thyroid hormones are versatile players. They regulate diverse cellular processes from mitosis to apoptosis, from metabolism to growth and development, with a well-established role in post-embryonic development across vertebrate species. Amphibian metamorphosis is the school case example of post-embryonic developmental process illustrating the essential role of thyroid hormones, where spectacular morphological and biochemical modifications have similarities with the perinatal period in mammals. Tadpole transformation is marked by numerous changes, including *de novo* morphogenesis (limb), tissue remodelling (brain, intestine...) and organ resorption through apoptosis (tail). These changes involve tissue specific cascades of gene regulation initiated by thyroid hormones and their receptors. By analyzing transcriptomic data, we found that thyroid hormones regulate the expression of genes coding for DNA methylation modifying enzymes. Pharmacological interventions confirm their central role during metamorphosis. DNA methylation changes are important means of regulating gene expression and a mechanism for coordinating developmental transitions. Therefore, we profiled the thyroid hormone-induced DNA methylation dynamic along the genome of an Anuran amphibian, *Xenopus tropicalis*. Following treatment with triiodothyronine, we have captured methylated DNA genome-wide using MethylCap procedure combined with high-throughput sequencing for two organs with contrasted fate during metamorphosis (either proliferation for the hindlimbs or cell death for the tail fin epidermis). In addition, transcriptome variations were measured using RNA-Seq on hindlimbs and tail fin skin. Direct response genes were further sorted out by chromatin interaction analysis by paired-end tag sequencing for tail fin epidermis. In both organs, we found a strong tendency for DNA demethylation following treatment with T_3, with a more pronounced effect in the tail fin epidermis. In hindlimbs, 3,519 loci were demethylated and 582 methylated, while in tail fin, 14,656 loci were demethylated and 643 methylated. The majority of differential methylated regions were also organ specific. Finally, T_3 induced variations of DNA methylation are generally not localize near genes regulated by the hormone, but overlap with repeated sequences. In conclusion, thyroid hormone treatments lead to DNA demethylation with mainly targeted loci that are enriched for repeated sequences.

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OP-14-04

Effect of time-restricted feeding on memory and the regulation of oxidative stress VIA XCT in a mice model of diet-induced obesity

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Pediatric obesity has been associated with specific comorbidities such as cognitive impairments and circadian rhythm alteration. Time-Restricted Eating/Feeding (TRE/TRF), a nutritional intervention focusing on meal timing, has demonstrated significant metabolic benefits, and our team has shown its positive impact on memory impairment caused by juvenile obesogenic diet. A series of initial analyses highlighted a local hippocampal hypothyroidism associated with memory impairment in mice fed a High-fat High-sucrose diet (HFS) since weaning, both of which were restored following 4 weeks of TRF. Further analyses of hippocampal ps6-TRAP-RNA sequencing performed at two different time points and in basal versus memory consolidation conditions revealed that several genes involved in oxidative stress regulation were differentially expressed across experimental groups. Among these, xCT is particularly interesting because it allows the entry of cystine into the astrocyte, then forming cysteine, which is a limiting factor in the biosynthesis of glutathione (the main antioxidant in cells). Specifically, xCT showed a day/night rhythm and an increased memory-induced expression in both control and HFS TRF mice, but not or less in the HFS *ad lib* group. We then looked at the expression of hippocampal xCT at several time points and noticed that the rhythmicity of hippocampal xCT gene expression was blunted in HFS *ad lib* mice and restored in their TRF counterparts. Then, in order to complement our findings on local hippocampal hypothyroidism, we assessed the hippocampal xCT gene response to T3 infusion in HFS *ad lib* mice, revealing a significant upregulation of xCT expression. Furthermore, imidazole ketone erastin (IKE), an inhibitor of xCT, was co-infused with T3 directly into the hippocampus. The results showed that mice receiving both IKE and T3 exhibited memory impairments, whereas a single infusion of T3 was sufficient to restore memory performance. These results provide a better understanding of the signaling pathways involved in the restoration of memory deficits by TRF involving the regulation of oxidative stress via XCT through thyroid hormone regulation.

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OP-14-05

Novel enzymes and metabolites in the thyroid hormone side chain metabolism

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Objectives
Thyroid hormones are crucial for the normal development and metabolic functions of nearly all tissues across various species. The current dogma holds that modification of the thyroid hormone molecule through removal of iodine atoms (a process called deiodination) is the primary pathway for thyroid hormone metabolism However, several observations indicate that modification of the alanine side chain of the thyroid hormone molecule (side chain metabolism) is a relevant, novel pathway. In this study, we seek to understand the biochemical cascade of thyroid hormone side chain metabolism.
Methods
Lysates of COS-1 cells transfected with Aminoadipate aminotransferase (AADAT), Aminocarboxymuconate-semialdehyde decarboxylase (ACMSD) and/or Malate dehydrogenase 1 (MDH1) were used for in-vitro conversion of T3. Rat kidney homogenate (RKH) was also included for these enzymatic assays. Expression of the enzymes was confirmed by western blot. High resolution LCMS/MS was used to determine exact masses of the enzymatic products.
Results and Conclusions
AADAT catalyzed the conversion of T3 into its thyropyruvic acid derivative (TK3) and this conversion was time and concentration dependent. Triiodothyroacetic acid (Triac; TA3) was rapidly generated from TK3 upon addition of H_2O_2. Moreover, co-transfecting AADAT with ACMSD resulted in the formation of an extra metabolite that might be the aldehyde form (TO3). The possible lactic acid form (TL3) was generated from TK3 by dehydrogenation in presence of MDH1 and/or NADH. High-resolution LCMS/MS confirmed the identity of these

metabolites formed by alanine side chain modification of T3. Two novel, previously unknown peaks corresponding to different products were observed in T3 sample exposed to RKH as determined by LCMS/MS indicating the presence of multiple relevant enzymes in the homogenate. Our findings highlight thyroid hormone side-chain metabolism as a previously underappreciated yet relevant component of overall thyroid hormone regulation. Our study indicated several enzymes, not implicated in the current dogma of thyroid hormone metabolism, that can modify the side chain of thyroid hormone, resulting in various metabolites, including Triac. By delineating the metabolic steps of this pathway, this work provides a foundation to explore its role in (patho)physiology or its potential to modulate for clinical purposes.

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OP-14-06

KEAP1 modulates thyroid enlargement during dietary iodine deficiency in mice

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Objective
To investigate how constitutive activation of Nrf2 signaling via Keap1 knockdown influences thyroid enlargement in response to dietary iodine deficiency in mice.
Methods
Young adult wild-type (WT) and Keap1 hypomorphic ($Keap1^{hypo/hypo}$; Keap1 knockdown, constitutively activating Nrf2) mice were maintained for 3 months on either a normal iodine or iodine deficient diet. At the end of the intervention, thyroid glands were harvested and weighed. Genotype, diet, and sex dependent effects on thyroid weight were evaluated using factorial ANOVA followed by appropriate post hoc tests.
Results
Under normal iodine diet, thyroid size was similar between WT and $Keap1^{hypo/hypo}$ mice in both males and females, indicating that constitutive Nrf2 activation alone is not sufficient to induce major thyroid enlargement (no significant genotype effect within normal iodine groups). In contrast, under iodine deficient diet, Keap1 knockdown caused pronounced goitrous enlargement in both sexes, with a more pronounced increase in males, revealing a strong synergy between impaired Keap1 signaling (constitutive Nrf2 activation) and chronic thyroidal iodine shortage. Consistent with this pattern, factorial ANOVA showed a very strong overall effect of genotype [$F(1,41) \approx 1591$, $P < 0.0001$], together with significant genotype$\times$diet [$F(1,41) \approx 23$, $P < 0.001$] and genotype$\times$sex [$F(1,41) \approx 31$, $P < 0.001$] interactions and a moderate genotype$\times$diet$\times$sex interaction [$F(1,41) \approx 6.7$, $P \approx 0.01$], indicating that the impact of Keap1 loss on thyroid enlargement under iodine deficiency is more marked in males but clearly present in females as well.
Conclusions
These findings suggest that Keap1 constrains thyroid growth under iodine deficiency-induced thyroidal stress and that constitutive Nrf2 activation markedly enhances susceptibility to goiter when iodine supply is limited, while thyroid size remains comparable between genotypes under adequate iodine intake. Overall, the data support a critical role for balanced Keap1/Nrf2 signaling in maintaining thyroid size homeostasis under nutritional stress and indicate that sex modulates the magnitude of the goitrous response to impaired Keap1 function in the setting of iodine deficiency. We will present the detailed hormonal and molecular characterization of these phenotypes.

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OP-14-07

Nodule-specific upregulation of NRF2-target genes in patients with keap1 mutations and familial multinodular goiter

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Objectives
Genetic abnormality in KEAP1 have been implicated with familial multinodular goiter. KEAP1 regulates NRF2 by promoting its degradation under physiological conditions. This study aimed to investigate how germline KEAP1 mutations contribute to thyroid nodule formation through altered expression of NRF2 target gene.
Methods
Thyroid specimens were obtained from both the nodules and the surrounding nonnodular parenchyma in two patients harboring heterozygous KEAP1 mutations (L136P and G477S) and in three control patients with follicular adenoma or adenomatous nodule lacking KEAP1 mutations. Genetic status was verified by next-generation sequencing, and histological examination was subsequently performed. The expression levels of 42 NRF2-target genes were analyzed using the Affymetrix whole transcript expression array. Differentially expressed genes containing NRF2 binding site were identified based on a P value <0.05 and a fold change value $\geq$|2.0|.
Results
Histologically, all nodules, including those harboring KEAP1 mutations and those from control patients, were benign and exhibited a low Ki-67 labeling index ($<5\%$). In KEAP1-mutant nodules, somatic allele frequencies exceeded 80%, suggesting loss of heterozygosity. Among the 42 NRF2 target genes, antioxidant genes were most frequently upregulated in KEAP1-mutant nodules (10/12 genes), whereas such upregulation was rarely in controls (1/12). For example, GPX2 expression increased by 496.6-fold and 1556.3-fold in KEAP1-mutant nodules, compared with only -1.0 to 1.2-fold changes in controls. More than half of the detoxification-related genes were also upregulated in KEAP1-mutant nodules (6/11), while such changes were uncommon among controls (1/11). In contrast, PTGS2 gene, a representative inflammatory cytokine, was significantly down-regulated in both KEAP1-mutatant and control nodules.
Conclusions
Germline heterozygous KEAP1 mutations lead to excessive NRF2 activity in the thyroid, potentially providing cytoprotective effects even under the high oxidative stress associated with thyroid hormone synthesis. The gene expression profiles of KEAP1-mutant nodules differ markedly from those of typical benign thyroid nodules, highlighting a distinct molecular mechanism underlying familial multinodular goiter.

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Poster Presentations

Poster High Lights - Session 1 - Flash Talks
Basic Highlights 1

PS1-01-01

Theo Visser Prize 2026: Molecular mechanism of thyroid hormone transport by monocarboxylate transporters

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Thyroid hormones (THs), specifically the prohormone thyroxine (T4) and the active form triiodothyronine (T3), are essential for vertebrate development and metabolic homeostasis. Their cellular uptake is primarily mediated by Monocarboxylate Transporter 8 (MCT8), which is recognized as the most specific TH transporter in humans. Unlike the closely related MCT10, which also transports aromatic amino acids, MCT8 is evolutionarily refined for the exclusive transport of THs. Mutations in the SLC16A2 gene encoding MCT8 cause Allan-Herndon-Dudley syndrome (AHDS), a severe X-linked neurodevelopmental disorder. Despite its clinical importance, the molecular basis for MCT8's high specificity and its transport mechanism remained unknown. Using cryogenic electron microscopy (cryo-EM), we determined high-resolution structures of human MCT8 in ligand-free and T4-bound outward-open states, and human MCT10 in a T4-bound inward-open state. Our results reveal that the MCT8 binding pocket is uniquely tailored to the iodinated thyronine backbone. We identified a critical network of residues, including Arg371 and Asp424, that coordinates the T4 carboxyl and amino groups, while a hydrophobic pocket accommodates the iodine atoms. Comparison with MCT10 shows that MCT8's specificity arises from a constrained binding environment that precludes substrates different from THs. Structural analysis of the pathogenic D424N mutation reveals that while the protein folds correctly, the mutation disrupts the salt bridge required for the "rocker-switch" transition between conformational states, effectively halting TH delivery. We also resolved the structure of MCT8 bound to the inhibitor silychristin, which locks the transporter in an outward-facing state. This study provides the first structural blueprint of the most specific TH transporter, explaining how MCT8 selectively captures T4 and T3. These insights clarify the molecular basis of AHDS and provide a framework for the rational design of targeted therapies.

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PS1-01-02

Sort1 knock-out impairs lipid trafficking affecting thyroid gland development and thyroid hormone production

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The thyroid gland produces thyroid hormones (TH), which are essential regulators of metabolism, growth, and development. TH synthesis occurs through iodination of thyroglobulin (TG) within the extracellular lumen of thyroid follicles. For hormones to be released into the circulation, TG must be internalized from the follicular lumen, degraded in lysosomes, and processed to liberate TH. Efficient TG endocytosis is therefore a critical step in thyroid hormone availability. Sortilin, encoded by Sort1, is a multifunctional endocytic receptor involved in protein trafficking and proteostasis and has been reported to interact directly with TG. However, its role in thyroid biology remains unclear. To investigate this, we combined 2D cellular models with embryonic stem cell–derived 3D mouse thyroid organoids. Using CRISPR-generated Sort1 knockout (KO) embryonic stem cells, we generated thyroid organoids to examine the role of sortilin in thyroid development and function. Although KO organoids formed follicle-like structures, they exhibited impaired maturation, characterized by altered expression of thyroid-specific genes, reduced lumen size, and intracellular lipid accumulation. Functionally, KO organoids showed decreased TG levels and a significant reduction in T4 production and secretion compared with wild-type controls. Transcriptomic analysis further revealed downregulation of key genes involved in thyroid differentiation and hormone biosynthesis, suggesting that sortilin contributes to proper thyroid lineage maturation. To assess sortilin function in mature thyrocytes, we examined TG trafficking using both 2D cellular models and pharmacological perturbations in organoids. Imaging analyses indicate that sortilin promotes TG internalization via clathrin-dependent endocytosis. Pharmacological inhibition of this pathway impaired TG uptake, supporting a role for sortilin in TG endocytic trafficking. Together, these findings reveal a dual role for sortilin in thyroid maturation and TG handling. By integrating thyroid organoid models with cellular trafficking assays, this study identifies an unexpected role of sortilin in thyroid hormone homeostasis.

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PS1-01-03

Zebrafish SBP2 deficiency reveals disrupted thyroid hormone conversion with preserved HPT axis function

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Objectives
SECISBP2 (SBP2) regulates the selenoproteome, enabling co-translational insertion of selenocysteine into the catalytic centers of selenoproteins, including iodothyronine deiodinases (DIO1-3). These selenoenzymes govern systemic and intracellular thyroid hormone (TH) metabolism. Biallelic *SBP2* variants in patients trigger a multisystem disorder with impaired DIO activity, yielding a hallmark thyroid profile: elevated T4/T3 ratio and low reverse T3 (rT3), despite a structurally normal thyroid gland and near-normal TSH levels. Here, we used the zebrafish model to explore how sbp2 deficiency influences thyroid development, hypothalamic-pituitary-thyroid (HPT) axis control, and TH metabolism.
Methods and Results
Systemic *sbp2* knockdown was induced by injecting antisense morpholino oligonucleotides (sbp2MO) at the 1–2 cell stage. Thyroid primordium assessment via WISH and qPCR for pharyngeal endoderm (*foxa2*) and anlage markers (*nkx2.4*, *pax2a*), showing normal pattern at 24 hpf. Follicle differentiation, marked by *tg* and *nis* expression at 48–72 hpf, confirmed *sbp2*-independent organogenesis. By 120 hpf, sbp2MO larvae showed an increase in thyroid follicle T4 synthesis and *tshb* expression, analyzed by IF and fluorescent WISH, respectively. In a TSH suppression test with graded LT4 doses (25–100 nM), pituitary feedback remained normal, suppressing *tsh* dose-dependently and confirming HPT axis preservation. Notably, total TH concentration measured by ELISA revealed a significant increase of T4/T3 ratio in *sbp2* MO whole-body larvae compared to controls. Consistent with a crippled T4-to-T3 conversion, maximal LT4 exposure didn't boost T3. To probe further dio2 activity, control and sbp2MO received 200 nM db-cAMP, a *dio2* mRNA inducer, from 6 to 120 hpf. qPCR revealed equivalent *dio2* mRNA surges in both, but T3 increased significantly only in controls, supporting dio2 enzymatic failure in sbp2MO.
Conclusion
Zebrafish *sbp2* knockdown maintains thyroid organogenesis but impairs deiodinase-driven TH activation, producing high T4, low T3, and TSH compensation, mimicking the thyroid signature of human SBP2 disorder. This model validates selenoprotein functional defects in TH conversion, establishing it as a preclinical model for SBP2-related conditions.

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PS1-01-04

Structural and biochemical studies of the human IRP2 in complex with RAP reveal multiple regulatory sites

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LRP2 (megalin) is a giant single-pass transmembrane glycoprotein belonging to the LDL receptor (LDLR) family that mediates ligand uptake through clathrin-mediated endocytosis. LRP2 is expressed at the apical membrane of epithelial cells in several organs, including the kidney, brain, and thyroid. In the thyroid, LRP2 plays a key role in hormone production by acting as a receptor for thyroglobulin (TG), the precursor of thyroid hormones, mediating its endocytic uptake from the follicular lumen into thyrocytes. Following ligand binding, LRP2 internalizes TG into endosomes, where ligands are released upon vesicle acidification, after which the receptor is recycled back to the apical membrane. Unlike other members of the LDLR family, LRP2 can interact with a broad spectrum of ligands, from secreted proteins to hormones and small molecules. How newly synthesized LRP2 avoids premature ligand binding during trafficking through the secretory pathway remains unclear. LRPAP1 (or RAP) is an endoplasmic reticulum–resident chaperone for LDLR family members. It has been proposed to prevent these receptors from interacting with ligands during their transport to the plasma membrane. However, the mechanism by which LRPAP1 interacts with LRP2 in the secretory pathway, as well as how this interaction dissociates before the receptor reaches the apical membrane, remains poorly understood. Previous studies have suggested an intricate relationship among TG, its endocytic receptor LRP2, and the ER-resident chaperone LRPAP1. Here, we combined cryo-electron microscopy, crosslinking mass spectrometry, and biochemical approaches to characterize: 1. The structure of the human LRP2 receptor and identification of hotspots for ligand binding. 2. The interaction landscape and stoichiometry of the ER chaperone LRPAP1 with human LRP2. We observed multiple copies of LRPAP1 binding to LRP2 at sites overlapping with ligand-binding regions, suggesting that LRPAP1 competes with ligand recruitment and may shield ligand-binding sites during receptor maturation. 3. The molecular competition between LRPAP1 and TG for the same binding site on LRP2. In contrast to previous reports, our data suggest that TG does not directly interact with LRPAP1, supporting a model in which LRPAP1 protects LRP2 from premature TG binding during its trafficking through the secretory pathway. To bridge these molecular insights with a physiological context, we established mouse thyroid organoids, which present co-localization of LRP2 and TG, consistent with LRP2's role as the TG endocytic receptor. In parallel, we are developing LRP2-mediated endocytosis assays to monitor TG uptake, establishing the first functional framework to study LRP2-mediated TG endocytosis in thyroid tissue. Together, our results provide structural and mechanistic insight into how LRP2 ligand binding is regulated during receptor maturation and highlight the molecular basis of TG recognition by its receptor in the thyroid. These findings will be of broad interest to biochemists and cell biologists studying receptor trafficking, endocytosis, and thyroid hormone production.

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PS1-01-05

Impact of thyroid hormone transporters Mct8 and Oatp1c1 in stem cell niche cells on adult hippocampal neurogenesis

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Adult hippocampal neurogenesis (AHN), the continuous generation of new neurons from neural stem cells in the subgranular zone (SGZ) of the hippocampus, is essential for cognitive flexibility and emotional regulation and is strongly influenced by thyroid hormones (TH). Adult-onset hypothyroidism, a common endocrine disorder, is associated with anxiety, depression, cognitive impairments, and deficits in learning and memory, symptoms linked to hippocampal dysfunction. Cellular uptake of TH is mediated by transmembrane transporters, such as the monocarboxylate transporter 8 (Mct8) and organic anion transporting polypeptide 1c1 (Oatp1c1). Our previous work demonstrated the expression of both TH transporters at distinct stages of the murine neurogenic lineage, and their absence impairs the generation of new hippocampal neurons in mice. Our findings pointed to the existence of non–cell-autonomous effects of Mct8/Oatp1c1 within the neurogenic niche. Astrocytes, endothelial cells, and neurons are components of the neurogenic niche in the SGZ and also express both TH transporters. Here, we investigated whether Mct8 and Oatp1c1 exert non–cell-autonomous effects on AHN through their expression in neurons. To this end, we generated conditional Mct8/Oatp1c1 double-knockout mice with targeted deletion of both TH transporters in either glutamatergic (using Vglut2-Cre) or GABAergic neurons (using Gad2-Cre). AHN was assessed by immunofluorescence analysis of progenitor cell development and neuronal maturation. Moreover, hippocampus-dependent behaviors were assessed using the elevated plus maze test for anxiety-like behavior and the novel object recognition test for memory and exploratory activity. Deletion of Mct8/Oatp1c1 in both neuron types did not affect AHN, anxiety-like behavior, or recognition memory. This indicates that Mct8 and Oatp1c1 in mature neurons do not execute non-cell-autonomous regulation of AHN. A similar approach is being applied to astrocyte- and endothelial-specific knockouts, using Aldh1l1-CreERT2 and Tek-CreERT2, respectively. These studies will reveal how Mct8/Oatp1c1-dependent TH transport regulates adult hippocampal neurogenesis thereby providing novel insights into the mechanisms of how TH deficiency leads to cognitive deficits in adult-onset hypothyroidism.

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PS1-01-06

Integrated transcriptomic and machine learning analysis identifies peripheral immune signatures and biomarkers associated with active moderate-to-severe thyroid eye disease

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Objective
Thyroid eye disease (TED) is a heterogeneous autoimmune inflammatory disorder closely associated with Graves' disease. Patients with active moderate-to-severe TED usually show greater immune dysregulation, stronger inflammatory responses, and poorer clinical outcomes than those with milder disease. However, the systemic peripheral immune features underlying disease severity remain insufficiently understood. This study aimed to identify key immune pathways and peripheral blood biomarkers associated with active moderate-to-severe TED through integrated transcriptomic and machine learning analyses.
Methods
Patients with active moderate-to-severe TED, patients with inactive mild TED, and healthy controls were enrolled. Peripheral blood mononuclear cells (PBMCs) were isolated for bulk RNA sequencing. Differentially expressed genes were identified using DESeq2, followed by Gene Ontology enrichment analysis with clusterProfiler. Weighted gene co-expression network analysis (WGCNA) was used to construct gene co-expression networks and identify modules significantly associated with active moderate-to-severe TED. The overlap among differentially expressed genes, key module genes, and inflammation-related genes was further analyzed. Least absolute shrinkage and selection operator (LASSO) regression and random forest (RF) algorithms were applied to identify hub genes, and receiver operating characteristic (ROC) curves were used to assess their diagnostic performance. CIBERSORT was used to evaluate immune cell infiltration patterns in PBMCs and their correlations with hub genes. RT-qPCR was performed to validate hub gene expression.
Results
Compared with inactive mild TED, PBMCs from active moderate-to-severe TED patients showed significant upregulation of multiple inflammation- and innate immunity-related genes, including NOD2, TLR1, TLR2, IL18, S100A8, IFNG, and FOS. Enrichment analysis indicated that active moderate-to-severe TED was mainly associated with innate immune response, myeloid leukocyte activation, inflammatory mediator production, and interleukin-related processes, whereas mild TED was more related to immune cell migration, chemotaxis, and stress responses. WGCNA identified the sienna3 module as significantly positively correlated with active moderate-to-severe TED. By integrating differentially expressed genes, key module genes, and inflammation-related genes, and then applying LASSO and RF, NOD2, IL18, and PTPRO were identified as three hub genes. All three were significantly upregulated in active moderate-to-severe TED and showed good discriminatory performance, with area under the curve values of 0.910, 0.885, and 0.873, respectively. Single-gene GSEA suggested that high expression of these genes was associated with mitochondrial energy metabolism, transmembrane transport, organelle-related pathways, and extracellular matrix-related processes. CIBERSORT analysis revealed a myeloid-skewed peripheral immune landscape in active moderate-to-severe TED, characterized by increased monocytes, activated dendritic cells, and neutrophils. These hub genes were positively correlated with monocyte infiltration, and RT-qPCR further confirmed their upregulation.
Conclusion
NOD2, IL18, and PTPRO are potential immune biomarkers for active moderate-to-severe TED and are closely associated with immune activation and myeloid cell expansion, providing new clues for disease stratification and targeted intervention.

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PS1-01-07

Identification of new genes involved in thyroid morphogenesis by pooled-library CRISPR/Cas9 screen on Esc-derived thyroid organoid

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Congenital hypothyroidism affects approximately one in 3000 newborns and represents one of the most common endocrine disorders detected at birth. In the majority of cases, the disease results from thyroid dysgenesis, characterized by abnormal development of the thyroid gland. Although several genes involved in thyroid organogenesis have been identified, the genetic basis of most cases remains unresolved, highlighting a significant gap in our understanding of the molecular mechanisms controlling thyroid development. A deeper characterization of the genetic networks governing thyroid lineage specification and differentiation is therefore essential to better understand the origins of thyroid dysgenesis and to identify new molecular actors potentially implicated in congenital hypothyroidism. Pluripotent stem cell models of thyroid differentiation provide a powerful system to investigate these developmental processes in a controlled experimental context. The objective of this project is to identify novel genes involved in thyroid lineage specification using an unbiased genome-wide loss-of-function approach. To achieve this, a CRISPR/Cas9-based screening strategy was implemented in pluripotent stem cells undergoing forced differentiation toward the thyroid lineage. A genome-scale single-guide RNA library was introduced into the cells to enable systematic gene inactivation, after which the cells were subjected to a thyroid differentiation protocol. Populations committed to the thyroid lineage were subsequently isolated and the representation of integrated guide RNAs was analyzed by next-generation sequencing. Comparative analysis between thyroid-committed and control cell populations allows the identification of genes whose disruption affects thyroid lineage specification. During the first phase of the project, the experimental pipeline required for large-scale CRISPR screening was successfully established and validated, including library amplification, optimization of viral delivery conditions, scaling of the differentiation protocol, and genomic DNA preparation and sequencing for screen analysis. A first genome-wide screen was performed and preliminary analysis of the dataset identified several candidate genes potentially involved in thyroid differentiation. Among the top candidates emerging from this initial screen were Guanylate Binding Protein 1 and Arylsulfatase Family Member H, suggesting a possible role for these genes in early thyroid specification. Further validation studies are currently underway to investigate the function of these candidate genes through the generation and characterization of knockout cell lines. In parallel, additional independent screens are being prepared to strengthen the identification of novel genetic regulators involved in thyroid lineage development.

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PS1-01-08

USP47 is essential for normal thyroid development

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Objectives
A cysteine-type deubiquitinase Usp47 is a modulator of cell growth, genome integrity and transcription through its N-terminal catalytic domain. Its known targets include beta-catenin, which regulates cell proliferation and adhesion, and Yap1, which controls organ size by restricting proliferation. Usp47 also regulates NLRP3 inflammasome activation, being essential for maintaining the stability and function of regulatory T-cells. Usp47 is expressed in glandular epithelial cells, including thyrocytes, and its variants have been identified in Finnish patients with hypothyroidism. To explore its role in thyroid biology, we generated mice models carrying either a human USP47 N1133S-variant or a frameshift K1120fs-mutation, and additionally created Usp47-knockout FRTL5 thyrocytes.
Methods
Homozygous N1133S, K1120fs, and wild-type mice were fed either high-iodide (HI) or sufficient-iodide (SI) chow. Thyroid growth response was assessed after one-month goiter induction with sodium perchlorate and methimazole in drinking water. Thyroid and body weights, body length, and serum TSH and T4 levels were measured. Thyroids were examined by immunohistochemistry and RNA sequencing. Usp47-KO FRTL5 cells were analyzed by western immunoblotting for thyroid- and growth-related protein targets.
Results
Untreated Usp47-variant mice showed no general abnormalities but had reduced thyroid weight (females: N1133S -27%, $P = 0.018$; K1120fs -29%, $P = 0.042$; males: -16% and -12%, respectively). In goiter-treated K1120fs-mice, thyroid weight was further reduced (females -38%, $P < 0.001$; males -29%, $P = 0.001$), while body weight, body length, and T4 levels remined unaffected. A modest TSH elevation was observed in goiter-treated K1120fs-mice compared to controls. Immunohistochemistry showed high Usp47 expression in developing thyrocytes of wild-type mice, with reduced staining in Usp47-variant carriers. Follicular morphology was altered in Usp47-variant mice, most prominent in K1120fs-animals and those receiving SI diet. Immunostaining for beta-Catenin, Ki67, Grk5, Nis and Slc26a7 was reduced in goiter-treated K1120fs-mice. RNA-analyses revealed broad gene-expression alterations in goiter treated K1120fs thyroids, with more pronounced alterations in males. Western blotting analyses of Usp47-KO FRTL5-cells confirmed reductions in beta-Catenin, Ki67, Nis, Slc26a7, TPO and Pendrin, while Thyroglobulin was slightly increased compared to control FRTL5-cells.
Conclusions
Usp47 modifications lead to impaired thyroid growth and altered follicular morphology, associated with reduced expression of beta-Catenin, Ki67, Nis, Slc26a7, TPO and Pendrin. Therefore, normally functioning Usp47 is essential for normal thyroid development, and its dysfunction may predispose to hypothyroidism.

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PS1-01-09

Heightened food reward motivation, reduced opioid sensitivity and gene expression shifts in the dopaminergic systems following developmental thyrotoxicosis

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To investigate the role of thyroid hormone (TH) in programming adult reward systems during development, we utilized global *Dio3* knockout (*Dio3* KO) mice, which model developmental TH excess due to the loss of the enzyme DIO3, which breaks down TH into inactive metabolites. We hypothesize that developmental TH excess programs adult behaviors and gene expression of relevance to the reward system. We used adult male and female WT and *Dio3* KO littermates bred on a hybrid background with C57BL/6J fathers and 129X1/SvJ mothers. Food reward motivation was measured using a palatable food reward self-administration runway assay and palatable food conditioned place preference (CPP). Opioid sensitivity was assessed using twice-daily morphine injections over 72 hours with nociceptive testing (hot-plate tail-flick latency) at baseline, 30 minutes post-morphine, and after three days of morphine treatment, followed by naloxone-precipitated withdrawal scoring. We used qPCR to quantify reward-related gene expression in hypothalamus, striatum, and amygdala. *Dio3* KO mice exhibited increased palatable food motivation and significant resistance to extinction in the palatable food reward self-administration runway. *Dio3* KO also showed an increased CPP for palatable food reward. In the opioid assay, *Dio3* KO mice exhibited higher tail-flick latency after three days of morphine treatment, consistent with reduced tolerance, and displayed significantly fewer total jumps following naloxone administration. Notably, the subset of *Dio3* KO mice that jumped were all female, with no *Dio3KO* males showing withdrawal-dependent jumping. Post-morphine withdrawal, *Dio3* KO mice showed significantly higher amygdalar and hypothalamic corticotropin-releasing hormone(*Crh*), which trended down in the striatum. RNA-seq analysis revealed 545 differentially regulated genes (DEGs) within the amygdala and 50 DEGs in the striatum with a p-value of <0.5. RNA-seq of the amygdala and striatum show upregulation of *Ppp1r1b* and *Gpr88* in the amygdala and striatum. *Ppp1r1b*, also known as DARPP-32, encodes a signaling molecule that regulates dopaminergic circuits. *Gpr88* is an orphan G-protein receptor known to play a role in reward and impulsivity. *Crh* and *Nr4a2* were downregulated. *Nr4a2*, also known as Nurr1, is a critical dopamine neuron maintenance gene. These results were confirmed via qPCR. Developmental TH excess leads in adulthood to heightened palatable food motivation and attenuated opioid tolerance/withdrawal and altered reward-related behaviors that were associated with significant amygdalar and striatal gene expression alterations.

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Basic Highlights 2

PS1-02-01

Theo Visser Prize 2026: Effectiveness of early treatment with thyroid hormone analogue TRIAC on neurocognitive outcomes in young paediatric male patients with MCT8 deficiency: an international single ARM trial

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Background
Monocarboxylate transporter (MCT)8 deficiency is a rare, X-linked, genetic disorder characterized by severe motor and intellectual disability, combined with chronic T3-mediated thyrotoxicosis in peripheral tissues. Treatment with the T3 analogue Triac can effectively and safely alleviate features of thyrotoxicosis in paediatric and adult male patients with MCT8 deficiency. Early postnatal administration of Triac to mice modelling MCT8 deficiency fully rescues the brain phenotype in these animals. The effects of early treatment on motor and cognitive outcomes in patients with MCT8 deficiency are unknown.
Methods
We performed a phase II, open-label, multicentre, clinical trial (NCT02396459), which investigated the effect of Triac treatment on the motor and cognitive development of male patients with MCT8 deficiency, aged 0-30 months at baseline. Exclusion criteria included previous treatment with Triac or other (anti-) thyroid medication. Patients were treated for 96 weeks with Triac doses up to 200 mg/kg/day, targeting T3 concentrations between 10% of the lower limit of normal (LLN) and the LLN. Primary outcomes were neurodevelopmental changes as measured by the Gross Motor Function Measure (GMFM)-88 and the Bayley Scales of Infant Development (BSID)-III gross motor domain, compared to untreated historical cohort patients aged 0-9 years. Post-hoc analyses focused on other neurodevelopmental domains. Secondary outcomes included the effect of Triac on clinical and biochemical features related to thyrotoxicosis, and safety outcomes.
Results
Between Dec 3, 2020, and Jun 22, 2022, we screened 23 male patients. One patient was excluded due to previous levothyroxine treatment and another discontinued treatment because of personal circumstances. A total of 21 patients (median age 16 months at baseline) completed the 96-week treatment period. Compared to untreated historical cohort patients, there was no improvement in GMFM-88 total score (mean difference -2.42, 95%CI -4.36 to -0.48, $P = 0.02$) or BSID-III gross motor domain (mean difference 0.21, 90%CI -0.19 to 0.61, $P = 0.38$) after 96 weeks of treatment. Post-hoc analyses suggested small, significant, improvements in expressive language, fine motor, and cognition compared to untreated historical cohort patients. A decrease in serum T3 concentrations was observed during Triac treatment (mean difference -3.24 nmol/l). No patients discontinued due to severe adverse events.
Conclusions
In this phase II, open-label, multicentre, clinical trial, we found no significant treatment effect of Triac on gross motor outcomes in young paediatric male patients with MCT8 deficiency. Post-hoc analyses suggested small improvements in expressive language, fine motor, and cognition. Our findings validate the safety of Triac on outcomes related to peripheral thyrotoxicosis.

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PS1-02-02

Thyroid transcriptome differs between two NON-autoimmune hyperthyroidism mouse models

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Objectives
Constitutively activating mutations (CAMs) of the TSH receptor (TSHR) are the most common genetic cause of nonautoimmune hyperthyroidism (NAH). TSHR CAMs lead to increased thyroid hormone (TH) production and gland enlargement, yet the molecular mechanisms by which specific TSHR mutations drive NAH, and how dietary iodide modulates disease expression, remain incompletely understood. Here we investigate the thyroid transcriptome in two patient-derived TSHR CAM knock-in mouse models with distinct G-protein signaling profiles.
Methods
Thyroidal gene expression was compared between two knock-in mouse models carrying either the TSHR M453T or D633H mutations, which preferentially activate Gαs or both Gαs and Gαq/11 signaling, respectively. Both models included two-month-old male and female mice as wild-type (WT) controls or homozygote (HOM) mutation carriers. Both models were maintained on a sufficient iodide diet (SID) mimicking physiological dietary conditions. The M453T model included an additional high iodide diet (HID) group. Thyroid total mRNA was isolated, sequenced and reads were normalized using the DESeq2 R package.
Results
Under SID conditions, M453T mice displayed a strong hyperthyroid phenotype with suppressed TSH and elevated T4, whereas HOM D633H mice presented a comparatively milder phenotype. Under HID conditions M453T mice presented an unexpectedly attenuated hyperthyroid phenotype, particularly in males. Both mutations expressed thyroidal genes in differential patterns, with significant modifying effects of sex and dietary iodide. However, in HOM M453T mice thyroidal genes were expressed more potently. Thyroid function genes *Pendrin, Nis and Dio1* were strongly upregulated in HOM M453T mice and similarly though less markedly, in HOM D633H mice. SID further amplified upregulation of these genes in M453T mice compared to HID. Only in HOM M453T *Tshr, Tpo, Duox2 and Tg* were also upregulated, although more modestly. Notably, the *Slc26a7* gene, with substantially higher basal expression than *Pendrin*, showed no significant differential expression in either model. *Duox1* was the only thyroid-related gene consistently downregulated in both models. In both models, females consistently showed stronger differential expression than males.
Conclusions
These findings demonstrate that TSHR mutation type and dietary iodide availability critically influence thyroidal transcriptional responses in NAH. The sex-dependent differences in gene expression further highlight the importance of

considering both sex and diet when modeling thyroid diseases in vivo. Importantly, the conditional modulation of TSHR CAM activity by dietary iodide suggests potential of iodide-based strategies to refine the clinical management of NAH.

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PS1-02-03

Iodide availability controls thyroid cell identity, ERK signaling, and redox balance

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Introduction
Iodine deficiency (ID) is still a major global public health concern. The effects of ID on thyroid function have been mainly attributed to increased TSH levels secondary to impaired thyroid hormones production. However, the direct effects of ID on thyroid follicular cell gene expression, intracellular signaling, and redox regulation remain poorly understood.
Objective
To investigate the molecular effects of moderate and severe ID on thyroid cell differentiation, intracellular signaling pathways, epigenetic regulation, and oxidative stress-related genes *in vitro*.
Methods
PCCl3 cells (normal rat thyroid follicular cells) were cultured for seven days under three conditions: control (C: 10?? M NaI), moderate iodine deficiency (MID: 10?? M NaI), and severe iodine deficiency (SID: iodide-free medium/PBS). TSH concentration remained constant across all groups. To evaluate the role of the MAPK/ERK signaling pathway on ID-induced effects, cells were treated with the MEK inhibitor PD0325901. Gene expression was assessed by qPCR and protein levels by Western blotting.
Results
Both MID and SID significantly increased the expression of thyroid differentiation markers *Slc5a5 (NIS), Tpo, Tg* and *Tshr*. The thyroid transcription factors *Foxe1* and *Pax8* were also upregulated under ID conditions. At the protein level, *NIS* expression was increased in MID and SID groups. Interestingly, ID also modulated genes involved in epigenetic regulation, including *Dnmts, Hat1, Hdac3, Kdm5c, Kdm6a* and *Ezh2*. Moreover, *Sod1* and *Sod2* mRNA levels were reduced in both ID groups compared with controls, whereas *Gpx1* mRNA expression was reduced only in the SID group. In parallel, MID and SID reduced phosphorylated ERK and AMPK protein levels. Notably, pharmacological inhibition of ERK signaling abolished the ID-induced upregulation of *Slc5a5*, *Pax8* and *Foxe1*, indicating that ERK signaling contributes to the transcriptional response to iodide availability.
Conclusions
ID directly modulates thyroid cell differentiation, epigenetic regulatory pathways, redox-related enzymes, and intracellular signaling pathways independently of TSH. These data reinforce the concept that iodide is not only required for thyroid hormone synthesis, but also actively participates in the maintenance of thyroid follicular cell identity and cellular homeostasis.

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PS1-02-04

Thyroid hormone activation drives fibroblast identity and tumor remodeling in cutaneous squamous cell carcinoma

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Cutaneous Squamous Cell carcinoma is a major cause of cancer-related mortality. Although immune checkpoint blockade has improved outcomes, nearly half of patients fail to respond or develop resistance. Cancer-Associated Fibroblasts (CAFs) are central drivers of tumor progression and immunotherapy resistance, yet the molecular signals that reprogram fibroblasts into tumor-promoting states remain poorly understood. We identify Thyroid Hormone (TH) signaling, mediated by type 2 deiodinase (D2), as a critical regulator of CAF activation. Single-cell transcriptomics and spatial RNA profiling identified a D2-positive fibroblast subpopulation, overlapping with immunomodulatory and matrix CAFs. RNAseq analysis provided a strong functional and mechanistic evidence that D2 is required to sustain the activated and metabolically competent CAF phenotype. *In vivo* fibroblast-specific D2 deletion impaired CAF activation and suppressed tumor expansion. Functionally, spatial metabolomics revealed that D2-positive regions promoted metabolic remodeling of the tumor microenvironment (TME) and collagen-rich matrix deposition, exacerbating aggressive tumor behavior. These findings identify TH signaling as a previously unrecognized driver of fibroblast reprogramming in cancer and suggest that its inhibition represents a novel therapeutic vulnerability.

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PS1-02-05

Perchlorate potentiates IODIDE accumulation in human thyroid cells VIA pendrin blockade

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Introduction
Pendred syndrome (PS) is the most common syndromic form of congenital deafness, frequently associated with goiter and subclinical hypothyroidism caused by pathogenic variants in *SLC26A4* (Pendrin). In the thyroid follicular epithelium, Pendrin mediates apical iodide efflux into the lumen, while basolateral NIS (SLC5A5) drives active influx. Despite its clinical relevance, functional characterization of patient-derived Pendrin variants in dynamic iodide transport remains technically challenging: classical assays rely on radioactive iodide and cannot recapitulate the polarized human follicular epithelium. The net pharmacological effect of NIS inhibitors such as sodium perchlorate (NaClO?) in intact human thyroid cells where both transporters coexist has never been characterized.
Objective
To determine the functional consequences of perchlorate on iodide transport in human thyroid follicular cells expressing endogenous, polarized NIS and Pendrin, and to compare these with non-polarized HEK293 models.
Methods
A non-radioactive Sandell-Kolthoff iodide assay was validated in HEK293 cells transfected with NIS, Pendrin (WT or two Pendred syndrome-associated pathogenic variants), or combinations thereof. Results were extended to primary human thyroid follicular cultures from the TIROCHUS biobank [Bravo *et al*., PMID:23539720] maintained under h7H hormonal conditions, and to T-NT2 cells (spontaneously immortalized human normal thyrocytes) and their isogenic Pendrin-knockout derivative T-NT2-KO-PDS (CRISPR-Cas9). The role of h7H stimulation vs hormone deprivation was evaluated.

Results
In HEK293 cells expressing NIS alone, NaClO? inhibited iodide uptake as expected. Strikingly, in HEK293 cells expressing Pendrin-WT alone (without NIS, at high iodide concentrations allowing passive entry), NaClO? potentiated intracellular iodide accumulation, demonstrating direct Pendrin blockade independent of NIS. This potentiation was proportional to functional Pendrin activity: markedly reduced with S28R-Pendrin (trafficking-competent but transport-impaired N-terminal variant) and absent with L236P-Pendrin (transmembrane domain variant lacking membrane targeting), establishing a mechanistic hierarchy. Michaelis-Menten kinetic analysis in HEK293 co-expressing NIS + Pendrin-WT vs pathogenic variants revealed significant Vmax and Km differences. In primary TIROCHUS cultures under h7H and in T-NT2 cells, NaClO? paradoxically potentiated iodide accumulation reaching levels equivalent to T-NT2-KO-PDS, strictly dependent on h7H stimulation and Pendrin expression. 3D thyronoid structures amplified all findings.
Conclusions
We propose that perchlorate acts sequentially: entering thyrocytes via NIS then blocking Pendrin-mediated apical efflux, trapping iodide intracellularly and preventing transfer to the colloid. This mechanism explains the goitrogenic component of perchlorate exposure and the organification defect in Pendred syndrome, providing a robust non-radioactive platform for functional classification of patient-derived *SLC26A4* variants in human follicular epithelium. *Funded by AEI PID2022-140149OB-I00*.

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PS1-02-06

Thyroid hormone–mediated modulation of testicular mitochondrial homeostasis in high-fat diet rats

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Objectives
Obesity is a multifactorial condition characterised by excessive body fat accumulation resulting from the interaction of endocrine-metabolic and environmental factors. In recent decades, an obesity-induced progressive decline in sperm quality and male fertility has been reported. Metabolic alterations induced by a high-fat diet (HFD) can impair testicular function, affecting both spermatogenesis and mitochondrial quality, which are essential for male fertility. Mitochondria provide energy for cellular maturation and differentiation during spermatogenesis and are critical for sperm motility, capacitation, and fertilising ability. In this context, mitochondrial integrity and the regulation of processes such as mitochondrial biogenesis, mitophagy, and oxidative balance are particularly vulnerable. In animal models, both 3,5-diiodo-L-thyronine (3,5-T2) and 3,5,3′-triiodo-L-thyronine (T3) have been shown to ameliorate metabolic alterations induced by HFD through modulation of mitochondrial function, nevertheless the underlying mechanisms remain incompletely understood. This study investigated the effects of 3,5-T2 and T3 administration in a rat model of HFD-induced obesity, focusing on testicular mtDNA oxidative damage, base excision repair (BER), and mitochondrial quality control mechanisms.
Methods
Male rats were fed a HFD for 14 weeks; 3,5-T2 or T3 was daily administered by intraperitoneal injection during the last 4 weeks of the experimental period. Testicular histology, steroidogenesis and spermatogenesis, and oxidative stress were evaluated, together with mtDNA damage, mtBER components, markers of mitochondrial biogenesis, dynamics and mitophagy, and the cGAS/STING pathways.
Results
HFD-fed rats exhibited marked testicular alterations, including impaired testicular architecture, hormonal imbalance, increased oxidative stress, mitochondrial dysfunction and inflammatory activation. Moreover, HFD significantly increased mtDNA oxidative lesions. Treatment with 3,5-T2 or T3 exerted a partial recovery of testicular architecture and protective effect on mitochondrial integrity, significantly reducing mtDNA oxidative damage and testicular stress.
Conclusions
3,5-T2 and T3 can positively modulate testicular morphology and mitochondrial homeostasis under metabolic stress, suggesting a potential role for thyroid hormone derivatives in preserving male reproductive function in obesity-related conditions.

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PS1-02-07

Effects of TR-β selective thyromimetic TG68 on FNDC5/irisin axis in a mouse model of diet-induced obesity

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Background
TG68 has emerged as a promising metabolic modulator, displaying lipid-lowering and neuroprotective properties [doi: 10.3390/cells14080580]. Previous studies have suggested that TG68 can influence energy metabolism and inflammatory pathways, but the mechanisms underlying its systemic metabolic effects remain only partially understood. Given the recognized role of the myokine irisin in regulating energy expenditure, adipose browning, and central metabolic homeostasis [doi.org/10.1016/ j.drudis.2022.03.019], we investigated whether TG68 could modulate the FNDC5/irisin axis in a mouse model of diet-induced obesity.
Methods
Male CD-1 mice were fed a high-fat diet (HFD) for 10 weeks to induce obesity and insulin resistance, followed by TG68 administration (10 mg/kg/day) for 2 weeks via drinking water. Circulating irisin levels were quantified (Elisa assay), and gene expression of thermogenic and metabolic markers (PGC-1α, FNDC5, UCP1) was assessed by qPCR in metabolically relevant tissues, including adipose tissue and hypothalamus. These analyses were performed to evaluate both peripheral and central components of metabolic regulation potentially influenced by TG68 treatment.
Results
HFD mice showed reduced circulating irisin levels, associated with reduced expression of *PGC-1α* and *UCP1* in adipose tissue, and downregulation of *FNDC5* and *PGC-1α* in the hypothalamus, suggesting an overall impairment of metabolic and thermogenic pathways. TG68 treatment significantly increased the expression of selected genes in both adipose tissue and hypothalamus, consistent with reactivation of oxidative metabolism and browning-related programs. In all animals, circulating irisin levels were strongly and inversely correlated with body weight ($r = -0.79$, $R^2 = 0.63$, $P < 0.0001$). Multiple linear regression/ANCOVA analysis revealed comparable slopes among groups but significant differences in intercepts ($P = 0.015$), indicating that TG68 increased irisin levels independently of body weight.
Conclusions
Overall, these findings suggest that TG68 may partially counteract obesity-associated metabolic and central alterations, potentially involving modulation of the FNDC5/irisin pathway. Further studies are currently ongoing to further clarify the underlying molecular mechanisms. Taken together, our results support the hypothesis that TG68 could act as a multitarget metabolic modulator with relevance for obesity-associated metabolic and neuroinflammatory disorders.

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PS1-02-08

Maraviroc attenuates orbital remodeling, inflammation, and lipid dysregulation in a murine model of thyroid eye disease

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Background
Graves' disease (GD) is an autoimmune disorder that can extend beyond the thyroid gland and cause thyroid eye disease (TED), which is characterized by orbital inflammation and tissue remodeling. Given the role of the CCL5-CCR5 axis in immune cell recruitment, this study aimed to evaluate whether the CCR5 antagonist maraviroc can reduce orbital inflammation and remodeling in a murine model of TED.
Methods
We investigated the therapeutic potential of maraviroc, a CCR5 antagonist, in a mouse model of TED induced by immunization with the human TSH receptor (hTSHR) A-subunit. Mice were immunized with the pTriEx1.1Neo-hTSHR A-subunit plasmid, and a subset received maraviroc via drinking water. Thyroid function, orbital tissue alterations, immune cell infiltration, and lipid metabolism were evaluated using serological assays, histological and immunohistochemical analyses, as well as untargeted lipidomics.
Results
Maraviroc treatment did not significantly alter anti-TSHR antibody levels or the degree of hyperthyroidism, although a modest improvement in thyroid histopathology was observed. Importantly, maraviroc markedly reduced key features of orbital disease, including brown adipose tissue expansion, infiltration of CCL5-positive immune cells, $CD4^+$ T cells, and $F4/80^+$ macrophages. Lipidomic profiling revealed distinct metabolic changes in treated animals, characterized by decreased triacylglycerol levels and increased carnitines, suggesting enhanced fatty acid utilization. Furthermore, composite Z-score analysis confirmed the beneficial effects of maraviroc on orbital inflammation and tissue remodeling.
Conclusion
Maraviroc emerges as a promising targeted therapeutic strategy for TED, exerting anti-inflammatory and anti-adipogenic effects while largely sparing thyroid autoimmunity. These preclinical findings provide a strong rationale for further clinical investigation of maraviroc as a potential treatment for TED. Data previously published in: [Front. Endocrinol.2026].

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PS1-02-09

Spatial transcriptomics reveals perinatal endocrine disruptor–induced reprogramming of hypothalamic circuits shaping adult metabolic responses to western diet

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Introduction/Aim
The worldwide rise in obesity cannot be solely attributed to sedentary lifestyles and Western dietary habits. Increasing evidence points to environmental exposure to endocrine-disrupting chemicals (EDCs) as an additional and underestimated contributor to metabolic dysregulation. Among these compounds, so-called obesogens have been shown to target central circuits controlling food intake, particularly within the hypothalamus—a key integrative hub regulating metabolism, energy balance, and the thyroid axis. This brain region is composed of distinct nuclei, each orchestrating specific aspects of metabolic and hormonal homeostasis.
Methods/Results
Here, we investigated the combined impact of perinatal exposure to the flame retardant tetrabromobisphenol A (TBBPA), a known disruptor of thyroid hormone signaling, and a high fat–high sucrose (HFHS) diet in adulthood, mimicking a Western dietary environment, on the hypothalamic transcriptome. Pregnant dams were exposed to TBBPA (10 mg/kg/day) or vehicle from late gestation through lactation. Offspring were subsequently challenged with an HFHS diet from 2 to 6 months of age. To capture hypothalamic nucleus-specific molecular responses, we employed spatial transcriptomics enabling the integration of whole-transcriptome profiling with anatomical resolution. We optimized an analysis workflow tailored to hypothalamic physiology, allowing the identification of transcriptional clusters aligned with histologically defined hypothalamic nuclei. Using a custom-built analytical pipeline, we compared spatial gene expression signatures across treatments and dietary conditions. Our results reveal that perinatal TBBPA exposure induces nucleus-specific transcriptional reprogramming within the hypothalamus, with distinct molecular pathways being differentially affected depending on the dietary context.
Conclusions
By resolving the spatial origin of transcriptomic signals, our study highlights how early-life exposure to an EDC can durably rewire hypothalamic circuits involved in thyroid and metabolic regulation. When combined with an obesogenic diet, this developmental reprogramming may compromise the adult organism's capacity to adapt to metabolic challenges, providing novel mechanistic insight into the developmental origins of metabolic diseases.

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PS1-02-10

Systemic metabolic reprogramming in graves' disease and orbitopathy: preliminary results of the MISS go study

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Objectives
The international study "Investigation of Novel biomarkers and Definition of the role of the microbiome In Graves' Orbitopathy" (INDIGO) investigated the role of gut microbiota in Graves' disease (GD) and Graves' Orbitopathy (GO). The metagenomics by 16S rRNA sequencing of fecal samples identified an imbalance in commensal bacteria (reduced Bacteroidetes, increased Actinobacteria) among GD and GO patients compared with healthy controls (CTRL). The subsequent study "Microbiota and Immune SignatureS of Graves' disease and Orbitopathy" (MISS.GO) aims to identify systemic metabolic pathways altered in GD and GO, possibly linked to specific gut microbiota alterations.

Methods
Metabolomics profiling using GC×GC TOFMS was performed on stored plasma samples of 35 GO, 33 GD and 5 CTRL from the INDIGO study. Multivariate statistical analysis including Principal Component Analysis (PCA) and Partial Least Square Discriminant Analysis (PLS DA) were applied.
Results
PCA and PLS DA analyses revealed global metabolic variation between CTRL, GD and GO samples. Disease groups tended to cluster separately from controls, indicating systemic metabolic alterations associated with autoimmune thyroid disease. Volcano plot analysis revealed several metabolites of oxidative stress and lipid metabolism significantly altered in GD compared with CTRL, such as gamma tocopherol, 4 hydroxybutanoic acid, stearic acid and 1,5 anhydroglucitol. GO patients, compared with CTRL, had altered L tryptophan levels, an important amino acid involved in immune regulation and inflammatory responses. Direct comparison between GO and GD patients revealed specific alterations of fatty acid metabolism and mitochondrial energy metabolism associated with orbitopathy development, including metabolites 9 octadecenoic acid, L glutamic acid, pentanoic acid and 3 hydroxybutyric acid. Pathway enrichment analysis highlighted alterations of linoleic acid metabolism, tryptophan metabolism, glycerolipid metabolism, taurine metabolism, alanine–aspartate–glutamate metabolism and nicotinate metabolism, linked to oxidative stress regulation, immune signaling and mitochondrial energy production.
Conclusions
Several systemic metabolic alterations were identified in GD and GO patients compared with CTRL. Especially lipid metabolism of fatty acids (stearic acid), and amino acid metabolism (tryptophan and glutamate), both involved in immune regulation and inflammatory responses. Other alterations affected several pathways associated with carbohydrate metabolism and energy metabolism, closely linked to oxidative stress and immune mediated tissue remodeling processes. These findings suggest systemic metabolic reprogramming in autoimmune thyroid disease and identify potential metabolic signatures associated with orbitopathy development. We are currently working to link such metabolomic signature with the gut microbiota profile derived from shotgun analysis, aiming to cluster gut bacteria and their function with specific pathways, and identify potential diagnostic and prognostic markers, or therapeutic targets, of thyroid autoimmunity.

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Basic Cancer 1

PS1-03-01

Genetic characterization of RET fusion genes in papillary and poorly differentiated thyroid cancer

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Background
RET is a receptor tyrosine kinase that has been found altered in multiple thyroid cancer (TC) subtypes. Whilst mutations are the most common alteration in medullary thyroid cancer, *RET* fusions are long known to be involved in papillary thyroid cancer (PTC). Such fusions, however, are yet to be fully characterized. Here, we investigated the role of fusion genes as a RET activating mechanism in PTCs and poorly differentiated thyroid cancers (PDTCs).
Methods
To identify and characterize *RET* fusions, we interrogated 315 PTCs and 132 PDTCs, previously subjected to targeted sequencing, from the cBioportal database, and 531 PTCs previously subjected to whole-exome (TCGA) and whole-genome sequencing (PCAWG). The frame status and fusion driver probability were evaluated using Oncofuse. Breakpoint locations in the gene sequence and protein domain were also assessed. The TCGA RNA sequencing data taken from PTC cases harboring *RET* fusions was examined to measure the expression levels of RET. The tumor infiltrating immune cells profile of TCGA samples was examined using Cybersort.
Results
RET fusion genes were identified in 44 primary and 17 metastatic PTCs (61/846, 7,2%), and in 1 primary and 6 metastatic PDTCs (7/132, 5,3%). Of the 68 RET fusions identified, 64 were in-frame (94%), and 4 were out-of-frame (6%). In PTCs, 52% of RET fusions had a driver probability of 99%, while in PDTCs, all *RET* fusions displayed a driver probability lower than 50%. All of the 68 fusion genes were found to affect the coding region of RET transmembrane domain, with 91% affecting the exon 12 ($n = 62$), and 9% affecting the exon 11 ($n = 6$) of *RET*. Recurrent fusion genes included those affecting *CCDC6* ($n = 43$, 63%), *NCOA4* ($n = 9$, 13%), and *ERC1* ($n = 4$) genes. RNA sequencing data showed that PTCs harboring *RET* fusions had a significantly higher expression of the *RET* gene than those not harboring any *RET* genetic alteration (median z-score 2.2 vs -0.4, $P < 0.0001$). PTCs harboring *RET* fusions had a significantly higher CTA (Cancer-testis antigen) score than those not harboring any *RET* genetic alteration (median score 1.65 vs 1.35, $P < 0.0001$), associated with enhanced responsiveness to immunotherapy in other cancer types.
Conclusion
Fusion genes affecting *RET* were found in primary tumors and metastases from both PTCs and PDTCs, with significant differences detected in RNA levels and immune scores in PTCs harboring *RET* fusions. These findings thus broaden the spectrum of molecular mechanisms of RET activation in thyroid cancer, with diagnostic and potentially therapeutic relevance.

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PS1-03-02

Functional characterization of cancer stem-like properties in anaplastic thyroid carcinoma and the contribution of JAK/STAT3 pathway

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Objective
This study aimed to functionally characterize cancer stem-like cells (CSC) properties in anaplastic thyroid carcinoma (ATC) and to evaluate the involvement of the JAK/STAT3 pathway in stemness using nifuroxazide (NFZ).
Methods
ATC cell lines KTC-2, HTH83 and 8305c, the non-tumoral cell line Nthy-ori 3-1 and *STAT3* knockout (KO) KTC-2 and HTH83 were applied. ALDH activity and fluorescence-activated cell sorting (FACS) were assessed by flow cytometry using ALDEFLUOR reagent. The expression of nine CSC biomarkers was analyzed by real-time PCR. Functional assays included sphere formation, self-renewal, cell proliferation, cell cycle, cell viability, and colony formation. Autophagy was evaluated by western blot.
Results
Higher ALDH activity was observed in all ATC cells compared to Nthy-ori 3-1, particularly in HTH83 cell line. Increased expression of CSC biomarkers and enhanced sphere formation capacity were also observed compared to non-tumoral cell line. After FACS, HTH83 showed a higher proportion of ALDH+ (80%) than KTC-2 (30%). ALDH+ cells also showed increased expression of CSC biomarkers, including *ALDH1A3*, along with an enhanced sphere formation capacity and self-renewal compared with ALDH-. Functionally, ALDH1 inhibition by DEAB reduced cell proliferation, cell cycle progression, cell viability, and clonogenicity only in KTC-2 cell line. *STAT3* KO decreased sphere formation and CSC biomarkers expressions in HTH83 cell. In all ATC cells, NFZ reduced ALDH activity, sphere formation, and CSC biomarkers expression. NFZ also decreased ALDH activity in KTC-2 and HTH83 *STAT3* KO cells. Additionally, NFZ induced autophagy in KTC-2, even in the presence of an autophagic flux inhibitor.
Conclusion
Together, these results indicate that ATC cell lines exhibited pronounced CSC features, suggesting that JAK/STAT3 contributes to CSC maintenance in HTH83 cells. The pharmacological treatment with NFZ attenuated CSC properties, possible through inhibition of JAK/STAT3, MAPK or PI3K pathways, as previously observed by our group. Moreover, ALDH activity appears to be relevant in KTC-2 stemness. Targeting CSC biomarkers, including ALDH, in combination with JAK/STAT3 inhibition, may represent a promising therapeutic strategy for ATC.

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PS1-03-03

Single-cell mapping of thyroid development reveals a notch–heyl axis in tumorigenesis

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Objective
To generate a single-cell transcriptional map of early thyroid development and identify regulatory pathways linking developmental programs to thyroid tumorigenesis.
Methods
Single-cell RNA sequencing (scRNA-seq) was performed on mouse embryonic thyroid tissues across key stages of organogenesis (E9.5–E12.5). Computational trajectory inference and gene regulatory network (GRN) analyses were used to reconstruct lineage relationships and identify transcriptional regulators of thyroid follicular and ultimobranchial body (Ubb/C-cell) development. Distinct cellular populations and intermediate progenitor states were characterized based on transcriptional signatures. Candidate regulators were validated using RNAscope in situ hybridization in embryonic thyroid tissues. Comparative analyses were also conducted to assess gene expression in BRAFV600E-mutant and wild-type thyroid cells in adult mice.
Results
Single-cell transcriptomic profiling identified transcriptionally distinct populations corresponding to thyroid follicular and ultimobranchial body lineages, as well as intermediate progenitor states representing transitional developmental stages. Lineage trajectory reconstruction provided a framework for thyroid lineage specification during early organogenesis. GRN analysis identified several candidate regulators, including Heyl, a transcriptional effector of Notch signaling, as a key regulatory node within the thyroid lineage network. RNAscope confirmed the spatial expression of Heyl in developing thyroid tissues. Additionally, Heyl expression was increased in BRAFV600E-mutant thyroid cells compared with wild-type cells, and its upregulation was dependent on mutant Braf kinase activity in Tg-CreERT2;-BrafCA/+ mice.
Conclusions
This study provides a high-resolution single-cell framework of early thyroid development and identifies the Notch–Heyl axis as a potential regulatory pathway linking developmental transcriptional programs to thyroid tumorigenesis.

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PS1-03-04

Circulating cell-free dna as a potential biomarker for defining disease status in patients with differentiated thyroid cancer

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Introduction and Background
Cell-free DNA (cfDNA) consists of DNA fragments released by dying cells (apoptosis and necrosis) into body fluids and reflects genetic and epigenetic alterations associated with pathological states. Circulating cfDNA analysis (liquid biopsy) is increasingly used in cancer genomics and features such as cfDNA concentration and fragmentation patterns, have shown potential diagnostic and prognostic value in oncology.
Aim
To evaluate whether plasma cfDNA concentration and fragmentation patterns are associated with disease status and tumor burden in patients with differentiated thyroid cancer (DTC).
Patients and Methods
We conducted a cross-sectional evaluation involving 41 patients diagnosed with DTC who had undergone total thyroidectomy ± radioiodine therapy. Our cohort included patients with no evidence of disease (NED) after treatment, patients with stable distant metastases (SD), and patients with progressive distant metastases (PD) receiving Lenvatinib therapy. For each patient, clinical data were retrospectively collected and a liquid biopsy was performed, followed by cfDNA extraction, quantification, and fragmentation analysis through assessment of the fragmentation index (FI: short fragments 100–300 bp/medium + long fragments 300–700 bp).
Results
The mean age was 59.9±15.9 years; 25 (61%) patients were female and the majority (90.2%) had DTC. At evaluation 14 (34.1%) patients had NED, 17 (41.5%) had SD without systemic therapy, and 10 (24.4%) had PD receiving Lenvatinib. cfDNA concentration significantly differed according to disease status ($p=0.0001$), with mean values of 10.5 ± 3.5 ng/ml in NED, 13.5 ± 5.3 ng/ml in SD without systemic therapy, and 31.1 ± 15.6 ng/ml in PD receiving Lenvatinib. cfDNA levels also increased with disease burden (micro-metastases: 15.7 ± 11.5 vs macro-metastases: 22.2 ± 13.9 ng/ml; $p=0.003$ and 1 metastatic site: 15.3±5.8 vs >1 metastatic sites: 27.4 ± 14.8 ng/ml; $p=0.006$). Similarly the FI increased according to disease status (NED: 3.3 ± 0.7; SD: 4.1 ± 1.8; PD receiving Lenvatinib: 5.8 ± 1.4; $p=0.0008$) and disease burden (micro-metastases: 3.96 ± 1.4 vs macro-metastases: 4.9 ± 1.6; $p=0.02$; 1 metastatic site: 3.9 ± 1.2 vs >1 metastatic sites: 5 ± 1.7; $p=0.03$).
Discussion and Conclusions
Patients with PD, macro-metastases and multiple metastatic sites showed the highest circulating cfDNA concentrations and FI values, clearly discriminating them from patients with NED, who displayed lower cfDNA concentration and fragmentation levels, comparable to those reported for healthy controls in the literature. These findings suggest that cfDNA analysis through liquid biopsy may represent an additional tool for assessing disease status in patients with DTC.

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PS1-03-05

Lysicamine: a potential redifferentiation agent for thyroid cancer cells identified via a non-radioactive iodide uptake screening

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Objective
This study aimed to screen compounds capable of redifferentiating thyroid cancer cells through increased iodide uptake using a non-radioactive assay.
Methods
NThyOri 3.1(non-tumoral), HTH83 and KTC2 (anaplastic thyroid cancer, ATC) cell lines were employed for drug screening, NThyOri 3.1 cell with ectopic human NIS expression was generated by transfection with a plasmid encoding the NIS gene using Lipofectamine. A stable clone was selected with geneticin and used to standardize the iodide uptake assay. Redifferentiation gene expression was assessed using real-time PCR. Pd184352 and Ly294002, ERK and PI3K inhibitors respectively, were used as positive controls.
Results
A stable clone (NB6) was selected, exhibiting a high-fold increase in NIS expression. In the non-radioactive iodide uptake assay NB6 cells and PI3K and ERK inhibitors showed an increase of 81%, 46%, and 52% in iodide uptake, respectively, compared with non-transfected NThyOri 3.1. Among the 21 tested drugs, lysicamine increased iodide uptake at 1,5X IC50 in NThy-ori 3-1 and HTH83 cells, by 65% and 110%, respectively. The expression of NIS, TG, and TPO was increased in lysicamine-exposed cells; however, PAX8 expression was reduced.
Conclusion
Lysicamine promoted iodide uptake and upregulated key thyroid differentiation markers in both non-tumoral and anaplastic thyroid cancer cells, highlighting its potential as a novel redifferentiation agent. Since lysicamine inhibits the PI3K/AKT pathway, as previously demonstrated by our group, this mechanism may contribute to the enhancement of NIS expression and function. Thus, lysicamine may represent a promising strategy to restore radioiodine responsiveness in aggressive thyroid tumors. Further studies are needed to clarify the molecular mechanisms involved in these effects.

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PS1-03-06

Modulation of oxidative stress and metabolic burden in papillary thyroid cancer by SGLT2 and DPP-4 inhibitors

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Papillary thyroid cancer (PTC) shows metabolic reprogramming consistent with the Warburg effect, including enhanced glycolysis, redox imbalance and reliance on anti-apoptotic mechanisms such as XIAP stabilization. Modulation of glucose metabolism and oxidative status with SGLT2 or DPP-4 inhibitors may reveal vulnerabilities in this metabolic–apoptotic axis. This study evaluated their effects on oxidative stress, glucose-dependent metabolic activity and XIAP-mediated cytoprotection in thyroid-derived cell models. Two PTC (SCC147, MDA-T32) and a normal thyroid line (NTHY-ORI) were exposed for 48 hours to an SGLT2 inhibitor (10?? M), a DPP-4 inhibitor (10?? M), or vandetanib (10?? M), with doses selected by MTT viability profiling. Reactive oxygen species (ROS), lipid peroxidation (MDA), total antioxidant capacity (TAC), intracellular and extracellular XIAP, and glucose-normalized metabolic indices (IG, MS) were quantified. Metabolic profiling showed that SGLT2 inhibition markedly increased IG and MS in SCC147 and NTHY-ORI, reflecting stimulation of glycolysis and glucose consumption. In contrast, in MDA-T32 SGLT2 inhibition lowered IG/MS values, indicating reduced metabolic activity and a less glycolytic phenotype. Both inhibitors diminished oxidative stress. SGLT2 inhibition reduced ROS levels in SCC147 ($P < 0.01$), while in NTHY-ORI both inhibitors decreased ROS ($P < 0.05$). Lipid peroxidation (MDA) declined after SGLT2 inhibition in all lines (MDA-T32 and SCC147 $P < 0.05$; NTHY-ORI $P < 0.01$). TAC increased under vandetanib and rose further after SGLT2 inhibition in MDA-T32 ($P < 0.0001$), SCC147 ($P < 0.01$) and NTHY-ORI ($P < 0.05$). The stress condition generated the highest extracellular XIAP levels, indicating membrane compromise, whereas treatment with either inhibitor consistently increased intracellular XIAP across all cell lines. SCC147 and NTHY-ORI exhibited marked glycolytic stimulation following SGLT2 inhibition, whereas MDA-T32 showed reduced metabolic workload and a less glycolytic phenotype. SGLT2 (10?? M) and DPP-4 (10?? M) inhibitors mitigated oxidative damage, modulated glucose-dependent metabolic activity and enhanced XIAP-mediated cytoprotection. However, these effects were strongly cell-line–dependent.

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PS1-03-07

Hypothyroid milieu alters expression of oncogenes and tumour suppressors in pre-neoplastic mammary cells

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Background
Hypothyroidism is the most common thyroid disorder, while breast cancer (BC) remains the leading malignancy in women. The link between thyroid dysfunction and BC risk is unclear, with studies showing increased, decreased, or unchanged risk. This highlights the need to understand how altered thyroid hormone (TH) levels affect breast epithelial biology. Here, we investigated how serum from hypothyroid patients influences the transcriptome of mammary epithelial cells, potentially shaping their future cellular fate.
Methods
Serum was collected from women with hypothyroidism ($n = 10$) and healthy control volunteers ($n = 10$). Premalignant MCF10AT breast epithelial cells were cultured under four conditions: with hypothyroid or control serum, with or without added T3. Transcriptomic analysis was done using Clariom™ S microarrays and validated by qPCR, and compared with breast tumour transcriptomic data from the TCGA BRCA dataset involving >1,000 patients.
Results
Exposition of MCF10AT cells to hypothyroid serum altered expression of 301 genes (185 upregulated, 116 downregulated), when compared with controls. Over half of the FDR?<?0.05 genes showed the same expression direction as in TCGA breast tumours. Hypothyroid serum upregulated several BC related oncogenes (e.g.,?AGR2, KRT14) and downregulated tumour suppressors (ACSL5, FBXO32, KLF9) as well as the TH receptor THRB. Supplementation with T3 reversed these alterations, indicating that reduced TH availability drives the observed transcriptomic changes.
Conclusions
A hypothyroid systemic environment induces marked transcriptional changes in premalignant breast epithelial cells, upregulating T3 responsive oncogenic pathways while suppressing T3 regulated tumour suppressor genes. These results provide molecular evidence that hypothyroidism may influence early breast carcinogenic processes. Further studies are needed to determine whether these changes ultimately influence malignant progression in vivo.

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PS1-03-08

Macrophage polarization-mediated remodeling of the tumor immune microenvironment regulates NIS expression in thyroid cancer cells

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Background
Radioiodine (RAI) therapy is a cornerstone of treatment for metastatic differentiated thyroid cancer (DTC); however, a substantial subset of tumors become radioactive iodine refractory (RAIR), leading to poor clinical outcomes. Although tumor-associated macrophages (TAMs), particularly M2-polarized macrophages, have been implicated in thyroid cancer progression, their role in regulating RAI avidity remains incompletely understood. In this study, we hypothesized that remodeling of the tumor immune microenvironment (TIME), driven by macrophage polarization, actively contributes to RAI avidity of DTC.
Materials & Methods
Immune infiltration patterns, macrophage polarization signatures, and NIS expression were analyzed using TIMER3 across TCGA-THCA and independent thyroid cancer cohorts. Based on the bioinformatic observations, *in vitro* co-culture experiments were conducted to functionally interrogate the effects of macrophage polarization on thyroid cancer cells. TPC-1 cells were co-cultured with RAW 264.7–derived macrophages polarized toward M0, M1, or M2 phenotypes, and expression of iodine-metabolism genes (NIS, TPO, Tg) and the dedifferentiation marker CD97 was assessed by qRT-PCR and western blotting. Differential macrophage-associated gene expression was further analyzed.
Results
On TCGA data analysis, increased infiltration of M2-polarized TAMs was associated with reduced NIS expression, whereas M1-like macrophage signatures correlated with relatively high NIS levels in PTC-1 cells. Guided by these findings, *in vitro* experiments also demonstrated that macrophage polarization exerts direct and opposing effects on thyroid cancer differentiation. Co-culture with M2 macrophages resulted in decreased expression of NIS, TPO, and Tg at both mRNA and protein levels in TPC-1 cells, accompanied by upregulation of the dedifferentiation-associated marker CD97. In contrast, co-culture with M1 macrophages increased expression of NIS, TPO, and TG while suppressing CD97 expression.
Conclusion
M1- and M2-polarized macrophages are associated with opposing effects on expression of iodine-handling genes in PTC1 cells. Targeting macrophage polarization may provide novel therapeutic strategies to restore radioiodine avidity in DTCs.

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Basic Cancer 2

PS1-04-01

SIGLEC-15 as novel potential immune target in thyroid cancer

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Background
Thyroid cancer, particularly the aggressive anaplastic subtype, is highly infiltrated with tumor-associated macrophages (TAMs), which correlates with tumor

progression and poor prognosis. Siglec-15 is highly expressed on TAMs in thyroid cancer and promotes the immunosuppressive macrophage phenotype. The function of Siglec-15 in the tumor microenvironment, its ligands and downstream signaling pathways remain poorly understood. The aim of this study is to identify how Siglec-15 regulates TAM differentiation and immune suppression in thyroid cancer and other solid tumors.
Methods
Tumor conditioned medium from thyroid cancer cells lines (TPC-1, FTC-133, B-CPAP, Cal-62, and 8505C) were cocultured with human monocyte cell lines and primary CD14+ monocytes from healthy donors. Siglec-15 expression and TAM differentiation markers were assessed by flowcytometry. Tumor conditioned medium was profiled using targeted proteomics, and additional proteomic analysis was performed on conditioned medium from human monocyte cell lines over-expressing Siglec-15 to identify Siglec-15 dependent secreted factors.
Results
Thyroid cancer-conditioned medium from multiple thyroid cancer cell lines induced Siglec-15 expression in peripheral blood monocytes. Proteomic analysis showed that Siglec-15 overexpression markedly altered the secretory profile toward a pro-inflammatory, tumor-promoting phenotype, with increased production of CXCL10, IL-8, and CCL4. In line, these factors were significantly elevated in serum from patients with anaplastic compared to differentiated thyroid cancer.
Conclusion
Siglec-15 upregulation in monocytes, promotes a pro-tumor macrophage phenotype and potentially contributing to TAM differentiation. Future research should aim to identify tumor-derived glycan ligands and downstream Siglec-15 signaling pathways that regulate TAM polarization and immune suppression. These findings will help to develop novel strategies to limit TAM-mediated immune suppression, in solid tumors including thyroid cancer enriched in Siglec-15^+ TAMs.

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PS1-04-02

Altered NIS trafficking machinery in thyroid tumor cells: insights into impaired functional iodide uptake

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Introduction
Iodide uptake is mediated by the sodium-iodide symporter (NIS), located on the basolateral membrane of thyrocytes. In tumors, NIS dysfunction is mainly associated with altered expression or its retention in the cytoplasm. Recent studies show that NIS associates with proteins involved in its cytoplasmic trafficking and anchoring to the plasma membrane (PM).
Objective
To investigate the expression of genes encoding proteins previously reported to be involved in the subcellular localization of NIS in normal and tumoral thyrocytes.
Methods
Normal human thyrocytes (Nthy-ori-3-1) and thyroid tumor cell lines (TPC1, BCPAP, and KTC2) were cultured, and the expression of genes encoding proteins involved in NIS trafficking was evaluated by qPCR. These included the cytoplasmic proteins ARF4 and COPA, as well as the plasma membrane protein EZR. The findings were then compared with genomic and transcriptomic data from TCGA datasets. In addition, cells were transfected with the pcDNA3.1-HA-NIS vector, and NIS function was assessed using non-radioactive iodide uptake assays. Reactive oxygen species (ROS) production was measured by flow cytometry, and MAPK pathway activation was analyzed by Western blotting.
Results
Compared with Nthy-ori-3-1 cells, COPA expression was reduced in BRAF-mutant cells, but not in TPC1 cells. EZR expression was decreased in BCPAP and KTC2 cells, but increased in TPC1 cells. In contrast, ARF4 expression was reduced in TPC1 and BCPAP cells. These findings were consistent with results from tumor and normal samples in the TCGA dataset. Dimensionality reduction analysis also revealed a clear separation between the analyzed tissues, with BRAF-mutant tumors showing a more distinct transcriptomic profile, similar to that observed in the tumor cell lines, whereas tumors harboring other mutations displayed greater heterogeneity. Interestingly, although NIS overexpression increased iodide uptake in all cell lines compared with controls, this effect was not proportional to SLC5A5 mRNA expression levels, suggesting impaired NIS translocation to the PM in tumor cells. Finally, NIS overexpression increased ROS production and ERK phosphorylation in Nthy-ori-3-1 cells, whereas it reduced both parameters in KTC2 and BCPAP cells, with no significant changes observed in TPC1 cells.
Conclusion
NIS overexpression alone is not sufficient to restore its function in thyroid tumor cells. Defects in the machinery that controls NIS trafficking to the PM may represent an important barrier to iodide uptake in thyroid tumors and a potential target for strategies to restore radioiodine responsiveness. Furthermore, differences observed across distinct tumor backgrounds suggest that NIS trafficking depends on the tumor's molecular context.

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PS1-04-03

Clinical actionability of molecular testing in advanced thyroid cancer: a real world cohort study

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Objectives
Molecular testing is increasingly used in thyroid cancer (TC) to complement diagnostics and guide systemic therapy choices. However, real-world data on its clinical impact remain limited. We evaluated the molecular landscape, clinical actionability, and outcomes of matched therapy in patients with advanced TC.
Methods
We retrospectively assessed 103 patients with advanced TC who underwent panel-based molecular testing with potential treatment consequences at Radboud University Medical Center, Nijmegen, the Netherlands, between 2014 and 2024. Alterations were classified using the European Society of Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT), and details on matched treatment and follow-up were collected.
Results
Molecular testing was performed at diagnosis (51.5%; primarily anaplastic TC) or upon disease progression (48.5%; primarily differentiated and medullary TC). Most frequent alterations were *TP53* (39.8%), *NRAS* (17.5%), *BRAF* (16.5%), *PTEN* (16.5%), and *RET* (11.7%). Potential targetable alterations (ESCAT level I-III) were detected in 62.1% of patients, and 32.0% harboured ESCAT level I or II alterations considered clinically actionable. Matched systemic therapy was initiated in 16 patients, and demonstrated an objective response rate of 56.3% and disease control rate of 68.8%. Durable responses were predominantly observed in patients with ESCAT level I or II alterations (*BRAF*, *RET*, *NTRK*). Matched therapy was associated with a trend towards longer overall survival (123.0 vs 57.0 months; $P = 0.058$).
Conclusions
Molecular testing frequently revealed targetable alterations in patients with advanced TC, and matched therapies yielded meaningful clinical benefit. These findings underscore the value of precision medicine in TC and support broader implementation of molecular-guided treatment strategies.

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PS1-04-04

Multimodal liquid biopsy (MMLB) in sporadic medullary thyroid carcinoma (SPMTC) patients: a pilot study

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Objectives
Distant metastases (DM) and/or biochemical persistent disease (BPD) in MTC, adversely affect disease prognosis. MMLB (cell free DNA (cfDNA) and circulating tumor cells (CTCs) analysis) represents a non-invasive tool providing real-time disease monitoring and information on tumor biology. We aimed to investigate whether CTCs' molecular characterization, CTCs-derived genomic (g)DNA and cfDNA characterization at the level of the most common spMTC somatic mutation (*RET*-M918T) as well as, cfDNA methylation, provides prognostic information in spMTC patients.
Methods
Twenty spMTC patients (DM:12, BPD:8) were included. In 12/20 information on tumor mutational status was available ((*RET* ($n = 9$), *RET*-M918T (5/9), *HRAS* ($n = 3$)). Peripheral blood (10mL-EDTA) was obtained every 3-6 months depending on disease progression. In a total of 81 samples, EpCAM-based CTCs-enrichment was performed while cfDNA was extracted (Qiagen Circulating Nucleic-Acid Kit) followed by Sodium-Bisulfite conversion. CTCs-derived total RNA was used for gene-expression analysis of, *Calcitonin-CALCA*, *CXCR4* and *Vimentin-VIM*, using RT-qPCR. Paired plasma-cfDNA was analyzed for established DNA methylation markers (*RASSF1A, NALCN, MGMT*) using real-time methylation-specific PCR. A highly sensitive droplet-digital PCR was developed for the detection of *RET*-M918T in CTC-derived gDNA and in paired plasma cfDNA samples of *RET*-M918T patients. Calcitonin, CEA DTs and disease status were recorded. 17 healthy donors' samples were used as controls.
Results
Calcitonin and CEA DTs were >24 months in all but two patients with Calcitonin DTs 12.6 and 15 months, respectively, (mean f-up:31.3 months). Structural disease progression (SDP) was documented in eight patients (2/8 *RET*-M918T). *CALCA* was overexpressed in 13 samples related to 13 patients, including those with SDP, at time-points 1-6 months before calcitonin levels showed a mean percentage increase from the preceding time point of $60.58 \pm 85.64\%$ vs $21.14 \pm 24.46\%$, $P < 0.05$, which was observed in 18 samples without *CALCA* overexpression. ROC-analysis revealed a cut-off value of percentage increase:8.52% (sensitivity:100%, false-positive rate-FPR:73.7%, AUC:0.717). *CXCR4* was overexpressed in 7 samples related to 5 patients (3/5 SDP, 0-6 months before SDP). *RET*-M918T was detected only in CTCs-derived gDNA in 2/29 samples related to 2/5 *RET*-M918T patients 6 months before SDP; interestingly only in these 2/5 *RET*-M918T patients SDP was documented. *VIM* was overexpressed in 41/81 samples (50.62%) related to all but one patient without DM, while methylation status showed a trend of hypermethylation in 43.75% DM vs 18.75% BPD patients (non-significant).
Conclusions
MMLB analysis in spMTC might provide complementary insights into tumor biology and disease monitoring. Larger patients' series and for longer follow-up periods are needed so that potential clinical significance may be unraveled.

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PS1-04-05

Somatic pathogenic variants in cancer tissues and medullary thyroid cancer grading results – retrospective analysis

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Objectives
The introduction of the International Medullary Thyroid Carcinoma Grading System into risk stratification has influenced the approach to medullary thyroid cancer (MTC), given the differences in patient outcomes between low-grade (LG) and high-grade (HG) MTCs. Evidence on the association between the molecular profile and grading is scarce and conflicting, yet it suggests a higher frequency of RET-M918T somatic variants in the HG group.
Methods
We performed a retrospective analysis of a consecutive series of patients with sporadic MTC who were hospitalized at the University Hospital in Krakow. Pathological and molecular data were collected, and patients were eligible for analysis if both somatic mutation status and MTC grade information were available. The cohort was then divided into high-grade (HG) and low-grade (LG). The molecular status was assessed based on the presence of RET and RAS pathogenic somatic mutations into four categories: RET-M918T+, RET-other, RAS+, and wild-type (WT). The negative outcome was defined as proven structural recurrence or progression. The statistical analysis was performed using Fisher's exact test.
Results
35 patients were included in the analysis - 26 were LG and 9 were HG. There was a significant difference between the LG and HG groups regarding their molecular profiles. HG MTCs were more often RET-918+ (6/9, 66,7%), whereas the RAS+ was exclusive to LG MTC (12/26). All HG/RET-918+ and none of the HG/WT patients experienced a negative outcome. In the LG subgroup, 4 patients experienced a negative outcome, of whom 3 were RAS+, and the remaining one was RET-918+. In the exploratory analysis, both HG and RET-918+ MTCs were associated with involvement of lateral neck lymph nodes, extranodal extension, metastases at diagnosis, and negative outcomes.
Conclusions
The results underscore the importance of tumor grading, together with molecular profiling, in the full risk assessment of sporadic MTC. Our results, similarly to the available scarce evidence, point to an association between HG and RET-M918T+ mutation and exclusiveness of RAS mutation in LG group.

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PS1-04-06

Redefining tumor vascularization in thyroid cancer: from endothelial cells-dependent angiogenesis to vascular mimicry

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Objectives
Tumors can adopt alternative vascularization strategies beyond classical endothelial cell-dependent angiogenesis under adverse conditions. Vasculogenic mimicry (VM) consists of perfusable vascular-like channels formed by tumor cells lacking endothelial lining but positive for Periodic Acid-Schiff (PAS) staining, while mosaic vessels

(MoV) contain both endothelial and tumor cells. These patterns are associated with tumor aggressiveness, adverse prognosis, and resistance to anti-angiogenic therapies in several neoplasms. Their presence in thyroid carcinomas (TCs) has not been previously investigated. This study aimed to assess usual and alternative vascularization patterns in TCs.

Methods

Neoplastic vasculature was evaluated by CD31/PAS double-staining in 5 normal thyroid tissues (NTs), 5 follicular adenomas (FAs), 15 papillary thyroid carcinomas (PTCs), 6 of which exhibiting aggressive features, 6 follicular thyroid carcinomas (FTCs), 6 poorly differentiated thyroid carcinomas (PDTCs), 3 anaplastic thyroid carcinomas (ATCs), 8 lymph-node and 7 distant metastases. Results were expressed as the proportion of CD31+ vessels within the analyzed area and categorized as $\leq$30%, 31–60% and >60%. Glycophorin A/PAS double-staining was used to confirm intraluminal erythrocytes and assess perfusion in alternative vessels.

Results

The proportion of CD31+ vessels progressively decreased with increasing TCs aggressiveness if compared to NTs and FAs, which were entirely composed of CD31+ vessels ($P = 0.001$). In parallel, MoV and VM channels increased, becoming predominant in dedifferentiated tumors and metastases. Non-aggressive PTCs retained relatively high proportions of CD31+ vessels, whereas aggressive PTCs displayed a heterogeneous pattern. FTCs, PDTCs, ATCs, and distant metastases more frequently exhibited $\leq$30% CD31+ vessels. Blood perfusion within alternative vascular structures was confirmed by intraluminal erythrocytes.

Conclusions

This is the first study demonstrating the presence of alternative vascularization beyond classical angiogenesis in TCs. Tumor progression is associated with a reduction in CD31+ vessels and a concomitant increase in mosaic vessels and vasculogenic mimicry, suggesting their potential role in tumor aggressiveness and resistance to anti-angiogenic therapies in TCs.

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PS1-04-07

Modeling of patient-derived 3D organoids of thyroid cancer: from cells to care

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Objectives

Recent advances in three-dimensional (3D) organoid technology derived from patient tissues provide a more accurate representation of cancer biology, offering an effective tool compared to traditional two-dimensional (2D) models. This study aimed to develop patient-derived 3D organoid models for refractory and anaplastic thyroid cancer, with the long-term goal of guiding personalized treatment strategies and improving patient outcomes.

Methods

Tumor tissues from refractory and anaplastic thyroid cancer patients were collected, dissociated, and embedded in Matrigel for 3D culture. The cells were then incubated with specific growth factors to establish organoid models, monitored for cell growth, and subcultured.

Results

The TCO001 sample, derived from an anaplastic thyroid cancer, showed substantial growth up to passage 11 over five months, while the TCO002 sample, derived from a refractory thyroid cancer, exhibited limited proliferation and stopped at passage 4 after four months.

Conclusions

Despite the considerable challenges in cultivating patient-derived 3D organoid models for thyroid cancers, this study achieved meaningful progress by establishing viable cultures. This achievement is expected to provide the foundation for advancing personalized treatment strategies and supporting improved patient outcomes in thyroid cancer.

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PS1-04-08

Comparison of long-term survival associated with C228T vs C250T TERT promoter mutations in differentiated thyroid carcinoma

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Background

Telomerase reverse transcriptase (TERT) promoter mutations, specifically C228T and C250T, are recognized drivers of adverse outcomes in differentiated thyroid carcinoma (DTC). However, the distinct prognostic implications of each hotspot mutation remain insufficiently characterized. The aim of this study was to compare the clinicopathological and prognostic features associated with C228T and C250T mutations in patients with DTC.

Methods

We retrospectively reviewed 561 patients with DTC (1997–2021). TERT promoter status was analyzed in primary tumor tissues, identifying 155 patients with C228T, 16 with C250T, and 390 with wild-type (WT) alleles.

Results

C228T was associated with significantly worse overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) compared with WT ($P < 0.001$). While C250T did not significantly differ from WT in OS curves, it was associated with markedly reduced 10-year DFS (40% vs. 83%, $P = 0.005$). Importantly, landmark analyses at 10 years showed that C228T conferred significantly poorer OS (76% vs. 94%, $P = 0.022$) and CSS (79% vs. 94%, $P = 0.047$) compared with C250T.

Conclusion

C228T mutation leads to more aggressive long-term clinical outcomes compared with C250T mutation. Mutation-specific risk stratification should be considered in the clinical management of DTC.

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PS1-04-09

The BRAFV600E/ELK3/UHRF1 axis reprograms the epigenome of thyroid cancer

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Background

BRAF V600E, the most frequent oncogenic mutation in thyroid carcinoma (TC), is associated with tumor progression and dedifferentiation. Although it had been linked to aberrant DNA methylation profiles, how this driver mutation reprograms the epigenome is still largely unknown.

Methods

We analyzed thyroid cancer cohorts and performed knockdown experiments using siRNA, drug treatment, luciferase reporter assays and ChIP-qPCR to identify key regulatory mediators. *In vitro* functional assays and mouse models were used to assess tumor growth and malignant phenotypes. Integrative multi-omics analyses, including Illumina EPIC v2 DNA methylation profiling, RNA sequencing, H3K27ac ChIP-seq and HiChIP, were performed to characterize epigenetic alterations, chromatin interaction dynamics and transcriptional regulation.

Results

The BRAF V600E/MAPK signaling activated the expression of transcription factor ELK3, which directly bound to the promoter of UHRF1 (a key regulator of genomic DNA methylation) and promoted its transcription. Elevated UHRF1 maintained aberrant DNA methylation patterns, driving promoter hypermethylation and reduced expression of several tumor suppressor genes (TSGs), including SP140, ID3 and DICER1. Interestingly, further exploration showed that UHRF1 depletion reshaped the H3K27ac landscape and altered enhancer activity. HiChIP analysis revealed reduced enhancer–promoter (E–P) chromatin interactions with

the loss of UHRF1, accompanied by decreased expression of a set of oncogenic genes such as MDK, S100A1, S100A2 and S100A6. Consistently, UHRF1 silencing markedly inhibited thyroid cancer cell proliferation, migration and invasion and induced cell-cycle arrest.
Conclusion
These findings reveal a BRAFV600E/ELK3/UHRF1 regulatory axis linking the oncogenic MAPK signaling to DNA methylation maintenance and chromatin interaction in thyroid cancer. Aberrant DNA methylation not only silences TSGs but also modulates enhancer activity and E–P interactions, thereby shaping oncogenic transcriptional programs. Targeting UHRF1 may therefore represent a promising therapeutic strategy for BRAF V600E-driven thyroid cancer.

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PS1-04-10

Differential functional role of HOXA9 in follicular vs papillary thyroid carcinoma: implications for cancer type-specific carcinogenesis

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Objectives
HOXA9 regulates RUNX2 expression and promotes migration and invasion in papillary thyroid carcinoma (PTC). However, its role in follicular thyroid carcinoma (FTC) remains unexplored. This study aimed to investigate whether HOXA9 exhibits similar oncogenic functions in FTC.
Methods
We established HOXA9-overexpressing FTC cell lines (FTC-133 and ML1) using lentiviral transfection. The effect of HOXA9 overexpression on cell migration was assessed by wound-healing assay. Additionally, five downstream target genes (AKR1B1, LDHA, RPL7, RPL13A, RPS21), previously identified through transcriptomic analysis in PTC cells, were knocked down in HOXA9-overexpressing FTC cells to evaluate their functional contribution. To validate clinical relevance, immunohistochemistry (IHC) for HOXA9 and RUNX2 was performed on tumor tissues from 17 patients with FTC.
Results
In contrast to findings in PTC where HOXA9 promotes cell migration, HOXA9 overexpression in FTC cell lines (FTC-133 and ML1) resulted in reduced migratory capacity compared to control cells. Knockdown of the five downstream target genes in HOXA9-overexpressing FTC cells did not significantly enhance migration, suggesting that the HOXA9-mediated regulatory pathway observed in PTC does not operate similarly in FTC. Interestingly, IHC analysis demonstrated that both HOXA9 and RUNX2 were expressed in the majority of FTC tissues ($>$ 80% positivity), indicating that despite abundant expression, HOXA9 may not functionally contribute to FTC progression.
Conclusions
Our findings reveal a striking difference in HOXA9 function between FTC and PTC. While HOXA9 promotes migration and invasion in PTC, it appears to have a suppressive or neutral effect on FTC cell migration despite being expressed in human FTC tissues. These results suggest cancer type-specific regulatory mechanisms of HOXA9 in thyroid carcinogenesis and indicate that molecular pathways driving FTC may fundamentally differ from those in PTC.

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Clinical Cancer 1

PS1-05-01

Longitudinal trends of BASAL calcitonin in moderate risk RET GCS patients under active surveillance

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Objectives
In multiple endocrine neoplasia type 2A (MEN2A), early thyroid surgery is pursued in *RET* gene carrier patients (GCs). The type of *RET* mutation and the level of calcitonin (CTN) usually guide the timing of surgery. However, less is known about the trend of CTN levels in GCs followed with active surveillance, according to the type of *RET* mutation.
Methods
We evaluated genetic, clinical, and biochemical data on 102 RET GCs followed in a tertiary referral center between 1993 and 2025. Patients were followed for a median of 6.7 years (IQR 4–9.5) and had a median of 6 bCTN measurements per patient (IQR 4–8).
Results
RET mutations at codon 804 were the most frequently observed (50/102 - 49%). Due to the low number of *RET C634X* cases (4/102 – 4%), these patients were excluded from further analyses. The final cohort included 98 patients (49 males and 49 females). At the first evaluation after *RET* positivity, the median age was 18 years (IQR 10–37) and the median basal CTN levels were 2.5 ng/l (IQR undetectable–5.9). Baseline bCTN levels were influenced by age, being higher in older patients, and *RET* mutation type, being higher in GCs with mutation in cysteine codons. Each 1-year increase in age was associated with a 2% increase in bCTN levels. After adjustment for age, patients harboring cysteine codon mutations showed 72% higher bCTN levels than those carrying *RET 804* or other non-cysteine mutations, whereas no differences were observed between patients with *RET 804* and those with other non-cysteine mutations. During the follow-up, basal CTN levels increased by approximately 7% per year, with similar trends across different *RET* mutation groups, regardless of their initial value.
Conclusions
In moderate risk RET GCs patients, the yearly increase in basal CTN levels is $<$ 10%, regardless of their initial value. The duration of active surveillance and the timing of surgical indication are mainly determined by bCT levels at the first evaluation.

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PS1-05-02

Estrogen and thyroid hormone receptor expression in thyroid cancer co-occurring with breast cancer

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Background
Breast and thyroid cancers frequently co-occur in women, suggesting shared hormonal pathways in their tumorigenesis. However, the hormonal receptor landscape of thyroid cancer arising in patients with breast cancer remains poorly defined. We investigated whether estrogen receptors (ERs) and thyroid hormone receptors (TRs) are differentially expressed in thyroid cancer co-occurring with breast cancer.
Methods
Tissue microarrays were constructed from paired normal and tumor tissues of 57 thyroid cancer patients with co-occurring breast cancer (TC + BC) and 92 thyroid cancer controls. Immunohistochemical staining for ERα, ERβ, TRα, and TRβ was performed and evaluated using the Allred scoring system. Associations with clinicopathological features and prior breast cancer treatment were analyzed.
Results
Thyroid cancers in TC + BC patients showed a distinct receptor profile characterized by increased ERα expression and reduced ERβ and TRβ expression compared with controls. ERα positivity was significantly higher in TC + BC cases (66.7% vs. 43.5%, $P = 0.007$), whereas ERβ (76.8% vs. 97.8%, $P < 0.001$) and TRβ (19.6% vs. 45.1%, $P = 0.002$) were significantly less frequently expressed.

ERα positivity was associated with postmenopausal status ($P = 0.037$). Loss of ERβ was more common in tumors ≥1 cm ($P = 0.003$) and those with lymph node metastasis ($P = 0.009$), while reduced TRβ expression was also associated with larger tumor size ($P = 0.006$). Among patients who developed thyroid cancer after breast cancer, prior anti-estrogen therapy (tamoxifen or aromatase inhibitors) was associated with higher ERα and ERβ expression in thyroid cancer tissue.

Conclusion

Thyroid cancer arising in patients with breast cancer exhibits a distinctive hormonal receptor signature characterized by ERα predominance and loss of ERβ and TRβ. These findings suggest that hormonal receptor imbalance may contribute to the biological link between breast and thyroid cancers and may reflect both shared endocrine pathways and adaptive responses to anti-estrogen exposure.

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PS1-05-04

Familial status modulates the stability of excellent response in non-medullary thyroid carcinoma: implications for tailored surveillance

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Objective

The clinical impact of familial history on the prognosis of non-medullary thyroid cancer (NMTC) remains controversial. This study aimed to investigate whether familial NMTC (*f*NMTC) is associated with different patterns of response-to-therapy evolution over time compared to sporadic NMTC (*s*NMTC), using a dynamic risk stratification (DRS) approach.

Methods and Results

We analyzed 795 consecutive NMTC patients (665 *s*NMTC and 130 *f*NMTC) followed at our Center. Response to therapy was assessed at the first follow-up (6-12 months after initial therapy) and at the last outcome. Univariate and multivariate analysis were used to assess the role of family history as a modifier of response reclassification, independently of established prognostic factors. A significant difference in the dynamic pattern of response evolution was observed between *f*NMTC and *s*NMTC ($P = 0.003$), with familial cases showing higher response variability. Among patients with an initial excellent response ($n = 558$), familial status remained the only independent predictor of losing excellent response ($P = 0.002$). The worsening in *f*NMTC was primarily driven by transitions to indeterminate or biochemical incomplete responses ($P = 0.006$), while structural progression remained rare and similar between groups (2.5% vs. 1.3%, $P = 0.33$). Moreover, 50.2% of patients with an initial non-excellent response achieved an excellent response, with no significant difference between familial and sporadic cases (61.2% vs. 47.3%, $P = 0.1$). Intermediate-high ATA risk class was independently associated with a lower probability of achieving an excellent response ($P = 0.01$).

Conclusions

These findings suggest that "Excellent Response" could be more fragile in a familial thyroid cancer cases. Familial NMTC might require a more vigilant biochemical surveillance than sporadic form, even when they appear to be in remission.

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PS1-05-05

Effect of thyroid nodule location on various risk stratification systems for thyroid malignancy: a multicenter retrospective study

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Objectives

The purpose of our study was to validate whether thyroid nodule location on US is an independent predictor for thyroid malignancy, and to evaluate the effect of thyroid location on various international risk stratification systems.

Methods

We retrospectively evaluated 5,708 thyroid nodules (≥1 cm) in 5,081 patients who underwent US from 26 hospitals in South Korea from June to September 2015. US features of thyroid nodules were evaluated, and thyroid nodules were classified according to 4 different kinds of Thyroid Imaging Reporting and Data System (TIRADS)s. We compared malignancy rate of each TIRADS categories according to thyroid nodule location. Univariate and multivariate logistic regression analysis were applied to evaluate the association between thyroid nodule location and the risk of malignancy.

Results

Of the 5,708 thyroid nodules, 1,111 (19.5%) were malignancy. Malignancy rates varied according to location within the same TIRADS category. In the highest category of each TIRADS systems, malignancy rates were highest in isthmus location (K-TIRADS; 84.5%, EU-TIRADS; 61.5%, AACE-TIRADS; 62.2%, ACR-TIRADS; 79.0%) and lowest in lower location (K-TIRADS; 54.1%, EU-TIRADS; 29.8%, AACE-TIRADS; 30.4%, ACR-TIRADS; 47.6%). Thyroid nodule location was an independent risk factor in predicting thyroid cancer ($P < .001$). In a multivariate regression analysis using age, sex, nodule size, location and American College of Radiology (ACR) TIRADS, the isthmus nodules had the highest risk of malignancy (Or = 2.88, 95% CI: 2.00–4.15, $P < .001$), followed by upper thyroid nodules (Or = 2.27, 95% CI: 1.76–2.93, $P = 0.019$) and then middle thyroid nodules (Or = 1.75, 95% CI: 1.44–2.12, $P = 0.457$) compared with lower thyroid nodules.

Conclusion

Thyroid nodule location is an independent risk factor in predicting the thyroid malignancy. Isthmic location carries the highest risk for malignancy and lower pole has the lowest risk. However, the location did not change the TIRADS category classification.

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PS1-05-06

Clinical and biochemical predictors of permanent hypoparathyroidism in papillary thyroid cancer: the role of disease stage and postoperative PTH

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Introduction
Permanent hypoparathyroidism (PH) after thyroidectomy is a significant issue. Postoperative PTH levels are commonly used to identify patients at risk of hypoparathyroidism after surgery, although the optimal predictive threshold remains undefined. This study aimed to identify clinical and biochemical risk factors associated with the development of PH in a large cohort of patients surgically treated for papillary thyroid cancer (PTC).
Methods
We conducted a retrospective monocentric study of 407 patients with PTC (median follow-up 44 months, IQR 17-87 months). PH was defined as the persistence of hypoparathyroidism for more than 12 months post-surgery. We analyzed clinical, pathological, and biochemical parameters, including postoperative PTH levels (measured between 12 hours and one month after surgery).
Results
The cohort (322 women, 79% and 86 men, 21%; median age 53 years [42–63]) included patients who underwent total thyroidectomy (TT) alone ($n = 268$), TT with central neck dissection ($n = 121$), of whom 60 also underwent lateral neck dissection, and hemithyroidectomy ($n = 18$). Overall, PH occurred in 34 patients (8%). Multivariate analysis, excluding postoperative PTH values, identified T4a stage (OR 35.78, 95% CI 3.37–380.1) and N1b stage (OR 5.37, 95% CI 2.24–12.84) as independent predictors of PH, independent of the surgical extent. Furthermore, a postoperative PTH level >13 pg/mL demonstrated a negative predictive value of 100% in identifying patients who would not develop PH (AUC = 0.972, $P < 0.001$).
Conclusion
Advanced oncological stage (T4a and N1b) significantly increases the risk of PH in PTC patients. Our findings suggest that postoperative PTH levels >13 pg/mL may serve as a potential marker to identify patients at low risk for PH, though these preliminary results warrant further validation.

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PS1-05-07

Changes in clinical presentation and prognosis in patients with sporadic medullary thyroid cancer: a 50-year experience from a referral center

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Background
Medullary thyroid cancer (MTC) is a rare endocrine malignancy arising from thyroid C cells and may occur in either sporadic (sMTC-75%) or hereditary form (hMTC-25%). Its aggressiveness is related to the ability to metastasize through the hematic and lymphatic vessels. Early diagnosis is crucial, and prognosis depends on several factors. This study aimed to evaluate whether clinical presentation and disease-specific survival (DSS) of patients with sMTC have changed over time.
Methods
From a prospectively maintained database, we evaluated data of sMTC diagnosed from 1961 to 2025 and followed up at the Endocrine Unit of the Pisa University Hospital. We divided patients into 3 groups based on year of diagnosis: group 1 (≤2000), group 2 (2001–2012), and group 3 (2013–2025).
Results
A total of 1020 patients with sporadic MTC were included. Median age at diagnosis significantly increased (47.5 vs 54 vs 56, $P < 0.01$), while tumor size progressively decreased (2.3 vs 1.5 vs 1.2 cm, $P < 0.01$) from group 1 to 3. Patients with central compartment lymph node metastases (N1a) (5.5 vs 13.7 vs 23.1%, $P < 0.01$) increased while those with laterocervical lymph node metastases (N1b) (42.3 vs 29.9 vs 21.9%, $P < 0.01$) and distant metastases (M1) (12.4 vs 9.4 vs 6.1%, $P < 0.01$) significantly decreased from group 1 to 3. During follow-up (median 72 months), the need for additional surgeries after the initial one also declined ($P < 0.01$). Disease-specific survival (DSS) significantly improved from group 1 to 3 (65.9 vs 86.8 vs 95.5%, $P < 0.01$). Overall, patients with N0 and N1a had higher DSS (96% and 100%, respectively) than patients with N1b (73%) or M1 (41.2%) at diagnosis ($P < 0.01$). However, in group 3, significantly higher DSS was observed also in N1b patients compared to groups 2 and 1 (97.2% vs 67.8 vs 52.5%, $P < 0.01$). In contrast, in M1 patients, DSS did not significantly differ between groups 1 and 3 (31.8 vs 45.9 vs 42.3%, $P = 0.217$).
Conclusions
Increased detection of smaller tumors, with fewer N1b and M1 cases, and a decrease in additional surgeries, has been observed over time. In agreement, overall DSS improved over the decades. The presence of N1a at diagnosis showed a negligible impact on DSS. Conversely, the impact of N1b on DSS seems to be less relevant in recent years. The prognosis of patients with distant metastatic disease at diagnosis, although reduced in terms of prevalence, remains the most critical challenge.

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PS1-05-08

The impact of proactive nursing care on quality of life in thyroid cancer patients post-radical surgery: a randomized controlled trial using QLQ-C30 and QLQ-THY34 questionnaire

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The Impact of Proactive Nursing Care on Quality of Life in Thyroid Cancer Patients Post-Radical Surgery: A Randomized Controlled Trial Using QLQ-C30 and QLQ-THY34 Questionnaire.
Background
Thyroid cancer represents a common endocrine malignancy with increasing incidence rates, presenting substantial public health challenges due to its impact on patient health and the associated economic burden. This study aimed to assess the effects of proactive nursing care on the quality of life of patients following radical thyroidectomy.
Methods
Participants were randomly assigned to either a proactive nursing care group or a routine nursing care group. Quality of life was evaluated using the QLQ-C30 and QLQ-THY34 scales at baseline and at 1, 3, 6, 9, and 12 months postoperatively. A linear mixed model was employed to compare differences between the groups.
Results
A total of 228 patients were enrolled in the study. The analysis revealed no significant differences between the groups in terms of baseline characteristics, surgical management, or postoperative complications. However, the proactive nursing care group exhibited significant improvements in global health status, as well as emotional, cognitive, and social functioning, and experienced reduced severity of fatigue and insomnia ($P < 0.05$) compared to the control group. Furthermore, particular symptoms, including head and neck discomfort, difficulty swallowing, and shoulder function, were significantly alleviated in the proactive nursing group ($P < 0.05$) at certain measurement points.

Conclusions
This study underscores the beneficial effects of proactive nursing care on the quality of life of thyroid cancer patients undergoing surgery, indicating its potential applicability in broader cancer care contexts.

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PS1-05-09

Does an increase in the size of T1A papillary thyroid carcinoma require surgical intervention? a single-center study on tumor growth during active surveillance of 10–20 mm papillary thyroid carcinoma

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Introduction
Active surveillance (AS) for low-risk papillary thyroid microcarcinoma ($\leq$10 mm) has become widely accepted due to the low incidence of disease progression. However, the clinical course and optimal management of tumors that enlarge beyond 10 mm remain unclear. This study aimed to evaluate tumor growth and clinical outcomes in patients with papillary thyroid carcinoma (PTC) measuring 10–20 mm who underwent non-surgical observation.
Subjects and Methods
We conducted a retrospective analysis of patients diagnosed with PTC by fine-needle aspiration cytology between 2010 and 2014. These patients had tumors measuring 10–20 mm and opted for active surveillance instead of immediate surgery, depending on their preferences and background. We defined disease progression as tumor enlargement of at least 3 mm, the appearance of lymph node metastasis, or the development of new distant metastasis.
Results
A total of 91 patients were included, representing 1.4% of cytologically diagnosed PTC cases and 13% of patients who selected non-surgical management. The cohort included 12 men and 79 women, with a mean age of 63 years (range 25–91 years) and a mean tumor diameter of 13.2 mm (range 10.1–19.6 mm). The median observation period was 4.0 years (range 0.5–13.6 years). The 2-, 5-, and 10-year progression-free survival (PFS) rates were 81%, 66%, and 53%, respectively. When stratified by tumor size, the 2-, 5-, and 10-year PFS rates were 89%, 78%, and 68% in the $\leq$15 mm group ($n = 52$) and 68%, 36%, and 28% in the $>$15 mm group ($n = 31$), demonstrating a significant difference ($P = 0.0008$). Seven patients (8%) eventually underwent surgery, including three due to disease progression. No patients experienced dedifferentiation or disease-specific death. Overall survival rates were 99% at 5 years and 95% at 10 years.
Conclusion
PTC measuring 10–20 mm showed a moderate risk of tumor progression during active surveillance, particularly in tumors larger than 15 mm. Although disease-specific mortality was not observed, careful monitoring is required, and surgical intervention should be considered for tumors showing progression or larger initial size. For patients with progressive PTMC under AS, surgical intervention should be considered. However, urgent surgery might not be necessary.

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PS1-05-10

Critical evaluation of ETA basal calcitonin cut-offs in the preoperative diagnosis of medullary thyroid carcinoma (MTC): data from a single-center cohort

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Objectives
Medullary thyroid carcinoma(MTC) is a rare malignancy arising from parafollicular C cells.Basal calcitonin(CT) measurement represents a key diagnostic tool, but the optimal cut-off values remain debated.This study aimed to evaluate the diagnostic accuracy of the basal CT cut-offs(30 pg/mL for women, 34pg/mL for men) proposed by the ETA guidelines and to assess their clinical impact in monocentric cohort of patients with thyroid nodules.
Methods and Results
We evaluated 3045 patients with thyroid nodules referred to our Center.Basal CT was measured in all patients.In those with CT$>$10pg/mL ($n = 70$), a calcium stimulation test was performed.Patients with suspicious findings underwent total thyroidectomy, and histological examination was available in 18 cases.In 77.8% of these cases we found a MTC.In 64% of these cases, MTC was lower than 0.5cm of diameter, in 36% of cases was grater than 0.5cm of diameter. Applying ETA cut-offs to our cohort, the positive predictive value was 83.3%, while the negative predictive value was 25%.Basal CT$>$30pg/mL was associated with MTC in 83.3% of cases, and concordance with the stimulation test was 100%.Basal CT levels between 10–30 pg/mL were associated with MTC in 75% of cases, with 89% concordance after stimulation testing. Histological data showed that in micro-MTCs($<$0.5 cm)(Group1),33.3% of cases had basal CT$>$30 pg/mL, whereas 66.7% had values between 10–30pg/mL;in micro-MTCs($\geq$0.5 cm) (Group2),40% of cases had basal CT$>$30pg/mL, whereas 60% had values between 10–30 pg/mL.Using ETA cut-offs,64.3% of MTC cases would not have been identified.Stimulation test peaks were consistently elevated in confirmed cases(peak of CT$>$79pg/mL in all women and $>$466pg/mL in all men in Group2 while in all women and in 50% of men in Group1).
Conclusions
Applying only basal CT cut-offs may fail to identify a substantial proportion of MTCs, in particular micro-MTCs with mildly-elevated basal CT levels.The combination of basal CT and calcium stimulation testing significantly improves diagnostic accuracy.However, the clinical significance and potential progression of micro-MTC toward more aggressive disease remain uncertain.Long-term follow-up and prospective studies are needed to better define their biological behavior and prognostic implications.

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Clinical Cancer 2

PS1-06-01

Prospective evaluation of follow-up de-escalation to primary care in differentiated thyroid cancer with excellent response to therapy

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Objetives
Dynamic risk stratification (DRS) enables response-adapted follow-up in differentiated thyroid carcinoma (DTC). However, prospective data supporting surveillance de-escalation and discharge to primary care (PC) after an excellent response (ER) are lacking.
Methods
We conducted a longitudinal cohort study with a prospectively conducted post-discharge reassessment including 154 patients with DTC treated with total thyroidectomy, with or without radioiodine ablation, who completed $\geq$5 years of specialist follow-up and were discharged to PC after achieving ER. A small subset ($n = 9$) of clinically stable patients was also discharged despite a persistent indeterminate response (IR), based on clinical judgment. Patients underwent a standardized reassessment $\geq$5 years after discharge to PC. DRS was assessed at three predefined time points: 6 months after initial therapy, final pre-discharge specialist visit, and post-discharge reassessment. Outcomes included recurrence, additional interventions, real-world PC follow-up practices, referrals back to specialist care, and patient-reported outcomes collected at reassessment using a study-specific 5-point Likert-type questionnaire.
Results
Baseline ATA-2025 recurrence risk was low 78/154 (50.6%), intermediate-low 44/154 (28.6%), intermediate-high 23/154 (14.9%), and high 9/154 (5.8%). ER increased from 118/154 (76.6%) at 6 months to 145/154 (94.2%) at pre-discharge and to 148/154 (96.1%) at post-discharge reassessment ($P < 0.001$). At last pre-discharge visit, 9/154 (5.8%) had an IR, decreasing to 6/154 (3.9%) at post-discharge reassessment. No biochemical or structural recurrences were observed

over a mean post-discharge follow-up of 70.3 ± 10.6 months. All non-ER findings at reassessment occurred exclusively in patients already classified as IR at discharge, with no deterioration from ER. During specialist follow-up, 8/154 (5.2%) required additional interventions. PC surveillance was characterized by low-intensity follow-up, with thyroglobulin testing in 11/154 (7.1%), no routine neck ultrasound, and stable levothyroxine dosing. Premature re-referral to specialist care occurred in 13/154 (8.4%) without evidence of recurrence. Despite favorable outcomes, 66/154 (42.9%) reported high fear of recurrence and most preferred specialist follow-up.

Conclusions

Patients with DTC who complete ≥5 years of specialist follow-up and achieve ER can be safely transitioned to PC. ER represents a stable clinical state, with minimal risk of clinically meaningful recurrence even with markedly reduced biochemical and imaging surveillance. These findings support a response-adapted long-term care model centered in PC, focused on thyroid hormone replacement and TSH monitoring. Further studies are warranted to confirm these findings.

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PS1-06-02

Active surveillance for small low-risk papillary thyroid cancer can be safely offered also to young patients and those with a pericapsular nodule

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Background and objectives

Active surveillance (AS) is an established management strategy for low-risk papillary thyroid microcarcinoma (mPTC). In most reported series, the overall risk of disease progression during AS is low, around 5%. However, the use of AS remains debated in certain subgroups, particularly in patients aged ≤40 years and in those with pericapsular tumors, due to concerns about higher progression rates and the potential risk of surgical complications if surgery is delayed. This study aimed to evaluate the risk of disease progression in these subgroups and to assess the outcomes of delayed surgery performed only after documented progression.

Methods

From November 2014 to November 2024, adult patients admitted at our referral center for a single low-risk mPTC (maximum ultrasound diameter ≤13 mm) and who voluntarily chose AS were prospectively enrolled. Patients underwent neck ultrasound and biochemical evaluation every 6 months for the first 2 years and annually thereafter. Disease progression was defined as tumor growth beyond 13 mm, an increase ≥3 mm in all three diameters, or the appearance of lymph node metastases. For this analysis, three subgroups were considered: (Group 1) patients ≤40 years with non-pericapsular mPTC ($n = 50$), (Group 2) patients >40 years with pericapsular mPTC ($n = 77$), and (Group 3) patients ≤40 years with pericapsular mPTC ($n = 47$). Patients with progression were recommended to have surgery. Postoperative complications and treatment outcomes were evaluated.

Results

Among 174 eligible patients, median follow-up ranged from 28 to 51 months across groups. Disease progression occurred in 2/50 (4.0%) patients in Group 1, 7/77 (9.1%) in Group 2, and 5/47 (10.6%) in Group 3. In Group 3, larger baseline tumor diameter was significantly associated with progression ($P = 0.004$), while no predictive clinical or ultrasound features were identified in the other groups. Overall, 14 patients underwent surgery after progression. After a median postoperative follow-up of 43.5 months, all showed an excellent response to treatment and were in clinical remission. No recurrent laryngeal nerve injury occurred; only one patient developed permanent hypoparathyroidism.

Conclusions

Although younger patients and particularly those with pericapsular mPTC show a slightly higher risk of progression during AS, the overall progression rate remains low (< 10-11%). Furthermore, delayed surgery performed at progression provides excellent oncologic outcomes and a very low complication rate also in these subgroups. These findings support the feasibility and safety of AS even in these higher-risk subgroups, provided that careful and regular ultrasound follow-up is maintained.

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PS1-06-03

Impact of hashimoto's thyroiditis and parenchymal hypoechogenicity on the diagnostic performance of EU-TIRADS risk stratification

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Background

Hashimoto's thyroiditis (HT) can alter the ultrasound (US) appearance of the thyroid, with a hypoechoic and heterogeneous pattern that may interfere with US risk classification. Given the high prevalence of HT in our region, we aimed to assess the impact of HT and parenchymal hypoechogenicity on EU-TIRADS diagnostic performance in a prospective, cytology-based cohort.

Methods

We prospectively evaluated 534 consecutive diagnostic thyroid nodules that underwent US and fine-needle aspiration cytology in our center. US and cytological evaluations were performed by the same experienced endocrinologist and cytopathologist. US findings were classified according to EU-TIRADS. The presence of HT was defined based on at least two of the following alterations: hypothyroidism, positive thyroid autoantibodies, and parenchymal hypoechogenicity on US. Furthermore, hypoechogenicity was classified into three degrees (mild, moderate and severe). Cytological diagnoses were reported according to the Bethesda system classification. Statistical analyses included Fisher's exact test, ROC curve analyses and DeLong test.

Results

Cytological distribution was: Bethesda-II, $n = 332$; Bethesda-III, $n = 90$; Bethesda-IV, $n = 76$; Bethesda-V, $n = 19$; and Bethesda-VI, $n = 17$, with a malignancy rate, excluding intermediate cytology, of 9.8%. Overall, 232 nodules (44%) occurred in patients with HT. Diagnostic performance was assessed by comparing EU-TIRADS categories with benign (Bethesda-II) and suspicious/malignant (Bethesda-V + Bethesda-VI) cytology. No statistically significant difference was found between HT and non-HT nodules. In HT nodules, the area under the ROC curve (AUC) was 0.780 (sensitivity 88.8%, specificity 76.8%, PPV 26.6%, NPV 98.6%, accuracy 77.8%), while in non-HT nodules AUC was 0.704 (73.3%, 71.1%, 25.5%, 95.1%, 71.4%), with no significant difference between ROC curves ($P = 0.1863$). Furthermore, the analysis of single ultrasound features (hypoechogenicity, irregular margins, microcalcifications and taller than wide shape) did not show significant differences between HT and non-HT nodules. Similarly, for Bethesda-III and Bethesda-IV nodules, the distribution of EU-TIRADS categories did not differ between HT and non-HT nodules. Finally, we compared EU-TIRADS results of non-HT vs HT nodules according to the three degrees of parenchymal hypoechogenicity. Due to the limited number of cases with severe hypoechogenicity, moderate and severe categories were merged. Sensitivity, specificity, accuracy and AUC were respectively, 64%, 71%, 70.8% and 0.657 in normoechoic parenchyma of non-HT; 100%, 73.4%, 75.9% and 0.839 in mild hypoechogenicity of HT and 83.3%, 78%, 78.6% and 0.773 in moderate-to-severe hypoechogenicity of HT, with no significant differences in AUC between all groups. No interferences on diagnostic accuracy of nodule hypoechogenicity was caused by any degree of HT hypoechogenicity.

Conclusions

Hashimoto's thyroiditis does not affect the diagnostic performance of EU-TIRADS. Moreover, its performance appears to remain consistently reliable across different degrees of parenchymal HT hypoechogenicity.

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PS1-06-04

Pheochromocytoma and hyperparathyroidism are rarely present in non-cysteine ret mutated men 2a patients: evidence from a multicentric italian study

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Objectives
The clinical management of MEN 2 patients with non-cysteine RET mutations who rarely present other endocrinopathies than medullary thyroid cancer (MTC), raises the question of the real prevalence of pheochromocytoma (PHEO) and hyperparathyroidism (hyperPTH). The aim of this multicentric study was to determine this prevalence in a big series of non-cysteine RET positive patients.
Methods
We collected data of patients affected with hereditary MTC and harboring a non-cysteine RET mutation from 10 Italian Centers. The type of RET mutation, the number of investigated family members, the number of RET positive cases and the number of MTC, PHEO and hyperPTH affected patients were registered.
Results
526 non-cysteine RET positive subjects, 177 index cases and 349 gene carriers, were analysed. The V804M RET mutation was the most frequent mutation (n = 123/177,69.5%), followed by S891A (n = 17/177,9.6%), L790F (n = 15/177,8.5%), p.Glu768Asp (n = 11,/177,6.2%) and V804L (n = 7/177,3.9%). Moreover, the mutations S904F, M918V, K666E and K666N were each found in a single index case (0.6%). 302/526 (57%) RET positive patients were clinically affected by MTC. 2/526 patients (0.4%), both carrying the V804M mutation, were also affected by hyperPTH and 4/526 (0.8%) by PHEO. The two patients with hyperPTH and the V804M mutation had a single parathyroid adenoma, and both were the only case affected by hyperPTH within their respective families. Among the 4 patients affected by PHEO, one patient had the L790F mutation and was the only affected member of the family: PHEO was unilateral. The 3 patients with the V804M mutation were members of a same large family; however, the genealogical tree clearly demonstrated that they belonged to a specific branch, whereas none of the RET-positive members from another branch showed an association between MTC and PHEO.
Conclusions
This study confirms that the prevalence of PHEO and hyperPTH in non-cysteine RET mutated patients are almost negligible. The rarity of this association could also be explained by other hypotheses such as a random association of a sporadic hyperPTH or PHEO to hereditary MTC, at least in cases with only one family member affected. For the family with multiple patients with PHEO the hypothesis that another germline mutation, involved in the development of PHEO and restricted to the affected branch, may be considered. The possibility that the isolated familial MTC (FMTC) could be an independent syndrome respect to MEN 2A when sustained by non-cysteine RET mutation should be considered.

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PS1-06-05

Development of an ultrasound risk stratification system for large (> 2cm) low-risk thyroid nodules: a comparison with five societies' systems using a standardized ultrasound lexicon

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Objectives
Biopsy criteria for large (>2 cm) low-risk thyroid nodules vary significantly across different ultrasound (US)-risk stratification systems (RSSs). This study aimed to develop a US-RSS for large (>2 cm) low-risk thyroid nodules using the standardized international expert consensus lexicon, and to compare its diagnostic performance with that of five international societies' RSSs.
Methods
We retrospectively analyzed 1,228 consecutive large (>2 cm) low-risk thyroid nodules with final diagnoses. The cohort included Korean (K)-Thyroid Imaging Reporting and Data Systems (TIRADS) 3 (low suspicion) nodules (partially cystic or iso-/hyperechoic nodules without suspicious features) and K-TIRADS 2 (benign) nodules, excluding cysts (spongiform appearance or intracystic echogenic foci with comet-tail artifacts). The US features were assessed during real-time examinations. Independent US predictors of malignancy were utilized to develop a novel US-RSS and to assign an estimated malignancy risk score (range: 0–3) for stratifying the risk of each nodule. The diagnostic performance of the biopsy criteria derived from the developed US RSS was compared with that of the American Thyroid Association (ATA) system and the European (EU)-, K-, American College of Radiology (ACR)-, and Chinese (C)-TIRADSs.
Results
Among the 1,228 nodules, 52 (4.2%) were malignant. Independent predictors of malignancy included hypoechogenicity or mixed echogenicity, the presence of a halo or smooth margin, and marked intranodular vascularity (all $P \leq 0.01$). Based on the Echogenicity, Margin, and Vascularity (EMV) score derived from the three predictive features, nodules were stratified into three risk groups with the following malignancy rates: 0.0% (benign; score 0), 1.3% (very low suspicion; score 1), and 11.7% (low suspicion; score 2–3). Biopsy was recommended only for very low suspicion nodules >3 cm and low suspicion nodules >2 cm. The developed US-RSS demonstrated a sensitivity of 92.3% and an unnecessary biopsy rate of 52.0%. This sensitivity was significantly higher than those of ACR-TIRADS (46.2%) and C-TIRADS (32.7%) (all $P < 0.001$), and the system demonstrated a substantially lower unnecessary biopsy rate compared to the ATA (100%), EU-TIRADS (99.4%), and K-TIRADS (92.0%) (all $P < 0.001$). The developed US-RSS yielded the highest diagnostic odds ratio (11.1) among all evaluated systems.
Conclusions
The EMV score-based US-RSS provides a significantly higher sensitivity (>90%) than ACR-TIRADS and C-TIRADS and reduces unnecessary biopsies by over 40% compared with the ATA system, EU-TIRADS, and K-TIRADS. This system may enhance biopsy decision-making and provide a more effective approach to managing large (>2 cm), low-risk thyroid nodules than existing RSSs.

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PS1-06-06

Distinct metastatic phenotypes in primary vs PTC-derived anaplastic thyroid carcinoma

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Objectives
Anaplastic thyroid carcinoma (ATC) is a rare but highly aggressive malignancy with extremely poor survival. Increasing evidence suggests that ATC may arise through distinct evolutionary pathways, either de novo (primary ATC) or through dedifferentiation from pre-existing papillary thyroid carcinoma (PTC). However, whether these evolutionary trajectories influence metastatic phenotype and clinical characteristics remains incompletely understood. We aimed to compare clinical features, metastatic patterns, and genomic alterations between primary ATC and PTC-derived ATC in a real-world cohort.
Methods
We conducted a retrospective cohort study of patients with histologically confirmed ATC diagnosed at a tertiary referral center between 2014 and 2024. Patients were classified into two groups based on disease evolution: primary ATC and PTC-derived ATC. Clinical variables included age, sex, metastatic sites at diagnosis, treatment patterns, and overall survival. Targeted next-generation sequencing (NGS) was performed in a subset of patients to assess genomic alterations. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher's exact test. Overall survival was estimated using the Kaplan–Meier method.
Results
A total of 24 patients were included (median age 70 years; 50% female). Fourteen patients had primary ATC and ten had PTC-derived ATC. Among patients with PTC-

derived ATC, the median interval from the initial PTC diagnosis to ATC transformation was 206 months. Distant metastases were present in 87.5% of patients at the time of ATC diagnosis. Distinct metastatic phenotypes were observed between the two groups. Bone metastasis occurred significantly more frequently in PTC-derived ATC than in primary ATC (80% vs 21%, $P = 0.011$), and brain metastasis was also more common (50% vs 7%, $P = 0.050$). In contrast, lung metastasis was common in both groups. Surgical intervention after ATC diagnosis was performed in 50% of primary ATC but in none of the PTC-derived ATC cases. Targeted NGS was performed in 15 patients and revealed frequent genomic alterations including BRAF (60%), TERT promoter (67%), TP53 (27%), and PIK3CA (27%). The median overall survival for the entire cohort was 8 months (9 months in primary ATC and 4 months in PTC-derived ATC).

Conclusions

ATC demonstrates clinical heterogeneity related to its evolutionary origin. PTC-derived ATC is characterized by a prolonged latency from differentiated thyroid carcinoma and a higher burden of bone and brain metastases at diagnosis, often limiting surgical eligibility. These findings highlight the importance of considering evolutionary disease history and support early comprehensive molecular testing to guide therapeutic strategies in patients with ATC.

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PS1-06-07

Intermediate- and long-term adverse effects of radioiodine therapy in pediatric patients with differentiated thyroid carcinoma: a systematic review

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Background

Long-term survival with current therapies for pediatric differentiated thyroid carcinoma (DTC) exceeds 98%. Given these outcomes, attention shifts from cure to minimizing treatment-related toxicity, and evidence suggests that selected low-risk pediatric patients may achieve favorable outcomes without routine I-131. While harms of I-131 have been suggested, pediatric-specific evidence remains scarce, limiting the ability to guide risk-adapted strategies that maximize survival while minimizing harm. This systematic review synthesizes evidence regarding intermediate- and long-term I-131 toxicity in children.

Methods

PubMed was searched up to January 2025 for original studies with ≥ 3 years follow-up reporting intermediate- or long-term adverse effects of I-131, including salivary gland, lacrimal, and gonadal dysfunction, reproductive outcomes, bone marrow suppression, pulmonary fibrosis, cardiac dysfunction, and second primary malignancies. Risk of bias was assessed using the Cochrane Childhood Cancer Risk of Bias criteria for observational studies.

Results

Eleven studies were included. The number of studies reporting on potential adverse effects of I-131 were: salivary gland dysfunction ($n = 2$), pulmonary fibrosis ($n = 1$), bone marrow suppression ($n = 1$), cardiac dysfunction ($n = 1$), female fertility/ovarian function ($n = 5$), and second primary malignancies ($n = 3$). One study contributed data to multiple outcomes. No studies reported on male fertility or lacrimal outcomes. Higher cumulative I-131 activity was associated with salivary gland dysfunction, bone marrow suppression, pulmonary fibrosis in patients with lung metastases, and inconsistent changes in AMH levels in females, while fertility and pregnancy outcomes remained unaffected. Salivary gland dysfunction was the most frequently reported adverse effect, with subjective prevalence ranging from 2% to 35.5-37.1% and an objective prevalence of 47.6%. Pulmonary fibrosis and bone marrow suppression were rarely reported (5% and 4%, respectively). Diastolic dysfunction was observed in 21.2% of patients; however, no increased risk of cardiac dysfunction attributable to cumulative I-131 activity was found. Overall, the risk of second primary malignancies was not increased, although limited evidence suggested a possible association with secondary salivary gland malignancies (prevalence: 1.4% and 0.4%, respectively).

Conclusion

I-131 in pediatric DTC is associated with intermediate- and long-term toxicities, though evidence is limited and heterogeneous. Systematic, long-term collection of variables, including organ-specific toxicity, reproductive outcomes, and second primary malignancies, is needed to guide pediatric-specific treatment strategies balancing excellent survival with harm minimization.

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PS1-06-08

Trends in paediatric differentiated thyroid carcinoma surgery before and after the 2015 ATA paediatric guidelines in the sydney children's hospitals network, australia

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Objectives

To report the surgical approaches and outcomes for paediatric differentiated thyroid carcinoma (DTC) in the largest paediatric centres in Sydney, Australia, over the last 17 years.

Methods

Retrospective study of patients undergoing surgery for DTC between 2009-2025. Patients were stratified into Group 1 (surgery 2009-2015, prior to ATA paediatric guidelines), and Group 2 (surgery 2016-2025).

Results

Demographics and disease classification are shown in Table 1. In both groups 1 and 2, 71% (15/21 and 20/28) of patients underwent total thyroidectomy (TT) and 29% (6/21 and 8/28) underwent subtotal thyroidectomy (ST). Ten of 14 (71%) STs proceeded to completion thyroidectomy (CompT). There was no significant change in the proportion of TT to ST between 2009-2025 when analysed by year of surgery. All patients who underwent ST without CompT had ATA low-risk disease and no evidence of recurrent disease at last visit.

Conclusions

Despite excellent survival, morbidity from paediatric DTC remains significant in those with advanced disease. ST and CompT were associated with less complications than TT, likely in part due to less invasive disease in patients selected for ST. A reduction in Level III sentinel node excision in patients without ultrasound evidence of LN disease was observed after 2015, with no detriment to outcomes. No other significant change in surgical practice or outcomes was observed over the 17 years of this study, which is limited by small numbers in this preliminary analysis. An Australia-wide study is underway and will provide greater insights and detail.

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Different stimulated thyroglobulin cut-offs at remnant ablation for predicting persistent disease in thyroid cancer: RHTSH vs LT4 withdrawal

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[Abstract PS1-06-07]

Outcomes Main- and suboutcomes	No. of studies (No. of participants)	Subconclusions: Prevalence, if known	Conclusion effect I-131 on outcome measure (No. of studies/ total no. of studies)	Comments
SGD > Objective SGD > Subjective SGD	2 (170) > 1 (63) > 2 (170)	 Prevalence: 47.6% Prevalence: 2-35.5/ 37.1%	Cumulative I-131 activity is consistently and independently associated with both symptomatic (2/2) and objective (1/1) SGD, whereas the number of I-131 administrations correlates with symptomatic SGD (2/2) but shows no correlation with objective SWS measures (0/1) and is not a consistent independent predictor in multivariable analyses across studies (1/2)	
Lacrimal apparatus dysfunction	0 (0)	-	-	
Lung fibrosis	1 (105)	Prevalence: 5%	Cumulative I-131 activity and the number of I-131 administrations are associated with lung fibrosis in patients with metastatic lung disease, although a contribution of the metastases to the observed fibrosis cannot be excluded (1/1).	No corrections were made for metastatic lung disease.
BMS	1 (105)	Prevalence: 4%	Cumulative I-131 activity and the number of I-131 administrations are associated with BMS (1/1).	
Decreased cardiac diastolic function	1 (66)	Prevalence diastolic dysfunction: 21.2%	Cumulative I-131 activity is not associated with decreased cardiac diastolic function (1/1).	Number of I-131 administrations not analyzed.
Female fertility Pregnancy (outcome) > Fertility/ pregnancy rate > Live birth rate > Median time to first birth > Stillbirth > Preterm birth > Congenital abnormalities > Miscarriage > Fertility problems Ovarian reserve > AMH levels	 2 (185) 2 (274) 1 (218) 1 (64) 1 (64) 1 (64) 1 (64) 1 (56) 3 (134)	 Prevalence: 0% Prevalence: 2.2% Prevalence: 0% Prevalence: 4.4% Prevalence: 10.9%	Cumulative I-131 activity and the number of I-131 administrations show inconsistent relationships with AMH levels (1/2, 1/2, resp.) and cumulative I-131 activity is not correlated with AMH levels (0/1). However, neither factor appears to influence fertility rates (0/1 and 0/2, resp.). Furthermore, I-131 treatment did not affect live birth rates and median time to first birth. For more outcomes: see 'comment' section.	Ped-DTC patients treated with I-131 treatment seem to have normal fertility/ pregnancy rates (2/2), live birth rates (2/2), still birth rates (1/1), preterm birth rates (1/1), children with congenital abnormality rates (1/1), rates of miscarriages (1/1), rates of fertility problems (1/1), and AMH levels (1/1).
Male fertility	0 (0)	-	-	-
SPM > Overall SPMs > Site-specific salivary gland SPMs	 3 (3702) 1 (519)	 Prevalence: 1.4% Prevalence: 0.4%	I-131 treatment does not significantly affect overall SPM occurrence (3/3). Site-specific salivary gland SPM occurrence is significantly higher compared to the general population (1/1), but it is not known if this is due to the I-131 treatment.	In 1/3 studies, both overall SPM occurrence and site-specific salivary gland SPM occurrence were compared to the SEER reference population, and not to a non-I-131 treated cohort.

Table 1. Summary of findings table: potential adverse effects of I-131 in pediatric DTC patients <21 years.I-131: Radioiodine; DTC: Differentiated Thyroid Carcinoma; SGD: Salivary Gland Dysfunction; SWS: Stimulated Whole Saliva; BMS: Bone Marrow Suppression; AMH: Anti-Müllerian Hormone; SPM: Second Primary Malignancy; SEER: Surveillance, Epidemiology and End Results.

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Background

Serum thyroglobulin (Tg) measured under TSH stimulation is a key biomarker for detecting residual or recurrent disease in patients with differentiated thyroid carcinoma (DTC). However, the prognostic value of stimulated Tg (sTg) at the time of radioactive iodine (RAI) remnant ablation

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	Whole group	Group 1 (2009-2015)	Group 2 (2016-2025)	Total thyroidectomy	Initial subtotal thyroidectomy	Completion thyroidectomy
n	49	21	28	35	14	10
Female	34 (69%)	15 (71%)	19 (68%)	24 (69%)	10 (71%)	7 (70%)
Median age in years (range)	13 (5-16)	12 (7-15)	14 (5-16)	12 (5-16)	14 (9-15)	14 (9-15)
ATA low-risk	23 (47%)	9 (43%)	15 (54%)	11 (31%)	12 (86%)	8 (80%)
ATA intermediate-risk	12 (24%)	6 (29%)	5 (18%)	10 (29%)	2 (14%)	2 (20%)
ATA high-risk	14 (29%)	6 (29%)	8 (29%)	14 (40%)	0	0
Complete response	18 (37%)	9 (43%)	9 (32%)	11 (31%)	7 (50%)	4 (40%)
Biochemically incomplete response	20 (41%)	6 (29%)	14 (50%)	15 (43%)	5 (36%)	5 (50%)
Structurally incomplete response	8 (16%)	5 (24%)	3 (11%)	8 (23%)	0	0

Table 1. Demographics, ATA paediatric risk classification and disease status/response at last visit. Among patients with no evidence of lymph node (LN) disease on pre-operative ultrasound, 9/13 (69%) in Group 1 and 10/18 (56%) in Group 2 underwent central neck dissection ($P = 0.2$). A level III sentinel node was excised in 5/13 (38%) and 2/18 (11%) respectively ($P < 0.05$), while 2 patients in Group 1 had additional lateral LNs excised. There was no significant difference in outcome at last visit between these subgroups. Disease status at last visit is shown in Table 1. There were no statistically significant differences between Groups 1 and 2. Among patients with TT, transient hypoparathyroidism was observed in 49% (17/35); permanent hypoparathyroidism in 14% (5/35) and recurrent laryngeal nerve (RLN) complications in 9% (3/35), with no significant differences between Groups 1 and 2 or by year of surgery. Both initial hemithyroidectomy and CompT were associated with low incidence of transient hypoparathyroidism (2/13 (15%) and 2/10 (20%) respectively; $P < 0.01$ cf TT) and no occurrence of permanent hypoparathyroidism or RLN complications.

remains incompletely defined, particularly when TSH stimulation is achieved with recombinant human TSH (rhTSH) or thyroid hormone withdrawal (THW).

Aim

To identify a sTg cut-off measured at the time of RAI remnant ablation that predicts long-term outcomes in a large DTC cohort, and to evaluate the utility of sTg in predicting an excellent response (ER).

Methods

We retrospectively analysed 696 consecutive DTCs (633 Papillary and 63 Follicular TCs) who underwent thyroidectomy followed by RAI. TSH stimulation was achieved using either rhTSH ($n = 291$) or THW ($n = 405$), and Tg was measured after RAI administration using a sensitive immunometric assay. Patients were followed for a median of 92 months (range 12–485). Outcomes were classified according to response-to-therapy categories. Receiver operating characteristic (ROC) analyses were used to evaluate the prognostic value of sTg.

Results

During follow-up, 67% patients achieved an excellent response, 3% an indeterminate response, 6% a biochemical incomplete response, and 24% a structural disease. The median TSH level achieved at stimulation was 78 mIU/l (91 with THW and 72 with rhTSH, $P = 0.004$), and the median RAI activity was 100 mCi (range 30–110). Median sTg at ablation was significantly lower in patients with an ER compared with those with non-excellent outcomes (1.6 ng/mL *vs* 20.5 ng/mL, $P < 0.0001$). ROC analysis identified a sTg (with THW) cut-off of 9.8 ng/mL (AUC 0.83; 95% CI: 0.792 to 0.874; sensitivity 78%, specificity 82%, $P < 0.001$) and a sTg (with rhTSH) cut-off of 5.7 ng/mL (AUC 0.81; 95% CI: 0.76 to 0.85; sensitivity 69%, specificity 81%, $P < 0.001$) as the optimal predictor of biochemical and structural response.

Conclusions

The thresholds able to identify patients with higher risk of persistence/recurrence differ according to the preparation used for remnant ablation. In the present series we found that Tg threshold of 9.8 and 5.7 effectively stratifies patients after THW and rhTSH, respectively, and support their crucial role for therapeutic decision-making.

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Histology/Translational

PS1-07-01

The ongoing challenge of preoperative pathologic recognition of medullary thyroid carcinoma in the bethesda classification ERA

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The Ongoing Challenge of Preoperative Pathologic Recognition of Medullary Thyroid Carcinoma in the Bethesda classification Era.

Introduction

Fine needle aspiration cytology (FNAC) is used to diagnose medullary thyroid cancer (MTC), but the reported sensitivity is only 56%. Preoperative confirmation of MTC ensures adequate extent of surgery and reduces the risk of reoperation. This nationwide study evaluates whether historical implementation of the Bethesda System improved FNAC performance, identified cytological pitfalls associated with missed diagnoses, and assessed clinical consequences of unrecognized MTC.

Methods

All Dutch histology reports for MTC from 1989 to 2025 were reviewed and matched with corresponding cytological data from PALGA (Dutch Pathology Registry). Cytology, histology, immunocytochemistry (ICC) use, and surgical outcomes were analyzed. FNAC sensitivity was compared between the pre

Bethesda (1989–2013) and Bethesda (2014–2025) eras. Cytological features and clinical outcomes were compared between recognized and unrecognized MTC cases. Standardized sensitivity was calculated to adjust for changes in ICC use.
Results
Among a total of 818 patients, 515 underwent FNAC. Of these, 236 had thyroid FNACs that met the inclusion criteria. Maximum pre-operative Bethesda scores were I (6%), II (9%), III (9%), IV (14%), V (24%), VI (38%). MTC was cytologically suspected or confirmed in 49% of cases. Sensitivity increased from 44% to 56% after Bethesda implementation ($P = 0.089$), but this improvement disappeared after adjustment for the increased ICC use. ICC, particularly calcitonin, CEA, and TTF 1, was applied in 67% of recognized vs 9% of unrecognized cases. Cytologically unrecognized patients less often underwent initial total hemithyroidectomy (45% vs. 86%), and lymph node dissection (83% vs. 94%), leading to more additional hemithyroidectomies ($P < 0.001$).
Conclusions
Cytological diagnosis of MTC remains challenging and was not improved by Bethesda classification. Increased ICC use accounts for recent diagnostic gains. Liberal application of ICC in cases with features suggestive of or overlapping with MTC is essential to reduce missed diagnoses and avoid suboptimal initial surgery.

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Pathological predictors of oncocytic thyroid carcinoma outcome: KI67-index as an adjunct for event free survival stratification

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Objectives
Oncocytic thyroid carcinoma (OTC) is a distinct follicular cell-derived malignancy with frequent radioiodine refractoriness (RAI-R) and incompletely defined pathological predictors. We assessed clinicopathological determinants of outcome, compared WHO high-grade criteria, with a Ki-67-augmented scheme, and explored a data-driven Ki-67 cut-off.
Methods
We retrospectively studied 73 OTCs managed at a referral cancer center (2003-2024) with centralized, blinded pathology review for mitosis, necrosis, extrathyroidal extension (ETE), lymphovascular invasion (LVI, including an "extensive" indicator for more than 4 emboli), capsular invasion, Ki67 proliferation index, margins, tumor grade and RAI-R. Endpoints were event-free survival (EFS) and overall survival (OS).
Results
The cohort included localized and metastatic presentations (pM1: 6.8%). Adverse pathological features were common, including LVI in 58.9% (extensive in 55.8% of LVI-positive cases), ETE in 19.2%, necrosis in 26.0%, mitotic count $\geq$5/2 mm^2 in 24.7%, and Ki-67 $\geq$5% in 46.6%; WHO high-grade tumors accounted for 35.6%. Over a mean follow-up of 5.7 years, 18 events and 6 deaths occurred; median EFS and OS were not reached. EFS was 75.5% at 3 years and 72.9% at 5 years; OS was 98.1% and 95.6%, respectively. On univariable analysis, shorter EFS was associated with ETE, necrosis, mitotic count $\geq$5/2 mm^2, Ki-67 $\geq$5%, higher grade (WHO or composite), and pT3–4. In penalized multivariable discrete-time models, ETE remained independently adverse for EFS. Ki-67 modeled continuously showed no linear association; an exploratory cut-point search identified 8% as the optimal threshold for EFS separation, and incorporation into a composite grade improved EFS discrimination. Among RAI-treated patients with documented activity ($n = 51$), 33.3% developed RAI-R; tumor size showed the most consistent univariable association.
Conclusions
In OTC, ETE and age are the most consistent independent predictors. Incorporating Ki-67 $\geq$ 8% into a composite grade enhances EFS risk stratification, whereas WHO high-grade best aligns with OS. Ki-67 should be considered an adjunct to, not a replacement for, established anatomic predictors; the 8% threshold is hypothesis-generating and warrants external validation.

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RET germline variant spectrum in subjects at risk for hereditary medullary thyroid cancer: analysis of 1,734 cases in a brazilian reference center

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Introduction
Medullary thyroid carcinoma (MTC) may occur sporadically or as part of hereditary syndromes associated with germline variants in the *RET* oncogene (MEN2A and MEN2B). The BrasMEN consortium, a national collaborative initiative, aims to characterize the clinical and molecular spectrum of these patients in Brazil. However, sequencing and case recruitment strategies may vary among participating centers.
Objective
To present the complete series of cases sequenced in a Brazilian reference center for MTC molecular diagnosis participating in BrasMEN.
Methods
Retrospective observational study including individuals referred for genetic investigation of RET due to clinical suspicion of hereditary MTC, either as index cases or at-risk relatives of carriers of pathogenic variants. Genetic analysis consisted of systematic sequencing of exons 5, 8, 10, 11, 13, 14, 15, and 16 of *RET* for index cases and exon-specific sequencing for at-risk relatives of patients with MEN2. Demographic variables, clinical classification, and the distribution of identified variants were analyzed.
Results
Between 2003 and 2026, 1,734 individuals were analyzed, of whom 1,659 had complete information and were included in this report. Among them, 235 (14.2%) presented sporadic MTC, while 728 (44%) carried germline *RET* variants, including 122 (16.8%) index cases and 606 affected family members. Among hereditary MTC cases, 677 (93%) were classified as MEN2A and 14 (1.9%) as MEN2B. In addition, 37 individuals (2.2%) harbored variants of uncertain significance (VUS), and 689 (41.7%) were family members with negative *RET* screening results. Overall, 41 distinct germline variants were identified, including 30 pathogenic variants and 11 VUS. The most frequent pathogenic variants were p.Gly533Cys (19.9%), p.Val804Met (14.4%), p.Met918Val (12.5%), p.Val804Leu (9.1%), p.Cys634Tyr (9.0%), and p.Cys634Arg (8.5%). Codon-level analysis showed higher frequencies at codons 804 (23.5%), 634 (20.0%), 533 (19.9%), and 918 (14.4%). Interestingly, the frequency of *RET* variants varied according to the geographic region within Brazil.
Conclusion
Our findings demonstrate a broad spectrum of *RET* germline variants in this Brazilian cohort, differing from patterns reported in European and other

international series. The higher prevalence of variants such as p.Gly533Cys, p.Val804Met, p.Met918Val, p.Val804Leu, and p.Cys634Tyr likely reflects the unique admixture of European, Amerindian, and African ancestries that characterizes the Brazilian genomic mosaic.

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PS1-07-04

Growth differentiation factor 15 (GDF-15) as a biomarker of tumor aggressiveness inpatients with differentiated thyroid cancer

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Introduction and Background
Growth Differentiation Factor 15 (GDF-15), a cytokine belonging to the TGF-β family, is emerging as a potential biomarker of tumor aggressiveness and cancer cachexia. However, its role in differentiated thyroid cancer (DTC) remains poorly explored.
Aim
The aims of this study were to analyze the correlation between serum GDF-15 levels and disease status and to identify a predictive threshold value for distant metastases.
Patients and methods
A total of 82 patients (69.5% women) with a diagnosis of DTC and treated with thyroidectomy ± lymphadenectomy ± radioiodine therapy were enrolled. During follow-up, a venous blood sample was collected from each patient and serum GDF-15 levels were measured using ELISA. Anthropometric, histological, and disease status data were collected concurrently.
Results
The mean age was 50.8 years and the mean BMI was 26.7 kg/m^2. Overall, 96.3% of patients had well differentiated thyroid carcinoma, with aggressive histological variants observed in 28% of cases. At the time of evaluation, 65 patients (79.3%) had no evidence of disease (NED), whereas 17 (20.7%) showed evidence of distant metastatic disease (PD). Higher GDF-15 levels were significantly associated with male sex (0.69 vs 0.44 ng/ml, $p=0.009$), age ≥55 years (0.73 vs 0.43 ng/ml, $p<0.0001$), high ATA risk class (0.84 vs 0.48 ng/ml, $p=0.04$), and the presence of distant metastases (0.78 vs 0.47 ng/ml, $p=0.009$). Patients with metastases were more frequently aged ≥55 years (64.7% vs 35.3%, $p=0.03$) and stratified in high ATA risk class (58.8% vs 7.7%, $p<0.001$), with no significant differences in sex distribution. At multivariate analysis, high ATA risk class and GDF-15 levels were independently associated with the presence of distant metastases. ROC curve analysis identified a GDF-15 threshold of 0.72 ng/ml (AUC: 0.71; 95% CI: 0.56–0.86; $p=0.007$), below which distant metastatic disease could be excluded with good diagnostic accuracy (NPV: 89.8%, sensitivity 64.7%, specificity 81.5%).
Discussion and conclusions
Serum GDF-15 levels may represent a biomarker associated with disease aggressiveness and distant metastasis in patients with DTC, similarly to other malignancies. These findings warrant further investigation in larger and prospective cohorts.

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PS1-07-05

KI-67 expression and its prognostic significance in relation to TERT promoter and braf V600E mutation status in papillary thyroid carcinoma

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Backgroun
Ki-67 is a nuclear protein expressed during active phases of the cell cycle and a well-established marker of tumor proliferative activity. In the 2022 World Health Organization (WHO) Classification of Endocrine and Neuroendocrine Tumours, Ki-67 was formally incorporated into the grading of medullary thyroid carcinoma (MTC); however, its prognostic role in papillary thyroid carcinoma (PTC) remains poorly characterized. In PTC, BRAF V600E and TERT promoter (TERTp) co-mutation is a well-established predictor of adverse outcomes, yet whether Ki-67 expression provides additional prognostic information beyond mutation status remains unknown.
Methods
We conducted a retrospective cohort study of 296 PTC patients classified into three mutation groups: Double wild-type (WT; $n = 62$), BRAF mutant (MT) only ($n = 207$), and Double MT (TERTp + BRAF; $n = 27$). Ki-67 was quantified by manual hot-spot counting on tissue microarray sections, with optimal cutoffs determined separately for each outcome using the maximally selected rank statistics (>5 cells/high-power field [HPF] for structural recurrence; >4 cells/HPF for thyroid cancer–specific mortality). Associations with Ki-67 expression, structural recurrence-free survival (median follow-up 12.4 years), and thyroid cancer–specific survival (median follow-up 13.8 years) were evaluated using logistic regression, Cox proportional hazards regression, and Firth's penalized likelihood method.
Results
Double MT was independently associated with Ki-67 high expression on multivariable logistic regression (OR 7.72, 95% CI 2.21–28.70; $P = 0.002$). Ki-67 high expression was significantly associated with structural recurrence on univariable analysis (HR 1.65, 95% CI 1.02–2.66; $P = 0.041$), but did not retain independent significance after adjustment for mutation status (HR 1.52, 95% CI 0.92–2.52; $P = 0.104$). Similarly, for thyroid cancer–specific mortality, Ki-67 high expression was significant on univariable analysis (HR 2.98, 95% CI 1.07–8.66; $P = 0.036$) but not on multivariable analysis (HR 2.20, 95% CI 0.71–7.06; $P = 0.169$). Double MT was the strongest independent predictor of both structural recurrence (HR 4.87, 95% CI 1.95–12.12; $P = 0.001$) and thyroid cancer–specific mortality (HR 48.32, 95% CI 5.09 to upper limit not estimable; $P < 0.001$), and no statistically significant interaction was observed between Double MT and Ki-67 expression for either outcome ($P = 0.362$ and $P = 0.581$, respectively).
Conclusion
In PTC, Ki-67 high expression is strongly associated with TERTp + BRAF co-mutation but does not provide independent prognostic information beyond mutation status, suggesting that Ki-67 serves as a histologic correlate of the aggressive molecular phenotype driven by Double MT rather than an independent prognostic driver. These findings suggest that mutation profiling may be sufficient for risk stratification in PTC, without the need for additional Ki-67 assessment.
Keywords: Ki-67; papillary thyroid carcinoma; TERT promoter mutation; BRAF V600E; prognosis; recurrence.

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PS1-07-06

Molecular tumor profiling in patients with advanced differentiated thyroid carcinoma (DTC)

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Objectives
Molecular testing for somatic variants in tumor tissue from differentiated thyroid carcinoma (DTC) pts supports diagnosis, prognostication, therapeutic decision making. Next generation sequencing enables multiple genes analysis to detect pathogenic - likely pathogenic variants.

Methods
We analyzed tumor tissue from 45/52 pts with locally advanced and/or metastatic DTC (7 samples inadequate). In 35/45 we performed comprehensive genomic profiling of >500 genes to identify likely oncogenic - oncogenic SNVs, insertions/deletions, gene rearrangements, CNVs. In 10/45 a targeted panel of > 45 DTC related genes was applied. Clinical, histopathological features, radioiodine refractoriness (RAI R), structural disease progression, systemic treatments were recorded.
Results
The cohort included 45 pts (18 men, age 43.4 ± 14.6 yrs, mean follow up 4.4 ± 2.7 yrs, median survival 6 yrs). Histology showed PTC & variants in 37/45, OTC in 6/45, FTC in 2/45; 26/45 tumors were poorly differentiated. RAI R cases were 55.6%, 47% received tyrosine kinase inhibitors (TKI). SNVs/Indels were detected in 32/45 (71.1%) pts (RAI R 91% metastatic 75%). The most frequent variants involved *BRAF* (27%), *TERT* (11%), *TP53* (6%), *NRAS* (6%), *KRAS* (3%). Less common variants in 10/45 pts affected *ATM* ($n = 4$), *TSHR, RAD51D, BCOR, APC, CDK1B, CDKN2A, NUP93, EGFR, SMARCA4* ($n = 1$ each). All 3 RAI avid pts carried *BRAF* variants; 18 received TKI with 13 achieving responses >1 yr. Rearrangements were identified in 7/45 (RAI R 43% metastatic 57%): *RET/PTC* ($n = 4$), *ALK, NTRK3, PAX8/KCNH1, ETV6/DLD* ($n = 1$ each). Those with metastatic *RET/PTC* positive tumors retained radioiodine avidity. CNVs were detected in 9/45 (RAI R 89% metastatic 78%) involving *CHEK2* ($n = 3$) *BRCA2, RAD54L, ATM* ($n = 2$ each) *CHEK1, RET, CDKN2A, CDKN2B, MTAP, TERT* ($n = 1$ each); 4/9 had durable TKI responses >1 yr. 5/45 (RAI R 40% metastatic 40%) had no genomic alterations.
Conclusions
Comprehensive genomic profiling reveals oncogenic - likely oncogenic alterations at high frequency in advanced DTC and provides clinically relevant information for prognosis - treatment selection. Multiple alterations (SNVs/Indels, CNVs) are associated with RAI R and metastatic disease, whereas RET/PTC rearrangements appear to be linked with preserved radioiodine avidity even in metastatic cases.

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PS1-07-07

Comparison between invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) and the infiltrative follicular and classic subtypes of papillary thyroid carcinoma regarding response to therapy: a retrospective cohort study

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Objectives
This study aimed to compare patients with Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (IEFVPTC), Infiltrative Follicular Papillary Thyroid Carcinoma (IFPTC), and Classic Papillary Thyroid Carcinoma (CPTC) regarding the achievement of an excellent response according to the ATA response-to-therapy classification one year after initial treatment and at the last follow-up evaluation.
Methods
This retrospective cohort study comparatively analyzed patients with the three aforementioned tumor types who underwent total thyroidectomy and were treated with or without radioactive iodine. The outcomes were the achievement of an excellent response to therapy one year after initial treatment and at the last follow-up visit. Statistical analyses of numerical variables were performed using the Gamma and Wald tests, and categorical variables were analyzed using the chi-square and proportion tests.
Results
A total of 164 patients were included in the analysis. The mean age was 50.7 ± 14.2 years, and most patients were women (134; 84.8%). The mean follow-up time was 70.7 ± 45.2 months. An excellent response at one year was observed in 10/13 (76.9%) patients with IEFVPTC, 39/49 (79.6%) with IFPTC, and 66/102 (64.7%) with CPTC ($P = 0.149$). At the last follow-up visit, the IFPTC group showed a higher proportion of excellent response compared with the other two groups [IEFVPTC: 9/13 (69.2%), IFPTC: 44/49 (89.8%), and CPTC: 72/102 (70.6%); $P = 0.029$].
Conclusions
Although the groups did not differ in the rate of excellent response to therapy one year after initial treatment, patients with Infiltrative Follicular Papillary Thyroid Carcinoma exhibited a higher rate of excellent response at the last follow-up visit compared with those with Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma and Classic Papillary Thyroid Carcinoma.

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PS1-07-08

High-grade differentiated thyroid carcinoma: epidemiology and clinicopathological features

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Objectives
High-grade differentiated thyroid cancer (DHGTC) is a histological subtype described by the WHO in 2022 as papillary (PTC), follicular (FTC), or oncocytic (OTC) carcinoma without a solid architecture, with ≥5 mitoses per 2 mm^2 and/or tumor necrosis. This study aims to define the prevalence of DHGTC and describe its clinical and pathological features.
Methods
We analyzed the prevalence of DHGTC in a series of consecutive patients (January 2023-Decembre 2025) and its clinicopathological features.
Results
Of 5224 cases of PTC, FTC, and OTC, only 39 (0.75%) were classified as DHGTC. Most patients (61.5%) were female. The median age at diagnosis was 53 years. Cytology was performed in 36/39 (92.3%) patients: most cases had indeterminate (TIR3B = 15/36 – 41.7%; TIR3A = 6 –16.7%) cytology, the remaining had malignant (TIR5 = 10 –27.8%) or suspicious for malignancy (TIR4 = 5 –13.8%). The median tumor size was 3.7 cm. Eleven patients (28.2%) underwent lobectomy followed by completion thyroidectomy in most cases (9/11 – 81.8%). PTC solid variant [$n = 12$ (30.8%)] was the most common histology followed by OTC [$n = 10$ (25.6%)] equally distributed between minimally ($n = 5$) and widely ($n = 5$) invasive. DHGTC was unifocal in most cases ($n = 38$ – 97.4%). Vascular invasion was present in 74.4% ($n = 13$ <4 and $n = 16$ ≥4 emboli). Extrathyroidal extension (ETE) was detected in 35.8% ($n = 15$) of cases: minimal ETE in 7 (46.7%) and gross ETE in 8 (53.3%). Thirteen patients (33.3%) had other histological types of differentiated thyroid carcinoma in the same gland. Lymph node dissection was performed in ten patients (10/39 – 25.6%), nine had lymph node metastases [N1a = 4, N1a/N1b = 4, N1b =1, N0=1]. Two patients (5.1%) had distant metastases at diagnosis (lung). Postoperative radioiodine treatment was performed in 33 (84.6%) cases, but only one case showed radioavid metastases (lung).
Conclusions
In our experience, DHGTC is an uncommon histological type with a heterogeneous clinical presentation. Cytology is not suggestive of malignancy in most cases and is clearly suspicious for thyroid cancer in less than half of cases. The tumor is generally large and unifocal but has a low rate of lymph node and distant metastases at the time of diagnosis.

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PS1-07-09

Clinical relevance of histological and molecular heterogeneity of multifocal papillary thyroid cancer (PTC)

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Objective
Multifocal papillary thyroid carcinoma (PTC) is characterised by tumour foci that may share identical or different histology to the main (largest) focus. Previously, we reported molecular data of 12 multifocal PTCs exhibiting different histological subtypes, finding a discordance rate of 83.3%. Aim of the present study is to compare molecular profile of multifocal PTCs with same (cohort 1) or different (cohort 2) histological subtype.
Methods
We analysed 37 cases (19 for cohort 1 and 18 for cohort 2), corresponding to a total of 124 tumour foci. Cases were included based on the following criteria: (1) a minimum of two foci per patient and (2) presence of at least two different histological subtypes (cohort 2). DNA and RNA were obtained from tumour tissues and analysed by NGS-targeted sequencing with two custom panels designed to detect alterations involved in thyroid carcinogenesis. *TERT* promoter mutations were investigated using ddPCR.
Results
Of the 37 cases analysed, 21/37 (56.7%) cases exhibited discordant molecular profiles across different foci, regardless of histological subtype. Discordance in mutational profile was observed in both cohorts with a higher prevalence in cohort 2 (42.1% vs 72.2% respectively). Conversely, we found concordance in 11/19 (57.9%) cases of cohort 1 and 5/18 (27.8%) of cohort 2. Within the discordant cases, we observed 3 patterns: 1) 1 case of cohort 1 and 8 cases of cohort 2 showed different mutations in different oncogenes across the foci; 2) in 1 case of cohort 1 and 5 cases of cohort 2 we observed the coexistence of mutated and negative foci and 3) in 2 cases of cohort 1, we observed foci showing different mutations in the same gene/codon. We also observed that if we consider only molecular profile to the main focus, we may miss actionable alterations in 9/21 (42.8%) discordant cases, as these were exclusively present in smaller foci.
Conclusions
Multifocal PTC shows intratumoral molecular heterogeneity, regardless of histological subtype. These findings support the coexistence of both intrathyroidal metastasis and clones with independent molecular origin thus highlighting the importance to perform the molecular analysis across all the tumour foci to avoid underestimating the presence of actionable alterations. The study was supported from MIUR (PRIN 2022WWY7AA).

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PS1-07-10

Pairwise analysis of TSHR promoter methylation levels and pathological factors in papillary thyroid cancer

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Introduction
Papillary thyroid carcinoma (PTC) accounts for approximately 80–85% of all thyroid cancer cases. Although most patients have a favorable prognosis, up to one-third may experience a more aggressive disease course. Identification of reliable minimally invasive biomarkers could improve risk stratification and monitoring of disease progression.
Aim
To evaluate changes in *TSHR* promoter methylation levels in plasma samples of patients with PTC before and after surgery and to assess their association with pathological characteristics of the tumor.
Methods
The study included 68 patients with histologically confirmed PTC. Peripheral blood samples were collected preoperatively and 4–6 weeks postoperatively. *TSHR* promoter methylation levels were determined using quantitative methylation-sensitive polymerase chain reaction. In multifocal PTC cases, total tumor size was calculated as the sum of the diameters of all tumor foci. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.
Results
TSHR methylation levels in plasma were significantly lower after surgery compared with preoperative levels ($p = 0.003$). Pairwise analysis demonstrated significantly decreased postoperative methylation levels in both classical and follicular PTC variants ($p = 0.034$ and $p = 0.002$, respectively). Lower postoperative methylation levels were also observed in patients younger than 55 years ($p = 0.029$), in tumors with a total size ≤ 2 cm ($p = 0.002$), and in patients with a single tumor focus ($p = 0.023$). In contrast, higher postoperative methylation levels were found in patients with multifocal PTC ($p = 0.034$).
Conclusions
Plasma *TSHR* promoter methylation may represent a promising minimally invasive molecular marker associated with PTC pathological characteristics and potentially useful for monitoring disease progression. Further studies are required to confirm these findings.

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Stratification

PS1-08-01

ATA 2025 risk reclassification in differentiated thyroid cancer may increase radioiodine eligibility

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Objective
The 2025 American Thyroid Association (ATA) guidelines introduced a revised recurrence risk stratification system for differentiated thyroid cancer (DTC), incorporating histology-specific features such as clinically relevant multifocality and posterior positive surgical margins, and subdividing the former intermediate-risk category into intermediate-low and intermediate-high groups. We aimed to quantify the magnitude of reclassification from ATA 2015 to ATA 2025 and to explore its potential clinical impact in a real-world cohort.
Methods
We conducted a retrospective cohort study of consecutive adults with DTC from an institutional database. Tumors were classified according to ATA 2015, ATA 2025, and AJCC/TNM 8th edition. Incidental low-risk papillary microcarcinomas were excluded. Multifocality was considered clinically relevant when the sum of maximal tumor diameters exceeded 10 mm. Clinical outcome during follow-up was defined as structural persistent/recurrent disease.
Results
A total of 225 patients were included (mean age 51 $\pm$ 15 years; 79.6% women), with a median follow-up of 81.2 months [IQR 38–120]. Multifocality was present in 104 patients (46.2%), including 27 (12%) with unilateral and 77 (34.2%) with bilateral disease. According to ATA 2015, 48.0% of tumors were classified as low risk, 36.3% as intermediate risk, and 14.8% as high risk. Under ATA 2025, this distribution shifted to 31.4% low risk, 17.9% intermediate-low, 31.4% intermediate-high, and 16.6% high risk. Rates of structural persistence/recurrence are summarized in Table 1. Overall, 35 (15.5%) tumors that were initially classified as ATA 2015 low risk were reassigned to higher-risk ATA 2025 categories: 15 (14%) to intermediate-low and 20 (21%) to intermediate-high. Reclassification to intermediate-low was mainly driven by unilateral multifocality, whereas reclassification to intermediate-high was exclusively driven by bilateral multifocality, a feature not considered in ATA 2015. Importantly, among

these reclassified tumors, 10/15 (66.7%) in the intermediate-low group and 6/20 (30.0%) in the intermediate-high group had not initially received radioactive iodine, highlighting the potential for ATA 2025 to modify postoperative treatment recommendations in a substantial subset of patients.
Conclusions
In this real-world cohort, ATA 2025 reclassified a substantial proportion of tumors previously considered low risk into intermediate-risk categories, largely on the basis of multifocality. The revised system appears to provide more granular risk separation, but may also increase the number of patients considered for more intensive postoperative management, particularly radioactive iodine.

	Structural recurrence	
Risk	ATA 2015	ATA 2025
Low	3%	1.4%
Intermediate	17.7%	
- Intermediate-low		10.3%
- Intermediate-high		17.4%
High	42.4%	40.5%

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PS1-08-02

Long-term outcomes of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a single-center cohort with follow-up up to eight years

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Background
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is considered a low-risk thyroid neoplasm with indolent biological behavior. However, real-world data regarding long-term outcomes and response to treatment remain limited.
Methods
A retrospective cohort study was performed, including patients with histological diagnosis of NIFTP identified in thyroid surgery specimens between February 2017 and May 2025, at a tertiary referral center. Patients with other concomitant thyroid neoplasms were excluded. Clinical, surgical and follow-up data were collected. Response to treatment was evaluated according to criteria from the 2025 ATA Guidelines for adult patients with differentiated thyroid cancer. Comparisons between groups were performed using the chi-square test, with statistical significance defined as $P < 0.05$.
Results
Among 274 patients with NIFTP identified in thyroid surgical specimens, 106 were excluded due to the coexistence of other thyroid neoplasms, 2 with hematological malignancies and 23 without follow-up were also excluded. The final cohort included 143 patients. Mean age was 55 $\pm$ 15 years and 71.3% were female. Median follow-up duration was 39.7 months [24.2 - 66.1], with a maximum follow-up of 100.7 months. The main indications for surgery were thyroid nodules with non-benign cytology [98 (68.5%)], multinodular goiter with benign cytology [22 (15.4%)], thyroid nodule with benign cytology [14 (9.8%)] and hyperthyroidism [9 (6.3%)]. Sixty-eight (47.6%) underwent total thyroidectomy and 75 (52.4%) lobectomy with isthmusectomy. Excellent response to treatment was achieved by 86.0% of patients [61 (89.7%) in the total thyroidectomy group and 62 (82.7%) in the lobectomy group] , while indeterminate, biochemically incomplete and structurally incomplete responses were observed in 3.5%, 1.4% and 0.7%, respectively. Eight-point-four percent of patients were submitted to lobectomy and had residual thyroid nodules in the remaining thyroid lobe classified as ACR-TIRADS $\geq$4 with no cytological assessment; therefore response classification was not performed in these cases.~ There were no statistically significant differences in treatment response according to surgical extent ($\chi^2 = 1.469$, $P = 0.226$) or indication for surgery ($\chi^2 = 2.157$, $P = 0.340$).
Conclusions
In this single-center cohort of patients with NIFTP, most patients achieved excellent response to treatment during follow-up extending up to approximately eight years. Outcomes were favorable regardless of surgical extent and indication for surgery, supporting the indolent behavior of NIFTP and more conservative treatment approaches.

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PS1-08-03

Association between multifocality and structural recurrence in differentiated thyroid cancer: is it time to reconsider our approach?

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Background
The prognostic value of multifocality in differentiated thyroid cancer (DTC) remains debated, although current guidelines consider it a recurrence risk factor.
Objective
To assess the association of multifocality with structural recurrence and final dynamic response in DTC.
Methods
We analyzed a retrospective cohort of low/intermediate-risk DTC patients followed in one center in Argentina (2015-2025). Baseline clinicopathologic variables, ATA 2025 risk, AJCC/UICC TNM 8th edition, type of surgery, radioiodine, and ATA dynamic response were analyzed. Structural recurrence was the primary endpoint. Univariable analyses and Cox models were performed.
Results
96 adult patients were included. Mean age was 46.4 +/- 13.6 years and 83.3% were women. Median follow-up was 41.5 months. Total thyroidectomy was performed in 86.5%, lymph node dissection in 42.7%, and radioiodine in 67.7% (median dose 100 mCi). Multifocality was present in 37.5% ($n = 36$) and bilaterality in 30.2% ($n = 29$). Final dynamic response was excellent in 69.8% ($n = 67$). Structural recurrence occurred in 8.3% ($n = 8$) with median time to recurrence 15 months. In the global cohort, recurrence was associated with younger age (median 37.5 vs 48 years; $P = 0.047$) and larger tumor diameter (median 3.30 vs 1.95 cm, $P = 0.049$). Recurrence was higher with bilaterality (17.2% vs 4.5%; $P = 0.038$), higher nodal status ($P = 0.011$; highest in N1b: 33.3%), positive margins (27.3% vs 5.9%; $P = 0.016$), and lymphatic invasion (25% vs 3.9%; $P = 0.009$). Multifocality was not associated with recurrence in either univariable (11.1% vs 6.7%; $P = 0.446$, OR 1.75, 95% CI 0.41-7.48) and multivariable analysis (HR 2.00 95% CI 0.45-8.97, $P = 0.362$). However, it was associated with worse ATA initial risk classification ($P < 0.001$), higher nodal involvement ($P = 0.006$) and more frequent radioiodine use (83.3% vs 58.3%; $P = 0.011$). Final dynamic response was similar between multifocal and unifocal tumors.
Conclusions
In this cohort, multifocality was not independently associated with structural recurrence and final dynamic response. Recurrence was primarily driven by baseline ATA risk and age, supporting an integrated risk–adapted approach rather than decisions based only on multifocality.

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PS1-08-04

Tumor focality drives subclassification of intermediate-risk papillary thyroid carcinoma in the 2025 ATA recurrence risk system

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Background
Tumor multifocality has been incorporated into the updated 2025 American Thyroid Association (ATA) recurrence risk (RR) stratification system. Unilateral multifocality (UM) is considered a low–intermediate risk, whereas bilateral multifocality (BM) (> 1 cm) is associated with high–intermediate RR in papillary thyroid carcinoma (PTC). The clinical implications of this refinement remain incompletely understood. This study evaluated how tumor focality influences classification within the intermediate-risk category and its association with clinicopathological features and response to therapy in PTC.

Methods
We conducted a retrospective study including 270 patients with confirmed PTC (total thyroidectomy with or without radioiodine therapy). Clinicopathological characteristics were compared among patients with unifocal, UM, and BM tumors. RR and response to therapy were assessed using the 2015 and the ATA 2025 systems. A subanalysis evaluated the relationship between tumor focality and tumor size ($\leq$1 vs. $>$1 cm). Associations were analyzed using chi-square or Fisher's exact tests.
Results
Among 270 patients, 154 (57.0%) had unifocal tumors, 33 (12.2%) UM, and 83 (30.7%) BM tumors. Mean age was 45.6 $\pm$ 12.9 years in unifocal, 43.7 $\pm$ 13.8 years in UM, and 50.1 $\pm$ 10.4 years in BM PTC ($P = 0.70$). Median tumor size was 1.5 cm (IQR 0.75–2.8) in unifocal, 1.7 cm (IQR 1.3–2.4) in UM, and 1.8 cm (IQR 1.0–3.1) in BM ($P = 0.16$). Multifocal tumors were significantly associated with vascular invasion ($P = 0.029$), lymph node metastasis ($P = 0.048$), extranodal extension ($P = 0.046$), and higher N stage ($P = 0.028$). Microcarcinomas ($\leq$1 cm) were more frequent in unifocal tumors, whereas tumors $>$1 cm were more common in multifocal PTC ($P = 0.018$). Using the ATA 2015 system, 92 patients were classified as low risk, 142 as intermediate risk, and 36 as high risk. Reclassification with the ATA 2025 system reassigned 32.6% of patients previously categorized as low risk to intermediate-low or higher risk categories. Among those initially classified as intermediate risk, 65.5% were reclassified as intermediate-high risk, 24.6% as intermediate-low risk, and 9.9% as high risk. BM was the sole determinant of intermediate-high risk classification in 20% of patients. Tumor multifocality, either unilateral or bilateral, was not associated with response to therapy at the last follow-up ($P = 0.19$ and $P = 0.95$, respectively).
Conclusions
Although multifocal tumors were associated with adverse pathological features, multifocality did not translate into differences in dynamic response to therapy. Multifocality alone may therefore have limited prognostic impact and should be interpreted alongside other clinicopathological factors when applying the ATA 2025 recurrence risk stratification.

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PS1-08-05

Comparison of ata 2015 and ATA 2025 risk stratification systems in differentiated thyroid cancer: a single-center retrospective analysis

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Objective
The 2025 recommendations of the American Thyroid Association introduced an updated recurrence risk-stratification system expanding the three-tier model into four categories by subdividing the intermediate-risk group. This study compared ATA_2015 and ATA_2025 risk stratification systems and evaluated their association with response to therapy and clinical outcome in a real-world cohort of DTC patients.
Methods
We conducted a single-center exploratory retrospective analysis of a consecutive series of histologically confirmed DTC patients attending routine follow-up visits at a tertiary referral center during 2025. All cases were systematically re-reviewed using original histopathological and clinical records and reclassified according to both ATA_2015 and ATA_2025 risk-stratification criteria. Response to therapy was assessed according to dynamic risk-stratification categories (excellent, indeterminate, biochemical incomplete, structural incomplete). Associations between risk categories and outcomes were assessed using χ^2 tests, and the probability trend of incomplete response across ATA_2025 categories using the Cochran-Armitage trend test.
Results
A total of 487 patients were included, all of whom underwent total thyroidectomy; 85% also received radioiodine therapy. According to ATA_2025 criteria, 65% of patients were classified as low risk (L-R), 15% as low-intermediate risk (LI-R), 16% as intermediate-high risk (IH-R), and 4% as high risk (H-R). Among patients formerly classified as intermediate risk, the ATA_2025 system redistributed 41.9% into the LI-R category and 55.8% into the IH-R category. Response to therapy was excellent in 82.5% of patients, indeterminate in 10.1%, and biochemical or structural incomplete in 2.1% and 5.3%, respectively. Both ATA_2015 and ATA_2025 classifications were significantly associated with distribution of response-to-therapy categories ($\chi^2 = 32.3$ and $\chi^2 = 42.8$, respectively, both $P < 0.001$). A significant increasing trend in incomplete response across ATA_2025 categories was observed ($Z = 2.82$, $P = 0.005$), whereas no significant trend was detected using the ATA_2015 classification ($Z = 1.73$, $P = 0.08$). Incomplete response occurred in 3.7% of LI-R patients and in 15.3% in the IH-R group, corresponding to an approximately fourfold higher rate in the latter group (Fisher's exact test, $P = 0.041$) . Outcome analysis including 410 patients with $\geq$36 months of follow-up showed that, within the ATA_2015 intermediate-risk group, disease occurred in 8.0% of patients reclassified as LI-R and in 17.2% of those reclassified as IH-R, indicating a higher rate of persistent disease in the latter group.
Conclusions
In this single-center DTC cohort, the ATA_2025 classification redistributed patients across four risk categories and showed a progressive increase in incomplete response across ATA_2025 risk groups, with subdivision of the intermediate-risk category identifying subgroups with distinct response profiles.

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PS1-08-06

Long-term follow-up of differentiated thyroid carcinoma: is routine ultrasound surveillance needed beyond 8 years in low-intermediate risk patients?

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Background
The 2025 American Thyroid Association (ATA) guidelines recommended discontinuing routine neck ultrasound after 5–8 years in low-risk patients with sustained excellent response. However, whether similar surveillance de-escalation is appropriate for low-intermediate-risk patients remains unclear. This study evaluated long-term recurrence patterns in patients with low-intermediate-risk DTC who achieved an excellent response after initial therapy.
Methods
We retrospectively analyzed 1,175 consecutive patients with DTC treated with total or near-total thyroidectomy and radioactive iodine (RAI) therapy between 2012 and 2015. Dynamic risk stratification was performed 6–12 months after RAI. Patients classified as low-risk or presenting with distant metastasis were excluded. Follow-up consisted of annual thyroid function tests, serum thyroglobulin and anti-thyroglobulin antibody measurements, and neck ultrasound. The primary endpoint was structural recurrence.
Results
Among 1,175 patients (78.0% female; mean age 45.9 $\pm$ 12.4 years), papillary carcinoma accounted for 94.5%. According to the 2025 ATA risk stratification system, 22.7% were low-intermediate risk, 52.6% intermediate-high risk, and 24.7% high risk. An excellent response at initial dynamic risk stratification was achieved in 897 patients (76.3%). During a median follow-up of 10.2 years (range 5.0 - 17.3), structural recurrence after excellent response occurred in 25 patients (2.8%). Only 1 of the 240 patients (0.4%) in the low-intermediate-risk group developed structural recurrence. In this patient, lateral neck lymph node metastasis was detected by ultrasound 7.9 years after initial therapy and was preceded by a rise in nonstimulated thyroglobulin (2.18 ng/mL) at 7.4 years.
Conclusion
Structural recurrence after sustained excellent response was rare in low-intermediate-risk DTC. Late recurrence was exceptionally uncommon and, in the single recurrent case, was preceded by biochemical elevation. These findings suggest that less intensive long-term ultrasound surveillance may be reasonable in selected patients with low-intermediate-risk DTC who maintain a durable excellent response.

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PS1-08-07

A 4-mm size of central lymph node metastasis is a better cut-off value than a 2-mm micro-metastasis for predicting post-lobectomy recurrence: a retrospective cohort study of 2,340 patients with papillary thyroid carcinoma

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Background
The biological behavior of papillary thyroid carcinoma (PTC) with micro-metastasis (N1a-mic) or macro-metastasis (N1a-mac) remains unclear, and there are conflicting data regarding the optimal cut-off value for immediate completion thyroidectomy in patients with N1a-mac compared with those with N1a-mic or isolated tumor cells (ITC).
Methods
We retrospectively analyzed 2,340 clinically node-negative (cN0) PTC patients who underwent thyroid lobectomy between 2007 and 2017. The proportion of patients upstaged to pathologically node-positive (pN1a) disease was 16.3% ($n = 381$). The optimal cut-off size of central lymph node metastasis associated with post-lobectomy recurrence was identified as 4.0 mm. The clinicopathological characteristics and oncologic outcomes of patients with pN1a <4.0 mm were compared with those with pN1a ≥ 4.0 mm.
Results
In the pN1a ≥ 4 mm group, there was a significantly higher proportion of younger patients, males, conventional thyroid lobectomy rather than endoscopic or robotic lobectomy, larger tumor size, and N1a stage. Post-lobectomy recurrence was significantly higher in the younger age group (6.2% vs. 1.7%). In Cox analysis, younger age (Hr = 3.22), larger tumor size (Hr = 1.78), and aggressive tumor variants (Hr = 12.0) were significant risk factors for post-lobectomy recurrence. Multivariate analysis revealed that younger age (Hr = 2.71), aggressive variants (Hr = 6.28), and central lymph node metastasis ≥ 4 mm (Hr = 5.49) were significant independent risk factors. Conversely, central lymph node metastasis <4 mm was not associated with an increased risk of post-lobectomy recurrence compared with N0 or Nx stage patients (Hr = 1.66, $P = 0.174$).
Conclusions
The optimal cut-off size of central lymph node metastasis associated with post-lobectomy recurrence was 4.0 mm. While younger age (<35 years), N1a stage, and central lymph node metastasis ≥ 4 mm were significant risk factors ($P = 0.001$), nodal metastases measuring 2–4 mm were not significant risk factors for post-lobectomy recurrence compared with ≤ 2 mm micro-metastasis ($P = 0.174$; log-rank $P = 0.194$).

Table 1. Cox regression analysis of risk factors for post-lobectomy recurrence in papillary thyroid carcinoma.

Variable	Category	Multivariate HR (95% CI)	p-value
Age	<35 vs ≥35 years	2.71 (1.53–4.79)	0.001
Sex	Female vs Male	1.12 (0.57–2.20)	0.745
Operation	Endoscopic/Robot vs Classic	1.35 (0.64–2.82)	0.430
	Minimal vs Classic	1.38 (0.74–2.59)	0.316
Tumor size	>7.5 mm	1.24 (0.68–2.24)	0.480
Aggressive variants	DSV / Hobnail / TCV	6.28 (1.68–23.4)	0.006
N1a metastasis	<4 mm vs N0/Nx	1.66 (0.79–3.47)	0.174
	≥4 mm vs N0/Nx	5.49 (2.60–11.6)	0.001

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PS1-08-08

Multiple foci, single question: does multifocality really predict papillary thyroid carcinoma recurrence? - a reassessment in the ATA 2025 ERA

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Introduction
The current American Thyroid Association 2025 risk stratification (ATA25) assigns a stronger impact to multifocality in predicting recurrence in papillary thyroid carcinoma (PTC) compared with the 2015 classification (ATA15). The aim of this study was to evaluate whether multifocality was an independent prognostic factor in our cohort.
Methods
Retrospective study of PTC patients from a Portuguese tertiary cancer center, with histologic diagnosis between January/2017-October/2018. Exclusion criteria: <1-year follow-up or distant metastasis at diagnosis. Univariable/multivariable logistic regression and Kaplan-Meier survival analysis were performed.
Results
Of 495 patients (76.8% female, median age 61), most had intrathyroidal disease (95.6% pT1a-3a) without nodal metastases (71.7%). Classic subtype predominated (54.5%); lymphovascular invasion was present in 38.1% and R1 margins in 19.9%. Total thyroidectomy was performed in 94.7% and radioactive iodine (I-131) in 74.7%. Median follow-up was 7.1years, with 11% experiencing recurrence (after a median of 3 years). Multifocality occurred in 53.7% (bilateral 66.9%). Compared to unifocal PTC, multifocality was associated with higher tumor burden (median 20vs28mm, $P < 0.001$), predominantly classic subtype (46.3%vs54.3%, $P = 0.042$) and R1 (36.2vs63.8%, $P = 0.018$). In patients with multifocal disease, recurrence rates were similar regardless of I-131 therapy (13.4vs4.2%, $P = 0.071$). Recurrence-free survival was also comparable between multifocal and unifocal groups ($P = 0.629$). In the multivariable analysis, the independent factors for recurrence were incomplete surgical resection (OR2.48, 95%CI1.08-5.70, $P = 0.032$), classic subtype (OR2.61, 95%CI1.11-6.12, $P = 0.027$) and number of lymph node metastases (OR1.17, 95%CI1.07-1.28, $P < 0.001$), after controlling for the significant variables in the univariable analysis (advanced stage, classic variant, higher tumor burden, number of lymph node metastases, extranodal extension, lymphovascular invasion, incomplete surgical resection and I-131). Among patients who recurred, ATA15 classified 48.1% as high-risk, 48.1% intermediate and 3.7% low-risk, while ATA25 classified 44.4% as high-risk, 46.3% intermediate-high, 7.4% intermediate-low and 1.9% low-risk ($P < 0.001$).
Conclusion
In our cohort, multifocality was not predictive of recurrence, while incomplete resection, histological subtype and number of nodal metastases emerged as the strongest prognostic factors. As I-131 therapy was not associated with recurrence, its routine use in patients with multifocal tumors without additional adverse prognostic factors appears unwarranted.

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PS1-08-09

Is multifocality a true risk factor for recurrence or persistence of disease in papillary thyroid carcinoma?

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Objectives
Multifocality has been incorporated into 2025 American Thyroid Association guidelines in the intermediate risk of recurrence of thyroid carcinoma. The prognostic significance of multifocality remains debatable. Our study aims to evaluate whether multifocality is a predictor of recurrence or persistence of disease (RPD) in patients with papillary thyroid carcinoma (PTC).
Methods
We conducted a retrospective study of patients diagnosed with PTC between January 2018 and January 2026. Clinicopathological features evaluated included age, sex, vascular invasion, node metastasis, tumor stage, extrathyroidal extension, total tumor diameter and RPD (defined as structural evidence of disease or biochemically incomplete response during follow-up). We performed a stratified analysis based on the administration of radioactive iodine (RAI) therapy to evaluate the impact of multifocality in both subgroups.
Results
We analyzed 173 patients (77.5% female, median age of 61 years at diagnosis). Median follow-up was 24 (0-92) months. Multifocality was present in 57 patients (32.9%). Eight patients experienced RPD, four of which were multifocal ($P = 0.293$) . A higher percentage of multifocal tumors underwent RAI (45.7% vs 29.7%), but this difference did not reach statistical significance. RAI was predominantly used in tumors with aggressive features such as vascular invasion ($P < 0.001$), node metastasis ($P < 0.001$) and extrathyroidal extension ($P < 0.001$) and these patients also presented with higher recurrence rate ($P < 0.001$). Within the RAI subgroup ($n = 35$), we had 19 unifocal and 16 multifocal PTC. One significant difference was observed regarding aggressive features, with larger total tumor diameter in multifocal PTC ($P = 0.02$). A 25% rate of RPD was observed in multifocal tumors, which did

not differ significantly from unifocal PTC ($P = 0.497$). Within the non-RAI subgroup ($n = 138$), 97 PTC were unifocal and 41 were multifocal. Again, the total tumor diameter was the only significant difference, with bigger diameter in multifocal group ($P = 0.02$). Only one patient with unifocal PTC presented with RPD ($P = 0.514$). Multivariate logistic regression demonstrated that multifocality was not independently associated with RPD (Or = 1.36; 95% CI: 0.28-6.43; $P = 0.697$) when controlled for tumor size and RAI.
Conclusions
In our cohort, multifocality did not appear to be related to higher RPD. The low RPD rates reinforce the excellent prognosis even in multifocal PTC. Within the RAI group, multifocality does not appear to be associated with a higher prevalence of other aggressive features. Given the indolent nature of PTC, longer surveillance is often required to accurately assess long-term recurrence. Multifocality should be incorporated along with other clinicopathological aspects, underscoring the challenge of individual therapeutic decisions.

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PS1-08-10

Comparison of the 2015 and 2025 american thyroid association risk stratification systems in predicting recurrence in differentiated thyroid cancer

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Background
Risk stratification systems are essential for individualized management of differentiated thyroid cancer (DTC) patients. This study compared the 2015 and 2025 American Thyroid Association (ATA) guidelines in predicting long-term recurrence risk in Korean DTC patients.
Methods
A retrospective cohort study was conducted on 2,816 adult patients with DTC who underwent total thyroidectomy at a tertiary academic medical center between 2010 and 2015. Patients were stratified according to 2015 and 2025 ATA guidelines. The primary outcome was disease-free survival (DFS).
Results
During a median follow-up of 9.7 years (interquartile range: 6.7–12.2 years), 153 (5.4%) patients underwent structural recurrence. Risk distributions differed significantly between systems and 693 patients (24.6%) up staged by the 2025 ATA. The 2025 ATA system assigned fewer patients to the low-risk group (14.8% vs. 29.5% in 2015 ATA) and more to the high-risk group (24.3% vs. 11.2%). While the 2025 ATA sub-classified intermediate-risk patients into low-intermediate and intermediate-high categories, the overall intermediate-risk proportion remained similar (60.9%) and most patients classified as having intermediate-high risk. Among low-risk patients, the recurrence rates were 1.6% according to the 2015 ATA and 0.5% according to the 2025 ATA system. For intermediate-risk patients, the 2015 ATA guidelines showed a recurrence rate of 4.2%. In the 2025 ATA system, recurrence rates were 0.8% for the low-intermediate and 3.6% for the intermediate-high groups, demonstrating more granular stratification within the intermediate spectrum. Among high-risk patients, recurrence rates were 14.1% for the 2015 ATA and 12.4% for the 2025 ATA.
Conclusion
Both guidelines demonstrated comparable performance, and the revised 2025 ATA guidelines showed improved specificity in identifying truly low-risk patients. However, the shift of patients toward higher-risk categories in the 2025 ATA guidelines raises concerns regarding potential overtreatment.

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Systemic Treatments

PS1-09-01

Lenvatinib outcomes across histologic subtypes of differentiated thyroid cancer

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Background
Lenvatinib is the first-line therapy for advanced/metastatic differentiated thyroid cancer (DTC) requiring systemic treatment, particularly in radioactive iodine-refractory disease. However, evidence on lenvatinib in DTC is mainly derived from histologically heterogeneous cohorts, while potential differences in response across distinct histologic subtypes remain insufficiently characterized.
Objectives
To evaluate whether lenvatinib outcomes differ by histology in advanced/metastatic DTC.
Methods
Retrospective analysis of DTC patients treated with lenvatinib at a tertiary center. Included histology groups (WHO 4th edition) were classical variant papillary thyroid carcinoma (cvPTC), follicular variant PTC (fvPTC), follicular thyroid carcinoma (FTC) and oncocytic thyroid carcinoma (OTC). Mixed PTC variants and other rare variants were excluded.
Results
77 patients were included: 41 (53.2%) cvPTC, 13 (16.9%) fvPTC, 13 (16.9%) FTC and 10 (13%) OTC. Mean age at diagnosis was 60.1 ± 13.5y and mean age at lenvatinib start was 67.9 ± 11.2y; 55.8% were female. Median treatment duration was 13 (1-68) months. At lenvatinib start, 71.4% of patients had N1 disease and 85.7% were M1. N1 status was more frequent in cvPTC patients (cvPTC: 82.1%, fvPTC: 31%, FTC: 53.8%, OTC: 50%, $P = 0.029$); sex, age at diagnosis, age at lenvatinib start, T stage, M stage, prior radioactive iodine and lenvatinib treatment duration did not differ across histology groups. Best objective response rate (ORR) differed significantly between groups (cvPTC: 52.6%, fvPTC: 22.2%, FTC: 75%, OTC: 10%, $P = 0.007$), and progressive disease events during follow-up were more frequent in OTC (cvPTC: 39%, fvPTC: 31%, FTC: 15.4%, OTC: 70%, $P = 0.049$). Best disease control rate (DCR), median estimate progression-free survival (PFS), disease-specific survival (DSS) and overall survival (OS) did not differ across histology groups. In multivariable analyses adjusting for age, T, N and M status at lenvatinib start, OTC was associated with lower odds of objective response (OR 0.1, 95% CI 0.01-0.61, $P = 0.018$). Histology was not independently associated with DCR, PFS, DSS or OS.
Conclusions
In this real-world advanced/metastatic DTC cohort, structural response with lenvatinib therapy differed across histologic subtypes, while survival outcomes did not. After adjustment for age and T, N and M status at treatment start, OTC was independently associated with lower odds of achieving objective response with lenvatinib, likely reflecting its distinct genetic profile. These findings suggest histology-related heterogeneity in lenvatinib response.

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PS1-09-02

Ten years of lenvatinib for advanced thyroid cancer: real-world experience at a tertiary care center compared to that of select trial

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Objectives
Lenvatinib is used for progressive, iodine-refractory thyroid cancer (RAIR-TC). This study evaluates the outcomes of patients treated with lenvatinib in the real world compared to SELECT trial.
Methods
We analyzed data of 207 RAIR-TC patients treated in a tertiary care center between 2014 and 2025 outside of clinical trials.
Results
Histotype distribution was like that of SELECT study for PTC (51.7% vs 50.6%) and FTC (17.9 vs 20.3%) but different for PDTC (23.2% vs 10.7%; $P = 0.01$) and OTC (7.2% vs 18.4%; $P = 0.03$). Median age (65 vs 64 years) and sex (53.6% male vs 47.9%) were similar. Our cohort presented a poorer performance status (ECOG $\geq$2: 42.2% vs 5%). While all SELECT patients initiated with 24 mg/day, only 57.8% of our cohort started with this dose. After a median follow-up of 7.4 years, 40% of patients were still alive: since the SELECT study was closed much earlier, we compared the number of alive patients at 28 months (data cut-off of SELECT): 55.1% in our study vs 60% in the SELECT study. The Disease-Specific-Survival (DSS) was 52.6 months (95%CI 35.9-69.4), with higher ECOG ($\geq$2 vs 0-1) significantly associated with shorter DSS. Unfortunately, the DSS was not calculated in the SELECT study. The progression-Free Survival (PFS) was 21 months (95%CI 11.7-30.3) longer than that found in the SELECT study (18.3 months). In our study histology was significantly associated with PFS: PDTC and OTC showing a PFS of 8 and 21 months, while FTC and PTC showed a longer PFS of 40 and 30 months, respectively. The SELECT PFS according to the histotypes was FTC = 18.8 months, PTC = 16.4 months, PDTC = 14.8 months and OTC = NE<: in both studies FTC was the most responsive hystotype. Best clinical response significantly diverged from SELECT ($P < 0.001$) since we had Stable Disease as the most frequent outcome (57.4%), then Partial Response (30.9%) and finally Progressive Disease 11.6%) while they were 23%, 63% and 6.9% in the SELECT study, respectively.
Conclusions
Ten years of clinical experience confirms Lenvatinib efficacy in advanced RAIR-TC even in the real world. As in the SELECT study FTC is the best responder histotype followed by PTC. The longer PFS is likely due to a higher number of stable disease. The lower prevalence of partial response may be due to the greater presence of elderly patients and ECOG > 2, in whom we started with lower doses of lenvatinib.

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Pharmacogenetics of lenvatinib in patients with advanced thyroid cancer: correlation with adverse events and clinical outcome

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Introduction and background
Around 10% of patients with differentiated thyroid cancer (DTC) are diagnosed with distant metastases. Radioiodine therapy remains the gold standard treatment in this setting; however, only about 40% of patients achieve disease control. Lenvatinib represents the first therapeutic option for progressive radioiodine-refractory disease (RAI-R), although treatment response and toxicity may considerably vary among patients. Recent data suggest that pharmacogenomic factors may contribute to variability in Lenvatinib plasma levels, potentially influencing both toxicity and efficacy.
Aim
To evaluate the association between pharmacogenetic polymorphisms in drug metabolism and transport genes and treatment-related adverse events (AEs) and clinical outcomes in patients with RAI-R DTC treated with Lenvatinib.
Patients Methods
We conducted a multicentric, retrospective analysis of a consecutive cohort of patients with RAI-R DTC treated with Lenvatinib. Clinical and treatment data were collected over a 12-month observation period. AEs were graded according to CTCAEv5.0 and radiological response assessed using RECIST1.1 criteria. Patients were genotyped for polymorphisms in CYP3A4(rs2242480), CYP3A5(rs776746), ABCB1(rs2032582, rs1045642, rs2235048), and ABCG2(rs2231142).
Results
48 patients were included (median age:65.5 years; 56.2% females). The majority had a DTC (72.9%) with distant metastases (87.5%). The initial Lenvatinib dose was 24 mg/day in 56.2% of patients and only 18.8% maintained the full dose. No associations were found between genotypes and dose intensity. Maximum tolerated dose was independently associated with body weight ($\beta = 0.093$; $P = 0.019$). The most frequent AEs were fatigue (75%), hypertension (75%), diarrhea (64.6%), anorexia (58.3%), oral mucositis (50%). ABCB1 rs2032582 GT/TT genotype was associated with mucositis (OR:5.32, 95%CI:1.56-20.67; $p = 0.01$), CYP3A4 GG genotype with longer mucositis duration ($p = 0.002$) and ABCB1 rs2235048 CT/TT genotype with anorexia (OR:6.82, 95%CI:1.68-35.5; $P = 0.01$) . Older age ($\geq$65 years) was associated with fatigue (OR:4.90, 95%CI:1.22–19.69; $P = 0.04$). Partial response to the treatment occurred in 64.6% of patients, disease stabilization in 33.3%, and progression in 2.1%. At a median follow-up of 47.7 months, median OS was not reached; worse OS was independently associated with age at Lenvatinib initiation and ECOG PS (HR:1.05; 95%CI:1.00-1.10, $P = 0.04$ and HR:10.7 95%CI:2.72-42.2; $P < 0.001$, respectively) whereas no significant association was found with the genotypes analyzed.
Conclusions
Our findings support the inclusion of readily available clinical variables, particularly body weight, in initial dosing strategies to personalize treatment and minimize AEs. Age at therapy initiation and ECOG PS also emerged as prognostic factors. Pharmacogenetic profiling of drug transport and metabolism may help predict treatment-related AEs, although prospective studies integrating therapeutic drug monitoring are needed to validate genotype-guided dosing and clarify exposure-toxicity relationships.

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PS1-09-04

Treatment patterns and outcomes for patients with RET-altered thyroid cancer treated with selpercatinib in europe: final results from the sprint-RET study

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Background
Selpercatinib is a selective rearranged during transfection (*RET*) inhibitor. Based on the efficacy demonstrated in the Phase 1/2 single-arm LIBRETTO-001 and Phase 3 randomised LIBRETTO-531 trials, selpercatinib was approved for advanced or metastatic thyroid cancer (TC) with *RET* mutation (in medullary TC; MTC) or fusion (in non-medullary TC; nMTC). Real-world European data on selpercatinib treatment patterns and outcomes remain limited.
Methods
SPRINT-RET was a European multi-country, observational, retrospective chart review study of selpercatinib-treated patients with advanced *RET* fusion-positive non-small cell lung cancer, nMTC, or *RET*-mutated MTC. This final analysis included adult and adolescent patients ($\geq$12 years) with *RET*-mutated MTC or *RET* fusion-positive nMTC across Germany, Italy, Netherlands, Spain, and UK. Data were collected from 9 sites between April23-July25 for patients who initiated selpercatinib outside clinical trials, at least 9 months before data collection period. Analyses were descriptive. Kaplan-Meier method was used to describe time-to-event outcomes among MTC patients.
Results
These analyses included 64 patients with MTC and 4 with nMTC. Of the patients with MTC, the majority were male (64.1%), diagnosed with stage IV disease (85.2%), and median (range) age at selpercatinib initiation was 58.2 (13.7-82.9)

years. Most patients ((90.6%) had only somatic mutation identified and 6 (9.4%) had germline mutation identified. The majority (57.8%) had *M918T* mutation. Selpercatinib was most commonly initiated in 2nd (48.4%) or 1st line (29.7%). Median follow-up time was 27.7 months. The majority of patients ($n = 54$, 85.7%) were still on selpercatinib treatment at the end of follow up. The 24-month overall survival rate was 92.8% (95% CI: 81.8, 97.2). The patients with nMTC were adults (≥56 years), majority ($n = 3$) female, with varying disease histology. All patients had a partial response to treatment. At a median follow-up time of 19.3 months, 3 patients remained on treatment with no documented disease progression, and 1 discontinued selpercatinib due to death after 14.9 months.Adverse events observed in both populations were consistent with selpercatinib's known safety profile.

Conclusion

Results confirm the real-world effectiveness of selpercatinib in treating *RET*-mutated MTC, demonstrating robust disease control and PFS. Findings in *RET* fusion-positive nMTC are from a small sample and should be interpreted cautiously. Overall, these findings reinforce the importance of genomic testing to identify *RET* alterations in patients with TC, and treatment with selpercatinib in this population.

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Treatment outcomes of multikinase and target therapy of the portuguese cohort of advanced thyroid carcinoma

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Introduction

Oral multikinase inhibitors and target therapies are the current backbone of systemic therapy for advanced thyroid cancer not amenable to surgery.

Objectives

The main aim of this study was to evaluate the outcomes and tolerability of the Portuguese cohort of advanced thyroid cancer treated with systemic therapy.

Methods

Centres belonging to the National Thyroid Study Group were surveyed for differentiated thyroid cancer (DTC) and anaplastic thyroid cancer (ATC) cases treated with oral systemic therapies. Main outcomes were overall survival (OS), progression-free survival (PFS), best objective response rate (ORR) and best disease-control rate (DCR).

Results

Twelve centres covering the whole country (6 in the north, 2 in the centre and 4 in the south and islands) included 307 patients which started treatment between 2009 and 2024: 59% female; median age 69.5 years; DTC in 75% (253) and ATC (54) in 18%; T4 stage in 49% and M1 in 82%. Molecular study was performed in 67.5% cases (29% BRAF, 13% RAS, 1% RET/NTRK and 23% not detected), in 89% before starting first line therapy. On first line 71% were treated with Lenvatinib and 10% Sorafenib while target therapy with Dabrafenib and Trametinib (DT) represented 18% of cases (50% in ATC cohort). Median OS/PFS was 1168/1007 days for DTC and 286/109 days for ATC. While 50% of DTC died of M1 disease, 75% of ATC died of local progression. In DTC patients treated with Lenvatinib and DT compared to Sorafenib, OS showed a trend for higher survival (1544 and 1419 vs 1091 days) and a significant increase in PFS (1540 and 1276 vs 583 days) ($P = 0.001$). Lenvatinib and DT also showed improved best ORR (62.5 and 77 vs 15.4% $P = 0.001$) and DCR (94 and 89 vs 69% $P = 0.001$). Oncocytic and high grade/poorly differentiated carcinomas had a trend towards decrease OS and PFS with Lenvatinib compared to classical DTC. In ATC, DT showed a significant increase in OS (588 vs 59 days), PFS (420 vs 51 days) ($P < 0.0001$), best ORR (65 vs 23 %) and best DCR (78 vs 50% $P < 0.001$). Dose interruptions occurred in 35% of cases, while discontinuation due to adverse events occurred in 17% of cases. DT therapy had significant less dose reductions (31 vs 67% $P < 0.001$) and permanent discontinuation (7.5 vs 19% $P = 0.048$) compared to Lenvatinib.

Conclusions

This is the first national wide assessment of Portuguese thyroid cancer patients treated with oral systemic therapy. Molecular testing was performed in a significant percentage of patients and mainly before first line therapy. In DTC Lenvatinib and DT showed improved anti-tumour activity compared to Sorafenib while DT had better clinical tolerability. In ATC DT was significantly superior to Lenvatinib in both OS and PFS.

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PS1-09-06

Dose optimization during lenvatinib therapy and subsequent cabozantinib treatment in radioiodine-refractory differentiated thyroid carcinoma: a real-world study

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Background

Lenvatinib is the standard first-line therapy for radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC), while cabozantinib is approved for subsequent disease progression. In clinical practice treatment-related adverse events (AEs) frequently require dose reductions or temporary treatment interruptions. The impact of dose optimization strategies on survival outcomes remains unclear.

Objectives

To evaluate the impact of dose reductions and scheduled treatment interruptions during lenvatinib therapy on survival outcomes in patients with RAIR-DTC, and to describe real-world outcomes of patients subsequently treated with cabozantinib.

Methods

We conducted a retrospective single-center study of patients with RAIR-DTC treated with lenvatinib. Dose modifications, scheduled treatment interruptions, progression-free survival (PFS), overall survival (OS), and treatment duration were analyzed. Outcomes were also evaluated in patients who later received cabozantinib after lenvatinib.

Results
Of seventy-six patients receiving lenvatinib, 43 (56.6%) were female. Median age at diagnosis was 61 [11;83] years and at treatment initiation was 70 [35;84] years. At treatment start 65 (85.5%) patients had metastatic disease. The most common indication for lenvatinib initiation was symptomatic or progressive metastatic disease (47.4%). Twenty-four patients (31.6%) started on full dose (24 mg/day), and 22 (91.7%) required dose reductions due to AEs, of which hypertension was the most reported (72.7%). The median administered dose was 14.1 [7.43;24.0] mg/day. Patients receiving lower doses (<14 mg/day) had significantly longer mean OS compared with those receiving higher doses (55.8 vs 38.2 months, $P = 0.026$), while PFS was similar between groups; median OS and PFS were not reached in the <14mg/day group. 70 (92.1%) patients started on a continuous regimen, but nearly half (47.1%) switched to a scheduled "weekends-off" regimen due to tolerability issues; this strategy was associated with longer median OS (50.5 vs 33.0 months, $P = 0.026$) and longer treatment duration (46.4 vs. 30.2 months, $p = 0.001$), without differences in PFS. Eleven patients subsequently received cabozantinib, most commonly due to disease progression on lenvatinib (6/11, 54.5%), followed by toxicity (2/11, 18.2%) or both (3/11, 27.3%). Median follow-up was 26 months, with a median PFS of 10.0 months (95% CI 3.3–16.7) and median OS of 22.0 months (95% CI 9.9–34.1). Dose reductions occurred in 90.9% of patients and the median daily dose was 33.5 [19.4;60] mg/day. Patients initiating cabozantinib at 60 mg showed numerically longer PFS and OS than those starting at lower doses, although differences were not statistically significant. Lower daily doses were not associated with inferior outcomes, likely reflecting dose adjustments during sustained treatment.
Conclusions
Dose reductions and scheduled treatment interruptions during lenvatinib therapy were common and enabled similar disease control. In real-world practice, tolerability-guided dose optimization may allow prolonged treatment exposure while maintaining clinical efficacy. Preliminary observations from patients treated with cabozantinib suggest that similar dose adjustments are frequently required.

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Donafenib in locally advanced or metastatic thyroid cancer: a retrospective real-world study

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Objectives
Locally advanced and metastatic thyroid cancer remains a formidable clinical challenge with limited therapeutic options and dismal prognosis. Donafenib, a novel approved multikinase inhibitor for thyroid cancer, has scarce real-world data on its efficacy, safety, and prognostic predictors in unselected clinical practice. This study aimed to evaluate the real-world clinical outcomes and prognostic factors of donafenib in patients with locally advanced/metastatic thyroid cancer.
Methods
We performed a retrospective, real-world cohort study enrolling consecutive patients with pathologically confirmed locally advanced or metastatic thyroid cancer who received donafenib treatment at West China Hospital of Sichuan University between June 2021 and March 2026. The primary endpoint was objective response rate (ORR) per RECIST 1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety profile, conversion resection rate, and prognostic factors.
Results
A total of 102 patients were initially enrolled, 22 were lost to follow-up, and 80 patients were included in the final analysis, with a median follow-up of 12 months (range, 3–34 months). Among these 80 patients, there were 38 males and 42 females, with a median age of 57 years (range, 18–89 years). Most patients (95.0%) were American Joint Committee on Cancer (AJCC) stage III–IV, and 76.2% had papillary thyroid carcinoma. The ORR was 22.5%, DCR was 93.8%, with a median change in maximum tumor diameter of -4.8%. Patients without detectable pathogenic gene mutations achieved a significantly higher ORR than those with gene alterations (45.5% vs 11.4%, $P = 0.025$). Additionally, patients with differentiated thyroid cancer exhibited a significantly higher DCR compared with those with highly aggressive thyroid cancer subtypes (including anaplastic and poorly differentiated types, 95.59% vs 72.73%, $P = 0.033$). Grade 3-4 treatment-related adverse events occurred in 22.5% of patients, with hand-foot skin reaction being the most prevalent adverse event (32.5%). Conversion surgery was achieved in 40 patients, with R0/R1 resection rate of 50.0%. Multivariate Cox regression analysis revealed that an Eastern Cooperative Oncology Group (ECOG) score ≥ 2 served as an independent adverse prognostic factor for both PFS and OS, while a highly invasive pathological subtype was an independent adverse prognostic factor for PFS. Kaplan-Meier survival curves for PFS and OS showed the median values were not reached in the whole cohort.
Conclusions
Donafenib exhibits favorable anti-tumor efficacy and manageable safety in real-world advanced thyroid cancer. ECOG performance status and pathological subtype are reliable prognostic biomarkers, providing robust real-world evidence for individualized donafenib-based precision therapy.

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PS1-09-08

Impairment in the hypothalamic–pituitary–gonadal axis in patients with advanced metastatic medullary thyroid carcinoma treated with highly selected RET inhibitor selpercatinib

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Objectives
Erectile dysfunction (ED) has been reported as peculiar adverse events during treatment with highly selective RET inhibitor selpercatinib. A potential pathogenic hypothesis underlying ED is impairment of the hypothalamic–pituitary–gonadal (HPG) axis. This study aims to analyze variations in the HPG axis in a cohort of male patients with advanced MTC treated with selpercatinib.
Methods
Between May 2019 and April 2025, 29 male patients initiated selpercatinib therapy for RET-mutant advanced MTC. Nineteen of them, having a complete HPG assessment before and after treatment initiation, were included in the study. FSH, LH, Total Testosterone (TT), and Sex Hormone Binding Globulin (SHBG) serum values were evaluated. Free Testosterone (FreeT) was estimated using Vermeulen's formula. In all patients (total group – T-Group), the HPG axis was evaluated before and after 12 months of selpercatinib initiation. In 7/19 (36.8%) cases (extended group – Ex-Group), data collection was extended beyond 24 months from the start of treatment, with evaluation of the HPG axis at each clinical visit for a total of 12 assessments per patient. Semen analysis was performed in accordance with the World Health Organization (WHO) laboratory manual for the examination and processing of human semen, 6th edition.
Results
18/19 (94.7%) patients experienced ED during selpercatinib treatment. Two of 18 (11.1%) had ED before starting selpercatinib, while 16 (88.9%) developed ED after starting selpercatinib. The median time to ED onset was 1 month (IQR 1-2) after starting selpercatinib. During the first year of treatment, a significant increase in FSH serum value ($P = 0.03$) was observed in the T-Group; no significant variations in LH, SHBG, TT and FreeT were registered. In the Ex-Group, a significant increase in FSH ($P < 0.01$), LH ($P < 0.01$), and SHBG ($P < 0.05$), and a decrease in TT ($P < 0.01$) and FreeT ($P = 0.003$) were observed. Semen analysis was available in 6/19 (31.6%) patients. Five patients showed a reduction in the volume of ejaculate, compared to normal values, and in all these patients, azoospermia was observed. The remaining patient had oligospermia, with a high rate of atypical cells (96%) and reduced motility (5%).

Conclusions
ED shows high prevalence in *RET*-mutant MTC during selpercatinib treatment with very early onset. Variations in the HPG axis and semen analysis can reflect damage to Sertoli and Leydig cells, leading to hypogonadism. Therefore, fertility counseling and sperm cryopreservation could be advisable in childbearing male before starting selpercatinib treatment.

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The role of liquid biopsy in monitoring treatment with tyrosine kinase inhibitors for patients with advanced thyroid carcinoma

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Although treatment with tyrosine kinase inhibitors (TKIs) has improved the prognosis of patients with advanced thyroid carcinoma, some cases experience disease progression, due to the emergence of resistance mutations. This study aimed to evaluate the role of liquid biopsy for disease monitoring in patients with advanced thyroid carcinoma treated with TKIs. Plasma was collected before the start of systemic therapy (baseline) and at the time of therapeutic response or disease progression in 3 papillary (PTC), 2 follicular (FTC), 2 poorly differentiated (PDTC), 1 anaplastic (ATC), 2 medullary (MTC) thyroid carcinomas. Cell free (cf) DNA was extracted and sequenced by a custom NGS panel able to detect most of the variants involved in thyroid cancer. Molecular alterations in the primary tumor and metastases at progression, when available, were also investigated. Serum thyroglobulin (Tg), anti-Tg antibodies for PTC and FTC and calcitonin and carcinoembryonic antigen for MTC were evaluated during the follow-up and disease response were defined using computer tomography (CT) scan or 18 FDG PET/CT. In all cases, the molecular alterations detected in the tumor tissue were also found in cfDNA at baseline. Five patients showed a partial response, while 5 patients showed disease progression. In 3 patients (2 PTC and 1 ATC) mutations found in cfDNA at baseline were also detected at the time of therapeutic response, but at a lower allelic frequency, indicating a reduction in tumor burden. At variance, in 2 MTCs harboring *RET*; ^{M918T} in the primary tumor, a novel variant in *RET* (T729F) and the *H-RAS*; ^{Q61R} mutation were found in cfDNA at disease progression, but not at baseline. Similarly, in a FTC without mutations in the primary tumor or in cfDNA at baseline, a *TP53* variant was found in cfDNA at disease progression. Interestingly, these mutations were also present in the corresponding metastases at progression, suggesting their involvement in therapeutic resistance. Our findings support the use of liquid biopsy for monitoring TKIs response in patients with advanced thyroid cancer, especially when conventional markers are not helpful (dedifferentiated disease or presence of anti-Tg antibodies) and for the promptly identification of resistance mutations in cases with disease progression, possibly guiding therapeutic change.

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Goitre & nodules & surgery

PS1-10-01

Risk of malignancy according to nuclear atypia, clinical and ultrasonographic features in indeterminate thyroid nodules

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Introduction
Thyroid nodules with indeterminate cytology, classified as Bethesda categories III and IV, pose a clinical challenge due to their variable malignancy risk. Detailed cytological evaluation, particularly nuclear atypia, may improve risk stratification and guide management.
Objectives
To evaluate malignancy risk in indeterminate thyroid nodules according to nuclear atypia, clinical variables, and ultrasonographic features.
Methods
Prospective study conducted at two tertiary referral hospitals (January 2019–January 2026). A total of 123 nodules (121 patients) with Bethesda III or IV cytology were included in the sample. Histopathology was available for 83 nodules and served as the reference standard. Atypia was classified as nuclear, architectural, combined nuclear and architectural, oncocytic, or nuclear changes not related to papillary carcinoma. A positive test was defined as isolated or combined nuclear atypia. Clinical, biochemical, and ultrasonographic variables were analyzed, including risk stratification by the ACR TI-RADS.
Results
Mean age was 54.6 ± 15.1 years, and 77.7% were female. Among nodules, 51.2% were Bethesda III and 48.8% Bethesda IV. Of the 83 nodules with definitive diagnosis, the malignancy rate was 30.1%. Nuclear atypia (isolated or combined) was present in 18 of 22 malignant nodules and was strongly associated with malignancy (OR 37.8; 95% CI 9.08–157.3; $P < 0.001$). Diagnostic performance showed sensitivity 81.8%, specificity 89.4%, positive predictive value 78.3%, negative predictive value 91.3%, and accuracy 87.0%. Male sex increased malignancy risk (OR 3.06; 95% CI 1.04–9.04; $P = 0.038$). No significant association was observed between malignancy and age ($P = 0.63$), BMI ($P = 0.59$), TSH levels ($P = 0.82$), or nodule size ($P = 0.087$). Malignancy rates increased across ACR TI-RADS categories: 18.8% in TR3, 30.2% in TR4, and 40.9% in TR5 ($P = 0.026$).
Conclusion
In indeterminate thyroid nodules, nuclear atypia is a powerful predictor of malignancy with high diagnostic accuracy. Integration of refined cytological assessment with clinical and ultrasonographic risk stratification may substantially improve individualized surgical decision-making. These findings support a multimodal approach to risk stratification in contemporary endocrine practice.

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PS1-10-02

Intraoperative decline in parathyroid hormone determines postoperative parathyroidfunction

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Introduction and objective
In patients undergoing total thyroidectomy (TT), the risk of postoperative hypoparathyroidism (hypoPT) determines clinical management. We aimed to estimate 1) the incidence of hypoPT and 2) assess the importance of intraoperative parathyroid hormone (ioPTH) decline on hypoPT development.
Methods
Retrospective cohort study of adults ($\geq$18 years) undergoing TT with ioPTH measurements from May 2021 to December 2024. We sampled baseline PTH after induction of anaesthesia and final PTH approximately 10 minutes after thyroid excision. We analysed the ioPTH decline (%) and used a 75% prespecified cutoff to determine high or low risk patients. The postoperative medical supplementation was guided by ionized calcium and subjective symptoms. HypoPT was defined as the requirement for alfacalcidol treatment at discharge. Transient hypoPT was defined as discontinuation of alfacalcidol within 12 months after TT and permanent hypoPT as continued use of alfacalcidol. We calculated determining factors for hypoPT development including receiver operating characteristic curves and univariable logistic regression estimated odds ratios (ORs).
Results
We included 272 TT patients in the cohort (mean age 53 years; 72% women). Postoperative hypoPT occurred in 47 patients (17%), including 27 (10%) transient and 20 (7%) permanent. Median ioPTH decline was higher in patients with hypoPT than without (92% vs 51%; $P < .001$). Using the 75% cutoff, we determined any hypoPT with a sensitivity of 96% (45/47), specificity 84% (190/225), positive predictive value 56% (45/80), and negative predictive value 99% (190/192). Discrimination was strong for the $\geq$75% cutoff (AUC, 0.89; DeLong P=.023). Optimal cutoffs of ioPTH to determine hypoPT was 78% for any hypoPT (sensitivity 93%, specificity 86%) and 79% for permanent hypoPT (sensitivity 100%, specificity 80%). An ioPTH decline $\geq$75% was by far the strongest risk factor for development of hypoPT (OR: 57; 95% CI, 16–204; $P < .001$).
Conclusions
Use of ioPTH decline $\geq$75% strongly discriminated the risk of postoperative hypoPT after TT. With this new risk stratification, we can allocate TT patients to

either high or low risk of postoperative hypoPT and ensure a sufficient medical and clinical support for patients at risk and reduce follow-up for low-risk patients.

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PS1-10-03

Evaluation of acr TI-rads and strain elastography repeatability in thyroid nodules: intra-observer variability

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Objectives

Ultrasound-based risk stratification systems and elastography are widely used in the evaluation of thyroid nodules; however, their clinical reliability depends on measurement repeatability. This study aimed to assess the intra-observer repeatability of the American College of Radiology Thyroid Imaging Reporting and Data System classification and strain elastography measurements in thyroid nodules, and to explore the potential clinical implications of measurement variability.

Methods

A total of 275 consecutive patients with solid thyroid nodules were prospectively evaluated and re-examined within one month. All nodules underwent standardized gray-scale ultrasound, color Doppler assessment, ACR TI-RADS classification, and real-time strain elastography. Elastography stiffness was expressed as the strain ratio between the thyroid nodule and the sternocleidomastoid muscle (E2/E1). Both examinations were performed by the same experienced operator, who was blinded to the initial results during reassessment. Intra-observer repeatability was evaluated using intraclass correlation coefficients (ICC), Bland–Altman analysis, Pearson correlation, and weighted kappa statistics.

Results

The study population consisted predominantly of women, with a high prevalence of autoimmune thyroiditis and hypothyroidism. Strain elastography demonstrated low-to-moderate repeatability, with an ICC of 0.27 (95% CI: 0.16–0.38). The Bland–Altman showed a small mean difference between repeated measurements, but wide limits of agreement, indicating substantial variability at the individual nodule level. Intra-observer agreement for ACR TI-RADS categorization was moderate (weighted $\kappa = 0.61$), while agreement for vascularity assessment was substantial (weighted $\kappa = 0.69$). Reclassification of nodules between ACR TI-RADS categories led to changes in fine-needle aspiration recommendations in a subset of cases, primarily driven by variability in echogenicity assessment.

Conclusions

Strain elastography shows limited intra-observer repeatability in thyroid nodule evaluation, while ACR TI-RADS demonstrates moderate classification consistency. Measurement variability may influence clinical decision-making, particularly for nodules near diagnostic thresholds.

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PS1-10-04

Effectiveness of laser thermoablation for benign thyroid nodules: impact of higher energy delivery and repeat procedures

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Objectives

Laser thermoablation (LTA) of benign thyroid nodules is an established treatment option for patients experiencing compressive symptoms. To achieve a satisfactory therapeutic effect (VRR (volume reduction ratio) $>50\%$), the recommended energy dose is approximately 500 J/ml. The aim of this study was to evaluate the effectiveness of LTA using a single ablation fiber, considering higher energy delivery per milliliter, higher total energy per fiber, and repeated procedures.

Methods

Procedures were performed at a single center in 195 patients. Forty patients underwent two procedures, seven three, and one four. Thermoablation was always performed using a single fiber with the pull-back technique under ultrasound guidance. In 120 procedures, the total energy delivered per ablation fiber exceeded the recommended value (6000 J per fiber). Additionally, in 67 patients the total delivered energy exceeded 600 J/ml. Treatment effectiveness was assessed by volume reduction and symptom improvement at the last follow-up (6–12 months).

Results

The mean energy delivered per milliliter was 530.4 $\pm$ 308.3 J/ml (median 476.5), the mean volume reduction was 53.5 $\pm$ 26.7% (median 58.6%; $P < 0.0001$), VRR $\geq 50\%$ was achieved in 62.6% of patients (23.6% achieved VRR $\geq 75\%$). Partial symptom improvement was observed in 108 patients (59%), complete resolution in 53 patients (29%), while 22 patients (12%) reported no improvement. Symptom outcome was strongly associated with VRR ($P < 0.001$). Patients without symptom improvement had markedly lower VRR (18.4%). Delivered energy per milliliter was not associated with symptom outcome ($P = 0.21$) or with VRR ($P = 0.75$). Among patients with VRR $<50\%$ after the first treatment ($n = 36$), repeat procedures significantly increased mean VRR from 18.3% to 46.9% ($P < 0.000001$). After subsequent treatments, 55.6% of these patients achieved VRR $\geq 50\%$. Patients requiring repeated treatments had larger baseline nodules (26.6 vs 14.8 ml), with the largest in those treated three times (mean 50.7 ml). Procedure with energy >6000 J per single fiber was not associated with differences in volume reduction ($P = 0.061$). Higher energy per milliliter and energy >6000 J per fiber were not associated with increased complication rates ($P = 0.66$ and $P = 0.98$).

Conclusions

The use of higher energy per milliliter did not result in greater VRR. Repeat procedures significantly improve outcomes in patients with VRR $<50\%$ after the first treatment and persistent symptoms. Higher-than-recommended energy per fiber was not associated with increased complications and resulted in satisfactory outcomes.

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PS1-10-05

Is persistent hyperthyroidism following thermal ablation of autonomous thyroid nodules always indicative of treatment failure? insights from functional imaging

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Context

Thermal ablation (TA), including radiofrequency ablation (RFA) and microwave ablation (MWA), has emerged as a minimally invasive treatment for autonomously functioning thyroid nodules (AFTNs). However, the clinical interpretation of persistent thyroid-stimulating hormone (TSH) suppression after ablation remains unclear, particularly when substantial nodule shrinkage is achieved.

Objective

In this study, we primarily aimed to assess the efficacy of TA, including both RFA and MWA, in restoring euthyroidism in patients with AFTNs. Particular attention was given not only to biochemical outcomes, namely the achievement of euthyroidism, but also to the clinical, structural, and functional characteristics of patients with persistent TSH suppression after treatment, in order to better characterize this subgroup.

Methods
We retrospectively evaluated patients with AFTNs treated with TA (RFA or MWA). Biochemical remission was defined as normalization of TSH with normal free T4 and total T3 levels in the absence of antithyroid drug therapy. In patients with persistent TSH suppression, post-treatment scintigraphy was performed to assess residual functional autonomy.
Results
Forty-seven patients (49 nodules) were included. Mean baseline nodule volume was 9.62 ± 6.77 mL. Euthyroidism was achieved in 42 patients (89.4%), with a median time to normalization of 2.0 months. Mean volume reduction rate was 62.4 ± 28.4%. Antithyroid therapy was discontinued in 92.9% of patients previously receiving medication. Five patients (10.6%) had persistent biochemical hyperthyroidism. Despite marked volume reduction (VRR range: 65.5–95.7%), two distinct functional patterns emerged in these patients. Patients 1 and 2 showed absence of residual focal autonomy on post-treatment scintigraphy, with no identifiable hyperfunctioning focus on the treated site and heterogeneous tracer distribution in the remaining thyroid parenchyma. In these cases, biochemical persistence was not clearly attributable to residual nodular autonomy. In contrast, Patients 3, 4, and 5 exhibited residual nodular autonomy, with persistent (although reduced) focal uptake within the treated area with or without suppression of the surrounding parenchyma, consistent with true functional non-response to thermal ablation.
Conclusions
TA provides high rates of biochemical remission in AFTNs. In patients with persistent TSH suppression despite structural response, functional imaging may help distinguish true treatment failure from non-nodular causes of biochemical persistence and guide follow-up and retreatment decisions.

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PS1-10-06

Clinical outcomes of active surveillance in bethesda iv thyroid nodules

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Background
Bethesda IV thyroid nodules, classified as follicular neoplasms, present a diagnostic challenge since cytology cannot reliably distinguish between benign and malignant lesions. Molecular testing is not always available and expensive. Diagnostic lobectomy is traditionally recommended; however, a significant proportion of these surgical interventions are unnecessary, particularly in contexts where molecular testing is not available. This study aimed to assess the outcome of active surveillance (AS) for selected Bethesda IV nodules in a setting with limited access to molecular testing.
Methods
We included 58 patients with Bethesda IV nodules ≤30 mm without extrathyroidal extension or locoregional metastasis. Patients were prospectively and retrospectively (i.e. those previously declined surgery fulfilling eligibility criteria and adequate medical records). Ultrasonographic surveillance was performed every 6–12 months using a standardized protocol. Surgery was recommended for clinically significant disease progression (CSDP): longest diameter increase >3 mm within 6 months or > 5 mm within 12 months, cytological progression to Bethesda V/VI, or locoregional metastases. Repeat FNAC was performed in selected cases based on growth or ultrasonographic changes.
Results
Six out of 58 patients underwent surgery during follow-up; the remaining 52 were analyzed under AS. Mean age was 53.9 ± 13.6 years and median follow-up was 25 (6–120) months. During follow-up, 17.3% ($n = 9$) of nodules demonstrated an increase of >3 mm in the longest diameter, while 26.9% showed a ≥50% increase in nodule volume. Repeat FNAC was performed in 47% ($n = 24$); reclassification to Bethesda II and Bethesda III was observed in 5 (20.8%) and 12 (50.0%) nodules, respectively. Surgical indications included patient preference ($n = 3$), cytological progression ($n = 2$), and CSDP ($n = 1$). Histopathology confirmed one malignancy (IEFVPTC), one NIFTP, and one well-differentiated tumor of uncertain malignant potential; no local or distant metastases were detected during follow-up.
Conclusion
AS for carefully selected Bethesda IV nodules was associated with a low rate of surgical intervention and an absence of metastatic events during follow-up. These findings suggest that AS may be a reasonable management approach in centers lacking access to molecular testing. However, conclusions regarding long-term safety are constrained by the small cohort and partially retrospective design. Larger prospective studies with extended follow-up and size-stratified outcomes are warranted to clarify the role of AS in Bethesda IV nodules.

Keywords
Bethesda IV; follicular neoplasm; active surveillance; thyroid nodule.
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PS1-10-07

Thyroid artery embolization for large symptomatic goiter in non-surgical candidates a retrospective single center study

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Objectives
Nodular thyroid disease (NTD) may lead to compressive symptoms, particularly when the gland extends into the thoracic cavity. Surgical thyroidectomy is the standard treatment; however, in elderly patients with multiple comorbidities, surgery and general anesthesia carry substantial risks. Radioiodine therapy and minimally invasive ablative techniques may also be limited in patients with large goiters or intrathoracic extension. Thyroid artery embolization (TAE) has emerged as a potential alternative capable of reducing thyroid vascularization and gland volume. This study aimed to describe our institutional experience with TAE as a palliative treatment for symptomatic NTD in patients who were not candidates for conventional therapies.
Methos
We performed a retrospective exploratory study including patients treated with TAE between 2022 and 2025 at a tertiary referral center. Eligible patients had symptomatic benign multinodular goiter with intrathoracic extension, contraindication to radioiodine therapy, or clinical conditions precluding surgery or ablative procedures. Preprocedural evaluation included clinical assessment, laboratory testing, thyroid ultrasound, and computed tomography (CT) to assess gland volume and compressive features. TAE was performed via a transfemoral approach under angiographic guidance, selectively embolizing thyroid arteries supplying the compressive component using polyvinyl alcohol particles. Patients were monitored clinically and biochemically after the procedure, with blood tests on days 4, 10, and 30, and subsequently every 3–6 months. Follow-up CT scans at 6 and 12 months were used to evaluate volumetric changes.
Results
Fifteen patients were included (mean age 79 years; 86% female), with a median baseline thyroid volume of 130.9 mL. Embolization was performed bilaterally in 9 patients and unilaterally in 6. Median hospital stay was 3 days. Minor complications included transient neck pain, hematoma, and hoarseness. Two major cardiovascular events occurred during follow-up, although their causal relationship to the procedure remained uncertain. Thyroid volume decreased significantly to 56.9 mL at 3 months, 63.4 mL at 6 months, and 48.3 mL at 12 months, corresponding to median reduction rates of 45.2%, 51.0%, and 55.0%, respectively ($P < 0.05$). Clinical improvement was observed in 86% of patients at 3 months, with most remaining asymptomatic at final follow-up. Transient hyperthyroidism occurred in 86% of patients early after the procedure but resolved within 30 days. No cases of permanent hypothyroidism were observed.
Conclusions
TAE appears to be a safe and effective minimally invasive option for symptomatic NTD in patients who are not surgical candidates. The procedure achieves substantial thyroid volume reduction and symptomatic improvement while preserving long-term thyroid function. These findings support TAE as a promising alternative in the multidisciplinary management of complex benign thyroid disease, particularly in specialized centers.

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PS1-10-08

Targeted molecular profiling of thyroid nodules using nexthyro 2.0: multicenter validation across surgical specimens and fine-needle aspiration samples

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Objectives
Targeted molecular profiling is increasingly used in the management of thyroid nodules and thyroid cancer, but few panels are optimized for thyroid tumors and applicable to both surgical and cytology specimens. NexThyro 2.0 is a focused DNA/RNA next generation sequencing panel targeting driver mutations, gene fusions and progression-associated alterations in thyroid neoplasia. This multicenter study evaluated its molecular profile and applicability in surgical tissues and fine-needle aspiration (FNA) samples.
Methods
A total of 124 thyroid surgical specimens from four tertiary centers were analyzed, including benign lesions, differentiated and advanced thyroid carcinomas. In addition, 45 thyroid FNA samples were analyzed. Molecular alterations were classified as BRAF-like, RAS-like or non-BRAF/non-RAS. Associations with American Thyroid Association (ATA) risk categories were assessed using Fisher's exact test.
Results
Pathogenic or likely pathogenic alterations were detected in 72/124 tumors (58.1%) with driver events in 62 cases (50%). The most frequent alterations involved NRAS (26.8%) and BRAF (22.0%), followed by TERT promoter mutations (14.6%) and KRAS (10%). Variant allele frequencies ranged from 4-82.5% (median 37.8%). PTCs harbored driver alterations in 26/40 cases (65.0%), predominantly BRAF-like, whereas FTCs most frequently showed RAS-like alterations. RAS-like events included NRAS (26.8%), KRAS (10%), HRAS ($n = 1$) and PAX8::PPARG rearrangements ($n = 2$); PAX8::GLIS1 fusions ($n = 2$) occurred in hyalinizing trabecular tumors. Molecular complexity (≥ 2 pathogenic variants) occurred in 13/72 tumors (18.1%) and was not associated with ATA risk ($P = 0.520$). TERT mutations were enriched in poorly differentiated and anaplastic carcinomas (6/13 PDTCs;1/2 ATCs). In cytology, adequate nucleic acid was obtained in 42/45 samples (93.3%) with alterations detected in 27/42 cases (64.3%).
Conclusions
NexThyro 2.0 reliably detects molecular alterations across thyroid tumor subtypes and performs robustly in both surgical and cytologic specimens, supporting its use for molecular characterization of thyroid nodule.

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PS1-10-09

A multimodal needle detection and tracking algorithm for robotic thyroid biopsy under ultrasound images

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Objectives
Accurate needle visualization during ultrasound-guided thyroid biopsy is critical for procedural safety and diagnostic accuracy. However, needle detection based solely on ultrasound images often shows limited accuracy due to image noise and acoustic artifacts. This study aimed to develop a robotic needle insertion device and a multimodal artificial intelligence algorithm integrating ultrasound imaging and device motion data to improve needle detection during ultrasound-guided thyroid biopsy.
Methods
A robotic device with two degrees of freedom (2-DOF) was designed to control needle angle and depth along the ultrasound imaging plane. A multimodal recurrent neural network was developed by combining YOLOv8 for needle detection in ultrasound images with a Long Short-Term Memory (LSTM) network to incorporate time-series motion data from the robotic device. Optical markers were attached to the device and tracked using an optical tracking system to generate ground-truth measurements of needle tip position and insertion angle. Bench-top experiments using ex vivo porcine tissue simulated ultrasound-guided thyroid biopsy procedures. Model performance was evaluated using the F1 score for needle detection and mean absolute error (MAE) for needle tip position and insertion angle estimation.
Results
Needle detection using ultrasound images alone with YOLOv8 achieved an F1 score of 0.5130. In contrast, the proposed multimodal network significantly improved the F1 score to 0.8969. In addition, the proposed approach reduced the MAE for needle tip position by more than 30% and the MAE for insertion angle by more than 60% compared with the image-only detection model. These results indicate that integrating motion data with ultrasound images improves detection accuracy.
Conclusions
The proposed multimodal needle detection and tracking algorithm combined with a robotic assistive device demonstrates feasibility for improving needle visualization during ultrasound-guided thyroid biopsy. Integration of imaging and motion information may enable safer and more precise biopsy procedures. Future work will focus on developing a motorized device and validating the system in clinical environments.

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PS1-10-10

Endoscopic thyroidectomy vs thermal ablation for symptomatic benign goiter: a multicenter propensity score-matched analysis

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Background/Objectives
Endoscopic thyroidectomy (ET) and thermal ablation (TA) are both minimally invasive alternatives for symptomatic benign goiter, yet direct comparative multicenter data remain scarce. We aimed to compare perioperative safety, volume reduction, and midterm outcomes between ET and TA using propensity score matching (PSM) across four tertiary referral centers.
Methods
This retrospective multicenter cohort study included consecutive adults undergoing ET (TOETVA or BABA) or TA (radiofrequency or microwave ablation) between January 2018 and December 2024 at four institutions, all beyond learning-curve thresholds. After 1:1 PSM on demographic and nodule-specific variables, 496 patients per group were analyzed. Primary outcomes were perioperative complications, hospital length of stay (LOS), and volume reduction rate (VRR) at 6 and 12 months. Secondary outcomes included symptom relief, retreatment rate, and hypothyroidism development. Mixed-effects models accounted for center-level clustering.
Results
ET required longer operative time (127 vs. 26 min; $P < .001$) and LOS (2.0 vs. 0.1 days; $P < .001$). Overall complication rates were comparable (3.2% vs. 1.2%; $P =$ NS). VRR was significantly greater after ET at both 6 months (100% vs. 67%; $P < .001$) and 12 months (100% vs. 81%; $P < .001$). Retreatment/reoperation rates were lower in the ET group (1.6% vs. 12%; $P < .001$). However, ET carried higher rates of permanent hypothyroidism (8% vs. 0.2%; $P < .001$). Treatment effects remained consistent across all centers (P for interaction = NS).
Conclusions
In this multicenter propensity-matched analysis, TA demonstrated perioperative advantages and superior thyroid function preservation, while ET offered more definitive nodule reduction and lower retreatment rates. Nodule size, patient preference regarding thyroid function, and institutional expertise should guide individualized treatment selection.

Keywords
thyroidectomy; thermal ablation; benign goiter; propensity score matching; multicenter.

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Hyperthyroidism 1

PS1-11-01

Subacute thyroiditis in denmark: a nationwide study of 1,763 cases

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Objective
Subacute thyroiditis (SAT) is a differential diagnosis in the clinical care of hypo- and hyperthyroid patients, but large-scale population data on the incidence, patient characteristics, and outcome are limited. Thus, the aim was to determine the incidence of SAT in the Danish population and to characterise patient demographics and the risk of permanent hypothyroidism.
Methods
This retrospective nationwide register-based cohort study included individuals diagnosed with subacute thyroiditis (SAT) at Danish hospitals between 1995 and 2016, covering the years before and after the implementation of mandatory iodine fortification in Denmark as of July 2000. Annual incidence rates of SAT were calculated overall and by geographical region (East and West Denmark). The development of permanent hypothyroidism following SAT was evaluated based on redeemed prescriptions of levothyroxine (L-T4) within a four-year follow-up period.
Results
A total of 1,763 individuals were identified with a diagnosis of SAT among 1,747,168 individuals at risk. The overall nationwide incidence increased from 3.3/100,000 individuals (95% confidence interval (CI): 2.5-4.4) in 1995 to 6.2/100,000 individuals (95% CI: 5.1-7.6) in 2016, with no regional difference ($P = 0.18$). SAT occurred more frequently during summer (incidence rate ratio (IRR): 1.21 (95% CI; 1.07-1.40), $P = 0.004$) and autumn (IRR: 1.31 (95% CI; 1.15-1.50), $P < 0.001$) compared with spring. Follow-up showed that 459 of 1,763 patients with SAT (26.0%) started treatment with L-T4, and in 224 of these patients (48.7%), the duration of L-T4 treatment exceeded 36 months.
Conclusions
In a Danish nationwide cohort, the incidence of SAT increased during a 22-year period without geographical difference. Notably, the frequency of long-term L-T4 treatment was high, emphasising a focus on the post-diagnosis management of patients with SAT.

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PS1-11-02

Phase 3 randomized-controlled trials evaluating efficacy and safety of subcutaneous efgartigimod PH20 using pre-filled syringes in patients with graves' disease inadequately controlled with antithyroid drugs: trials in progress

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Graves' disease (GD) is an immunoglobin G (IgG)-mediated, autoimmune disease with debilitating symptoms and multiorgan complications that impair daily function, significantly diminish patient quality of life (QoL) and cause significant morbidity. In GD, thyroid-stimulating hormone receptor (TSH) IgG autoantibodies (known as TRAbs) chronically stimulate TSHR causing hyperthyroidism which can impact multiple organ systems. The main extrathyroidal manifestation of GD is Graves' orbitopathy/thyroid eye disease. Preferred treatment is antithyroid drugs (ATD), but only ~50% of patients remain euthyroid 1 year after ATD discontinuation. There remains a significant unmet need for therapies that target the underlying GD pathophysiology. Efgartigimod (EFG) is a human IgG1 antibody Fc fragment that selectively reduces IgG by blocking neonatal Fc receptor-mediated IgG recycling. Based on its mechanism of action and the underlying pathophysiology of GD, EFG may provide therapeutic value for GD patients. Two parallel, phase 3 studies will assess EFG efficacy and safety in participants with active GD and suppressed TSH after $\geq$3 months of ATDs. After a screening period ($\leq$5 weeks), ~230 participants will be enrolled to a 24-week, double-blinded treatment period (TP) and randomized 2:1 to receive weekly subcutaneous (SC) EFG (coformulated with recombinant human hyaluronidase PH20 [rHuPH20]) 1000 mg or placebo PH20 SC via pre-filled syringe (PFS). Thereafter, participants will enter a second 24-week TP, dependent on their clinical response at week 24. The study will conclude with an 8-week safety follow-up after the final administration. The primary endpoint is the percentage of participants who are euthyroid and off ATDs at week 24. Key secondary efficacy endpoints include time to euthyroidism off ATDs at week 24, and percentage of participants who are euthyroid off ATDs and TRAb seronegative at week 24. Other secondary efficacy objectives include durability of response, ability to induce remission, impact on health-related QoL and patient-reported outcomes. Safety and tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of the EFG PH20 SC PFS will also be assessed. These parallel trials will explore the potential of EFG to target the pathogenic IgG antibodies underlying GD pathophysiology.

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PS1-11-03

AI-driven computational modelling for patient stratification in molecular radiotherapy: insights from a multicentre hyperthyroidism dataset

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Purpose/Objective
Artificial intelligence (AI) offers advanced computational tools for integrating complex clinical and dosimetric data, supporting improved patient stratification and outcome prediction in molecular radiotherapy. This study aimed to apply AI-based models to identify predictors of therapeutic response in hyperthyroid patients treated with radioactive iodine (RAI).
Materials and Methods
A multicentre retrospective analysis was performed on 1036 hyperthyroid patients treated with RAI across four clinical centres (median follow-up: 21 months; range 0.47–135). Variables included clinical presentation, aetiology, prior anti-thyroid therapy, biochemical markers (TSH, fT3, fT4), administered activity, dosimetric parameters, and outcomes. Data were harmonised into a unified database and z-score normalised using *StandardScaler*. Machine Learning (ML) models included a Random Forest Classifier (RFC) and a fully connected Neural Network (FcNN, Multi-Layer Perceptron) with $\alpha = 10$, three hidden layers (30–10–2 nodes), ReLU activation, *lbfgs* solver, and 1000 iterations. Regularisation was performed using LASSO with built-in cross-validation. Model performance was evaluated via 10-fold stratified cross-validation (*cross_val_predict*, scikit-learn) using confusion matrices and performance metrics.
Results
Absorbed dose, disease subtype, age, sex, basal TSH, and fT4 were identified as key predictors of post-therapy outcome (hypothyroid, euthyroid, hyperthyroid). Best model performance achieved Precision $= 0.91 \pm 0.18$, Accuracy $= 0.89 \pm 0.15$, F1-score $= 0.89 \pm 0.12$, and ROC AUC $= 0.97 \pm 0.03$.
Conclusion
AI-based computational modelling reliably predicts clinical outcomes following RAI therapy in hyperthyroidism. These results support the use of AI for precision-driven patient stratification and personalised optimisation of molecular radiotherapy.

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PS1-11-04

Sex differences in long-term sick leave after graves' disease: a population-based cohort study

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Objectives
Graves' disease (GD) commonly affects working-age adults and may impair long-term work ability. We aimed to investigate sex differences in the risk of long-term sick leave after GD diagnosis.
Methods
This register-based cohort study included patients with newly diagnosed GD from seven Swedish cities during 2003–2005 and matched individuals from the general

population without hyperthyroidism. The outcome was long-term sick leave, defined as >60 consecutive net days. Sex-stratified relative risks (RRs) with 95% confidence intervals (CI) were estimated for different follow-up periods after the index date. Models were adjusted for education level, marital status, comorbidity, sick leave during the year before diagnosis, number of children, and occupational skill level. Analyses were performed for long-term sick leave excluding and including ICD-10 code E05.
Results
GD was associated with an increased risk of long-term sick leave in both women and men, but men showed consistently higher relative risks throughout follow-up. During the first year after diagnosis, the adjusted RR was 4.16 (95% CI 3.37–5.13) in women and 11.66 (95% CI 5.47–24.84) in men. The excess risk remained significantly elevated at 2–5 years after diagnosis in both sexes, again with higher estimates in men than in women.
Conclusion
GD is associated with an increased risk of long-term sick leave, particularly during the first year after diagnosis. Although GD is more common in women, men demonstrated higher relative risks of long-term sick leave. These findings suggest that GD may have a greater impact on work capacity in men and highlight the importance of considering sex differences in the management and follow-up of patients with GD.

Table 1. Relative risk of long-term sick leave (>60 consecutive net days) after Graves' disease.

Follow-up period	Women RR (95% CI)	p-value	Men RR (95% CI)	p-value
Excluding ICD-10 code E05				
Up to 1 year after index date	1.46 (1.06–2.01)	0.022	3.33 (1.04–10.70)	0.043
2–5 years after index date	1.05 (0.88–1.26)	0.573	1.30 (0.85–2.01)	0.229
5–10 years after index date	0.93 (0.77–1.12)	0.457	1.15 (0.74–1.80)	0.529
Including ICD-10 code E05				
Up to 1 year after index date	4.16 (3.37–5.13)	<0.001	11.66 (5.47–24.84)	<0.001
2–5 years after index date	1.29 (1.10–1.52)	0.002	1.72 (1.19–2.49)	0.004
5–10 years after index date	0.98 (0.82–1.18)	0.833	1.15 (0.74–1.80)	0.529

Models were adjusted for education level, marital status, comorbidity, sick leave during the year before diagnosis, number of children, and occupational skill level.

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PS1-11-05

Psychometric evaluation of the mental fatigue scale in patients with graves' disease

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Background
Mental fatigue is common in Graves' disease (GD). In one of our previous studies 89% of hyperthyroid GD patients were classified as having mental fatigue according to the mental fatigue scale (MFS) scores. This scale was constructed for patients with stroke and traumatic brain injury and has high validity in these patient groups. Our clinical experience suggested that symptoms resembling mental fatigue were present also in GD. However, the scale was never evaluated for this patient group.
Methods
We used Item Response Theory (IRT) to evaluate MFS in 199 men and women with GD. Patients completed the MFS at inclusion when still hyperthyroid. Item response theory uses computorized methods to process ordinal data to evaluate the validity of a self-rating scale. The sum score of the 14 items in MFS is intended to measure mental fatigue. A sum score approach assumes that there exist one underlying latent trait (unidimensionality) representing mental fatigue, and that the scale has equidistant steps. In a nonparametric setting, this implies that all pairwise item correlations, as well as each items correlation with the sum of the other 13 items, are strongly positive. This was evaluated by a Mokken scalability analysis. The dimensionality was further investigated by the Automatic Item Selection Procedure. The sum score is an unweighted sum, all items have the same weight, which means that they have the same ability to discriminate between patients regarding the latent trait, mental fatigue (θ). This was evaluated by introducing a parametric probability function where such a weight (also transformed to an amount of relative information for each item) can be estimated. This can further identify non-contributing items (i.e. more noise than information). Item Characteristic Curve is a logistic model with an s shaped curve where X is the latent trait θ and Y the probability of correct response.
Results
Mokken analysis revealed a total scalability of H 0.507 (moderate to strong scale). Scalability increased when item number 14 was removed and increased for every item in Automatic Item Selection Procedure which confirms unidimensionality. The Item Characteristic Curves were better when the answer alternatives with half steps (0, 0.5, 1, 1.5, etc) without text were removed and the answer alternatives were reduced to only alternatives with text.
Conclusion
The MFS is a functioning scale that can be used in GD patients to evaluate the grade of mental fatigue although improved following the above modifications.

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PS1-11-06

Increased formation of neutrophil extracellular traps in hyperthyroidism, but not in hypothyroidism: effects of therapy

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Objectives
Neutrophil extracellular traps (NETs), net-like complexes consisting of DNA, histones and granular proteins released by neutrophils, are involved in venous and arterial thromboembolic events. NETs parameters, including citrullinated histone 3 (citH3), were found to be associated with several cardiovascular and autoimmune disorders. However, the relationship between NETs and blood coagulation in thyroid disorders remains largely unexplored. The objective of this study was to assess plasma citH3 concentrations before and after 3-month therapy of hyperthyroid and hypothyroid patients. We also investigated whether citH3 is associated with prothrombotic and fibrinolytic markers in thyroid disorders.
Methods
31 patients with hyperthyroidism and 29 with hypothyroidism matched for age and sex were recruited along with 29 controls. Patients with acute infections, prior thromboembolic events, chronic inflammatory diseases, or cancer were excluded. Before and after 3-month therapy leading to normalization of thyroid hormone levels, we measured citH3 concentrations using ELISA (Cayman, USA) along with thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and thyroxine (FT4), thrombin generation (using automated thrombogram), fibrinolysis proteins, fibrin clot parameters (including clot lysis time, permeation coefficient), and platelet activation markers.
Results
In hyperthyroid individuals citH3 was 106% and 88% higher than in controls and hypothyroid patients, respectively (both $P < 0.001$), without any significant difference between the 2 latter groups. There were no associations of pre-treatment citH3 with demographic, clinical variables, thrombin generation, fibrin clot parameters and platelet markers in patient groups. Pre-treatment citH3 in patients with hyperthyroidism was strongly associated with FT3 and FT4 ($r = 0.709$, $P < 0.001$ and $r = 0.870$, $P < 0.001$, respectively). Among hemostatic variables in hyperthyroid individuals, the only association was found for citH3 and plasminogen activator inhibitor-1 (PAI-1) antigen ($r = 0.538$, $P = 0.002$), indicating impaired fibrinolysis. In hypothyroid patients, citH3 was not associated with thyroid hormones or any hemostatic variables. Hyperthyroid patients were characterized by a 43% decrease in citH3 after treatment ($P < 0.001$), while no change in citH3 was found in hypothyroid patients in euthyroidism ($P > 0.05$). After treatment, citH3 did not correlate with thyroid hormones or prothrombotic markers in either group.
Conclusions
To our knowledge, the present study is the first to suggest that enhanced NETs formation occurs in hyperthyroid but not in hypothyroid individuals. After successful hormone normalization citH3 had decreased significantly in hyperthyroid patients to values observed in healthy controls. This study hints at novel mechanisms linking NETs with prothrombotic tendency in hyperthyroidism largely via reduced fibrinolysis mediated by PAI-1. Clinical relevance of these findings remains to be established in larger cohort studies.

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PS1-11-07

Real-world comparative outcomes of adjunctive selenium with methimazole vs methimazole alone in filipino patients with graves' disease: a retrospective cohort study

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Background
Selenium plays a fundamental role in thyroid hormone metabolism and antioxidant defense. Evidence regarding its efficacy as an adjunctive treatment for Graves' disease has yielded inconsistent results across different populations.
Objectives
To evaluate the association of adjunctive Selenium supplementation and treatment outcomes, including response, remission rates, time to remission, and adverse events among Filipino patients with Graves' disease.
Methods
This retrospective cohort study involved 240 patients with Graves' disease treated with either Methimazole alone or Methimazole plus Selenium (200 mg/day). Baseline demographic and clinical characteristics were compared between the groups. The primary outcomes measured included time to biochemical remission, remission maintenance at 12 months, relapse within 12 months, and adverse events. Kaplan–Meier analysis and log-rank tests were used to compare the time to remission. An exploratory multivariable Cox proportional hazards regression was performed to identify factors associated with the timing of remission.
Results
Baseline characteristics were similar between groups. All patients achieved biochemical remission during follow-up. Patients receiving Methimazole plus Selenium achieved remission significantly faster than those receiving Methimazole alone (median 13.0 vs 21.7 weeks; log-rank $p < 0.001$). Selenium supplementation was independently associated with earlier remission in exploratory Cox regression (adjusted HR 4.05, 95% CI 3.01–4.45; $p < 0.001$), whereas smoking was associated with delayed remission (HR 0.29, 95% CI 0.21–0.41; $p < 0.001$). Remission maintenance at 12 months and relapse rates did not differ significantly between groups. Adverse events were notably less frequent in the selenium group. (RR 0.29, 95% CI 0.10–0.84; $p = 0.025$), with skin rash as the most common event. No cases of serious adverse events were observed.
Conclusion
Adjunctive selenium supplementation was associated with more rapid biochemical remission and a lower incidence of adverse events; however, it did not significantly influence long-term remission or relapse rates. Selenium may be beneficial in accelerating early biochemical control, although its role in long-term disease modification remains uncertain.

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PS1-11-08

Post-treatment weight dynamics and predictors of excessive weight gain in graves' disease

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Background/Objectives
Hyperthyroidism often causes weight loss, with weight regain common after treatment. However, some patients experience excessive gain, which may impact health. Graves' disease has been suggested as a potential predictor of excessive gain compared with other aetiologies. This study aimed to assess weight changes after treatment initiation and to identify predictors of excessive weight gain in patients with Graves' disease.
Methods
Patients with Graves' disease from a tertiary center were retrospectively included if baseline weight and $>=2$ post-treatment measurements (one at $>=6$ months) were available. Patients were stratified according to maximum weight gain relative to baseline ($>=10\%$ vs. $<10\%$). Weight trajectories during follow-up were analysed, clinical characteristics were compared between groups, and logistic regression was used to identify predictors of excessive weight gain.
Results
A total of 101 patients (83.2% female; mean age 46 years) were included, with a mean usual body weight of 69.9kg (BMI 26.1kg/m^2) and a median baseline weight of 65.5kg (BMI 24.8kg/m^2). All patients started synthetic antithyroid drugs, and only 9 (8.9%) underwent definitive therapy after a mean of 29.6 months. Patients reached a maximum mean weight of 74.9kg (BMI 28.3kg/m^2) after a median of 14.4 months, with a final median weight of 71.4kg (BMI 27.0 kg/m^2) at a mean follow-up of 27 months. The mean maximum weight gain was 5.9% relative to usual weight and 11.8% relative to baseline, while at the end of follow-up, mean gains were 3.5% and 9.6%, respectively. Greater initial weight loss was not associated with subsequent maximum weight gain relative to usual weight. Overall, 60 patients (59.4%) experienced a maximum weight gain $>=10\%$ from baseline, while 41 (40.6%) had $<10\%$ peak gain. Those with $<10\%$ gain maintained a final body weight comparable to their usual (-0.1%), whereas patients with $>=10\%$ gain exhibited an approximate increase of 5.6%. Patients with greater peak weight gain had higher baseline body weight (median[IQR] 68.0[58.9–73.9] vs. 62.0[57.9–68.5]; $P = 0.048$), higher free T4 (median[IQR] 3.3[2.1–5.2] vs. 2.1[1.6–2.9]; $P < 0.001$) and TRAb levels (median[IQR] 11.7[4.2–23.0] vs. 5.1[2.9–14.2]; $P = 0.038$), required longer to achieve thyroid function normalization (median[IQR] 11.3[6.8–16.3] vs. 7.2[4.6–11.0]; $P = 0.001$), and more frequently developed hypothyroidism during treatment (90.0% vs. 70.7%; $P = 0.013$). No differences were observed in baseline metabolic comorbidities or smoking status. In multivariable logistic regression analysis, baseline free T4 levels (Or = 1.67 [95%CI: 1.15–2.42]; $P = 0.007$) and time to normalization of thyroid function (Or = 1.10 [95%CI: 1.01–1.20]; $P = 0.028$) were independent predictors of excessive weight gain.
Conclusions
Greater baseline hyperthyroidism severity and longer time to thyroid function normalization appear to independently predict excessive peak weight gain after treatment. Patients with higher peak weight gain tend to maintain above-usual body weight over time, highlighting the importance of early weight management.

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PS1-11-09

Comparative analysis of fracture risks associated with radioiodine therapy vs antithyroid drugs in patients with graves' disease: a nationwide cohort study

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Objectives
Graves' disease (GD) has been associated with increased bone turnover, reduced bone mineral density, and a consequent rise in fracture risk. However, the impact of different GD treatment modalities on fracture risk remains underexplored. This study aims to bridge this knowledge gap by assessing the fracture risks in GD patients treated with radioiodine therapy (RAI) vs antithyroid drugs (ATD).
Methods
Utilizing the comprehensive Korean National Health Insurance Service-National Health Information Database, our nationwide retrospective cohort study examined GD patients initially totaling 641,203 individuals from the period of 2002 to 2020. We refined our cohort by excluding those with a history of thyroid cancer, prior thyroidectomy, or with follow-up data spanning less than six months. Patients were then categorized based on their treatment regimen: those having undergone RAI therapy were allocated to the RAI group, whereas patients who exclusively received ATD therapy, without any history of RAI treatment, constituted the ATD group. This stratification resulted in 11,607 RAI-treated and 34,821 ATD-only patients. We conducted propensity score matching at a 1:3 ratio based on criteria including age, sex, history of osteoporotic fractures, and the availability of health-check data to ensure balanced comparison groups. To evaluate the risk of osteoporotic, vertebral, and non-vertebral fractures, we performed a robust multivariable Cox proportional hazards model approach, with median follow-up durations of 8.5 years for the ATD group and 8.6 years for the RAI group.
Results
The average age of participants was 44.5 ($\pm$13.7) years, with females representing 66.6% of the study group. After adjustment for confounders, the incidence rates per 1000 person-years for composite osteoporotic fractures were not significantly different, with 48.12 in the ATD group and 45.11 in the RAI group (adjusted HR 0.98, 95% CI: 0.85–1.12). Despite this overall similarity, a more detailed examination revealed treatment-specific disparities: patients receiving RAI exhibited a significantly higher risk of vertebral fractures compared to those on ATD (adjusted HR 1.41, 95% CI: 1.04–1.91). When stratified by gender, the heightened risk of vertebral fractures persisted in the female subset of the RAI cohort (adjusted HR 1.42, 95% CI: 1.03–1.96).

Conclusion
This study indicates that RAI treatment in GD patients does not increase overall fracture risk compared to ATD therapy. However, the specific increase in vertebral fracture risk associated with RAI underscores the need for targeted bone health monitoring and prevention strategies for GD.

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PS1-11-10

Comparison of the efficacy and safety of treatment protocol for graves' disease: a high-dose ptu monotherapy vs. a combination therapy of a low-dose ptu with potassium iodide

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Background
Propylthiouracil (PTU) has been one of the medications for Graves' disease (GD) for more than 70 years. Although its use has declined due to drug-induced liver injury, there is still a need for PTU for patients who cannot be treated with Thiamazole.
Objective
This study aims to compare the efficacy and safety of PTU between high-dose monotherapy and low-dose combination therapy with Potassium iodine.
Methods
This is a retrospective observational study including patients who were newly diagnosed with GD and received PTU as initial therapy between January 2005 and October 2024. Patients who received an initial dose of 300mg of PTU (high-dose group) and those who received 150mg of PTU combined with 50mg of potassium iodide (KI) (low-dose group) were included. The inverse probability weighting method was applied to adjust for confounders.
Results
The final analytical sample consisted of 1170 patients (high-dose: low-dose = 1,132: 38, all female). The median age and follow-up time were 32 years (Interquartile range (IQR):28-36), and 92.9 months (IQR: 46.4-154.9). Median levels of free thyroxine (FT4), TSH receptor antibody (TRAb), and thyroid volume were 4.97ng/dL (IQR:3.67-7.31), 12.4 IU/l (IQR:6.4-26.8), and 28.2 mL (IQR:21.2-38.6), respectively. Adverse effects occurred in 298 patients; 283 (25.0%) were treated with high-dose and 5 (13.6%) were treated with low-dose. Agranulocytosis occurred only in the high-dose group. In the propensity score-matched pair analysis, the FT4 level of the low-dose group at Week 2 was significantly lower than that of the high-dose group ($P = 0.014$). Time to FT4 normalization (35 vs. 45 days) and the prevalence of FT4 normalization in weeks 4 and 8 were not different ($P = 0.26$ and 0.8). The prevalence of inadequate treatment efficacy with the initial dose was significantly higher in the low-dose group (12.8% vs. 35.5%, $P = 0.002$).
Conclusion
The Combination protocol of low-dose PTU and KI demonstrated quicker efficacy in decreasing FT4 level, but a certain percentage of patients may require an increase in the dose. Our results also showed that the low-dose PTU protocol could prevent severe adverse effects related to PTU.

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Hypothyroidism & Autoimmunity

PS1-12-01

Does the use of reflex testing for thyroid function tests (TFTS) – that is only testing FT4 when TSH is out of range, effect the prescribing of levothyroxine (LT4): investigation using general practice level laboratory requests in england

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Objective
There has been a significant growth in LT4 prescribing over the last 20 years, most of which has been of lower dose tablets. Most decisions about initiation and dosing are based levels of TSH and FT4 measured in requested TFTs. We report here an exploratory exercise to determine if there is any difference at general practice level in the way that the amount of TFT data being presented affects the amount/doses of LT4 prescribed.
Methods
Data for total number of TSH(1.179million) and FT4(0.680million) tests in each of 763 GP practices was made available. The number of total FT4 as %total TSH was taken as amount reflex testing. Practices were split into 3-reflex classes by FT4 as % of TSH results in each practice, with High Reflex (<20%FT4+TSH), Moderate (20-79%) and Low (90+%). The actual monthly amount of LT4 prescribed was extracted from publicly reported annual prescribing data. To standardise for age and sex, data in 300 of the 763 GP practices where both prescribed patient demographic and prescribing data were available allowed the actual average prevalence of LT4 used/head of population in prescriptions, mg/prescription and tablets to be calculated for each age group and sex. These population prevalences were then applied to each practice population split by age group and sex to calculate the expected number of prescriptions, total mg and total number of tablets for LT4, % of actual vs expected standardised for the practice population size, sex and age mix.
Results
The laboratory number of TFT tests carried in 2023 was used for 731 general practices with over 2000-registered patients each. The table below reflects the levels of prescribing relative to expected for those practices with different levels of reflex testing. Total number of prescriptions analysed was 3.51million. This shows that when reflex testing is high i.e. often TSH alone, fewer prescriptions are being written, but the total mg LT4 are higher, so on average each prescription is for a higher dose.
Conclusion
Our findings suggest that general practices that are provided with less data (high reflex: TSH alone) are prescribing more LT4 to fewer patients than general practices that receive both FT4+TSH values. Thus, the level of information being provided might be being reflected into their prescribing decisions. We suggest that consideration be given to providing both TSH and FT4 levels to clinicians to enable the most appropriate initiation/adjustment of LT4 dose.

Reflex Level of FT4 % TSH	Number of Practices (% Total)	TFT ratio FT4/TSH	LT4 Prescriptions Actual/Expected	LT4 mg Actual/Expected
High reflex (<20%)	274 (37.5%)	13.7%	90.9%	106.2%
Moderate reflex (20%-89%)	224 (30.6%)	47.3%	96.7%	99.9%
Low reflex (≥90%)	233 (31.9%)	98.3%	98.4%	94.1%

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PS1-12-02

Patient-reported outcomes in liothyronine-treated patients: comparison to patients on levothyroxine-monotherapy

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Objectives
Persistent symptoms in levothyroxine (LT4) treated patients remain a major clinical challenge and have led to increasing use of Liothyronine (LT3) containing therapies.

The Thr92Ala polymorphism in the deiodinase type-2 (DIO2) gene has been proposed as a determinant of treatment response. We examined quality of life (Qol), treatment satisfaction, thyroid hormone profiles, and DIO2 genotype status, in a tertiary thyroid clinic cohort of patients receiving LT3-therapies and compared outcomes to a background community-based cohort of LT4-monotherapy treated patients.
Methods
The LT3 cohort comprised 85 individuals (mean age 56-years, 90% female) who received treatment with LT3-LT4 combination therapy, $n = 47$(55%), LT3 only, $n = 5$ (6%), or Natural Desiccated Thyroid Extracts (NDT), $n = 33$(39%) The background LT4-monotherapy cohort comprised 2071 LT4-treated patients from the community-based Genetics of Thyroid Hormone Replacement (GenThyr) study (mean age 58-years, 85% females). QoL was assessed using the General Health Questionnaire (GHQ-12), Hospital Anxiety and Depression Scale (HADS-A and HADS-D), and Thyroid Symptom Rating Questionnaire (ThySRQ-A and ThySRQ-B). Self-reported satisfaction scores were rated as completely-satisfied, partially-satisfied, or dissatisfied with treatment. Outcomes were compared using non-parametric tests, linear and logistic regression models, and propensity score matching analysis in which LT3 patients were age and sex-matched to LT4-monotherapy controls.
Results
Overall, 83% of LT3-treated patients reported complete or partial treatment satisfaction. Genotype frequencies did not differ between the LT3 and LT4-monotherapy cohorts (10% vs 15% with the homozygous CC variant, $P = 0.46$). QoL scores were worse in younger patients and females but did not differ by treatment (GHQ, HADS-A, HADS-D). Although LT3-treated patients reported a greater frequency of thyroid-specific symptoms (median ThySRQ-A, IQR, 9[7-11] vs. 8[5-10], $P = 0.02$, LT3 vs.LT4), thyroid-specific symptom burden (ThySRQ-B) was similar between LT3 and LT4-treated patients (14 [7–19] vs 12 [7–19]; $P = 0.36$).
Conclusions
The majority of patients receiving LT3-containing therapies reported satisfaction with treatment and had similar QoL scores compared to LT4-monotherapy, although they had more frequent thyroid-specific symptoms. The CC variant of D2 was not enriched among patients on T3.

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PS1-12-03

Practicing double standards: physicians with hypothyroidism treat themselves differently than their patients

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Background
Therapeutic decision-making is a complex process. Physicians' self-treatment choices are informed by their medical training, ongoing education, and clinical experience. Hypothyroidism guidelines allow room for triiodothyronine-containing treatment (LT3CT) if symptoms persist on levothyroxine monotherapy. It is unknown whether physicians' recommendations are the same for themselves as for their patients.
Methods
In the THESIS survey, 534 (13.3 %) of 4019 European thyroid experts reported to have hypothyroidism (HYPO group). Treatment choices for themselves and for their patients, and in the non-hypothyroid physician group (NONHYPO; $n = 3485$) for assumed self-hypothyroidism were surveyed. Links to the online survey were distributed via national professional thyroid or endocrine societies.
Findings
The majority of both HYPO and NONHYPO physicians chose thyroxine as initial treatment for hypothyroid patients (97.6% and 98.6%, respectively, $P = 0.07$). Both HYPO and NONHYPO physicians were more likely to treat patients than themselves with LT3CT (HYPO group: 27.1% vs 16.9%, $P < 0.001$, NONHYPO group: 28.0% vs 16.3%, $P < 0.001$). HYPO physicians were more likely than their NONHYPO counterparts to prescribe thyroid hormones for certain non-thyroid indications, and to prescribe LT3CT for their patients if symptoms persisted in treated hypothyroidism, despite perceiving the persistent symptoms as being of non-thyroidal origin. Of the HYPO physicians, 96 (37.3%) reported fatigue; the presence of fatigue among HYPO physicians was associated with preference for self-treatment with LT3CT (non-fatigued 10.3%, fatigued 27.6%, $P < 0.001$), while similar proportion of non-fatigued and fatigued HYPO physicians prescribed LT3CT for their patients (27.4% and 26.6% respectively).
Interpretation
Thyroid specialists' treatment choices for themselves differed substantially from their recommendations for their patients with hypothyroidism. This raises the possibility that they may offer some patients medications they themselves do not deem appropriate. The generalizability of these findings to other disease contexts remains to be determined.

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PS1-12-04

Thyroid function and autoimmunity in women with breast cancer and breast fibrocystic disease: preliminary results of the mamtir study

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Objectives
Epidemiological studies have highlighted a positive correlation between the prevalence of breast cancer (BC) and benign thyroid diseases, such as goiter, hypothyroidism and autoimmunity, in particular a posi-tivity for anti-thyroid peroxidase antibodies (TPOAb). The MAMTIR study aims to investigate this associa-tion more deeply, from both epidemiological and mechanistic perspectives.
Methods
So far we have recruited in the study 349 total women either undergoing mammographic screening or awaiting surgery for a recent diagnosis of BC (before any neo-adjuvant therapy): 130 with breast cancer (BC) and 219 non-cancer controls including 167 women with benign breast fibrocystic disease (BFD) and 52 women with negative mammography (NEG). Thyroid history and anthropometric measurements were collected, and a blood sample was taken for the dosage of thyroid-stimulating hormone (TSH) and TPOAb. The analysis of TSH concentrations was performed after excluding women taking thyroid drugs. Given the known influence of age and body mass index (BMI) on thyroid function, a multivariate linear regres-sion analysis was also employed, adjusting for these variables.
Results
BC patients, compared to BFD and NEG, were older (mean $\pm$ SD: 61.3 $\pm$ 12.0 vs 48.9 $\pm$ 12.4 vs 54.3 $\pm$ 15.5 years, respectively $P < 0.001$) and had a higher BMI (median [IQR]: 24.1 [22.1–28.1] vs 22.6 [19.9–25.6] vs 23.7 [19.7–26.8] kg/m^2, respectively $P = 0.001$). There was no difference in TPOAb positivity among the three groups of women (13% vs 13% vs 12%, $P = 0.951$). Both BC and BFD patients had higher serum TSH concentrations than NEG women (1.79 [1.37-2.32] vs 1.61 [1.13-2.27] vs 1.43 [0.99-2.01] mIU/l $= 0.007$), independently from TPOAb status. The multivariate analysis adjusted for age and BMI confirmed that BC and

BFD had higher TSH concentrations than NEG in all women ($P = 0.002$) and the subset with TPOAb positivity ($P < 0.001$), but not those who were TPOAb negative ($P = 0.224$).
Conclusions
Preliminary data from the MAMTIR study show higher serum TSH concentrations in women with BC and BFD compared to NEG, particularly among those with TPOAb positivity, independently of age and BMI. The prevalence of TPOAb was similar in all three groups. We can hypothesize that the TSH increase in BC patients is related to possible cell-mediated immunity that may act synergistically with other factors, such as iodine deficiency, a known risk factor for both thy-roid and breast disorders. The recruitment of further patients (study target 496), the analysis of thyroid volume, intra-thyroidal lymphocyte immunophenotyping and the measurement of iodine urinary concen-trations will provide further interpretative elements.

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PS1-12-05

Coronary flow reserve and left ventricular global longitudinal strain in subclinical hypothyroidism: a systematic review and meta-analysis

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Background
Subclinical hypothyroidism (SCH) is associated with an increased cardiovascular risk. Coronary flow reserve (CFR) and left ventricular global longitudinal strain (GLS) are markers of early myocardial and coronary microvascular dysfunction. This study aimed to evaluate CFR and GLS in patients with SCH and to assess the effect of thyroid hormone replacement therapy on these parameters.
Methods
Embase and MEDLINE databases were searched to February 2026 for studies evaluating CFR and GLS in patients with SCH (PROSPERO registration number: CRD420261282776). Risk of bias was assessed using Cochrane criteria (ROBINS-I V2 tool). Mean differences (MD) with 95% confidence intervals (CI) were calculated using random-effects models. Statistical heterogeneity was assessed using the I^2 statistic. Analyses were performed using Review Manager 5.4.1.
Results
Fifteen observational studies were included (1263 patients with SCH and 7579 healthy controls), of which five evaluated CFR and ten evaluated GLS. The mean age of participants ranged from 37 to 73 years; 13 of 15 studies reported a mean age $\leq$50 years. Patients were predominantly female (64%). Patients with SCH had significantly lower CFR compared with euthyroid controls (MD -0.54; 95% CI -0.86 to -0.21; $I^2 = 85\%$). In SCH patients who achieved euthyroidism after levothyroxine therapy, CFR significantly improved from baseline values (MD 0.76; 95% CI 0.10 to 1.41; $I^2 = 50\%$), reaching levels not statistically different from those of healthy controls (MD -0.25; 95% CI -0.85 to 0.34; $I^2 = 24\%$). Patients with SCH also had significantly impaired GLS compared with euthyroid controls (MD 1.51; 95% CI 0.74 to 2.29; $I^2 = 92\%$). In patients treated with levothyroxine who achieved euthyroidism, GLS significantly improved compared with baseline (MD -1.03; 95% CI -1.63 to -0.39; $I^2 = 0\%$), reaching values similar to those of healthy controls (MD 0.45; 95% CI -0.39 to 1.28; $I^2 = 42\%$).
Conclusion
SCH is associated with impaired CFR and GLS, suggesting early coronary microvascular and subclinical systolic dysfunction. Levothyroxine therapy significantly improves both parameters, restoring values comparable to those of euthyroid individuals and supporting the potential reversibility of early cardiovascular alterations in SCH.

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PS1-12-06

Predictive factors of early hypocalcemia and hypoparathyroidism at three months after thyroidectomy

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Introduction
Postoperative hypocalcemia is a common complication after thyroidectomy. In most cases it is transient, but it can also become persistent and clinically relevant. Several factors have been proposed to influence its development, although the literature has not yet reached consensus on the most reliable predictors.
Objectives
To identify predictive factors for postoperative hypocalcemia and hypoparathyroidism three months after thyroidectomy. The main variables analyzed were preoperative serum calcium, thyroid volume, and preoperative cholecalciferol supplementation. Secondary variables included sex, age, body mass index (BMI), type of thyroid disease, surgical procedure, and a diagnosis of osteoporosis.
Materials and Methods
We conducted a retrospective study including 718 consecutive adult patients who underwent total or partial thyroidectomy between 2015 and 2024, followed at the Endocrinology Unit of Varese. Parameters related to phospho-calcium metabolism were collected at three time points: preoperatively, within 72 hours after surgery, and three months postoperatively. Hypocalcemia was defined as serum calcium $\leq$ 8 mg/dl. Associations between clinical variables and outcomes were evaluated using logistic regression models.
Results
The study population was predominantly female (77.6%) with a mean age of 56 years. Postoperative hypocalcemia occurred in 21% of patients. Preoperative serum calcium emerged as the main predictive factor: each increase of one standard deviation (0.4 mg/dl) in serum calcium was associated with a 22% reduction (OR 0.78, 95% CI 0.66-0.91, $P < 0.001$) in the risk of developing early hypocalcemia and a 26% reduction (OR 0.74, 95% CI 0.61-0.90, $P < 0.001$) in the need for calcium supplementation at three months. The inclusion of demographic and clinical variables (sex, age, BMI, thyroid disease characteristics, surgical procedure, and osteoporosis) did not significantly modify this association. Thyroid volume and preoperative cholecalciferol supplementation were not significantly related to outcomes.
Conclusions
Preoperative serum calcium represents an independent predictor of both early postoperative hypocalcemia and persistent hypoparathyroidism three months after thyroidectomy. Optimization of calcium levels before surgery may help reduce the risk of these complications. Further prospective studies are needed to confirm these findings and to define effective preoperative management strategies.

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PS1-12-07

Is there a need for regular sonography control in patients with autoimmune thyroiditis?

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Objectives
The aim of our study was to evaluate the need for regular sonographic follow up in patients with autoimmune thyroiditis in relation to their risk of developing thyroid carcinoma. Evidence on optimal sonographic surveillance in this population is limited. Existing recommendations vary widely, ranging from annual ultrasound examinations in children to no routine imaging in adults with autoimmune thyroiditis.
Methods
Data from 610 randomly selected patients were extracted from our registry (1994 to present). Only individuals with both biochemical evidence and characteristic sonographic features of autoimmune thyroiditis, and without any thyroid nodules at baseline, were included. Follow up was discontinued for any patient in whom a thyroid nodule was detected during routine ultrasound examinations. Statistical analysis was performed using Wilcoxon's test and the Mann–Whitney U test.
Results
A total of 610 patients were included, with a median age of 37 years (range 2–82). The median duration of follow up was 15 years (range 1–31). Baseline TSH was 3.72 mIU/l (0.005–250) and median thyroid volume was 11.0 mL (0.8–55.7). At the final examination, TSH was 2.34 mIU/l (0.005–53.9) and thyroid volume had decreased to 6.3 mL (0.3–45.9). During long term follow up, 67 pseudonodules, 32 benign nodules (confirmed by FNA), and two malignant thyroid nodules were detected. New pseudonodules typically appeared after approximately 14 years of surveillance (median 14; mean 14.3), whereas benign thyroid nodules developed after about 10 years (median 9.5; mean 10.4). One case of papillary thyroid carcinoma was diagnosed after 16 years of regular ultrasound surveillance. One case of histiocytosis was identified by palpation after 19 years.
Conclusions
To our knowledge, this is the first report describing long term follow up of patients with typical sonographic features of autoimmune thyroiditis and no baseline thyroid

nodules. Our findings indicate that hundreds of ultrasound examinations are required to identify a single case of thyroid carcinoma in this population. These results suggest that routine sonographic surveillance in asymptomatic patients is not warranted. As an alternative, extending the interval between ultrasound examinations to approximately 10 years may be reasonable, while also taking into account the preferences and concerns of both patients and physicians.

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PS1-12-08

Quality of life in patients with benign thyroid disease: a population-based cross-sectional study

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Background and Aim
Thyroid diseases are associated with a wide range of symptoms, including cognitive and psychological symptoms, and approximately 10–20% of patients report persistent complaints despite treatment. However, comparative population-based data on long-term quality of life (QoL) across different benign thyroid diseases remain limited. We aimed to assess QoL among patients with different benign thyroid diseases and to compare these outcomes with those of a background population.
Methods
In this cross-sectional study, adults aged 18–65 years residing in the North Denmark Region with benign thyroid disease for at least one year were identified through ICD-10 and ATC codes and invited to participate via secure digital mail (e-Boks) between September and December 2025. Participants completed a questionnaire including self-reported disease type, duration, treatment, and sociodemographic factors. Disease classification was based primarily on self-reported diagnosis, supplemented by ICD-10 and ATC codes. QoL was assessed using the thyroid-specific ThyPRO questionnaire (0-100, higher scores indicate greater symptom burden). Data from a background population without known thyroid disease were also collected. Differences between thyroid disease groups and controls were evaluated using linear regression adjusted for age and sex.
Results
Of 10,671 eligible patients, 4,356 responded to the questionnaire (response rate 40.8%). After exclusions due to history of thyroid cancer, thyroid disease duration <1 year, or incomplete QoL questionnaires, 3,641 patients were included in the analysis. Median age was 54.3 years, median disease duration was 10 years (IQR 5–20), and 88.1% were women. The most common diagnoses were unspecified hypothyroidism ($n = 1{,}329$) and autoimmune thyroiditis ($n = 1{,}081$), followed by Graves' disease ($n = 513$). The control group was drawn from 3,639 individuals without known thyroid disease; 742 responded (response rate 20.4%), and five were excluded, leaving 737 controls (median age 57.0 years; 90.4% women). After adjustment for age and sex, all thyroid disease groups had higher ThyPRO composite scores than controls (all $P < 0.019$). Autoimmune thyroiditis was associated with a 12.8-point higher ThyPRO composite score compared with controls ($P < 0.001$), while Graves' disease and toxic multinodular goitre were associated with increases of 8.6 ($P < 0.001$) and 9.1 ($P < 0.001$) points, respectively. The largest differences between patients and controls were observed in the ThyPRO tiredness and cognitive complaints domains.
Conclusion
Patients with benign thyroid diseases reported lower QoL than the background population, particularly those with autoimmune thyroiditis, highlighting the need for increased clinical attention to persistent patient-reported symptoms.

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PS1-12-09

The association of thyroid status on incidence of chronic kidney disease and CKD progression: the tehran thyroid study (TTS)

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Objective
Thyroid hormones regulate systemic metabolism and renal hemodynamics, yet longitudinal evidence linking thyroid dysfunction to chronic kidney disease (CKD) incidence and progression is limited. This study aimed to investigate the prospective association between thyroid status and the risk of incident CKD and CKD progression in a large population based cohort.
Method
This prospective cohort study included 3,663 adults from the Tehran Thyroid Study, followed for a median of 18 years. Participants were categorized at baseline as euthyroid, overt hypothyroid, subclinical hypothyroid, overt hyperthyroid, or subclinical hyperthyroid based on thyroid function tests. CKD incidence was defined as an estimated glomerular filtration rate (eGFR) <60 during follow up. CKD progression was defined as a $\geq 25\%$ decline in eGFR accompanied by an eGFR <60 in accordance with KDIGO recommendations. Multivariable Cox proportional hazards models were used, adjusting for age sex smoking status physical activity education body mass index systolic blood pressure fasting blood sugar triglycerides highdensity lipoprotein cholesterol and diabetes.
Result
During follow up 873 participants developed incident CKD and 330 met criteria for CKD progression. In the total population, overt hypothyroidism was independently associated with a higher risk of CKD incidence (HR 1.61 95% CI 1.13–2.29) and CKD progression (HR 1.88 95% CI 1.12–3.16). Subclinical hypothyroidism and overt hyperthyroidism were not significantly associated with either outcome. Subclinical hyperthyroidism showed a borderline inverse association with CKD incidence (HR 0.74 95% CI 0.55–1.00). In sex stratified analyses of CKD incidence, associations were predominantly observed in women, with overt hypothyroidism associated with increased risk and subclinical hyperthyroidism associated with lower risk, whereas no significant associations were detected in men.
Conclusion
Overt hypothyroidism is prospectively associated with both the development and progression of CKD, while hyperthyroid states may mask underlying renal dysfunction. These findings highlight the substantial impact of thyroid status on long term kidney outcomes and support consideration of thyroid function in CKD risk assessment and interpretation of renal function measures.

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PS1-12-10

RNASET2 in chronic autoimmune thyroiditis

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Background
Chronic autoimmune thyroiditis (CAT) is characterized by progressive immune-mediated destruction of thyroid tissue. Although some patients remain euthyroid, chronic hypothyroidism may gradually develop following extensive tissue damage. The human ribonuclease T2 (RNASET2) gene exerts pleiotropic functions, including regulation of the immune response and tumor suppression. Experimental data suggest that RNASET2 acts as an alarmin of the innate immune system under specific triggering conditions. Genome-wide association studies have related RNASET2 polymorphisms to susceptibility to autoimmune diseases, including thyroid autoimmune disorders.
Methods
Seventy-five consecutive CAT patients (age, 18-75 years) were recruited at the Endocrine Unit, and classified as spontaneously euthyroids (EU-CAT), untreated hypothyroids (HYPO-CAT), or levothyroxine-treated hypothyroids (LT4-CAT). Age- and sex-matched healthy controls (HC) were included. Assessment included serum TSH, FT4, thyroid autoantibodies, and plasma RNASET2 levels (ELISA).

To determine whether the thyroid gland expresses RNASET2 and could be the source of circulating RNASET2, immunohistochemistry was performed on thyroid tissue microarrays and thyroidectomy specimens derived from an institutional case series; findings were validated by quantitative polymerase chain reaction (qPCR). Statistical analyses were performed using ANOVA with post-hoc tests and Pearson's correlation ($P < 0.05$).
Results
Plasma RNASET2 levels were significantly higher in HYPO-CAT patients (135.8 $\pm$ 36.8 ng/mL) compared to HC (96.6 $\pm$ 13.8 ng/mL, $P = 0.0005$), EU-CAT (92.8 $\pm$ 9.9 ng/mL, $P = 0.0002$), and LT4-CAT (106.1 $\pm$ 9.9 ng/mL, $P = 0.0057$) cohorts. RNASET2 was expressed in follicular and stromal thyroid cells, showing a perinuclear-apical distribution and a granular pattern. Quantitative real-time PCR confirmed the expression of RNASET2. In normal thyroid tissue, RNASET2 was mainly localized to thyrocytes and the follicular lumen, whereas in CAT tissue, RNASET2 expression was predominantly in the cytoplasm of residual follicular and stromal cells (more abundant) with weak colloid positivity.
Conclusions
Plasmatic RNASET2 levels are increased in CAT subjects who recently developed hypothyroidism, suggesting a role in the inflammatory processes which cause thyroid tissue damage and functional decline. Immunohistochemical and quantitative PCR data showed, for the first time, RNASET2 expression in thyroid tissue with a luminal gradient, consistent with the release of this protein in the bloodstream.

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Hypothyroidism 1

PS1-13-01

Dietary habits and supplement use among patients with thyroid disorders: preliminary results from a survey

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Background
diet recommendations are often reported by patients with thyroid disorders (TDs), despite limited supporting evidence. The aim of this survey is to evaluate dietary habits and supplement use among patients with TDs.
Methods
a cross-sectional survey was administered to 224 patients (192 F, 32 M) with TDs, attending a single Center. The questionnaire explored dietary habits and beliefs, supplement use and iodized salt intake. Sources of advice were also recorded. Associations between dietary beliefs and other variables were assessed with chi-square tests.
Results
Median age was 56.5 years (IQR 44.8–66.0). 45/224 patients (20.1%) were advised to avoid specific foods, most frequently soy products (31/45; 68.9%), cruciferous vegetables (9/45; 20.0%) and iodized salt (5/45; 11.1%). Sugar, fried foods, coffee, alcoholics and grapefruit were cited once. Seaweeds were not recommended in 4 patients. Advice mainly originated from internet (13/45; 28.9%) or physicians (12/45; 26.7%). Conversely, 11/224 (4.9%) were advised to consume iodine-rich foods such as fish and seaweeds (7/11; 63.6%), vegetables (3/11; 27.3%) or almonds (1/11; 9.0%). Advice mainly originated from internet (4/11; 36.4 %) or physicians (3/11; 27.3%). 9/224 (4.0%) usually assumed iodine- or selenium-containing supplements; 11/224 (4.9%) used non-evidence-based products, including desiccated thyroid preparations or commercial thyroid-targeted supplements. 33/224 (14.7%) reported not using iodized salt. Concerning dietary beliefs, 77/224 (34.4%) believed that soy should be avoided and 26/224 (11.6%) were uncertain; 14/224 (6.3%) considered gluten contraindicated and 20/224 (8.9%) were uncertain. Patients considering soy contraindicated commonly believed that also gluten should be avoided ($P < 0.01$). No significant associations were found between soy or gluten avoidance and age, sex or disease duration.
Conclusions
this survey highlights the importance of an evidence-based nutritional counselling for patients with TDs to avoid dietary restrictions or unnecessary supplement use. Misinformation appears to be widespread across population, as no association with demographic or clinical variables was observed. We are now recruiting more individuals in order to enlarge the survey sample.

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PS1-13-02

Levothyroxine therapy in older adults increases metabolomic markers associated with alzheimer disease risk

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Background
When to diagnose and treat subclinical hypothyroidism from isolated TSH elevations in older adults remains controversial, as the prevalence of this finding increases with age. Multiple observational studies do not show adverse outcomes with thyrotropin (TSH) <10 mU/l, and treatment trials have not demonstrated significant effects on symptoms. Conversely, overtreatment has been associated with adverse outcomes, including cognitive disorders. Mechanistic understanding of impact of treatment in at risk individuals is needed.
Objectives
Determine the impact of levothyroxine (LT4) on the metabolome in older adults initiating thyroid hormone therapy and compare treatment effects in a large cross-sectional cohort.
Methods
We conducted paired within-person metabolomic analysis of 55 treatment initiators from the Baltimore Longitudinal Study of Aging who had metabolomic profiling before and after LT4 initiation using Biocrates MxP Quant 500 (474 metabolites, 76 pathways). We compared these findings to cross-sectional analysis of treated and untreated individuals using linear regression with Benjamini-Hochberg FDR correction, adjusting for age, sex, BMI, race, education, smoking, and alcohol use.
Results
Among 55 participants initiating LT4 between study visits, TSH at the pre-treatment visit was 6.2 (IQR 4.8-8.1) mU/l compared to 2.1 (IQR 1.2-3.4) mU/l at the post-treatment visit. LT4 initiation was associated with robust metabolic changes: 31 metabolites and 10 pathways achieved FDR<0.05. Top findings included LDH Activity (+34.8%, FDR<0.001), Ornithine Synthesis (+39.6%, FDR<0.001), Arginine Availability (-25.7%, FDR<0.001), lactic acid (+24.4%, FDr = 0.008), and multiple triglycerides (-20% to -30%). Thyroid axis hormones were significantly different in treated participants (FT4 +13% ($P < 0.001$), FT3 -6% ($P < 0.001$), TSH +7% ($P = 0.024$)) compared to untreated participants. Similar but mostly non-significant (after FDR correction) differences were observed in adjusted cross-sectional analysis comparing levothyroxine users ($n = 160$, visit=347) vs euthyroid controls ($n = 755$, visits=1,973). Interestingly, among the 55 transitioning participants, pre-treatment assessments were more central in the range for untreated reference population than post-treatment values.
Conclusions
Thyroid hormone treatment produces coordinated but targeted metabolic reprogramming. Several of the top affected pathways have a strong relevance to cognitive function, for example increased arginine methylation is associated with tau hyperphosphorylation and reduced availability may contribute to cerebrovascular dysfunction in Alzheimer's Disease. These data provide a potential mechanism for observations that overtreatment is associated with cognitive disorders, supporting the need for further research to guide patient-centered decision-making.

Feature	Paired % Change	Paired FDR	X-section Delta Rx	X-section FDR	Alzheimer Disease Pattern
LDH Activity	+34.8%	0.0002	+0.7%	0.68	Elevated
Ornithine Synthesis	+39.6%	0.0004	+1.8%	0.84	
Arg Availability	-25.7%	0.0004	-8.3%	0.19	Lowered
NOS Activity	+25.6%	0.0016	+8.0%	0.35	
Homocysteine Synth.	+17.2%	0.0025	+6.2%	0.35	Lowered
Sum Arg Methylation	+24.5%	0.0060	+10.3%	0.16	Elevated
Symm. Arg. Met.	+27.6%	0.0060	+15.7%	0.05	Elevated
Cit Synthesis	-11.5%	0.0084	+3.5%	0.55	
Asym.Arg.Methyl.	+21.0%	0.0092	+4.4%	0.59	Elevated
OTC Deficiency	+12.1%	0.0101	-2.7%	0.64	

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PS1-13-03

Analysis of greater manchester population health records (2011–2024) to establish patient-level drivers of increased levothyroxine (LT4) prescribing and the consequences for levothyroxine cessation on thyroid hormone profile

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Objective

Levothyroxine (LT4) prescribing rates have risen dramatically in England, with community prescriptions increasing from 9 million annually in 2000 to 30 million in 2024. Understanding the clinical outcomes of patients who discontinue treatment, particularly those on low LT4 doses, can inform as to the causes of this rise.

Methods

This study utilised patient-level primary care data from the Greater Manchester Care Record (GMCR) between 2010 and 2024, encompassing 2.85million patients with recorded thyroid function tests (TFTs) and LT4 prescriptions.

Dose Classification

A cut-off of an average prescribed LT4 of 80 mg/day was derived from the recommended 1.6 mg/d/kg and BMI to distinguish between patients on lower doses (<80 mg/day) and those on higher doses (>= 80 mg/day).

Cohort Definition

Patients with prescriptions for LT4 were included, who started LT4 medication during the period 2011-2023. Codes for other thyroid disorders, including thyrotoxicosis, were excluded.

Results

In the period 2011-2023 of the total 1,097,586 population with recorded TFT results, 106,117 received LT4.

Treatment Growth

The number of patients prescribed LT4 in GMCR increased from 45,553 in 2011 (17.0/1,000 population) to 83,863 in 2023 (28.3/1,000 population), representing an Annual Average Rate of Increase (AARI)=4.4%. Low doses (<80 mg/day) grew significantly faster (AARI=7.9%) than higher doses (>=80 mg/day, AARI=2.2%). The largest increases were observed in older individuals (80+ years) and in males for both dose categories.

Cessation

Of 58,070 patients who started LT4 post-2010, 5,100 stopped medication and had subsequent TFTs available. Patients who stopped had a significantly lower median dose (50mg/day (Interquartile Range (IQR) 43-57mg/day) compared to those who continued (76mg/day (IQR 68-84mg/day) and were on low doses (<80 mg/day) more frequently (75.4% vs 56.4%). Median age at diagnosis for those who stopped was 45 years, lower than those who continued at 49 years). Median duration on medication for low-dose patients who stopped was 12-months. TFT Outcomes Post-Cessation: Thyroid stimulating hormone(TSH) remained within reference range post-treatment for 56% of patients who had stopped vs 52% when treated. % within reference range for FT4 was unchanged post-discontinuation at 80% ie they had a euthyroid FT4 off thyroid-replacement.

Conclusion

LT4 use increased by two-thirds over a 12-year period, primarily driven by broadening of prescribing patterns to specific patient groups, notably those started on very low doses/older individuals/males. A significant subset of patients-those started on lower doses of LT4, successfully discontinued treatment and maintained euthyroidism. This suggests that initial elevation of serum TSH may have been transient.

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PS1-13-04

Nationwide epidemiology and genetics of congenital hypothyroidism in finland: enriched genetic variants in CHR15-STR, TPO and SLC26a7

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Objective

To investigate the genetic etiology and phenotypic spectrum of primary congenital hypothyroidism (CH) in Finland.

Methods

Whole-exome sequencing was performed for a newly recruited cohort of 109 CH patients. Clinical data were collected retrospectively from medical records. Protein-coding variant analysis for all patients and copy number variant analysis for select individuals were performed. Sanger sequencing was done to identify a known pathogenic variant in the short tandem repeat (STR) non-coding region of chromosome 15 and to validate identified variants in patients and family members. Variants identified in the new cohort and a previously published CH cohort of 52 patients were used to evaluate genetic prevalence and other phenotypic associations in the Finngen database. Selected variants of uncertain significance (VUS) were functionally characterized.

Results

A genetic basis for CH was identified in 82% (n = 45/55) of familial and 13% (n = 14/106) of sporadic cases. Overall, ~36% (n = 59/161) of the patients harbored a pathogenic variant in across 6 genes and one non-coding region, listed in descending order of prevalence: STR (23.7%), *TPO* (23.7%), *SLC26A7* (16.9%), *PAX8* (15.2%), *TG* (11.8%), *TSHR* (5%) and *NKX2-1* (3%). Among the variant carriers, 75% had familial CH and 25% sporadic CH. VUS were additionally identified in *TPO, TG, DUOX1, DUOX2, SLC26A4* and *NKX2-5*. Preliminary functional assay data for *TPO* and *DUOX2* VUS showed impaired protein activity. Autosomal recessive inheritance predominated, consistent with the genetically isolated Finnish population. Thyroid imaging in variant carriers showed 10 gland in-situ (*TG, TPO*, STR), one goiter (*TPO*), one aplasia (STR) and two hypoplasia (STR). STR variant carriers frequently had only moderately elevated TSH at neonatal screening with free T4 within the reference range, resembling TSH-resistance. Levothyroxine treatment was initiated at an older age or temporarily discontinued in a subset of STR variant carriers due to uncertain screening diagnosis (6/14 cases). STR variant carriers also manifested subclinical hypothyroidism and gestational hypothyroidism.

Conclusions

Next-generation sequencing approach incorporating the STR region could identify the genetic basis of CH in nearly all familial Finnish CH cases. Population-level enrichment of variants in STR, *TPO* and *SLC26A7* was observed. STR variant frequently causes a milder CH phenotype with increased risk of missed neonatal screening or delayed diagnosis of CH.

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PS1-13-05

Prescribing of thyroid hormones in euthyroidism: aggregate data from a european survey of thyroid specialists

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Background
The THESIS (Treatment of Hypothyroidism in Europe by Specialists: An International Survey) collaboration has documented differing patterns in the use of thyroid hormones (TH) for individual non-hypothyroid indications across Europe. This aggregate analysis aims to further explore TH prescribing patterns in euthyroidism.
Methods
We performed an aggregate analysis of responses from 5,695 European thyroid specialists across 28 countries. Respondents were queried regarding their willingness to prescribe TH in biochemically euthyroid patients for six specific clinical scenarios: female infertility with positive thyroid peroxidase antibodies (TPOAb), simple goitre enlarging over time, unexplained fatigue, treatment-resistant depression (TRD), hypercholesterolemia and obesity. Multivariable Poisson regression was used to identify independent predictors of prescribing breadth.
Results
A substantial proportion of European specialists would consider TH therapy for euthyroid patients for at least one euthyroid indication (53.3%), most commonly for female infertility associated with elevated TPOAb (42.8%) and for enlarging simple goitre (28.0%). Prescribing for other indications was less common; unexplained fatigue (7.5%), TRD (6.1%), hypercholesterolemia (5.8%) and obesity (5.1%). Hierarchical clustering identified two distinct prescribing phenotypes: an infertility/goiter cluster and an obesity/fatigue/hypercholesterolemia cluster. In multivariable models, independent predictors of an individual thyroid specialist prescribing TH for three or more euthyroid indications (high volume prescribers) included older physician age ($P = 0.034$), practice location in Eastern Europe (IRR 1.13; $P < 0.001$), and lower Gross National Income per capita (GNIPC) ($P < 0.001$).
Conclusions
Our analysis has identified three novel findings. Firstly, a significant minority of European thyroid specialists prescribe TH for multiple euthyroid indications, with alarmingly high frequency in some European countries. Secondly, prescribing for euthyroid indications cluster around female infertility associated with elevated TPOAb/simple goiter and obesity/fatigue/hypercholesterolaemia. Thirdly, these practitioners tend to be older and practice in low income Eastern European countries. In multivariable Poisson regression, each $1,000 USD increase in gross national income per capita (GNIPC) was associated with a 0.3% decrease in the expected number of accepted euthyroid indications (IRR 0.997; 95% CI 0.996–0.998; $P < 0.001$). Across the $81,130 range of national income in the dataset, this translates to a 2.2-fold difference in prescribing breadth between lowest and highest-income countries. Eastern European physicians had a 13.2% higher expected number of accepted indications compared to their Western European counterparts (IRR 1.13; 95% CI 1.08–1.18; $P < 0.001$). The underlying drivers for these physician practices are unclear and likely to be complex, but our data highlight that socioeconomic factors may be important.

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PS1-13-06

FAT mass reduction independently predicts TSH changes after sleeve gastrectomy

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Objectives
Obesity is associated with mildly elevated thyroid-stimulating hormone (TSH) levels, yet the underlying mechanisms remain unclear. While weight loss after bariatric surgery influences thyroid homeostasis, whether these changes relate to total weight loss or body composition alterations is uncertain. The role of adipose tissue reduction in mediating thyroid function changes has not been fully clarified. This study evaluated thyroid function changes after sleeve gastrectomy and investigated the relationship between TSH changes and body composition parameters, focusing on the independent effect of fat mass reduction.
Methods
Patients who underwent sleeve gastrectomy between 2020 and 2025 were retrospectively screened. Among 170 patients, those with thyroid function tests and bioelectrical impedance analysis (Tanita) measurements before surgery and at postoperative follow-up were included. Patients with thyroid dysfunction, positive autoantibodies, or levothyroxine treatment were excluded, yielding 61 patients for analysis. Serum TSH and free thyroxine (fT4) were assessed preoperatively and at 6 months postoperatively. Changes in body weight, fat mass, visceral fat mass, fat-free mass, and muscle mass were calculated. Associations between ΔTSH and body composition changes were evaluated using Pearson correlation. Multivariable linear regression adjusted for age and sex determined whether fat mass reduction independently predicted TSH changes.
Results
Significant reductions occurred in body weight, fat mass, visceral fat mass, muscle mass, and fat-free mass (all $P < 0.005$). Mean TSH decreased from 2.4 ± 1.1 to 1.8 ± 0.8 μIU/mL at 6 months ($P = 0.005$), while fT4 remained unchanged ($P = 0.923$). ΔTSH correlated significantly with changes in fat mass ($r = 0.421$, $P = 0.004$), total weight ($r = 0.361$, $P = 0.015$), and visceral fat ($r = 0.299$, $P = 0.046$), but not with muscle mass or fat-free mass changes. In multivariable regression, fat mass reduction independently predicted ΔTSH after adjusting for age and sex ($\beta = 0.452$, $P = 0.007$).
Conclusions
TSH levels significantly decrease after sleeve gastrectomy, with this reduction more strongly associated with fat mass decrease than overall weight loss. Fat mass reduction independently predicts TSH changes, suggesting adipose tissue plays an important role in obesity-related thyroid function alterations.

Table 1. Changes in thyroid function and body composition after sleeve gastrectomy.

Parameter	Baseline ($n = 61$)	6 months ($n = 61$)	p value (0–6 months)	p value (0–12 months)
TSH (μIU/mL)	2.4 ± 1.1	1.8 ± 0.8	**0.005**	**0.005**
fT4	15.8 ± 2.2	15.7 ± 1.9	**0.923**	**0.817**
Weight (kg)	115.9 ± 18.4	84.2 ± 12.7	**0.000**	**0.000**
BMI (kg/m^2)	42.5 ± 4.9	30.8 ± 4.3	**0.000**	**0.000**
Fat mass (kg)	51.0 ± 1.2	27.8 ± 9.1	**0.000**	**0.000**
Visceral fat mass (kg)	15.0 (7–35)	7.0 (1–20)	**0.000**	**0.000**
Fat-free mass (kg)	64.6 ± 11.6	56.5 ± 9.3	**0.000**	**0.000**
Muscle mass (kg)	61.5 ± 11.0	53.6 ± 8.8	**0.000**	**0.000**
Metabolic age	47 ± 10.8	40.9 ± 10.8	**0.000**	**0.000**

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PS1-13-07

Association between GUT microbiome composition, autoimmune activity in hashimoto's thyroiditis, and the effects of a flavonoid-rich diet

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Objectives
The gut-thyroid axis represents an important pathway linking intestinal microbiota with immune regulation in autoimmune thyroid diseases. Emerging evidence suggests that dietary polyphenols, particularly flavonoids, may beneficially modulate gut microbiota composition and reduce inflammatory processes. This study aimed to evaluate the association between gut microbiome composition and autoimmune activity in Hashimoto's thyroiditis and to investigate the potential effects of a flavonoid-rich diet on microbiome balance and thyroid autoantibody levels.
Methods
In this prospective observational study, 80 patients with confirmed Hashimoto's thyroiditis and 40 healthy controls were enrolled. Patients with Hashimoto's thyroiditis followed a structured diet enriched in flavonoid-containing foods (including berries, citrus fruits, dark leafy vegetables, cocoa, green tea, and legumes) for 12 weeks. Thyroid function parameters, including serum thyroid-stimulating hormone (TSH), free thyroxine (fT4), and thyroid autoantibodies (anti-thyroid peroxidase [TPOAb] and anti-thyroglobulin [TgAb]), were measured at baseline and after the dietary intervention. Stool samples were

collected at both time points and analyzed using 16S rRNA gene sequencing to determine gut microbiota composition. Alpha and beta diversity indices were evaluated, and correlations between microbial taxa abundance and thyroid autoimmunity markers were analyzed.
Results
At baseline, patients with Hashimoto's thyroiditis demonstrated significantly reduced microbial diversity compared with healthy controls ($P < 0.05$), characterized by increased relative abundance of pro-inflammatory genera such as Prevotella and Escherichia/Shigella, and reduced levels of beneficial commensals including Lactobacillus and Bifidobacterium. Following the 12-week flavonoid-rich dietary intervention, significant improvements in gut microbiome diversity were observed ($P < 0.05$). The relative abundance of beneficial bacteria, particularly Bifidobacterium and Lactobacillus, increased, while pro-inflammatory taxa decreased. These microbiome changes were accompanied by a significant reduction in thyroid autoantibody titers, including TOAb and TgAb ($P < 0.05$). Higher baseline TOAb levels were positively correlated with Prevotella abundance ($r = 0.41$, $P < 0.01$) and negatively correlated with Bifidobacterium levels ($r = -0.36$, $P < 0.05$). Improvement in microbial diversity after the intervention was associated with a reduction in antibody levels.
Conclusions
Gut microbiome dysbiosis is linked to autoimmune activity in Hashimoto's thyroiditis and may be partly improved through diet. A flavonoid-rich diet was associated with greater microbial diversity, more beneficial bacteria, and reduced thyroid autoantibodies, suggesting dietary flavonoids may help modulate the gut–thyroid axis and support immune balance, pending confirmation in randomized trials.

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PS1-13-08

Clinical predictors of levothyroxine discontinuation in primary hypothyroidism: a prospective study

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Objectives
The optimal duration of thyroid hormone replacement in patients with primary hypothyroidism remains unclear. We aimed to identify clinical factors associated with successful discontinuation or dose reduction of levothyroxine (LT4) therapy.
Methods
This prospective study enrolled patients with primary hypothyroidism who agreed to participate. After maintaining a stable LT4 dose for more than one year, LT4 was gradually tapered by 12.5–25 μg/day over three months, and the patients were observed for two years from the start of tapering. Serum free thyroxine (free T4) and thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), thyroid ultrasonography, and clinical symptoms were assessed at diagnosis, immediately before tapering, and at 2 years after tapering.
Results
Among 77 patients, 27 patients (35.1%) successfully discontinued LT4 (T4-Discontinued) and 20 patients (26.0%) achieved dose reduction (T4-Reduced), whereas the remaining 30 patients (38.9%) did not reduce their LT4 dose (T4-Unchanged). Median TSH at diagnosis was 40.3 (10.6–108.9) mIU/l in the T4-Unchanged group, 22.6 (10.8–84.1) mIU/l in the T4-Reduced group, and 15.5 (7.4–59.8) mIU/l in the T4-Discontinued group; although TSH tended to be higher in the T4-Unchanged group, the difference was not statistically significant. The stable LT4 dose at the time of tapering was lower in the T4-Discontinued group than in the T4-Unchanged group (50.0 μg/day vs. 67.8 μg/day, $p = 0.001$). The T4-Discontinued group more frequently showed homogeneous echogenicity on ultrasonography and had lower TPOAb positivity at diagnosis and at tapering. Predictors of failure to reduce LT4 dose were TPOAb positivity at diagnosis (OR 2.9; 95% CI, 1.02–8.60), TPOAb positivity at tapering (OR 5.14; 95% CI, 1.35–19.61), and heterogeneous echogenicity at tapering (OR 10.07; 95% CI, 1.23–82.40).
Conclusions
TPOAb positivity at diagnosis and before tapering, as well as thyroid ultrasonographic findings at tapering, may help predict the likelihood of successful LT4 dose reduction or discontinuation in patients with primary hypothyroidism.

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PS1-13-09

Prevalence of hypothyroidism in the danish blood donor study and characterization of biomarkers: a population-based case–control analysis

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Objective
Hypothyroidism is a common endocrine disorder, yet biomarker patterns at the time of diagnosis are not well characterized in large population-based cohorts. We aimed to estimate the prevalence of hypothyroidism in the Danish Blood Donor Study (DBDS) and examine differences in biomarkers, lipid profiles, and lifestyle factors between hypothyroid cases and euthyroid controls.
Methods
Cases of hypothyroidism were identified based on levothyroxine (LT4) prescriptions. Individuals diagnosed with thyroid cancer, hyperthyroidism, non-toxic goitre, or thyroid surgery were excluded. Each case was matched with four controls by sex and age at time of diagnosis. Controls were defined by not having a thyroid-related diagnosis and not being treated with LT4. Biomarker levels, lipid profiles, and lifestyle variables from time-relevant questionnaires were compared between cases and controls using appropriate statistical tests.
Results
The final cohort consisted of 10,315 individuals, including 2,063 hypothyroid cases and 8,252 euthyroid controls matched by sex and age at time of diagnosis. Cases were predominantly female (84.7%), with a mean age of 44.4 years (median 43.6 years) at time of diagnosis. When compared against the total pool of available controls, the prevalence of hypothyroidism was 1.86%. At diagnosis, hypothyroid cases showed markedly higher thyroid-stimulating hormone (TSH) levels compared with controls (median 7.59 vs 1.58 mIU/l, $P < 0.001$) and lower thyroid hormone levels, including free thyroxine (FT4; median 11.4 vs 14.2 pmol/l, $P < 0.001$) and free triiodothyronine (FT3; median 4.00 vs 4.20 pmol/l, $P < 0.001$). Autoimmune activity was reflected by substantially elevated thyroid peroxidase antibody levels (median 277 vs 12 $\times 10^3$ IU/l, $P < 0.001$). Cases also show lipid metabolic differences, including higher triglycerides (median 1.20 vs 1.16 mmol/l, $P = 0.029$), total cholesterol (median 5.30 vs 5.00 mmol/l, $P < 0.001$), and LDL cholesterol (median 3.00 vs 2.80 mmol/l, $P < 0.001$). No significant differences were observed for HDL cholesterol, VLDL cholesterol, TSH receptor antibodies, or self-reported BMI.
Conclusions
In this large population-based cohort, hypothyroidism occurred predominantly in women and at time of diagnosis was associated with clear differences in thyroid function markers, autoimmune activity, and altered lipid metabolism at the time of diagnosis. These findings provide insight into early biological changes associated with hypothyroidism in otherwise healthy individuals.

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PS1-13-10

Optimal computation of combined LT4 + LT3 replacement therapies for primary hypothyroid patients individualized by sex, height & weight

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Objectives
Primary hypothyroidism is typically treated with single-hormone replacement using LT4, a fraction of which is converted to thyromimetically active T3 in tissues. This standard works well in most patients but fails to fully normalize TH levels or alleviate symptoms in ~15% of patients. Combination replacement therapy, with LT3 added to LT4 in daily dosing, better mimics thyroid hormone secretion, and is becoming increasingly utilized in clinical practice. Regional thyroid associations provide general guidance for combination dosing, with quantitative dosing regimens for replacement hormone in different patient populations are under investigation. We developed computational algorithms and user-friendly clinical software for optimizing combination LT4 + LT3 replacement therapy in hypothyroid patients, tailored to a patient's sex, height (H), weight (W) and hormone values: TSH, FT4 and FT3 or total T3.

Methods
The project builds on an updated version of p-THYROSIM, an individualized patient model for simulating thyroid hormone dynamics previously fitted and validated using published data from 655 patients; and a published method for computing residual thyroid function (RTF) analyzing 13 large clinical study data sets. Algorithms were devised for optimizing combination dosing using ~400 p-THYROSIM simulations fitted to ranges of residual thyroid function (RTF) estimates in simulated male and female individuals, for different Ws and Hs.
Results
Computed combined dosages in available pill sizes were implemented into a user-friendly software package (app), separately for both sexes, with BMIs ranging from ~ 15 to 40. The app computes dosages based on patient H, W and serum hormone concentrations provided as input data. Findings showed that both W and H affect dosing in a nonlinear manner. Sex had minimal impact on RTF computations and dosing recommendations. Optimal simulations of both LT4 monotherapy and combination LT4 + LT3 therapy indicated that LT4 alone does not normalize FT3 in plasma even with additional LT4.
Conclusions
In simulated same-BMI patients, different H & W combinations produced markedly different RTF values, leading to more accurate dosing predictions based on body size. LT4 monotherapy did not normalize FT3 as well as combination therapy, especially for heavier patients.

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Pregnancy & neonatal thyroid function

PS1-14-01

Apgar score in children born to mothers with thyroid disease: a systematic review and cohort study

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Introduction
Thyroid hormones are important regulators of fetal development, and the fetus is dependent on maternal thyroid hormones during pregnancy. Thus, abnormal levels in pregnancy are a concern, and a hypothesis of fetal programming by maternal thyroid disease is proposed. The hypothesis considers long-term outcomes of the child, however, evidence on the impact of maternal thyroid disease on the child at birth is important to substantiate the underlying mechanisms. We aimed to review the existing literature on the association between maternal thyroid disease and child Apgar score and to conduct a cohort study on the association within the Danish population.
Methods
A systematic review of original articles on maternal thyroid disease and Apgar score following PRISMA guidelines was conducted using PubMed, Embase, and Cochrane. Two independent authors assessed eligibility and methodological quality. A cohort study was conducted including all singleton live-births in Denmark from 1999-2015 (n = 1,004,475). Maternal hyper- and hypothyroidism were defined by hospital diagnoses and drug prescriptions, and Apgar score at 5 min after birth was retrieved from the Medical Birth Registry. The association between maternal thyroid disease and low Apgar score (<7) was calculated by logistic regression (adjusted odds ratio (aOR) with 95% confidence interval (CI)).
Results
In the review, 308 articles were screened and 9 were included. Heterogeneous definitions of maternal thyroid disease and reporting of Apgar score limited comparability. No articles on maternal hyperthyroidism met eligibility criteria. Findings regarding maternal hypothyroidism were inconclusive. In the cohort study, low Apgar score was found in 0.76% of non-exposed children and 0.82% of children exposed to maternal hyperthyroidism (aOR 1.04 (CI 0.83-1.32)). Children of mothers with hypothyroidism more often had low Apgar score (1.10%) as depicted by a higher risk (1.34 (CI 1.11-1.62)), especially when untreated in the pregnancy (2.07 (CI 1.38-3.10)).
Conclusion
Literature on the association between maternal thyroid disease and child Apgar score was inconclusive. In a large cohort study, maternal hypothyroidism, was associated with low Apgar score of the child, pointing towards a role of untreated maternal hypothyroidism in pregnancy.

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PS1-14-02

Do maternal zinc and copper status affect neonatal thyroid metabolism?

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Introduction
Microelement status in pregnancy, particularly iodine, iron, and selenium (Se), is crucial in thyroid metabolism and proper fetal development. However, the impact of zinc (Zn) and copper (Cu) on neonatal thyroid homeostasis remains poorly understood. Both Cu and Zn are constituents of essential enzymes and structural proteins and contribute to removing reactive oxygen species (ROS) through superoxide dismutase (Cu/Zn-SOD) activity. Similarly, glutathione peroxidase 3 (GPx3) is a Se-dependent enzyme involved in ROS degradation and antioxidative protection.
Materials and methods
A total of 114 women in their third trimester of pregnancy and 93 of their newborns were recruited from the obstetric department of a tertiary referral center in Poland before delivery. Maternal blood serum and neonatal cord blood samples were collected for analysis. Micronutrient status was assessed using Total Reflection X-ray Fluorescence (S4 T-STAR spectrometer Bruker Nano GmbH, Berlin, Germany). The activity of GPx3 was measured using a coupled enzyme assay with tert-butyl hydroperoxide as the substrate. Thyroid parameters were measured in mother-newborn pairs, while neonatal thyroid-stimulating hormone (TSHs) concentrations were obtained from dried blood spots during routine screening tests at 2-5 days of life.
Results
Newborns had higher Zn and lower Cu concentrations than their mothers (P < 0.0001). Maternal and newborn Zn levels were positively correlated (r = 0.37, P < 0.0001). Maternal Cu exhibited a bimodal distribution, with 51% below and 41% above the normal range. Maternal Zn correlated with neonatal free triiodothyronine (fT3) and free thyroxine (fT4) (r = 0.39, P = 0.01 for both), whereas maternal Cu with neonatal fT4 (r = 0.34, P = 0.03). A relationship was found between maternal trace element levels and TSHs (Zn: r = -0.37, P < 0.001; Cu: r = -0.25, P = 0.01). Maternal GPx3 activity was negatively correlated with TSHs (r = -0.28, P < 0.01) and was lower in Zn-deficient mothers compared to those with normal Zn levels (P < 0.01). Linear regression showed that both Cu [β = 0.02 (95% CI: 0.01 – 0.03)] and Zn [β = 0.07 (95% CI: 0.04 – 0.09)] were associated with increased GPx3 activity (P < 0.0001).
Conclusions
Adequate concentrations of Cu, Se, and Zn during gestation may help reduce oxidative stress in mothers and support the regulation of thyroid hormone feedback mechanisms in newborns during the early postnatal period. Further research is required to explain the differences in the placental transfer of these micronutrients.

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PS1-14-03

The impact of autoimmune thyroiditis on the outcomes of *in vitro* fertilization

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Objective
Hypothyroidism of autoimmune etiology is associated with an increased risk of unsuccessful *in vitro* fertilization attempts. The aim of this study was to compare IVF outcomes in patients with hypothyroidism who had positive and negative antibody titers.
Method
The first group included 46 women with AIT. The second group included 74 patients with hypothyroidism without autoimmune thyroiditis. Thyroid status and ovarian reserve were assessed, and general clinical and laboratory tests included in standard pre-IVF protocols were performed.
Results
Following treatment aimed at improving thyroid function, spontaneous pregnancy occurred in 7 (15.2%) women from the first group and in 25 (33.8%) from the

second group; the remaining women were referred to IVF programs. Among them, IVF cycles were unsuccessful in 15 (32.6%) women from the first group and 11 (14.9%) from the second group. In the group of women with AIT, repeated IVF attempts were three times more common than in women with hypothyroidism without AIT. All patients with unsuccessful IVF outcomes had reduced levels of serum ferritin (8.2 ± 2.3 ng/mL) and inhibin B (44.4 ± 12.3 pg/mL). In patients with AIT, AMH was lower (1.3 ± 0.3 ng/mL) than in the second group (1.8 ± 0.6 ng/mL).

Conclusion

In women with AIT, the likelihood of becoming pregnant is reduced due to the effect of antibodies on ovarian reserve. Additionally, patients with hypothyroidism have an increased risk of anemia, regardless of the presence of antibodies, which also negatively affect conception.

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PS1-14-04

Transient thyrotoxicosis in relation to nausea and vomiting symptoms and hyperemesis gravidarum

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Background

Data on the possible association between (transient) thyrotoxicosis (FT4 and TSH outside trimester specific 2.5th-97.5th percentiles, TT) and nausea/vomiting symptoms during pregnancy (NVP) and hyperemesis gravidarum (HG) are inconclusive, mostly to be explained by methodological issues: assessment of NVP, definition of HG, time of assessment. The current study investigated a possible association between NVP / HG and TT, adjusting for confounders (hCG, depression).

Methods

2033 healthy pregnant women, participating into the HAPPY-study, completed at 12 and 32 weeks gestation the adapted 4-item Pregnancy-Unique Quantification of Emesis scale (PUQE-scale, range 0-16) and the 10-item Edinburgh Depression Scale (EDS, range 0 – 30), simultaneously with assessment of TSH, FT4, TPO-Ab and hCG.

Results

At 12 weeks, there were 17 (0.8%) women with TT (none were TPO-Ab positive) and at 32 weeks 11 (0.5%) women (one TPO-Ab +) had TT. Throughout pregnancy, in total, there were 25 women with TT and 1700 women who remained euthyroid. These 25 women had significantly higher NVP scores compared to euthyroid women at 12 weeks (T-test, $P = 0.005$) but not at 32 weeks gestation ($P = 0.31$). 212 (10.4%) Women were depressed at 12 weeks gestation, 219 (10.8%) at 32 weeks gestation, and 336 (16.5%) women were at least depressed once (EDS score > 10) during pregnancy. Depression was the strongest predictor of high NVP scores, both at 12 and 32 weeks gestation. 24 (1.2%) Women developed HG throughout pregnancy (> 5% antenatal weight loss, dehydration resulting in hospitalization). These women had significantly higher NVP sores ($P < 0.001$), and significantly higher mean FT4 levels at 12 and 32 weeks gestation compared to those without HG (T-test, $P = 0.003$, $P = 0.004$, respectively). TSH and hCG concentrations did not differ between these two groups. The 25 women with TT throughout pregnancy were 8.1 times more likely to develop HG compared to those who remained euthyroid (O.R.: 8.1; 95% CI = 1.78–13.3, $P = 0.007$), adjusted for depression (O.R.: 4.0; 95%CI = 1.6-9.8, $P = 0.003$) and hCG ($P = 0.43$). Severe NVP negatively affect quality of life resulting in depression. Therefore, a sensitivity analysis (excluding the 336 women who were at least depressed once during pregnancy) showed that in the remaining group, TT throughout pregnancy was still significantly associated with HG: O.R.: 9.8; 95% CI: 4.25 – 18.6, $P < 0.001$), adjusted for hCG ($P = 0.56$).

Conclusion

Transient thyrotoxicosis is associated with higher levels of NVP symptoms at first trimester and with the development of HG throughout pregnancy.

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PS1-14-05

Thyroid function trajectories and autoimmune thyroid dysfunction after pregnancy loss: preliminary results of an ongoing prospective study

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Objective

Pregnancy is characterized by a state of relative immune tolerance that may attenuate autoimmune diseases, followed by immune rebound after delivery. Postpartum thyroiditis represents a well-recognized manifestation of this phenomenon. Whether a similar immune rebound may occur after early pregnancy loss remains largely unexplored, and data on thyroid function after abortion are scarce. The objective was to investigate the occurrence of autoimmune thyroid dysfunction after pregnancy loss and describe longitudinal thyroid function trajectories in women undergoing pregnancy termination.

Methods

We conducted a prospective observational study including women undergoing spontaneous pregnancy termination. The study was approved by the local Ethics Committee and is ongoing. At enrolment, participants were stratified according to autoimmune thyroid risk (history of Hashimoto's thyroiditis or risk factors vs no known risk). Thyroid function tests (TSH, FT4, FT3) and thyroid autoantibodies were assessed at baseline (day of pregnancy loss), and TSH, FT4 and FT3 at 4 weeks after pregnancy loss and at three subsequent 8-week intervals.

Results

Among 60 women initially enrolled, three withdrew consent and 18 had incomplete follow-up data; therefore, 39 were included in the longitudinal analysis. Pregnancy loss occurred at a median gestational age of 9 weeks (IQR 8–10.9). Baseline thyroid function was comparable between the high-risk (HR, $n = 14$) and low-risk (LR, $n = 25$) groups (TSH 1.42 ± 1.10 vs 1.71 ± 1.08 mIU/l; FT4 14.58 ± 3.64 vs 14.74 ± 3.74 pmol/l; FT3 2.92 ± 0.73 vs 3.11 ± 0.56, mean ± SD). During follow-up, women in the HR-group showed greater variability in thyroid function trajectories compared with the LR-group. Mean TSH declined from 1.41 mIU/l at baseline to 0.87 mIU/l at the first follow-up in the HR-group, whereas it remained relatively stable in the LR-group (1.71 to 1.65 mIU/l). FT4 and FT3 showed modest fluctuations without clear differences between groups. Three cases of autoimmune thyroid dysfunction were observed, all in the HR-group: two destructive thyroiditis compatible with post-abortive thyroiditis and one recurrence of Graves' disease. No autoimmune thyroid dysfunction occurred in the LR group.

Conclusions

Preliminary findings from this ongoing prospective study suggest that autoimmune thyroid dysfunction may occur after pregnancy loss in women with increased autoimmune susceptibility. In addition to clinically overt events, greater variability in thyroid hormone trajectories was observed in the high-risk group, suggesting a possible immune rebound phenomenon even after a relatively short duration of gestational immune tolerance. Completion of this study will allow a more accurate definition of the incidence, clinical spectrum, and risk factors of thyroid dysfunction following pregnancy loss.

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PS1-14-06

Iodine nutritional status in the italian pregnant women and neonatal TSH in the offspring (period 2022-2023)

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Objectives
The aim of the study was to evaluate iodine nutritional status in the Italian pregnant women and thyroid function in the offspring.
Methods
In the period 2022-2023, 2713 pregnant women were recruited at the 3rd trimester in 8 Italian regions representative of Northern, Central, and Southern Italy. A questionnaire was administered to collect information on the use of iodized salt (IS) and/or iodine- containing supplements (ICS) during pregnancy. Morning spot urinary samples for the measurement of UI/creatinine (UI_{Creat}; μg/g) were available from 2611 pregnant women, while neonatal TSH values from 2182 infants.
Results
Sixty-nine percent of the women used IS during pregnancy. Specifically, 45% used IS+ICS, 24% IS-only, 18% ICS-only, 12% NO-IS/NO-ICS. Among IS users, 88% were using IS since at least 2 years. Overall, a median UI_{Creat} of 142 μg/g (Q1=91, Q3=217) indicative of mild iodine deficiency, was found, while the median value of neonatal TSH in term infants screened at 49-72 h of life was 2.0 mIU/l (Q1=1.3, Q3=3.2). After stratifying by type of iodine supplementation during pregnancy, a significant U-shape relationship between median values of maternal UI_{creat} and neonatal TSH was found (R2=0.8005, $P < 0.001$):
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Conclusions
A mild iodine deficiency persists among Italian pregnant women. The simultaneous use of IS+ICS leads to iodine sufficiency, without apparently affecting neonatal thyroid function, although a significant U-shape relationship between maternal UI_{creat} and neonatal TSH was found. Further studies are necessary to confirm these data.

Iodine supplementation during pregnancy	maternal UI_{creat}(mg/g) median (Q1, Q3)	neonatal TSH (mIU/l) median (Q1, Q3)
NO-IS/NO-ICS	97 (60, 146)	2.0 (1.3, 3.2)
IS-only	115 (75, 162)	1.9 (1.3, 3.0)
ICS-only	151 (100, 236)	1.8 (1.1, 2.7)
IS+ICS	169 (114, 251)	2.1 (1.4, 3.3)

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PS1-14-07

Fertility in women with graves' disease

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Introduction
Thyrotoxicosis is associated with hormonal changes and menstrual disturbances in women. However, there is limited data on whether women with Graves' disease (GD) give birth to fewer children compared to the general population.
Objective
We aimed to compare the pregnancy rate in women with GD and age-matched women without GD.
Methods
This was a retrospective, age- and county-matched cohort study using prospectively collected data from medical records and multiple Swedish national registers among women aged 18-45 years at index date. Women with GD were selected from an incidence cohort study including patients with newly diagnosed hyperthyroidism in 2003-2005 across 13 Swedish centers. The current study included 773 women with GD, each matched through Statistics Sweden with up to 10 women without GD ($n = 7{,}692$). A covariate-adjusted piecewise Cox regression model stratified on matching sets was used to compare time to conception in women with GD and the matched cohort within 0-1, 1-5, and 5-10 years of follow-up after index date.
Results
268 (34.7%) women with GD and 2,44 (31.8%) in the matched cohort had ≥1 pregnancy within 10 years from the index date. Compared with the matched cohort, the pregnancy rate was lower in women with GD within the first year after the index date (HR: 0.59; 95% CI: 0.40-0.86; $P = 0.006$). Already during 1-5 years after index date, women with GD had a somewhat higher pregnancy rate (HR: 1.18; 95% CI: 0.99-1.40; $P = 0.065$) and within 5-10 years after the index date, the pregnancy rate was statistically significantly higher (HR:1.43; 95% CI: 1.10-1.85; $P = 0.007$). Analyses stratified by the initial GD treatment showed a similar pattern of associations: women with GD had a lower pregnancy rate in the first year but higher rates thereafter compared with the matched cohort, irrespective of initial treatment (anti-thyroid drugs, radioiodine, thyroidectomy or conservative). IVF within 10 years from the index date was recorded in 0.5% of women with GD vs 0.3% in the matched cohort (risk ratio: 2.1; $P = 0.219$).
Conclusion
The pregnancy rate was lower in women with GD than in the matched cohort during the first year after GD diagnosis, but the decline was followed by an increase in subsequent years.

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PS1-14-08

Levothyroxine dose adjustment in pregnant women depending on severity of hypothyroidism

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Introduction
According to current recommendations, women on levothyroxine (L-T4) replacement therapy should increase their dosage by 30-50% upon pregnancy. From a practical perspective, it is important to understand whether the dosage increase varies depending on the severity of hypothyroidism.
Objective
We aim of the study was to assess the need to increase L-T4 dose in pregnant women depending on the severity of hypothyroidism.
Materials and methods
A retrospective study included 210 pregnant women with subclinical (SH) or overt hypothyroidism (OH) due to autoimmune thyroiditis. Patients were prescribed L-T4 replacement therapy immediately after the diagnosis of hypothyroidism. L-T4 dose adequacy was monitored every 4-6 weeks based on TSH levels. Patients were divided into 2 groups: Group 1 - 189 women with SH, Group 2 - 21 women with OH. Group 1 was divided into 2 subgroups: 1a - 64 women with SH diagnosed before pregnancy, 1b - 125 women with SH diagnosed during pregnancy.
Results
During pregnancy, all women required an increase in the L-T4 dose. The absolute increase in the daily L-T4 dose during pregnancy (μg) was calculated. For the entire cohort, this value was 50 [50;75], for women with subclinical hypothyroidism - 56.25 [50;75] (subgroup 1a: 50 [25;75], subgroup 1b: 75 [50;75]), and for pregnant women with overt hypothyroidism - 50 [25;50] ($P < 0.05$). The L-T4 dose adjustment was accompanied by a statistically significant decrease in the TSH level ($P < 0.05$).
Conclusion
The results of the study demonstrated that an absolute increase in L-T4 dose is greater in subclinical hypothyroidism than in overt hypothyroidism. Moreover, for SH that developed during pregnancy, this value is also greater than for SH diagnosed before pregnancy.

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PS1-14-09

Repeated assessments of thyroid peroxidase antibody concentrations in pregnant women show fetal sex specific fluctuations

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Background
Elevated concentrations of thyroid peroxidase antibodies (TPO-Ab) occur in up to 8-15% of women of fertile age and have clearly been associated with poor obstetric outcome. Due to immune adaptations, there is a gradual decrease of TPO-Ab throughout gestation. The current study explored possible different patterns of TPO-Ab changes stratified for fetal sex. It is commonly known that a male fetus put less investment in placental reserves and show higher levels of inflammation parameters compared to female fetuses. (''Male fetuses live dangerously in the womb'').
Methods
2433 singleton pregnant women (with 1202 female and 1231 male fetuses) participated in the Brabant Study with assessments of TPO-Ab, TSH, and FT4 at 12, 20 and 28 weeks gestation. Possible trajectories of TPO-Ab titer changes throughout pregnancy were assessed with Latent Class Growth Analysis (LCGA).
Results
210 (8.6%) Women showed an elevated TPO-Ab titer (>35 kU/l) at 12 weeks gestation with similar fetal sex rate (male: 9.3%, female: 8%, $P = 0.24$). LCGA revealed a three-class solution of TPO-Ab changes: class 1, the *reference group* ($n = 2325$, 95.5%), with a stable low median TPO-Ab concentration of 10 kU/l at all trimesters; class 2 ($n = 70$. 2.9%), a *moderately high TPO-Ab-titer decreasing* group of median TPO-Ab from 159 kU/l to 94 kU/l; class 3 ($n = 38$, 1.6%), a *high TPO-Ab-titer decreasing* group of median TPO-Ab from 318 kU/l to 204 kU/l. Demographic features were comparable, but women of class 3 smoked significantly more often, were more often multiparous, carried more often a female fetus and showed the highest levels of TSH and TPO concentrations at all trimesters (P from 0.01 to < 0.001). In class 3, the 12 women with a male fetus showed a less pronounced decrease of median TPO-Ab throughout gestation (from 332 kU/l to 281 kU/l) compared to the 26 women of this class with a female fetus (from 318 kU/l to 181 kU/l), resulting in a significantly different TPO-Ab concentration at 28 weeks gestation (Mann-W-U, $P = 0.023$).
Discussion
LCGA showed 3 clear distinct TPO-Ab patterns throughout gestation. In women with the highest TPO-Ab titers, those carrying a male fetus showed a less pronounced decrease of elevated TPO-Ab titers throughout gestation compared to those carrying a female fetus. These preliminary findings further suggest that the increased vulnerability of male fetus for poor obstetric outcome could be related to differences of gestational immune changes as reflected by a different TPO-Ab pattern.

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PS1-14-10

Cord thyroglobulin is a more sensitive biomarker of neonatal iodine status than thyrotropin

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Background
Monitoring iodine status is essential to prevent iodine deficiency. Neonatal thyrotropin (TSH) measured during routine newborn screening programs has traditionally been used as a population indicator of iodine nutrition, although its sensitivity to mild iodine deficiency is limited. Thyroglobulin (Tg) is a promising indicator of iodine status in pregnant women and children, but its added value in newborns remains unclear. This study aimed to evaluate whether newborn Tg measured is associated with iodine status and to compare its performance with neonatal TSH.
Methods
Pregnant women were recruited during the third trimester of gestation. Thyroglobulin and urinary iodine concentrations (UIC) were measured in pregnant women and their newborns. Cord blood samples were collected to measure Tg in plasma and in dried blood spots along with TSH. After delivery, a blood sample was collected from newborns at 2-5 days of life to measure Tg and TSH in dried blood spots as part of routine neonatal screening.
Results
Median UIC was 117 μg/l in pregnant women and 107 μg/l in newborns ($P < 0.05$). Creatinine-corrected UIC was similar in pregnant women and newborns (142 and 143 μg/g, respectively). Median Tg concentrations were 19 μg/l in pregnant women during the third trimester, 31 μg/l in cord plasma, 30 μg/l in cord dried blood spots, and 32 μg/l in neonatal dried blood spots. Cord Tg concentrations were significantly associated with newborn UIC, whereas neonatal TSH was not. Pregnant women's Tg concentrations were associated with newborn Tg, while maternal UIC showed no association. None of the iodine status markers were associated with cord TSH or neonatal TSH.
Conclusion
Cord Tg is a more sensitive indicator of iodine status than newborn TSH. Therefore, incorporating cord Tg determination into maternity procedures may enable regular monitoring of iodine status, facilitating early identification and timely response to changes in population iodine intake.

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TED Clinical 1

PS1-15-01

FCRN blocker efgartigimod: unique FC fragment allowing rapid, sustained IGG reduction without reducing albumin or increasing cholesterol

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Efgartigimod, an engineered human IgG1 Fc fragment, selectively binds to the IgG-binding site of the neonatal Fc receptor (FcRn) with high affinity at both acidic and neutral pH, preserving natural pH-dependent binding. Efgartigimod outcompetes endogenous IgG for binding to FcRn, thereby promoting lysosomal degradation of IgG, including pathogenic autoantibodies, without affecting other immunoglobulins or IgG production. The FcRn regulates both IgG and serum albumin homeostasis. While FcRn is an attractive target for antibody-mediated autoimmune disorders, albumin reductions were observed with some FcRn blockers. Albumin maintains oncotic pressure, regulates fluid distribution, among other transporter functions, such as maintaining lipid homeostasis. We investigated different Fc mutations *in vitro* and *in vivo* to find the optimal binding affinities for FcRn at both pH 7.4 and 6.0. Cellular/molecular analyses of multiple FcRn antagonists were carried out to elucidate mechanisms underlying differential effects on albumin homeostasis. ABDEG mutations with high affinity at both neutral and low pH were the best for the subtle balance needed for optimal FcRn-inhibiting activity to reduce endogenous IgG levels. Further increases in affinity provided no benefit. Efgartigimod, being an Fc fragment, binds to FcRn in the same orientation as natural IgG, preserving FcRn's fate and functioning in albumin recycling. Some therapeutic anti-FcRn monoclonal antibodies reduce albumin levels through two potential mechanisms: decreasing FcRn protein levels and/or causing steric hindrance for albumin binding, limiting receptor availability. Transgenic mouse models confirm these differential effects, recapitulating the observed clinical findings. Unlike certain FcRn blockers in clinical development, no reductions in albumin levels, increases in cholesterol, or notable clinical manifestations of these laboratory changes were observed across efgartigimod studies, regardless of cyclic or weekly dosing, suggesting that differences in molecular interactions with FcRn are responsible for the impact on albumin. Efgartigimod's unique molecular structure and interactions with FcRn clinically avoid reductions of albumin levels, while effectively targeting IgG autoantibodies across dosing regimens.

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PS1-15-02

Computed tomography-derived orbital tissue parameters for differentiating active and inactive thyroid eye disease: a pilot study

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Objectives
To assess whether non-contrast CT-derived orbital tissue parameters distinguish active from inactive thyroid eye disease (TED).
Methods
This pilot retrospective study included 50 patients with TED who underwent non-contrast orbital CT. Patients were classified as having active TED when Clinical Activity Score (CAS) was $\geq$ 3 and inactive TED when CAS was $<$ 3. Image processing and semiautomatic/manual segmentation were performed in 3D Slicer. Patient-level analysis used the mean of both orbits. The orbit was segmented between the orbital rim anteriorly and the optic canal entrance posteriorly. A posterior orbital segment was defined as the 15-mm orbital compartment anterior to the optic canal entrance. Assessed CT parameters included extraocular muscle-to-fat volume ratio (EOM/FAT ratio), orbital fat attenuation, posterior EOM fraction (POST_EOM_FRAC = posterior EOM volume/posterior orbital volume (OV)), posterior orbital fat volume fraction (POST_FAT_FRAC = posterior orbital fat volume/posterior OV) and posterior higher-attenuation fat volume fraction (POST_HAF; calculated as the posterior orbital fat volume with attenuation between -40 and -30 HU divided by total posterior orbital fat volume (-120 to -30 HU)). Volumetric parameters were expressed in cm3. Group comparisons used Mann-Whitney U and Fisher's exact tests; exploratory clinico-radiological associations used Spearman correlation.
Results
27 patients had active TED and 23 had inactive TED. Age and sex distribution were similar between groups, whereas diplopia was more frequent in active TED. Compared with inactive TED, active TED demonstrated a higher EOM/FAT ratio (0.64 [0.51-0.88] vs 0.38 [0.31-0.53], $p<0.001$), higher POST_EOM_FRAC (0.50 [0.42-0.53] vs 0.33 [0.30-0.39], $p<0.001$), lower POST_FAT_FRAC (0.30 [0.24-0.35] vs 0.45 [0.36-0.49], $p<0.001$) and higher orbital fat attenuation (-70.82 [-76.13 to -67.07] HU vs -77.88 [-85.02 to -74.06] HU, $p<0.001$). Exploratory analysis showed a higher POST_HAF in active TED (15.44 [12.08-19.26] % vs 10.35 [8.95-12.08] %, $p=0.002$). CAS correlated positively with POST_EOM_FRAC ($\rho=0.67$) and EOM/FAT ratio ($\rho=0.66$) (both $p<0.001$).
Conclusions
Active TED demonstrates a muscle-dominant orbital phenotype on non-contrast CT, characterized by reduced relative posterior fat fraction and higher orbital fat attenuation. Exploratory posterior higher-attenuation fat analysis suggests additional tissue-composition differences between active and inactive disease. CT-derived orbital parameters may provide objective imaging markers for distinguishing active from inactive TED.

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PS1-15-03

Tocilizumab and sirolimus show higher response rates than methylprednisolone as first-line treatment for moderate-to-severe active graves' orbitopathy: a proof-of-concept study

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Objective
Tocilizumab and sirolimus have emerged as potential therapeutic alternatives for moderate-to-severe active Graves' Orbitopathy (GO). This study aimed to compare the clinical efficacy and safety of tocilizumab, sirolimus, and ivGCs in patients with moderate-to-severe active GO.
Materials and Methods
Fifty-two consecutive patients with moderate-to-severe active GO were retrospectively evaluated: 14 treated with sirolimus (2 mg on day 1, followed by 1 mg/day for 12 weeks), 14 with tocilizumab (8 mg/kg once monthly for 4 months), and 24 with methylprednisolone (500 mg/weekly for 6 weeks, followed by 250 mg/weekly for 6 weeks), as first line treatment. Sirolimus and tocilizumab were administered when methylprednisolone was contraindicated. Clinical assessments were performed at baseline and 12 weeks after treatment completion. Primary endpoint: overall GO outcome based on a composite evaluation. Secondary endpoints: proportion of responders and the change from baseline in 1) quality of life, evaluated by GO-QoL questionnaire; 2)proptosis; 3)Clinical Activity Score (CAS); 4)ocular motility; 5)eyelid aperture.
Results
The overall response rate was significantly higher with tocilizumab (85%, OR 14.6, 95% CI 2.49–72.3; $P = 0.002$) and sirolimus (71%, OR 6.07, 95%CI:1.39–21.2; $P = 0.018$) compared with methylprednisolone (29%). CAS response was significantly greater with tocilizumab (92%, OR 13.0,95%CI:1.94–148; $P = 0.012$) and sirolimus (71%)(OR 6.0, 95% CI 1.09–30.1; $P = 0.039$) vs methylprednisolone (50%). Proptosis response was significantly higher with tocilizumab (85%, OR 30.0,95%CI:4.27–153; $P < 0.0001$) and sirolimus (50%) (OR 6.67,95%CI:1.33–24.3; $P = 0.014$) vs methylprednisolone (16.6%). QoL response was significantly higher with tocilizumab(92%) (OR 18.0,95%CI:2.95–89.6; $P = 0.0005$) and sirolimus(65%) (OR 5.4,95%CI:1.24–22.7; $P = 0.037$) vs methylprednisolone (25%). Consistently, mean reductions in CAS, proptosis and QoL were significantly greater in both sirolimus($P = 0.01$, 0.02 and 0.003 respectively) and tocilizumab groups (all $P < 0.0001$) compared to with methylprednisolone. Eyelid aperture and diplopia response rates did not differ significantly across groups. However, ocular ductions showed greater improvement in tocilizumab ($P = 0.009$) and sirolimus ($P = 0.01$) groups compared with methylprednisolone. No significant differences in adverse effects were observed across groups. On multivariate logistic regression, treatment with tocilizumab (OR 28.5,95%CI 3.1-64.1) and sirolimus (OR 7.35,95%CI 1.33-53.5) were associated with a greater probability of response compared to methylprednisolone, regardless of baseline CAS, TRAb levels and smoking habit.
Conclusions
As novel therapies targeting precise molecular pathways are emerging in the treatment landscape of GO, both tocilizumab and sirolimus demonstrated significantly superior response rate compared to methylprednisolone, with comparable safety profiles and sustainable costs. If confirmed in randomized trials, these findings support the use of IL-6 inhibition and mTOR pathway modulation as first-line therapeutic strategies in GO.

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PS1-15-04

Time matters in graves' orbitopathy: longitudinal analysis reveals delayed therapeutic response to intravenous glucocorticoids

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Objectives
Intravenous glucocorticoids (ivGC) represent the first-line treatment for moderate-to-severe and active Graves' orbitopathy (GO), primarily due to their rapid anti-inflammatory effects. Current guidelines recommend evaluation of treatment response at 24 weeks. However, glucocorticoids exert both rapid non-genomic and slower genomic effects, which may contribute to delayed clinical improvement. The aim of this study was to investigate the temporal trajectory of response to ivGC and identify the time point at which treatment response reaches its maximum probability.
Methods
A total of 134 patients with moderate-to-severe and active GO treated with ivGC between 2022 and 2024 were included. Baseline characteristics are reported in Table 1. Clinical response at each visit was assessed using EUGOGO revised composite response index. Longitudinal analyses were performed using generalized estimating equations (GEE) with link logit and exchangeable correlation structure. Time since treatment initiation was modelled as linear and quadratic term to account for potential non-linear response trajectories. Multivariable models were adjusted for age, sex, smoking status, TRAb levels, treatment of hyperthyroidism, and cumulative ivGC dose.
Results
Probability of treatment response based on the revised composite index increased significantly over time following ivGC (OR: 1.96, 95%CI: 1.71-2.25; $P < 0.001$).

Inclusion of a quadratic time term revealed a significant deceleration of the response trajectory (OR: 0.97, 95%CI: 0.96-0.98; $P < 0.001$), indicating a non-linear pattern. Predicted probability of response increased progressively after treatment initiation, reached a maximum at approximately 15 months, and subsequently plateaued. These findings remained consistent after multivariable adjustment (OR: 2.03, 95%CI: 1.74-2.38; $P < 0.001$; quadratic term OR: 0.97, 95%CI: 0.96-0.98; $P < 0.001$). In contrast, disease activity assessed by CAS declined steadily over time. Time since treatment initiation was significantly associated with a reduced probability of active disease (CAS ≥ 3) (OR: 0.79, 95%CI: 0.69-0.89; $P < 0.001$), with no significant quadratic effect, indicating a linear temporal pattern. Similar results were observed after multivariable adjustment (OR: 0.83, 95%CI: 0.78-0.88; $P < 0.001$).

Conclusions

Clinical response to ivGC in GO follows a non-linear trajectory, with progressive improvement continuing beyond the currently recommended 24-week evaluation point. In contrast, disease activity decreases linearly over time. These findings suggest that early classification of patients as non-responders may underestimate the true therapeutic effect of ivGCs, as a subset of patients may experience delayed clinical response. Extended follow-up is necessary to accurately assess treatment response and avoid premature therapeutic escalation.

VARIABLE	VALUE
Age (*years*)	52.97 (11.44)
Sex	Males: 27.61% Females: 72.39%
Smoking Habit	Non-smokers: 34.33% Current-smokers: 32.84% Ex-smokers: 32.84%
TRAb (*IU/l*)	8.5 (2.5-23.71)
CAS (7-items)	4.23 (1.13)
Hyperthyrioidism duration (*months*)	19 (11-37)
Orbitopathy duration (*months*)	18 (11-36)
Current/previous thyroid treatment	MMI: 65.67% RI: 8.96% TX: 25.37%
ivGC cumulative dose (*g*)	5 (1.94)
Follow up (*months*)	10.92 (3.62)

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PS1-15-05

Treatment escalation after intravenous glucocorticoid therapy in moderate-to-severe graves' orbitopathy: a retrospective cohort study

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Background

Intravenous glucocorticoid (IVGC) is the recommended first-line therapy for active moderate-to-severe Graves' orbitopathy (GO). However, a substantial proportion of patients require additional treatment due to persistent or progressive disease. Real-world data on the need and timing of treatment escalation following an initial course of IVGC remain limited.

Methods

We conducted a retrospective cohort study of 106 patients with moderate-to-severe and sight-threatening GO treated with IVGC at a tertiary referral center between January 1st, 2014, and December 31st, 2024. Baseline characteristics, smoking status and cumulative IVGC dose were recorded. Indication for orbital decompression were classified as acute DON or active non-DON. Primary outcome was the need of additional active treatment within 6, 12, and 24 months after the first IVGC dose. Additional active treatment was defined as second IVGC, orbital radiotherapy, tocilizumab, or acute decompression.

Results

75% of patients were female, and median age was 56.5 years (IQR 48-65). 39% were current smokers and 28% were former smokers. 73% received standard cumulative IVGC dose of 4.5 g; median cumulative dose was 5.0g (range 0.5–10.5). Overall, 39% required additional active treatment after first IVGC course. The cumulative incidence of treatment escalation was 33% at 6 months, 40% at 12 months, and 43% at 24 months. Among individual treatment modalities, 15% received a second IVGC course, 27% underwent orbital radiation and 4% were treated with tocilizumab. In total, 35 patients (33%) underwent decompression during follow-up, of whom 46% were operated due to DON and 6% due to persistent active non-DON disease. Median time from first IVGC dose to acute decompression was 149 days (IQR 49–187). Four patients required a second acute decompression: three due to DON and one due to persistent active disease. Forty-three patients required more than one treatment modality. Rehabilitative surgery increased over time after the last IVGC dose (7 procedures at 6 months vs 33 at 24 months), predominantly strabismus ($n = 15$) and decompression surgery ($n = 13$).

Conclusion

In this cohort, 61% of patients with moderate-to-severe GO did not require additional active treatment following first-line IVGC. Treatment escalation occurred predominantly within the first year, with relatively few additional interventions thereafter. These findings are broadly comparable to recent reports and further support IVGC as an effective first-line treatment strategy in many patients with GO.

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PS1-15-06

Validation of algorithms to identify patients with thyroid eye disease in the central denmark region: relevance for multidisciplinary care

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Background and Objective

Thyroid Eye Disease (TED) is a progressive, debilitating autoimmune disease that can result in vision impairment and substantial negative impact on quality of life. Accurate identification of TED in healthcare databases is essential for clinical research; however, TED algorithms have not been formally validated. This study assessed the performance of code-based algorithms in identifying incident TED patients in Danish healthcare registers.

Methods

This study was set in the Department of Ophthalmology at Aarhus University Hospital in the Central Denmark Region from 2020–2025. We applied three clinician-developed algorithms to identify incident TED patients in patient registry data: 1) the Danish Endocrine Society recommended ICD-10 code (H06.2, dysthyroid exophthalmos); 2) exophthalmic condition codes combined with use of medications for thyroid disease; and 3) hyperthyroidism codes combined with TED-related eye symptom codes. To determine the positive predictive value (PPV) and sensitivity of algorithms, medical records for all algorithm-identified patients and for a random sample of 100 suspected TED patients were reviewed by experts to confirm clinical diagnosis and establish a reference standard. TED severity (EUGOGO, NOSPECs) and activity (CAS) were also extracted from medical records.

Results

During the study period, 51,832 unique patients were seen at Aarhus University Hospital's Ophthalmology Department Collectively, the three algorithms identified 132 patients. Of these,129 had chart-confirmed TED, yielding a PPV of 97.7% (95% CI 93.5–99.5). PPV was similarly high across individual algorithms (96-100%), indicating that these algorithms almost always identified true cases. Out of 100 patients with suspected TED, 93 patients had chart-confirmed TED. Only 17 were identified by the algorithms, yielding a sensitivity of 18.3% (95% CI 11.0–27.6). The 76 missed cases did not share a consistent alternative coding pattern but were mostly mild in presentation compared to cases identified by algorithms (NOSPECS (extraocular muscle signs: 19.7% vs. 50.4%, p-value <0.0001), EUGOGO (moderate-to-severe: 21.1%, vs 51.9%, p-value <0.0001). Notably, 15% ($n = 11$) of the missed cases were captured in endocrinology records with the recommended code H06.2.

Conclusion

This is the first study examining validity of code-based algorithms to identify incident TED patients in Denmark. All algorithms identified true TED cases with high precision but did not capture all TED cases, particularly milder presentations. Broader use of recommended coding across specialities may improve TED identification. Consistent coding and coordinated care across endocrinologists and ophthalmologists are essential to enhance recognition, timely diagnosis, improve coding accuracy, and ensure comprehensive management of TED.

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PS1-15-07

Online medical education can significantly improve physicians' knowledge, competence and confidence when using targeted immunotherapy for thyroid eye disease (TED) in clinical practice according to guidelines

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To determine if online medical education for ophthalmologists (Opht) and endocrinologists (Endo) could improve knowledge and competence on TED assessment and management, and confidence for treatment decisions according to current ETA/ATA and EUGOGO guidelines. Learners watched an on-demand, 30-minute, 3-expert video discussion, then completed a pre- and post-activity assessment (4 MC questions, self-assessed confidence 5-item Likert scale). Matched pair design compared average number overall correct responses pre/ post with paired samples t-test and proportion of questions answered correctly at question level pre/ post with McNemar's test ($P < .05$ significance level). Education effect size on number of correct responses estimated with Cohen's d with correction for paired samples ($<.20$ modest, .20-.49 small, .59-.79 moderate, $\geq .80$ large). Confidence compared pre/ post with paired samples t-test. Data Sep 2025 - Jan 2026 255 Opht and 265 Endo completed the pre- and post- assessment. Average proportion of correct responses increased from pre 39% Opht and 35% Endo to post 58% Opht and 61% Endo ($P < .001$; Cohen's $d = 0.76$ Opht and 0.89 Endo). Confidence when treating patients with moderate to severe TED in accordance with leading clinical guidelines increased in 29% Opht and 25% Endo ($P < .001$) Online medical education can significantly improve physicians' knowledge, competence and confidence in applying current guidelines when assessing and treating TED, in particular for use of targeted immunotherapy, with endocrinologists benefitting most from education on patient selection. Additional education is warranted, due to TED therapy with teprotumumab, as the first licensed immunotherapy, not yet being established outside of the US, and low overall knowledge and confidence levels.

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PS1-15-08

Burden of thyroid eye disease for caregivers: results from a survey in spain and germany

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Objectives
Thyroid eye disease (TED) is a progressive autoimmune disorder characterized by inflammation and expansion of orbital tissues. This study describes the multifaceted impact of moderate-to-severe TED on caregivers and the burden they experience.
Methods
A web-based survey was conducted via Carenity, an online patient community, in Spain and Germany between September and December 2025. It assessed caregivers' sociodemographic profile, patient medical characteristics, caregiving activities, and burden. Caregivers' QoL was assessed with Caregiver Quality of Life Index Revised (CQLI-R; range 0-40, higher scores indicating better QoL).
Results
Among the 60 participants, 40 (67%) were from Germany and 20 (33%) from Spain. Caregivers had a mean age of 40.6 years, were predominantly male (60%) and most commonly patients' partners (72%). Caregivers reported a mean of 4.2 TED-related symptoms per patient (median = 4.0) and rated the impact of TED on patients' daily activities at a mean of 6.3 (SD = 2.1) on a 0-10 scale (higher scores indicating greater impact). Most had provided care for 1–5 years (52%) and spent 2–7 hours per day on caregiving activities (60%). The majority of caregivers provided daily or frequent emotional support (90%) and treatment-related support (85%), with substantial proportions also assisting daily or frequently with daily tasks (78%), technology use (78%), medical appointment management (75%), navigation in hazardous environments (73%), transportation (72%), and administrative tasks (67%). Most reported that worsening patient symptoms necessitate increase in caregiving time (62%) and require additional responsibilities (50%). Median (IQR) CQLI-R score was 24.5 (19.8-29.0) and mean (SD) was 24.1 (7.8). Across emotional, social, financial, and physical domains (0–10), mean QoL was similar (6.0, 5.9, 6.2 and 6.0). The domains where caregivers most frequently reported more impact (defined as score ≤ 3.0) were social (20%) and physical (13%) QoL, followed by emotional (10%) and financial (8%) QoL.
Conclusion
Caregivers of patients with TED experience a substantial, multidimensional burden affecting all aspects of QoL. These findings demonstrate that the burden of TED extends beyond patients, with significant consequences for caregivers and potentially the society.

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PS1-15-09

Extraocular muscle fatty infiltration on MRI is associated with chronic thyroid eye disease

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Objectives
Thyroid eye disease (TED) is characterized by an "active" inflammatory phase followed by a chronic "inactive" stage. Differentiating between these phases is crucial for patient management. In the chronic stage of TED, structural remodeling of the extraocular muscles (EOM) may occur, including fibrosis and fatty replacement. Magnetic resonance imaging is increasingly used as an adjunctive tool in TED assessment. However, fatty infiltration of the EOM on conventional T1-weighted MRI has not been systematically investigated in TED. The aim of this study was to assess the prevalence, severity, and clinical significance of EOM fatty infiltration in patients with TED.
Methods
This retrospective study analyzed orbital MRI scans of 130 patients with TED. Fatty infiltration of the EOM was assessed by identifying areas of high signal intensity on conventional T1-weighted images. Fatty infiltration was graded using a semi-quantitative scale: 0 = no fatty infiltration, 1 = minimal fatty streaks, 2 = fatty infiltration involving $<50\%$ of the muscle cross-sectional area, 3 = fatty infiltration involving approximately 50% of the muscle cross-sectional area, and 4 = fatty infiltration involving $>50\%$ of the muscle cross-sectional area. Additionally, a composite fatty infiltration score was calculated by summing the fatty infiltration grades across all evaluated EOM.
Results
Moderate-to-severe fatty infiltration (grades 2–4) was observed in 63.08% of inferior rectus, 50.39% of superior rectus, 41.54% of medial rectus, and 35.77% of lateral rectus muscles. Patients with moderate-to-severe fatty infiltration in any EOM had a significantly lower Clinical Activity Score (CAS) compared with patients with absent or minimal fatty infiltration (2 [IQR 1–3] vs 4 [IQR 2–5], $P = 0.0040$). They also had a lower frequency of chemosis (24.74% vs 58.62%, $P = 0.0013$), conjunctival redness (31.96% vs 58.62%, $P = 0.0156$), eyelid edema (61.22% vs 86.21%, $P = 0.0132$), eyelid redness (24.49% vs 44.83%, $P = 0.0396$), and ocular hypertension

Abstract [PS1-15-07]

	Opth ($n = 255$)			Endo ($n = 265$)		
	Correct pre	Correct post	p	Correct pre	Correct post	
Knowledge: TED assessment clinical activity score	38%	58%	$P < .01$	29%	44%	$P < .01$
Knowledge: Patient selection for targeted immunotherapy using EUGOGO guidelines	100%	100%	$P = 1.0$	20%	100%	$P < .05$
Competence: Making treatment decisions in TED (improve eye motility using ATA/ETA guidelines)	36%	44%	$P < .01$	32%	60%	$P < .01$
Competence: Making treatment decisions in TED (identify best proptosis 2L option using evidence & guidelines)	42%	73%	$P < .01$	44%	77%	$P < .01$

(36.17% vs 62.07%, $P = 0.0180$). The composite fatty infiltration score correlated negatively with CAS ($\rho = -0.250$, $P = 0.0042$), TSH-receptor antibodies levels ($\rho = -0.228$, $P = 0.0098$), thyroid peroxidase antibodies levels ($\rho = -0.238$, $P = 0.0123$), the mean EOM to temporalis muscle signal intensity ratio (SIR) on STIR ($\rho = -0.493$, $P < 0.0001$), and the mean lacrimal gland to temporalis muscle SIR on STIR ($\rho = -0.233$, $P = 0.0076$). Positive correlations were observed with TED duration ($\rho = 0.494$, $P < 0.0001$) and Graves' disease duration ($\rho = 0.493$, $P < 0.0001$).

Conclusions

In this study, EOM fatty infiltration was consistently associated with well-established clinical, biochemical, and radiological indices of inactive TED. EOM fatty infiltration may represent a useful imaging marker of EOM remodeling and chronic TED.

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PS1-15-10

Real-world effectiveness of rituximab for graves' ophthalmopathy: patient-reported response and predictors of therapy escalation

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Objectives

Evidence for rituximab (RTX) in Graves' ophthalmopathy (GO) remains heterogeneous. We assessed real-world outcomes, TSH receptor antibodies (TRAb) trends over follow-up, and baseline factors associated with early response and need for treatment escalation.

Methods

We performed a retrospective single-centre cohort study of consecutive patients treated with RTX for GO (2017–2025). All patients received a total RTX dose of 2000 mg. The primary early outcome was patient-reported global change at first follow-up. The primary long-term outcome was the need for additional therapy for active GO after RTX. Secondary outcomes included change in TRAb and Modified Clinical Activity Score (mCAS) where available. Between-group comparisons used Fisher's exact and Mann-Whitney U tests; paired comparisons used Wilcoxon signed-rank tests. Longitudinal TRAb trend was analyzed using a linear mixed-effects model on log(TRAb) with months since RTX (random intercept per patient). TRAb values above assay upper limit were treated as right-censored and analyzed conservatively (ULn = 39 U/l). CAS trend was analysed with mixed-effects modelling.

Results

Thirty patients were included (mean age 55.2 ± 10.5 years; 70% female; 20% current smokers; 83% euthyroid at baseline). Baseline GO severity was moderate-to-severe in 77% and sight-threatening in 23%; diplopia was present in 73% and exophthalmos in 30%. At the primary follow-up (median 2 months), 20/30 (67%) reported "better", 7/30 (23%) "unchanged", 1/30 (3%) "worse", and 2/30 (7%) "initially better, then worse again". Over a median follow-up of 19 months, 3/30 (10%) required escalation to additional therapy for active GO after a median of 8 months. No patient with early stable improvement required escalation vs 3/10 without early improvement ($P = 0.030$). Responders (patient-reported "better" at primary follow-up) had shorter baseline GO duration (median 12 vs 19 months; $P = 0.036$). Patients requiring escalation to other therapies had longer baseline GO duration (median 20 vs 13 months; $P = 0.045$) and higher baseline TRAb (trend, median 32 vs 11 U/l; $P = 0.077$). TRAb declined over follow-up ($\beta = -0.0557$ log-units/month; $P < 0.001$). mCAS declined over follow-up (mixed model $P = 0.001$) and improved from baseline to primary follow-up ($P = 0.031$). Adverse events within 12 months occurred in 20%, mainly mild infusion reactions.

Conclusions

RTX treatment was followed by early patient-reported improvement in two-thirds of GO patients, sustained TRAb decline over follow-up, and a low need for subsequent treatment escalation. Shorter disease duration and early patient-reported improvement may help identify patients most likely to benefit.

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TH action & Miscellaneous

PS1-16-01

Impact of iron supplementation on thyroid-stimulating hormone levels in women with iron deficiency in AJARA, georgia

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Objectives

Iron deficiency has been increasingly recognized as a potential contributor to altered thyroid function, particularly subclinical hypothyroidism. Iron plays a critical role in thyroid hormone synthesis as a cofactor for thyroid peroxidase, an enzyme essential for iodination and hormone production. The present study aimed to evaluate the effect of short-term iron supplementation on thyroid-stimulating hormone (TSH) levels in women with varying degrees of iron deficiency.

Methods

A retrospective observational study was conducted in 27 women aged 35–44 years. Baseline laboratory assessments included serum ferritin, thyroid-stimulating hormone (TSH), free thyroxine (FT4), and anti–thyroid peroxidase antibodies (anti-TPO). All participants received oral iron supplementation, and TSH levels were reassessed after six weeks of treatment. Patients were stratified according to baseline ferritin levels to evaluate the relationship between iron status and changes in TSH concentrations following therapy.

Results

At baseline, decreased ferritin levels (< 15 ng/mL) were associated with elevated TSH concentrations, consistent with subclinical hypothyroidism in several patients. After six weeks of iron supplementation, a reduction in TSH levels was observed in the majority of participants. The most pronounced improvement occurred in women with ferritin levels between 8–11 ng/mL, where TSH decreased substantially (e.g., from 7.1 to 3.2 μIU/mL and from 8.1 to 3.1 μIU/mL) . In contrast, participants with ferritin levels above 20 ng/mL demonstrated minimal variations in TSH levels. Notably, individuals with markedly elevated anti-TPO antibodies showed persistent or increasing TSH levels despite iron supplementation (for example, anti-TPO 890 IU/mL with TSH rising from 4.7 to 10.2 μIU/mL), suggesting that autoimmune mechanisms may override the metabolic benefits of iron repletion.

Conclusions

These findings suggest that iron supplementation may contribute to the normalization of TSH levels in women with iron deficiency, emphasizing the importance of adequate iron status for optimal thyroid hormone synthesis and regulation. However, the therapeutic response appears limited in patients with autoimmune thyroiditis, as indicated by elevated anti-TPO antibodies. Routine evaluation of iron status may therefore represent a clinically relevant component in the assessment and management of patients presenting with elevated TSH levels. Larger prospective studies are warranted to further elucidate the complex relationship between iron metabolism and thyroid autoimmunity.

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PS1-16-02

Age- and sex-related differences in thyroid function tests in healthy blood donors: preliminary data from a large monocentric cohort

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Background

Physiological variations in thyroid function according to age and sex may influence the interpretation of thyroid function tests and contribute to misclassification of subclinical thyroid dysfunction. Defining age- and sex-specific distributions of thyroid hormones may improve diagnostic accuracy.

Methods

This cross-sectional study included 2,611 healthy blood donors (1,906 men and 705 women; mean age 49.4 ± 11.2 years) screened according to national transfusion criteria. Serum TSH, FT4, and FT3 were measured using

electrochemiluminescence immunoassays on a Roche Cobas platform (Roche Diagnostics). Participants were stratified by sex and by two age groups (18–45 and 46–70 years). Hormone levels were summarized as median and interquartile range (IQR) and compared using Mann–Whitney tests.
Results
In the overall cohort, thyroid hormone concentrations differed significantly between sexes for FT4 and FT3, whereas TSH values were similar. Median TSH levels were 1.64 mIU/l in men vs 1.68 mIU/l in women ($P = 0.41$). In contrast, men showed higher free thyroid hormone concentrations: FT4 15.8 pmol/l (IQR 14.0–17.2) vs 15.1 pmol/l (IQR 13.7–16.5) ($P = 0.002$) and FT3 3.24 pg/mL (IQR 2.96–3.52) vs 3.01 pg/mL (IQR 2.71–3.30) ($P < 0.001$). The largest sex differences were observed in individuals aged 46–70 years. TSH values were slightly higher in women but not statistically different (1.68 vs 1.61 mIU/l, $P = 0.18$). Men showed higher FT4 (15.4 vs 14.8 pmol/l, $P = 0.018$) and FT3 (3.16 vs 2.93 pg/mL, $P < 0.001$). Within-sex comparisons revealed significant age-related differences. In men, FT4 decreased from 16.2 pmol/l (IQR 14.7–17.6) in the 18–45 years group to 15.4 pmol/l (IQR 14.0–16.8) in the 46–70 years group ($P = 0.01$), while FT3 decreased from 3.32 pg/mL (IQR 3.10–3.55) to 3.16 pg/mL (IQR 2.96–3.38) ($P = 0.02$). In women, FT4 decreased from 15.5 pmol/l (IQR 14.3–16.9) to 14.8 pmol/l (IQR 13.7–16.5) ($P = 0.01$), and FT3 from 3.14 pg/mL (IQR 2.86–3.44) to 2.93 pg/mL (IQR 2.71–3.15) ($P = 0.02$). TSH showed a modest age-related increase ($P = 0.07$).
Conclusions
In this large cohort, thyroid function tests showed clear sex- and age-related differences, with women exhibiting lower FT3 and FT4 levels and older individuals showing higher TSH and lower free hormone concentrations. These findings support the need for age- and sex-specific reference intervals. Large multicenter studies are warranted to confirm these observations.

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PS1-16-03

Association between thyroid function with migraine and stroke risk: the rotterdam study

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Background
Migraine and thyroid dysfunction, particularly hypothyroidism, are common medical conditions among women. A bidirectional relationship between these conditions has been suggested; however, evidence regarding the association between thyroid function and migraine remains conflicting. Both conditions have been identified as risk factors for incident stroke, but their potential interaction on stroke risk is unclear. This study aimed to investigate the association between thyroid function and migraine, as well as their potential interaction in relation to incident stroke risk.
Methods
We included participants with available thyroid function measurements and migraine interview data from a prospective population-based cohort, the Rotterdam Study. Multivariable logistic regression models were used to examine the associations of thyroid function indicators—free thyroxine (FT4), thyroid-stimulating hormone (TSH), and thyroid peroxidase antibody (TPO-Ab) positivity—with migraine prevalence and migraine subtypes. The impact of thyroid dysfunction was also assessed. Subgroup analyses stratified by sex and median age (65 years) were conducted to evaluate potential effect modification. Sensitivity analyses were performed among euthyroid participants, including analyses restricted to the third cohort—which included younger participants—and using inverse probability weighting to address potential selection bias. Restricted cubic splines with three knots were applied to assess nonlinear associations. To evaluate the interaction between thyroid function and migraine on incident stroke risk, multiplicative interaction terms were included in multivariable Cox proportional hazards models.
Results
A total of 5,770 participants were included (mean age 65.5 $\pm$ 11.3 years; 54.2% women) in the study, of whom 845 were diagnosed with migraine. Neither FT4 nor TSH levels were significantly associated with migraine prevalence or migraine subtypes. Thyroid dysfunction was also not significantly associated with migraine. However, TPO-Ab positivity was associated with a higher prevalence of migraine (OR 1.25, 95%CI 1.00-1.56), particularly among women (OR 1.30, 95%CI 1.03-1.66). Sensitivity analyses yielded consistent results. No interaction was identified between thyroid function and migraine on incident stroke risk (FT4: p interaction = 0.599; TSH: p interaction = 0.906).
Conclusions
Our study found no evidence supporting an association between thyroid function and migraine or its subtypes. However, thyroid autoimmunity was associated with a higher prevalence of migraine. No significant interaction between thyroid function and migraine was observed in relation to incident stroke risk. Further longitudinal studies are required to untangle the association between thyroid function and migraine.

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PS1-16-04

A national referral service for discordant thyroid function tests facilitates rapid diagnosis of resistance to thyroid hormone beta

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Background
Resistance to thyroid hormone (TH) beta (RTHβ), caused by mutations in the T3-receptor (TR) TRβ, is characterized by elevated FT4 and FT3 concentrations with non-suppressed TSH concentrations. Clinical features arise from hypothyroid features in TRβ-expressing tissues such as the liver (e.g. dyslipidaemia and MAFLD) and from thyrotoxic features in TRα-expressing tissues such as the heart, predisposing to an increased risk of cardiovascular morbidity (e.g. up to 10-times increased risk of atrial fibrillation) and mortality. Treatment options that potentially mitigate disease features require disease awareness among physicians to avoid a delay in diagnosis.
Objective
To document the yield a of national referral service for discordant thyroid function tests.
Methods
We established a national referral service for discordant thyroid function tests. This entails a pipeline following principles of international guidelines to establish the origin of abnormal thyroid function tests, including assay interference or genetic causes, such as binding protein abnormalities and RTHβ, using protocols accredited according to ISO15189:2022 by the Dutch Accreditation Council. Referring physicians can participate online in monthly physical multidisciplinary meeting consisting of endocrinologists, clinical chemists and molecular biologists. We raised awareness in The Netherlands and Belgium by case presentations at endocrinologists' retreats. Thyroid function was determined with immunoassays (Siemens Atellica IM 1300) and UPLC-LC-MS/MS. Where deemed appropriate, serum was further tested using size exclusion chromatography, electrophoresis and/or equilibrium dialysis, and EDTA blood for gene variants by Sanger sequencing.
Results
We received 80 referrals since the launch of this national service in mid-2023, which has so far led to the diagnosis of 10 independent cases of familial dysalbuminemic hyperthyroxinemia, 4 of familial dystransthyretinemic hyperthyroxinemia, and 8 of RTHβ. Of the RTHβ cases, 2 revealed novel variants. Both cases presented with multinodular goiter and increased FT3 and FT4 with non-suppressed TSH concentrations. Case 1 is a woman heterozygous for a Lys443del variant. Case 2 is a woman heterozygous for an Ile250Asn variant. The variants were predicted as respectively likely pathogenic and pathogenic (according to the ACGS guidelines 2019) and will be tested for T3-sensitivity in a luciferase reporter assay.

Conclusions
The identification of 8 novel RTHβ patients since the start of a national referral service suggests that RTHβ is a still underdiagnosed syndrome. In spite of the many pathogenic variants reported in literature, our results show that the full spectrum has not yet been uncovered. Timely diagnosis of RTHβ is beneficial to mitigate clinical consequences of disordered thyroid hormone signaling.

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PS1-16-05

Effect of early in-hospital rehabilitation after robot-assisted transaxillary thyroidectomy: a randomized clinical trial

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Objectives
Postoperative shoulder dysfunction and pain are common after transaxillary robot-assisted thyroidectomy due to extensive soft-tissue dissection and retraction. However, structured in-hospital early rehabilitation is not routinely incorporated into postoperative care, and supporting evidence remains limited. To evaluate the efficacy of an in-hospital early rehabilitation program on postoperative shoulder function, pain, and psychological outcomes following transaxillary robot-assisted thyroidectomy.
Methods
This assessor-blind randomized clinical trial was conducted between July 2024 and April 2025 at a tertiary academic hospital. Adult patients with thyroid cancer scheduled for transaxillary robot-assisted thyroidectomy were enrolled and randomized 1:1 to a rehabilitation or control group. All participants received standardized postoperative education on postoperative day 1, including pain-related body awareness, cold therapy, desensitization techniques, and lymphatic massage. The rehabilitation group additionally received a structured in-hospital early rehabilitation on postoperative day 1, consisting of breathing and core-setting exercises, deep cervical muscle activation, pectoral muscle mobilization, and passive range of motion and stretching exercises for the neck and shoulder. The control group received standard postoperative care without therapist-delivered rehabilitation. Postoperative analgesic regimens were identical between groups. The primary outcome was passive shoulder range of motion. Secondary outcomes included postoperative pain, functional performance, and psychological outcomes. Outcomes were assessed preoperatively, through postoperative day 2, and at approximately 2 weeks in outpatient follow-up.
Results
A total of 56 participants were included in the final analysis (28 per group). Compared with controls, the rehabilitation group demonstrated greater improvements in shoulder flexion and abduction and lower pain scores during the early postoperative period. Median time to functional recovery was shorter in the rehabilitation group than in the control group for both flexion (1.94 vs 8.50 days) and abduction (1.91 vs 10.67 days). No significant between-group differences were observed for external rotation.
Conclusions
In-hospital early rehabilitation after transaxillary robot-assisted thyroidectomy accelerates recovery of shoulder function and reduces postoperative pain, supporting integration of structured early rehabilitation into postoperative care pathways.

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PS1-16-06

Comparative mathematical modeling of FT4 dynamics across three pediatric thyroid diseases using retrospective data from an international multicenter study

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Objectives
Congenital hypothyroidism (CH), Hashimoto thyroiditis (HT), and Graves' disease (GD) are the most common chronic primary thyroid disorders requiring long-term monitoring and treatment in pediatric endocrinology. Disease-specific mechanisms lead to heterogeneous treatment responses both between and within these disorders. The aim of this project was to (i) develop and refine disease-specific clinically practical mathematical models characterizing individual free thyroxine (FT4) dynamics under treatment and (ii) comparatively validate refined models with respect to predictive performance and clinical applicability.
Methods
Retrospective longitudinal data from pediatric patients with CH, HT, and GD from seven hospitals on three continents were used for model development and validation. Mechanism-based mathematical models describing individual FT4 dynamics over one year of follow-up were developed within a nonlinear mixed-effects framework accounting for inter-individual variability. Disease severity groups were defined according to disease-specific guidelines based on FT4 at diagnosis. Predictive performance during the first four months was assessed using (i) absolute prediction error and (ii) sensitivity and specificity for classifying FT4 concentrations as above or below the midpoint of the respective reference range. Classification was based on prediction intervals derived from model-based simulations (1000 samples per individual).
Results
Data from 521 children (3291 FT4 measurements) with CH ($n = 267$, mean age 24 days), HT ($n = 113$, mean age 11.2 years), or GD ($n = 141$, mean age 11.6 years) were analyzed. To describe FT4 dynamics, the diseases shared the same structural model, but for GD, an additional inhibitory drug-effect term on the endogenous T4 production was included. All models incorporate weight progression and rely exclusively on clinically relevant and routinely available information (age, gestational age, and disease severity at diagnosis, measured FT4 under treatment, and administered dose of levothyroxine or carbimazole/methimazole). In CH, weight progression directly affected FT4 dynamics. Median absolute prediction errors ranged from 1.5 to 3.0. pmol/l and were highest in the first month for GD and in the second month for CH and HT. Across all diseases, sensitivity and specificity were at least 85% and 92%, respectively.
Conclusion
Developed mathematical models for pediatric CH, HT, and GD accurately predict individual disease dynamics. In combination with dose optimization algorithms, these models are expected to facilitate personalized pharmacotherapy and have the potential to mitigate the risk for under- or overdosing in children with thyroid diseases, thereby avoiding drug-related side effects and improving quality of life. A randomized controlled trial has been initiated to further assess predictive performance in clinical practice.

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PS1-16-07

THRB splice site pathogenic variants lead to EXON 4 skipping and TRβ1 gain-of-function syndrome

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Objectives
In humans the *THRB* gene encodes for thyroid hormone receptor (TR)β1 and β2. Heterozygous c.283+1G>A and c.283G>A variants are thought to lead to autosomal dominant macular dystrophy (ADMD). We report the detailed clinical characterization of two first-degree relatives with ADMD, heterozygous for *THRB* c.283+1G>A, and an unrelated ADMD patient with a novel variant, c.283G>C. As the underlying pathomechanism remains elusive, we studied the genomic and molecular consequences of both variants.
Methods and Results
Clinical characterization included biochemistry, bone density and body composition, ECG, echocardiography, thyroid ultrasound, audiometry and color vision. The patients manifested no resistance to thyroid hormone beta (RTHβ) and had normal FT4 and TSH. Clinical studies in two patients showed no goiter, tachycardia, hypercholesterinemia or hepatic steatosis. Hearing was not impaired. However, both patients carrying the c.283+1G>A mutation had impaired color vision and reduced bone density. gDNA and mRNA were obtained from leukocytes and RT-qPCR from all three patients revealed skipping of exon 4 exclusive to TRβ1, producing a deletion of 87 amino acids in the N-terminal domain ($TR\beta1^{\Delta NTD}$). *In vitro* assays revealed, that DNA-binding affinity of $TR\beta1^{\Delta NTD}$ to DR4-TRE with or without RXRα was comparable to $TR\beta^{WT}$. Surprisingly, $TR\beta1^{\Delta NTD}$ was transcriptionally twice more active than $TR\beta^{WT}$ with a similar EC_{50} for T3, demonstrating gain-of-function of $TR\beta1^{\Delta NTD}$. Unlike in RTHβ patients, *THRA* expression in leukocytes was increased by 3-fold compared to unrelated controls.
Conclusion
Here we show that these *THRB* variants (c.283+1G>A and c.283G>A) produce a TRβ1-specific phenotype distinct from RTHβ. On molecular level, the mutations affect the donor splice site of TRβ1-exclusive exon 4. This promotes exon skipping and ultimately generates a gain-of-function mutant ($TR\beta1^{\Delta NTD}$). This explains the dominant ADMD phenotype and suggests a novel TRβ1 gain-of-function syndrome.

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PS1-16-08

Near-infrared autofluorescence improves parathyroid outcomes in oncologic thyroidectomy with lymph-node dissection: propensity-matched multi-surgeon cohort and nested single-surgeon learning-curve analyses

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Background and Objective
Oncologic thyroid surgeries, particularly total thyroidectomy with central neck dissection (TT+CND), carry a high risk of inadvertent parathyroidectomy (IP). Near-infrared autofluorescence (NIRAF) aids parathyroid gland (PG) identification, but its effect on IP and related outcomes in complex oncologic procedures and along the learning curve remains unclear. We assessed NIRAF's impact on IP, frozen section examination (FSE), PG reimplantation, and operative time in oncologic thyroid surgery, focusing on TT+CND and learning-curve dynamics.
Methods
We retrospectively analyzed thyroid lobectomies, total thyroidectomies (TT), and TT+CND performed at Lausanne University Hospital (2016–2022). Data on IP, FSE, PG reimplantation, and operative time were extracted from operative and pathology reports. The multi-surgeon cohort ($n = 136$) was analyzed using standard and Covariate Balancing Propensity Score methods. A nested single-surgeon subcohort ($n = 98$) underwent multivariable linear regression including NIRAF use, case order, surgery type, and interactions to model learning-curve effects.
Results
In the full cohort, NIRAF use was associated with substantially fewer IP and FSE in both unweighted and weighted analyses, while PG reimplantation rates and operative times were similar. In the TT+CND subcohort ($n = 44$), these reductions were more pronounced, again without differences in reimplantations or duration. In the single-surgeon analysis, NIRAF showed no strong overall effect on IP or FSE but significantly improved both in TT+CND. Introduced at the 33rd operation, NIRAF rapidly reduced PG reimplantations early in the learning curve across surgery types, with no effect later. Operative time remained unaffected. Results were consistent across sensitivity analyses.
Conclusions
NIRAF was associated with fewer IPs and FSE in oncologic thyroid surgery, particularly TT+CND. Single-surgeon analyses confirmed that benefits are concentrated in complex procedures and that NIRAF may reduce PG reimplantations early in the learning curve, without prolonging surgery.

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Poster Session 2 TH Action

PS2-01-01

Optimization of the thyroid peroxidase inhibition assay in protein extracts derived from EX VIVO

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Thyroid peroxidase (TPO) is a pivotal enzyme for synthesizing thyroid hormones. A recent assay known as Amplex UltraRed (AUR) has been developed for the detection of TPO activity. In this report, a step-by-step protocol was optimized for the extraction of TPO-rich protein from fresh and frozen thyroid tissue samples obtained from surgical procedures. The tissue was divided into two fractions (frozen and fresh), followed by lysing and sonication. The quantification of total protein extracts was performed using the BCA Protein protocol. A comparative analysis was conducted on the protein extracts, utilising the AUR assay, in basal condition and following treatment with specific TPO inhibitors, MMI (methimazole) and PTU (propylthiouracil). By applying this optimized assay, TPO activity can be detected in lysates from fresh and thawed human thyroid tissues, with no statistically significant differences between the two conditions evaluated. Furthermore, the TPO activity present within both lysates, derived from fresh and thawed human thyroid tissues, is similarly suppressed by both MMI and PTU. Our new approach offers a biological context that more closely reflects the *in vivo* human system while reducing the need for large cell batches, costs and procedures that can alter cellular phenotype over time. More importantly, it facilitates the storage of tissue samples collected at different time points, thereby eliminating the necessity for immediate processing. Consequently, experiments can be planned and organized more efficiently.

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PS2-01-02

Cell-specific functions of thyroid hormone transporters Mct8/Oatp1c1 in myelin formation and repair in the murine CNS

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Abnormal myelination is a key hallmark of patients with an inactive thyroid hormone (TH) transporter MCT8 (Allan-Herndon-Dudley syndrome (AHDS)). Similarly, a combined inactivation of TH transporters Mct8 and Oatp1c1 in mice (DKO mice) causes a persistent hypomyelination and reduced expression of myelin associated genes. Since TH is well-established to regulate oligodendroglia differentiation, this phenotype may be explained by the profound TH deficient state of the CNS in DKO mice. Additionally, combined Mct8/Oatp1c1 deletion may also lead to an impaired TH uptake into mature oligodendrocytes and/or oligodendrocyte precursor cells (OPC), independent of the brain TH content. Here, we aim to clarify the exact cell-specific function of TH transporters within oligodendroglia maturation. Such knowledge is not only of clinical relevance for AHDS patients, but also important for patients with demyelinating diseases, as TH application is considered as a therapeutic option for promoting re-myelination. To determine the cell-specific function of Mct8/Oatp1c1 in myelination, so-called OL CKO mice were generated that lack both transporters only in cells of the oligodendroglia lineage. Neural maturation and myelination were assessed by immunofluorescence and*in situ* hybridization studies at different postnatal time points, while oligodendrocyte precursor cells (OPC), pre-myelinating and myelinating oligodendrocytes were visualized by co-immuno-labeling. Abundance of myelin sheaths-related proteins Mbp and Cnp was found to be significantly reduced in OL CKO mice at postnatal day P12, but reached normal levels at P21 and P120, indicating a transient hypomyelination in these animals. In line with these findings, quantification of OPC, pre-myelinating and myelinating oligodendrocytes disclosed a strongly reduced number of mature oligodendrocytes at P6 and P12, while cell numbers normalized in adult OL CKO mice. Altogether, these data indicate an oligodendroglia differentiation blockage in young OL CKO mice and indeed point to a critical cell-autonomous function of Mct8/Oatp1c1 in oligodendroglia lineage progression. We wondered whether a similar blockage would also occur in adult mice lacking Mct8/Oatp1c1 in the oligodendroglia lineage. To test this hypothesis, both TH transporters were specifically inactivated either in neural stem cells (NSC) or in OPC in adulthood. After inactivation, the animals were fed cuprizone for six weeks, which leads to the death of mature oligodendrocytes and subsequently triggers the activation of NSC. These activated NSC then differentiate into OPC which finally mature into new myelinating oligodendrocytes. Ongoing studies are expected to reveal to which extent the deletion of Mct8/Oatp1c1 in either NSC or OPC compromises oligodendroglia maturation and therefore proper myelin repair.

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PS2-01-03

Development of transcriptomic scores to characterize thyroid hormone deficiency and levothyroxine treatment response

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Primary hypothyroidism results from impaired thyroid hormone production and is commonly treated with levothyroxine therapy. Although serum thyroid-stimulating hormone (TSH) remains the standard clinical biomarker for monitoring treatment adequacy, systemic molecular changes associated with thyroid hormone deficiency remain poorly characterized. They could be useful for adequate thyroid hormone tissue evaluation, especially in situations with non-trustworthy TSH, such as macroTSH or heterophil antibody. This study aimed to identify transcriptomic signatures associated with distinct thyroid functional states and to develop transcriptomic scores reflecting both the molecular signature of thyroid hormone deficiency and the systemic response to levothyroxine therapy.

Methods

A total of 320 individuals were initially evaluated, and 16 participants were included in the final analysis. Participants were classified into four clinically thyroid functional groups: euthyroid controls without thyroid disease (Control), levothyroxine-treated patients within the therapeutic target (LT4 on target; TSH 0.5–2.0 mU/L), levothyroxine-treated patients outside the therapeutic target (LT4 out of target; TSH 4.0–20.0 mU/L), and untreated overt hypothyroidism (Hypothyroidism), with samples collected at the time of diagnosis (TSH $>$ 20 mU/L) before initiation of therapy. Peripheral blood RNA was collected in PAXgene tubes and extracted using the PAXgene Blood RNA Kit (Qiagen). Transcriptome libraries were generated using the Ion AmpliSeq™ Human Gene Expression panel and sequenced on the Ion Proton platform. Differential gene expression analysis was performed using PyDESeq2, and gene annotations were obtained from the MyGene database. Significant genes were defined using FDR correction (FDR $<$ 0.05). A weighted transcriptomic score was generated from normalized expression values weighted by log2 fold changes. Two transcriptomic scores were derived: a disease score based on differential expression between Control and Hypothyroidism, and a treatment response score based on comparisons between LT4 on target and LT4 out of target. Group differences in transcriptomic scores were evaluated using one-way ANOVA followed by Tukey's post hoc test.

Results

Unsupervised analyses demonstrated clear separation between Control and Hypothyroidism for the disease score and between LT4 on target and LT4 out of target for the treatment response score. Principal component analysis explained 65.9% of the variance in PC1 for the disease score and 82.5% for the treatment response score. The disease score showed a graded distribution across groups. Differences in the disease score among groups were statistically significant, and confirmed the contrast between Control and Hypothyroidism ($P < 0.001$). The treatment response score significantly differentiated LT4 on target from LT4 out of target ($P = 0.001$).

Conclusion

Circulating transcriptomic profiles capture both hypothyroidism and the response to levothyroxine therapy. These findings support the potential of transcriptomic biomarkers to complement biochemical monitoring and improve molecular stratification of patients with hypothyroidism.

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PS2-01-04

T3 reverses hippocampal microglial activation and exploratory deficits in diabetic rats

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Alloxan-induced diabetes causes central hypothyroidism and hippocampal neuroinflammation, potentially contributing to behavioural impairment. The therapeutic potential of T3 supplementation remains unclear. We investigated whether T3 modulates plasma thyroid hormones, exploratory behaviour, and hippocampal microglial activation in diabetic Wistar rats. Male Wistar rats received alloxan monohydrate (150 mg/kg i.p., dissolved in 10 mM sodium citrate pH 4.5, after 16h fasting) to induce diabetes, confirmed by tail vein puncture (fasting glucose $\geq$250 mg/dl). Groups were: healthy controls (C, vehicle 10 mM sodium citrate pH 4.5 i.p.), untreated diabetic (DM, vehicle), and T3-treated diabetic (T3, 1.5 µg/100g body weight i.p. for 60 days, n = 28-30 total). Serum thyroid hormones were measured by Luminex assay (pg/ml). Exploratory behaviour was assessed in Open Field (5 min). IBA-1 immunohistochemistry quantified microglial density (arbitrary units) in hippocampal CA1 and dentate gyrus. Data were analysed using parametric (ANOVA, t-tests) or non-parametric tests following Shapiro-Wilk normality assessment ($P < 0.05$). Diabetes was confirmed by fasting hyperglycaemia and central hypothyroidism in DM rats [T4: 38655$\pm$5284 vs 66881$\pm$10901 pg/ml ($P = 0.001$); TSH: 870.5$\pm$496.1 vs 2033$\pm$1233 pg/ml ($P = 0.035$)], with unchanged T3 [3448$\pm$531 vs 3634$\pm$941 pg/ml ($P = 0.905$)]. Diabetic rats showed reduced exploratory behaviour in Open Field [zone entries: 8.7$\pm$5.2 vs 16.6$\pm$8.5 ($P = 0.047$); rearings: 8.7$\pm$5.2 vs 20.1$\pm$6.8 s ($P = 0.004$)]. T3 treatment restored exploration to control levels

[zone entries: 19.8 ± 6.3 ($P = 0.004$ vs DM); rearings: 21.1 ± 8.4 s ($P = 0.002$ vs DM)]. Hippocampal IBA-1 density was increased in diabetic rats [CA1: 9424 ± 2974 vs 4744 ± 5203 ($P = 0.047$); dentate gyrus: 5992 ± 3881 vs 1175 ± 1064 ($P = 0.019$)], and T3 reduced microglial activation [CA1: 3299 ± 1566 ($P = 0.047$ vs DM); dentate gyrus: 1368 ± 720 ($P = 0.023$ vs DM)]. T3 reverses hippocampal microglial activation and exploratory deficits despite no change in systemic T4/TSH levels. These findings demonstrate direct CNS thyroid hormone effects independent of peripheral hormone restoration, supporting thyroid signalling as a therapeutic target for diabetes-related neuroinflammation.

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PS2-01-05

Novel insights into the neuroprotective action of synthetic thyronamine-like TAAR1 agonists

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Background
Alzheimer's disease (AD) is a progressive neurodegenerative disorder that acts as a complex multifactorial process, involving protein homeostasis disruption, microglia-mediated inflammation, and metabolic dysfunction. This pathological complexity represents a major barrier in the quest for AD therapies. Recently developed thyronamine-like analogue **SG2**, and its prodrugs **SG22** and **SG23** have been proposed as promising multi-target therapeutics for AD [doi: 10.3390/ph14121330]. To gain more insights into the working mechanisms responsible of the pleiotropic neuroprotective action of these novel drug candidates, in the present study we investigated the ability of **SG2**, **SG22** and **SG23** to prevent microglia pro-inflammatory (M1) response induced by LPS/ TNFα or Amyloid-beta25-35 (Aß25-35), and to promote fitness recovery in *C. elegans* models of AD.
Methods
Human microglial cells (HMC3) were exposed to pretreatment with increasing doses (0.1, 1.0 and 10 μM) of test compounds for 1h followed by stimulation with LPS (10 μg/ml)/ TNFα (50ng/ml) for 24h or with 10μM $A\beta_{25-35}$ for 24h. Then, culture media were collected and the concentrations of pro-inflammatory (IL6) and anti-inflammatory (IL10) interleukins were determined by specific ELISA assays. A previously developed C. elegans strain, which expresses full-length human Aß1-42 in muscle cells [doi: 10.3390/ph14121330], was utilized as a model to assess the ability of test compounds to mitigate Aβ-induced paralysis. Double transgenic C. elegans strain expressing both Aβ1-42 and GFP-tagged LGG-1 (the worm orthologue of human LC3) [doi: 10.3390/ph14121330], was used as a key model to study the interplay between Aβ-induced proteotoxicity and autophagic activity (ATG).
Results
Thyronamine-like agents were found to have a significant ($P < 0.05$) TAAR1-mediated ability to decrease the inflammatory phenotype of HMC3 cells stimulated with LPS/ TNFα or $A\beta_{25-35}$. Treatment of *C.elegans* expressing Aβ1-42 with 10 μM **SG2** confirmed previously observed results [doi: 10.3390/ph14121330), with a significant recovery of motility ($P < 0.01$) starting at Day 5 of treatment. Administration of **SG22** or **SG23** at 10 μM dosage revealed a delayed onset of recovering effects, with analog **SG22** resulting almost ineffective. Real time quantification of ATG-related genes displayed that treatment with 10 μM **SG2** or **SG23** may contribute to promote fitness recovery by ATG activation in double transgenic C. elegans model.
Conclusions
These results indicate that thyronamine-like TAAR1 agonist **SG2** and its prodrug **SG23** could represent valuable pharmaceutical tools against AD.

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PS2-01-06

Dietary iodine strongly modulates hepatic transcriptome in hyperthyroid mice with a constitutively active TSHR M453T variant

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Objectives
Thyroid hormones are key regulators of systemic metabolism and strongly influence hepatic lipid metabolism and energy homeostasis. Hyperthyroidism is associated with metabolic alterations and liver dysfunction, yet the hepatic transcriptional programs underlying these effects remain poorly understood. This study aimed to identify liver gene expression changes in a non-autoimmune hyperthyroid (NAH) mouse model carrying a human-derived constitutively activating TSHR M453T variant under sufficient and high iodine conditions.
Methods
Liver transcriptomes were analysed in 2-month-old female and male mice homozygous for the constitutively active TSHR M453T mutation (HOM) and compared with wild-type (WT) controls under sufficient (0.3 mg/kg) or high (6 mg/kg) iodine diets. Differential gene expression analysis was performed using DESeq2.
Results
HOM vs WT comparisons revealed substantially more differentially expressed genes (DEGs) under sufficient iodine diet (448 DEGs in Female, 527 in Male) than under high iodine diet (48 DEGs in Female, and 3 DEGs in Male), with no key thyroid-specific, liver-specific lipid, bile, or energy metabolism genes differentially expressed under high iodine conditions. Under sufficient iodine diet, HOM mice of both sexes showed strong upregulation of the thyroid hormone-activating deiodinase *Dio1* and metabolic genes *Cyp4a31* and *Acot11*. Bile acid synthesis regulators *Cyp7b1* and *Sult2A1* as well as cAMP-producing *Adcy10* were upregulated exclusively in HOM females, whereas liver stress response genes *ERK7, JunB, USP2, Aldh3b3*, the detoxification regulator *Ugt1a9*, and the fatty liver disease-linked *NR1H4* were downregulated in HOM females. *SLC16A10*, encoding the thyroid hormone transporter MCT10, was upregulated in HOM females, while *Serpina7*, encoding thyroxine-binding globulin (TBG), was downregulated in HOM mice of both sexes. KEGG pathway analysis detected no enriched pathways in high iodine samples. Under sufficient iodine conditions, metabolic pathways, retinol metabolism, and chemical carcinogenesis pathways were enriched in HOM of both sexes. Steroid hormone biosynthesis, arachidonic and linoleic acid metabolism were enriched exclusively in HOM females, whereas thermogenesis, oxidative phosphorylation, and diabetic cardiomyopathy pathways were enriched in HOM males.
Conclusions
Constitutive TSHR activation induces broad hepatic transcriptional changes reflecting altered bile acid and fatty acid metabolism, with the magnitude and nature of these responses strongly dependent of dietary iodine intake. Notably, iodine restriction in our model, amplifies transcriptional responses to hyperthyroidism thus highlighting the important modulatory role of dietary iodine in the NAH thyroid and thyroid hormone-driven hepatic gene regulation.

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PS2-01-07

Unravelling the complex relationship between thyroid function and depression: a BI-directional mendelian randomization study

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Objectives
Observational studies have shown associations between thyroid function and depression. However, the underlying biological mechanisms remain unclear. Thyroid dysfunction may contribute to the development of depression, while conversely, depression could also influence thyroid function. As observational studies are prone to residual confounding and reverse causality, we performed bi-directional Mendelian Randomization (MR) analyses to investigate potential causality between depression and concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and the FT3/FT4 ratio.
Methods
Independent, genome-wide significant genetic variants were selected from the latest genome-wide association study (GWAS) of depression conducted by the Psychiatric Genomics Consortium (European ancestry only, N_{cases} = 412,305, $N_{controls}$ = 1,588,397). For thyroid hormone levels, variants were selected from GWAS in euthyroid individuals of European ancestry conducted by the ThyroidOmics Consortium (N_{TSH} = 271,040, N_{FT4} = 119,120, N_{FT3} = 59,061, $N_{FT3/FT4}$ = 51,095). MR-PRESSO and Steiger filtering were applied to exclude invalid

instrumental variants. Causal effects were estimated using the inverse variance weighted method, with a significance threshold of $P < 0.0125$ to correct for multiple-testing. Additional sensitivity analyses were employed to assess the robustness of the findings.
Results
Genetic liability to depression was associated with a decrease of 0.042 standard deviations (SD) in TSH levels (95%CI = [-0.066, -0.019], $P = 3.94\times10^{-4}$). In the reverse direction, a 1 SD increase in TSH levels was associated with an increased risk for depression (odds ratio (OR) = 1.028, 95%CI = [1.010, 1.045], $P = 1.56\times10^{-3}$). Additionally, a 1 SD increase in FT3 levels was nominally associated with reduced depression risk (OR = 0.942, 95%CI = [0.892, 0.995], $P = 0.032$).
Conclusions
Our MR results suggest a bidirectional relationship between thyroid hormone levels and depression. Genetic liability to depression was associated with lower TSH levels, which is also biologically plausible as the lower TSH levels can be due to non-thyroidal illness. Vice versa, higher TSH levels were linked to increased depression risk, which is in line with previous studies showing that lower thyroid function is associated with a higher risk of depression. Higher FT3 showed a nominally significant protective effect. Although effect sizes were small, they might be clinically relevant as they reflect a lifelong exposure. These findings highlight potential causal links between depression and thyroid function that warrant further investigation to clarify underlying mechanisms.

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PS2-01-08

FOXE1 and Dyrk1A interaction: a mechanism of primary hypothyroidism in down syndrome

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Background
Non-autoimmune hypothyroidism is frequent in Down syndrome (DS) (1/141 births). Dyrk1A located on chr21 is a candidate gene to thyroid dysgenesis. Our previous work showed altered thyroid development in a transgenic mouse model overexpressing Dyrk1A. This study investigates whether Dyrk1A interacts with molecules directly involved in thyroid development leading to hypothyroidism.
Methods
Thyroids from transgenic embryos and wild-type were examined at E13.5 and E15.5. A DYRK1A consensus phosphorylation site (RPX(S/T)P) was identified on FOXE1. Human immortalized thyroid Nthy-ori-3.1 cells were transfected with pFlag-hFOXE1, pGFP-Dyrk1A. Expression of key thyroid developmental genes (*NKX2-1, FOXE1, PAX8, TG, TPO, NIS*), co immunoprecipitation after transfection with pGFP-Dyrk1A, pFlag-hFOXE1 or pFlag-mutant hFOXE1 lacking the consensus site were performed.
Results
At E15.5, Foxe1 protein was increased in Dyrk1A overexpressing murine thyroids. In Nthy cells, pGFP-Dyrk1A transfection significantly upregulated *TG, NIS*, and *TPO* expression with additive significant increases in *TG* and *NIS* when co-transfected with pFlag-hFOXE1. Co immunoprecipitation confirmed a physical interaction between DYRK1A and FOXE1, absent with the mutant FOXE1. However, transfection with pGFP-Dyrk1A and pFlag-mutant hFOXE1 still displayed *TG* and *NIS* upregulation, suggesting that loss of physical interaction does not diminish the transcriptional effects. Human foetal thyroids confirmed increased NIS staining level in DS foetal thyroids compared to controls.
Conclusions
Murine foetal thyroids overexpressing Dyrk1A exhibited increased FoxE1 protein. Dyrk1A overexpression leads to *TG* and *NIS* overexpression, with an additive effect with FOXE1 overexpression. For the first time, we show an interaction between Dyrk1A and FOXE1, leading to NIS activation which can explain hypothyroidism of DS patients.

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TED Basic

PS2-02-01

Expression pattern of chemokine CCL21 in thyroid eye disease and its potential inflammation-related role

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Objective
Thyroid eye disease (TED) is an autoimmune disorder characterized by immune-inflammatory responses and orbital tissue remodeling. Chemokines play important roles in regulating the immune microenvironment in TED, but their precise mechanisms remain to be fully elucidated. In our previous transcriptomic analysis, chemokine CCL21 was found to be significantly upregulated in retro-orbital tissues from patients with active TED. This study aimed to further validate the expression pattern of CCL21 in TED and to preliminarily investigate its potential inflammation-related role.
Methods
CCL21 protein expression in retro-orbital tissues from TED patients was assessed by immunohistochemistry. Serum CCL21 levels were measured by enzyme-linked immunosorbent assay (ELISA). Gene set enrichment analysis (GSEA) was further performed to explore the potential biological functions associated with CCL21. In addition, primary cultured orbital fibroblasts (OFs) were stimulated with recombinant CCL21 *in vitro*, and the expression changes of inflammation-related factors were evaluated to assess the inflammatory regulatory role of CCL21.
Results
Immunohistochemical analysis showed that CCL21 expression was markedly higher in TED orbital tissues than in normal controls, with even higher expression in active TED. Serum analysis likewise demonstrated significantly elevated CCL21 levels in TED patients. GSEA indicated that genes associated with high CCL21 expression were mainly enriched in pathways related to keratinization, keratin filament organization, ion channel activity, and regulation of signaling receptor activity. *in vitro* experiments further showed that CCL21 stimulation upregulated the expression of multiple inflammation-related factors in orbital fibroblasts, suggesting that CCL21 may participate in TED-related inflammatory responses.
Conclusion
CCL21 is significantly elevated in both orbital tissues and peripheral blood of TED patients and may contribute to TED pathogenesis by promoting inflammatory responses in orbital fibroblasts. CCL21 may serve as a potential inflammation-related biomarker in TED and provides a new clue for further investigation of the immune-inflammatory mechanisms underlying the disease.

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PS2-02-02

Prostaglandin analogues attenuate hyaluronan accumulation in orbital fibroblast cultures

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Objectives
Secondary glaucoma often accompanies thyroid eye disease (TED) and is treated with prostaglandin analogues (PGAs). Long term PGA treatment leads to deepening of the upper eyelid sulcus through altered adipogenesis of orbital fibroblasts (OFs). However, pleiotropic effects of PGAs beneficial in TED has not been investigated. Besides adipogenesis, hyaluronan (HA) accumulation is a critical factor in TED. Our *in vitro* study examines the effect of PGAs on HA metabolism of OFs.

Methods
Primary OFs from TED patients ($n = 4$) and non-TED subjects ($n = 4$) were used. Cells were cultured in the presence or absence of PGAs: latanoprost, tafluprost or bimatoprost, or prostaglandin F2α (PF2α), with or without PDGF-BB (10 ng/ml) stimulation of HA synthesis. Pericellular HA and HA secreted into the culture media, as well as mRNA expressions of hyaluronan synthases (HAS1, HAS2 and HAS3) and hyaluronidases (HYAL1, HYAL2 and CEMIP) were measured by ELISA and RT-PCR, respectively. The effect of PGAs on proliferation and metabolic activity were measured using BrdU incorporation and MTT assay, respectively.
Results
While both PF2α and PGAs reduced the HA content in the pericellular coat of the fibroblasts after 72 hours ($P < 0.001$), PGAs also lowered the HA concentration in the supernatant ($P < 0.001$). Of the PGAs, only the latanoprost decreased HAS2 mRNA expression ($P < 0.001$), while all PGAs and PF2α induced the mRNA expression of CEMIP ($P < 0.001$). Various PGAs exert distinct effects on HA production following PDGF-BB stimulation. Stimulated HA content in the supernatant was reduced to or below untreated level by tafluprost and latanoprost, respectively ($P < 0.0001$ for each). Bimatoprost and PF2α were unable to counteract the stimulatory effect of PDGF-BB. However, even under PDGF-BB stimulation, PGAs and PF2α treatment led to constant decrease in HA concentration in the pericellular coat ($P < 0.0001$). The PDGF-BB induced HAS2 expression was suppressed only by latanoprost ($P < 0.001$). Basal and PDGF-BB stimulated metabolic activity and proliferation potential declined after latanoprost treatment ($P < 0.05$ and $P < 0.05$, respectively).
Conclusion
PGAs modulate HA levels in orbital fibroblasts not only by suppressing synthesis but also by promoting degradation. This dual action may offer therapeutic benefits in TED, where the progression of the disease is driven by pathological HA accumulation.

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PS2-02-03

Plasma lipidomic profiling in thyroid eye disease based on untargeted lipidomics and its association with disease activity

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Objective
Thyroid eye disease (TED) is an autoimmune disorder mainly characterized by orbital inflammation and tissue remodeling, with a complex pathogenesis. At present, studies investigating systemic lipid metabolic alterations in TED remain limited. This study aimed to systematically characterize the plasma lipidomic profile of patients with TED using untargeted lipidomics and to identify potential lipid biomarkers associated with disease activity.
Methods
A total of 80 patients with TED were enrolled in this study, including 40 patients with active moderate-to-severe TED and 40 patients with inactive mild TED. Peripheral blood plasma samples were collected and subjected to untargeted lipidomics analysis using liquid chromatography–mass spectrometry (LC–MS). Principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), and orthogonal partial least squares discriminant analysis (OPLS-DA) were performed to evaluate the overall differences in lipid metabolic profiles between the two groups. Differential lipid species were screened based on variable importance in projection (VIP) > 1 and $P < 0.05$. In addition, lipid subclass composition, carbon chain length, and degree of unsaturation were systematically analyzed.
Results
Untargeted lipidomics identified a broad range of lipid species, covering multiple lipid classes, including glycerolipids, glycerophospholipids, sphingolipids, and fatty acyls. Multivariate statistical analyses demonstrated a clear separation between active and inactive TED patients in their lipid metabolic profiles, indicating substantial lipid metabolic reprogramming associated with disease activity. Further differential analysis revealed significant alterations in several lipid subclasses between the two groups, among which triglycerides (TG), diglycerides (DG), phosphatidylcholines (PC), lysophosphatidylcholines (LPC), and sphingomyelins (SM) showed the most prominent changes. Structural analysis of fatty acids further showed marked differences in carbon chain length distribution and degree of unsaturation between the two groups, suggesting that alterations in lipid composition and structural characteristics may be involved in the inflammatory and tissue-remodeling processes of TED.
Conclusion
This study revealed significant plasma lipidomic differences across distinct disease activity states of TED, providing new insights into TED-associated metabolic abnormalities. The identified differential lipid species may serve as potential biomarkers for assessing TED disease activity and may also provide an important basis for further elucidating disease mechanisms and developing precision therapeutic strategies.

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PS2-02-04

Metabolic and lipidomic alterations underlying orbital pathology in graves' disease-associated thyroid eye disease

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Background
Graves' disease (GD) is an autoimmune disorder that can extend beyond the thyroid to cause thyroid eye disease (TED), a condition marked by orbital inflammation, adipogenesis, and tissue remodeling. While TSHR-immunized mouse models reproduce key pathological features of GD/TED, circulating thyroid hormone levels are often variable. We aimed to investigate metabolic alterations in orbital tissue, focusing on lipid and metabolite dysregulation, and their potential link to systemic thyroid hormone metabolism.
Methods
Mice were immunized with the human TSHR A-subunit plasmid to induce GD/TED or with a β-Gal control plasmid. Thyroid function was assessed via serum TT4, FT4, and FT3 measurements, and liver expression of Dio1 and Serpina7 was analyzed to evaluate thyroid hormone metabolism. Orbital tissues were collected for untargeted lipidomic and metabolomic profiling using UHPLC-QTOF mass spectrometry. Data were processed with MetaboAnalyst v6.0, including pathway and composite Z-score analyses.
Results
TSHR-immunized mice displayed thyroid histopathology consistent with hyperthyroidism, -significant alterations in circulating fT4 and fT3. Liver expression of Dio1 and Serpina7 was dysregulated, indicating altered thyroid hormone metabolism. In orbital tissue, lipidomics revealed significant changes in triglycerides (TGs), diglycerides (DGs), and ceramides, with heatmap analyses distinguishing TSHR and control groups. Metabolomics identified disruptions in folate biosynthesis, lysine degradation, and proline metabolism, with notable increases in hydroxyproline and sepiapterin. Composite Z-score analysis confirmed coordinated alterations in lipids and metabolites associated with inflammation, adipogenesis, and fibrotic remodeling.
Conclusion
Our results highlight profound lipidomic and metabolomic remodeling in the orbit of GD/TED mice, linking metabolic alterations to orbital pathology and systemic thyroid hormone dysregulation. These findings underscore the value of metabolic profiling for identifying biomarkers and therapeutic targets in TED, providing a framework for future translational studies.

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PS2-02-05

Transcriptomic analysis reveals the transcriptional features of CD34$^+$ orbital fibroblasts as key effector cells mediating trab-induced tissue remodeling in thyroid eye disease

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Objective
Thyroid eye disease (TED) is an autoimmune disorder characterized by retro-orbital inflammation and tissue remodeling. Thyrotropin receptor antibodies (TRAb) are considered key drivers in the pathogenesis and progression of TED; however, direct evidence is still lacking regarding how TRAb induces pathogenic transcriptional reprogramming in specific subsets of orbital fibroblasts. $CD34^+$ orbital fibroblasts (OFs), which exhibit distinct subset-specific features and strong tissue-remodeling potential, may represent critical cellular targets through which TRAb promotes orbital fibrosis and amplification of inflammation.
Methods
Primary OFs were isolated and cultured from retro-orbital tissues obtained from patients with TED. $CD34^+$ OFs were purified by fluorescence-activated cell sorting (FACS). To mimic TRAb stimulation, cells were treated with the stimulatory TSHR antibody M22, with unstimulated cells serving as controls. Total RNA was extracted after treatment and subjected to transcriptome sequencing. Differential expression analysis was performed using DESeq2, followed by pathway enrichment analysis to identify the key biological processes induced by TRAb stimulation.
Results
Compared with the control group, M22 stimulation induced marked transcriptional changes in $CD34^+$ OFs. Differential gene expression analysis showed that multiple genes related to extracellular matrix (ECM) structure and remodeling were significantly upregulated after TRAb stimulation, including MGP, MFAP4, FBLN1, AEBP1, PODN, SPOCK1, TIMP1, and TIMP2. In addition, the adhesion/receptor-related molecule ITGB5 and the metabolism/survival-related factor IGFBP4 also showed an upward trend. Pathway enrichment analysis revealed that differentially expressed genes were mainly enriched in ECM-receptor interaction, integrin signaling, and cytoskeleton in muscle cells, suggesting that TRAb stimulation enhances matrix sensing, adhesion signaling, and structural remodeling in $CD34^+$ OFs. Furthermore, complement and coagulation cascades and lysosome pathways were also significantly enriched, indicating that TRAb stimulation may simultaneously potentiate innate immune amplification and organelle turnover-related programs.
Conclusions
Using a FACS-purified $CD34^+$ OF model derived from patients with TED, this study demonstrates that TRAb-mimicking stimulation drives significant transcriptional reprogramming in $CD34^+$ OFs, preferentially activating an ECM–integrin–cytoskeleton tissue-remodeling program, accompanied by enhancement of complement-related innate immune and lysosomal pathways. These findings provide cell subset-level molecular evidence supporting the TRAb-driven inflammation-to-fibrosis continuum in TED and suggest that the ECM–adhesion signaling axis, represented by molecules such as MFAP4 and ITGB5, warrants further mechanistic investigation and therapeutic exploration.

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PS2-02-06

PIEZO1 receptor activation in orbital fibroblasts during adipogenic induction diminishes the accumulation of hyaluronan

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Objectives
Intraorbital tissue expansion in the pathogenesis of thyroid eye disease (TED) is the consequence of increased proliferation of orbital fibroblasts (OFs), adipocyte differentiation and accumulation of hyaluronan (HA). These processes, in the constraint of the anatomical structure of the orbit, lead to increased intraorbital pressure, resulting in the anterior displacement of the eyeballs. Increased pressure may activate various mechanical receptors on the surface of OFs, such as the Piezo1 channel. Previously, we have confirmed that functional Piezo1 receptor is expressed in OFs. We have found that Piezo1 activation inhibits adipogenesis in TED OFs. Our aim has been to study the effect of Piezo1 activation on HA production in response to adipogenic stimulation.
Methods
OFs were obtained from control subjects (non-TED, $n = 6$) and TED patients ($n = 5$). Mechanical stimuli were modelled by addition of the synthetic agonist of Piezo1, Yoda1 during the 12-days of adipogenic stimulation. The produced HA into the cell culture medium and into the pericellular coat were measured using ELISA. Gene expressions related to HA metabolism were evaluated by RT-PCR; HA molecular weight distribution was examined by agarose gel electrophoresis.
Results
Adipogenesis induction led to HA accumulation both in the medium ($P < 0.001$) and in the pericellular coat ($P = 0.026$), which was hindered by the Yoda1 treatment in both sites ($P = 0.005$ and $P = 0.001$, respectively), and in both TED and non-TED OFs, regardless of the absence of adipocyte differentiation in non-TED OFs. Adipogenic stimuli elevated HAS2 mRNA expression ($P = 0.011$) and decreased CEMIP expression ($P = 0.005$). Piezo1 activation reduced HAS2 ($P < 0.0001$) and elevated HYAL1 ($P = 0.004$) and CEMIP ($P = 0.015$) expressions. Gel electrophoresis analysis revealed that the application of adipocyte-stimulating medium induces the production of high molecular weight HA in orbital fibroblasts ($P < 0.001$). Yoda1 treatment led to a shift in HA fragment distribution: high molecular weight HA decreased ($P < 0.001$) while low molecular weight HA ($P = 0.003$) increased.
Conclusion
Piezo1 activation during the course of TED leads not only to diminished de novo adipogenesis but also the inhibition of HA production under adipogenic stimuli. Based on the results in non-TED OFs, this HA-modulating effect of Piezo1 is independent of whether adipogenesis actually occurs. A potential role of its HA-lowering effect in the Piezo1 mediated inhibition of adipogenesis cannot be excluded.

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PS2-02-07

Machine learning-based identification of fibrosis-related biomarkers in thyroid eye disease with experimental validation

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Objective
Fibrosis is a critical pathological feature of tissue remodeling and disease progression in thyroid eye disease (TED). However, the underlying molecular mechanisms and reliable molecular biomarkers remain incompletely understood. Bioinformatics approaches enable the identification of disease-related differentially expressed genes through transcriptomic analysis and facilitate the discovery of potential key molecular regulators. Nevertheless, distinguishing biologically meaningful and diagnostically relevant genes from complex gene expression datasets remains challenging. Integrating machine learning algorithms can improve feature selection accuracy and provide powerful tools for identifying novel disease-related biomarkers.
Methods
In this study, fibrosis-related differentially expressed genes (FR-DEGs) were first identified based on a fibrosis-related gene set. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were subsequently performed to explore their potential biological functions and signaling pathways. Multiple machine learning algorithms, including least absolute shrinkage and selection operator (LASSO), support vector machine–recursive feature elimination (SVM-RFE), and random forest (RF), were applied to identify key fibrosis-related diagnostic genes. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of candidate genes. Furthermore, single-gene gene set enrichment analysis (GSEA) was performed to investigate the potential functional mechanisms of the identified core genes. Single-sample gene set enrichment analysis (ssGSEA) was used to estimate the relative levels of immune cell infiltration in each sample and to analyze the correlations between key genes and infiltrating immune cells. Finally, immunohistochemical staining was performed on orbital tissues from TED patients and normal controls, followed by quantitative analysis using an automated image analysis system.

Results
A series of FR-DEGs were identified based on the fibrosis-related gene set. GO and KEGG enrichment analyses indicated that these genes were primarily involved in biological processes such as cell chemotaxis, regulation of angiogenesis, cytokine signaling pathways, and growth factor–related signaling pathways, suggesting that inflammatory responses and tissue remodeling play crucial roles in TED-associated fibrosis. By integrating three machine learning methods (LASSO, SVM-RFE, and RF), three key fibrosis-related genes—COMP, SLC38A1, and CHI3L1—were identified. ROC curve analysis demonstrated that these genes exhibited promising diagnostic potential. Immune infiltration analysis and correlation analysis further revealed significant associations between these three fibrosis-related genes and multiple infiltrating immune cell populations. Immunohistochemical validation further confirmed that COMP, SLC38A1, and CHI3L1 were significantly upregulated in orbital tissues from TED patients compared with normal controls.
Conclusion
By integrating bioinformatics analysis, machine learning approaches, and immune infiltration analysis, this study identified COMP, SLC38A1, and CHI3L1 as potential fibrosis-related key genes in TED. These findings provide new insights into the molecular mechanisms underlying fibrosis in TED and suggest that these genes may serve as potential diagnostic biomarkers and therapeutic targets for the disease.
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PS2-02-08

Expression of mtor in orbital tissue from patients with graves orbitopathy and relationship with severity and activity
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Objectives
mTOR (molecular target of rapamycin) is a ubiquitous serine/threonine kinase belonging to the phosphatidylinositol 3-kinase-related kinase (PIKK) family and involved in the regulation of cell metabolism and growth, and of the immune system. mTOR binds to several proteins, thereby forming two distinct complexes, namely mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), being their downstream networks mutually linked. Several studies have shown that mTOR is involved in the pathogenesis of Graves' orbitopathy (GO). Based on this evidence, rapamycin, better known as sirolimus, a common mTOR inhibitor, has been used as a second-line treatment in GO patients, with rather successful outcomes. Recently, we found that a soluble form of mTOR is present in the serum of GO patients to a greater extent than in patients with Graves' hyperthyroidism without GO, with a significant correlation with GO severity, activity, and with serum anti-TSH receptor autoantibodies. In the present study, we investigated mTOR expression in orbital tissues from patients with GO by immunohistochemistry.
Methods
Fibroadipose orbital tissues samples were collected at surgery from 12 patients with previously untreated GO [four men and eight women, age 43.4 yr. (12.6)], who underwent orbital decompression for disfiguring proptosis, (ten patients, five with mild GO and five with moderate-to-severe GO), or for sight-threatening GO (two patients). Tissue samples were fixed in formalin and embedded in paraffin and immunohistochemistry was performed using the Ventana Benchmark system. To detect mTOR, a monoclonal antibody was used.
Results
Staining for mTOR was observed in orbital fibroblasts of 7/12 patients (58.3%), mainly intracellularly. mTOR was detected in 6/7 patients (85.7%) with moderate-to-severe GO, as per European Group on Graves' Orbitopathy guidelines, whereas it was present only in 1/5 patients (20%) with mild GO, with a statistically significant difference (OR: 24; 95% CI from 1.1 to 505.2; $P = 0.0409$). Moreover, there was a trend towards a more frequent positive staining for mTOR in patients with active GO, than in those with inactive GO, although the difference did not reach statistical significance (OR: 10; 95% CI from 0.6 to 154.4; $P = 0.099$), presumably because of the limited number of patients.
Conclusions
To our knowledge, this is the first report of mTOR in orbital tissues of patients with GO. Its association with disease severity and trendily with disease activity support a role for mTOR in GO pathogenesis and further establish a background for the use of sirolimus for GO treatment.
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PS2-02-09

The effect of hyaluronidase treatment on adipogenesis and hyaluronan accumulation of orbital fibroblasts under adipogenic stimuli
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Objectives
In thyroid eye disease (TED) hyaluronan (HA) production and adipocyte differentiation of orbital fibroblasts (OFs) increase. Adipogenesis further exacerbates HA accumulation, but the contribution of undifferentiated fibroblasts and adipocytes in heterogeneous OF cultures to the increased HA production, and the effect of HA elimination on the differentiation process has not been investigated. The aim of our study was to examine HA turnover during adipogenesis in OF cultures as a whole and in separated cell types, as well as to clarify how HA deprivation by external hyaluronidase (HYAL) affects the adipocyte differentiation in OF cultures.
Methods
We examined adipocyte differentiation in OFs derived from the orbital connective tissue of TED patients ($n = 7$). Adipogenic induction was used for 12 days, in the presence or absence of HYAL. HA concentration in the supernatant and in the pericellular coat was measured by ELISA. The lipid accumulation was verified by Oil Red O (ORO) staining. The mRNA expression of the enzymes of HA metabolism, HA synthases and hyaluronidases, and regulators of adipogenesis, peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (CEBPα), as well as the terminal marker fatty acid binding protein 4 (FABP4), were measured by RT-PCR. On day 12, the different cell types were separated by gradient centrifugation and examined separately.
Results
A proportion of TED OFs were able to differentiate into adipocytes within 12 days accompanied by HA accumulation, and characterized by increased HAS2 ($P < 0.05$) and decreased HYAL1 ($P < 0.01$) and CEMIP ($P < 0.05$) expression. Compared to undifferentiated fibroblasts, in the separated adipocytes the expression of HAS2 was not different, HAS1 was increased ($P < 0.05$), while HAS3 ($P < 0.01$) and HYAL1 ($P < 0.05$) were decreased; a downward trend was found in CEMIP ($P = 0.07$). After HYAL treatment, HA in the supernatant was completely degraded ($P < 0.001$), while a marked decrease was observed in the pericellular HA ($P < 0.01$). ORO staining confirmed that adipogenesis was diminished by HYAL treatment. Among the transcription factors, PPARγ ($P < 0.01$) and CEBPα ($P < 0.05$) as well as FABP4 ($P < 0.05$) expressions were decreased.
Conclusion
Our findings indicate that both adipocytes and undifferentiated fibroblasts contribute to the HA accumulation with higher synthesis by the dominant synthase HAS2 under adipogenic stimuli, while adipocytes express less amount of hyaluronidases. Adipogenesis can be inhibited by HA degradation using exogenous hyaluronidase. Two important contributors to the pathogenesis of TED, HA accumulation and adipogenesis, can be reduced by HYAL treatment.
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PS2-02-10

Plasma proteomics reveals protein expression profiles and potential biomarkers across different disease stages of thyroid eye disease
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Objective
Thyroid eye disease (TED) is an autoimmune disorder characterized primarily by orbital inflammation and tissue remodeling. Its pathogenesis is complex, and there is still a lack of systemic biomarkers that can effectively assess disease activity and severity. This study aimed to systematically characterize the plasma proteomic profiles of TED at different disease stages and to identify potential disease-related molecular biomarkers.
Methods
Peripheral blood plasma samples were collected from patients with TED and healthy controls. High-throughput quantitative proteomic analysis was performed using data-independent acquisition (DIA)-based proteomics on the Astral platform. Multivariate statistical analysis and bioinformatics approaches were applied to systematically analyze protein expression profiles, including differential protein screening, functional annotation, and pathway enrichment analysis, in order to explore the molecular features of TED across different disease stages.
Results
A total of 4,232 proteins were identified by proteomic analysis, of which 3,925 were reliably quantified. Differential expression analysis demonstrated marked differences in plasma protein profiles between TED patients and healthy controls, as well as distinct expression changes across different disease stages. Pairwise comparisons identified hundreds of differentially expressed proteins, while multigroup analysis further revealed 1,222 significantly differentially expressed proteins. Functional enrichment analysis showed that these proteins were mainly involved in biological processes such as immune and inflammatory responses, complement and coagulation cascades, extracellular matrix remodeling, and metabolism-related pathways, suggesting that the onset and progression of TED may be accompanied by systemic alterations in immune regulation and tissue remodeling-related protein networks.
Conclusions
This study systematically delineated the plasma proteomic landscape of TED across different disease stages, revealed potential molecular pathways associated with disease activity, and identified a series of candidate protein biomarkers with possible diagnostic and mechanistic relevance. These findings provide an important basis for further elucidating the molecular mechanisms of TED and for developing novel strategies for disease evaluation and therapeutic targeting.
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Basic Cancer 3

PS2-03-01

Expanding the spectrum of anti-cancer effects of the antibiotic clofoctol in human thyroid cells *in vitro*

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Purpose
Clofoctol showed anticancer activities in several type of cancers. However, whether it could modulate chemokines secreted in thyroid cancer microenvironment is still unknown. The present study aims to evaluate whether Clofoctol exerts anti-cancer effect and modulates the secretion of two pro-tumorigenic chemokines (CXCL8 and CCL2) on thyroid cancer cells.
Experimental design: Nthy-ori 3-1, BCPAP and TPC-1 were treated by increasing concentrations of Clofoctol (0; 5; 10; 15; 30; 100 μM) for 24-48-72 hours. Cell viability, proliferation and colonies were assesed by WST-1 and cristal violet, respectively. Oxidative stress was evaluated by confocal microscopy. CXCL8 and CCL2 levels were measured by ELISA and their mRNA levels were measured by RT-PCR.
Results
Clofoctol reduced cell viability in Nthy-ori 3-1 and BCPAP only at the highest concentration at all time points. In TPC-1 the viability was reduced already starting from 30μM after 72 hours. Cell proliferation was reduced at high concentrations at all time points in all the cells. Clofoctol inhibited the colonies formation in both BCPAP and TPC-1 cells. Increasing concentrations of Clofoctol induced vacuolization and oxidative stress in all cells. After Clofoctol treatment the secretion of CXCL8 and CCL2 and their mRNA expression levels were reduced in all conditions tested.
Conclusions
Clofoctol reduces the viability, proliferation and the ability to form colonies in the thyroid cell lines. Clofoctol induces endoplasmic reticulum stress with a marked vacuolization. Finally, it inhibits the expression and secretion of CXCL8 and CCL2 in thyroid cells. These results expand the spectrum of Clofoctol anti-cancer effects.
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PS2-03-02

PPARGC1A as an epigenetic biomarker of differentiation in differentiated thyroid cancer

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Although most differentiated thyroid cancer (DTC) patients have a favourable prognosis, some patients become refractory to standard radioiodine treatment. Identifying effective prognostic biomarkers and long-term therapies is key to improve the management of these patients. Radioiodine-refractory patients present dedifferentiated tumours, having lost some or most of their thyrocyte-specific features. As DTC typically shows few genetic alterations, epigenetics has been considered as a field to be explored in this disease, but its role in thyroid cancer dedifferentiation is poorly understood. Our aim is to study the epigenetic mechanisms involved in DTC dedifferentiation to identify new prognostic biomarkers as well as potential therapeutic targets. We identified a set of epigenetic-related genes whose expression correlates with thyroid differentiation levels by analysing the association between DTC tumour differentiation and epigenetics-associated gene expression in publicly available datasets. Tumour differentiation was defined using the Thyroid Differentiation Score (TDS) from TCGA. We selected *PPARGC1A*, an epigenetic and metabolic master regulator, as our main candidate to be a prognostic biomarker in DTC. Its expression strongly correlates with TDS in patient samples and multiple *in vitro* models, suggesting its role in DTC dedifferentiation. Moreover, *PPARGC1A* expression is also associated with other clinical prognostic markers, such as risk of recurrence. Consistent with these observations, *PPARGC1A* expression increases during thyroid development, as shown by RNA-seq analysis of thyroid follicle differentiation from human embryonic stem cells. Similarly, thyroid cancer redifferentiation models, including treatments with LY294002 (PI3K inhibitor), PD325901 (ERK/MAPK inhibitor), Trichostatin A (histone deacetylase inhibitor) and 5-azacytidine (DNA methyltransferase inhibitor), also resulted in an increased *PPARGC1A* expression alongside the TDS, reinforcing the link between *PPARGC1A* and differentiation state. Modifying the expression of our candidate *in vitro* resulted in a change in the expression of TDS-associated genes, indicating that this factor may influence the differentiation status of thyroid cancer cells. Ongoing studies on PPARGC1A localisation and function will elucidate the role of PPARGC1A in DTC. In conclusion, we have identified PPARGC1A as an epigenetic factor with a great potential as a biomarker of differentiation in DTC. Understanding its role may provide new insights into tumour dedifferentiation and open new avenues for therapeutic strategies in advanced thyroid carcinomas.
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PS2-03-03

Selective early genetic screening for targetable gene fusions in papillary thyroid carcinoma: clinical predictors and a predictive model

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Objectives
Papillary thyroid carcinoma (PTC) shows a low rate of somatic mutations, with BRAF V600E being the most common alteration and ~15% of cases driven by gene fusions. Although prognosis is excellent, a subset develops advanced disease requiring systemic therapy. Molecularly targeted treatment may improve outcomes, but DNA degradation in paraffin-embedded tissue and high costs make universal next-generation sequencing (NGS) unfeasible. Early identification of patients who may benefit from molecular profiling is therefore required. This study evaluates clinical factors enabling selective genetic screening in PTC.
Methods
Since 2022, molecular profiling of cancer tissues using NGS has been performed in 83 PTC patients. Patients were selected based on features suggestive of aggressive disease, including extensive lymph node metastases, early recurrence, distant metastases, or repeated surgery. The cohort included 26 males and 57 females with a mean age of 47 years. Clinical variables included among others age at diagnosis, sex, extranodal extension (ENE), lymph node metastasis size (categorized), and lateral lymph node involvement. Associations with gene rearrangements were assessed using nonparametric tests, chi-square analyses, and logistic regression. A multivariable predictive model evaluated combined clinical predictors.
Results
Gene fusions were identified in 25 patients. Fusion-positive patients were significantly younger than fusion-negative individuals (median 36 vs. 49 years; $P < 0.001$). Logistic regression showed each additional year of age decreased the odds of fusion by approximately 6% (Exp(B) = 0.94, 95% CI 0.91–0.98). Fusions were more frequent in females than males (38.6% vs. 11.5%, $P = 0.013$). Increasing lymph node metastasis size was associated with higher odds of fusion ($P = 0.003$), with metastases >10 mm conferring a 4.5-fold increased risk (OR = 4.53, 95% CI 1.60–12.87). Extranodal extension was also associated with fusions (46.4% vs. 23.5%, OR = 2.82, 95% CI 1.05–7.54). Lateral lymph node involvement similarly increased the likelihood of fusions (45.0% vs. 16.3%, OR = 4.21, 95% CI 1.52–11.69). A multivariable model incorporating age, sex, lymph node metastasis size, and lateral lymph node involvement showed good predictive performance (AUC = 0.815). At the optimal cutoff value, the sensitivity was 75%, and specificity 81.6%.
Conclusions
Gene fusions in PTC are associated with a distinct clinical phenotype characterized by younger age and aggressive nodal disease. A simple clinical model combining age and nodal characteristics predicts fusion likelihood with good accuracy and may guide early selective molecular testing in patients most likely to benefit from targeted therapy.

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PS2-03-04

Abstract Withwrawn

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PS2-03-05

Genetic landscape of a series of sporadic differentiated thyroid carcinoma (SPDTC) patients: clinical utility of next generation sequencing (NGS) in therapeutic strategy

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Objectives
DTC is characterized by clinical and genetic heterogeneity, with histopathological examination playing a crucial role in prognosis and therapeutic management. Tumor molecular identity provides additional prognostic information as well as data for targeted therapy in cases of metastatic or locally advanced/unresectable disease. The aim of our study is to present the genetic landscape of a series of patients with locally advanced, recurrent, and/or metastatic DTC and the cilinical utility of NGS in therapeutic strategy.
Methods
In 18/23 patients referred to our clinic (Sept. 2023 – March 2026) with locally advanced, recurrent and/or metastatic DTC, FFPEs from primary and/or metastatic site, were obtained. DNA/RNA isolation and library preparation for analysis by NGS (Oncomine™ Focus Assay, Thermo Fischer Scientific or AmoyDx® HANDLE Classic-NGS-Panel) were performed.
Results
In the majority of our patients (21/23) aggresive histological type/subtype was documented. In 7/18 patients (38.89%) with: (a) differentiated high-grade TC (DHGTC) and/or poorly differentiated TC (PDTC) ($n = 5/7$), (b) oncocytic-TC (OCA) ($n = 1/7$), (c) papillary-TC (PTC) columnar cell variant (CCV) ($n = 1/7$), and metastatic disease in: brain/lungs ($n = 1/7$), lungs/mediastinum ($n = 2/7$), locally unresectable recurrence ($n = 2/7$), local recurrence ($n = 2/7$), a **BRAF^{V600E}** mutation was found (variant allele frequency-VAF: 8.83 - 38.85%). In 3/18 patients (16.67%) with infiltrative follicular-PTC and lung metastases, a **NRAS^{Q61K}** mutation was found, VAF: 8.74-46.69%. In 1/18 patient (PDTC-70% & DHGTC-30%, bone and lung metastases), a **PTEN** deletion was found, VAF: 4.5%. In 1/18 patient (PDTC, locally unresectable recurrence) **BRAF^{V600E}** coexisted with a mutation in **PIK3CA**. In 1/18 patient (OCA widely invasive, locally unresectable recurrence) a mutation of unknown clinical significance was found in **MTOR**. Rearrangements were found in 3/18 patients: (i) patient A with lung metastases, PTC-classical variant, harbouring **NCOA4-RET**, (ii) patient B with local recurrence and intraluminal trachea impression, lung metastases, PDTC, harbouring **NTRK3-ETV6**, (iii) patient C with local recurrence and multidissemination in the resected thyroid gland, PTC-classical variant, harbouring **TFG-MET**. In 3/18 patients no mutation was found. In 3/7 **BRAF^{V600E}** patients Dabrafenib in combination with Trametinib was initiated ($n = 2$ patients with partial response, $n = 1$ patient with initially mixed response, finally succumbed to the disease). In the **PTEN** patient, Lenvatinib plus Pembrolizumab was initiated with mixed response for a period of 18 months before disease progression was documented. In the **NTRK3-ETV6** patient Larotrectinib was initiated with complete structural remission.
Conclusions
Clinical utility of NGS in aggressive DTC provides information regarding prognosis while in locally advanced and/or metastatic disease is the *"sine qua non"* of precision medicine implementation as, apart from targetable mutations, it unravels targetable rearrangements, as well.

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PS2-03-06

Genomic profiling of brazilian anaplastic thyroid cancer identifies canonical driver alterations and a potential novel BRAF variant

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Objectives
Anaplastic thyroid carcinoma (ATC) is a rare but highly aggressive thyroid cancer, representing 2–3% of cases and associated with near-universal mortality. Unlike differentiated thyroid carcinomas (DTC), ATC is undifferentiated, often locally

invasive, and frequently metastasizes to lymph nodes and distant sites. It may arise from DTC progression or develop de novo. ATC is characterized by extensive genetic and genomic instability, with recurrent alterations in *BRAF*, *RAS*, *TERT* promoter, *TP53*, the most frequent genetic drivers. Ethnic background may influence the molecular landscape of ATC. This study aimed to characterize molecular alterations in Brazilian ATC cases.

Methods

ATC samples were analyzed using next-generation sequencing (NGS). Libraries were prepared from 100 ng of RNA or 100–300 ng of DNA using Illumina RNA Prep with Enrichment and DNA Prep with Enrichment kits. Sequencing was performed on the NextSeq 2000 platform, and data were analyzed with DRAGEN Enrichment v4.3.6 and CNV Baseline for SNV/indel and copy number alteration (CNA) detection and annotation.

Results and Conclusion

Canonical molecular alterations were identified in two ATC cases. Case 1, DNA and RNA sequencing revealed HRAS p.Q61R and *TERT promoter* C228T, in addition to copy number alterations (CNA) and loss of heterozygosity (LOH) in 1p and, 22q. Case 2, NRAS p.Q61R, alongside alterations in key signaling pathways, including PI3K/AKT/mTOR and Hippo pathways, were detected. Notably, a potential novel BRAF variant, previously described in melanoma and lung adenocarcinoma but not in thyroid carcinoma, was identified. Our findings confirm known molecular drivers of ATC and suggest the presence of a potentially novel BRAF variant in Brazilian patients. These results highlight the relevance of ethnic and population-specific genomic features in ATC. Further validation and analysis of a larger cohort are warranted to expand our understanding of ATC's molecular heterogeneity.

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PS2-03-07

Performance of a microrna and DNA-based molecular classifier in pediatric patients with indeterminate thyroid nodules

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Background

Thyroid nodules are frequently detected in adults but are uncommon in children and adolescents. Despite their lower prevalence, pediatric thyroid nodules carry a substantially higher risk of malignancy (RoM), particularly when cytology is indeterminate. In pediatric patients, the RoM for Bethesda III nodules has been reported to be significantly higher than in adults, and Bethesda IV nodules also demonstrate markedly elevated malignancy rates. Molecular testing has been proposed as a useful tool in the evaluation of these cases; however, evidence supporting the use of molecular classifiers in pediatric patients remains limited.

Objective

To assess the diagnostic performance of a microRNA and DNA-based molecular classifier (mir-THYpe full) in pediatric patients with indeterminate thyroid nodules.

Methods

This multicentric study included FNA smear slides from 23 pediatric thyroid nodules previously analyzed using the mir-THYpe full molecular test, comprising 14 Bethesda III and 9 Bethesda IV cases. The assay integrates microRNA expression profiling with detection of key genetic alterations, including point mutations (BRAF V600E and TERT promoter C228T/C250T) and gene fusions (PAX8/PPARγ, RET/PTC1 and RET/PTC3), using quantitative PCR (qPCR). Histopathological diagnosis following surgery was used as the reference standard to evaluate the test performance.

Results

Among the 23 nodules analyzed, the molecular test correctly classified 19 cases, corresponding to an overall accuracy of 82.6%, sensitivity reached 100% and specificity was 69.2%. Nine nodules were classified as negative for malignancy, and all were confirmed as benign, yielding a negative predictive value of 100%. Fourteen nodules were classified as positive for malignancy, of which 10 were confirmed as malignant by histopathology, resulting in a positive predictive value of 71.4%. All malignant cases corresponded to papillary thyroid carcinoma or papillary microcarcinoma, including one tumor harboring the BRAF V600E mutation. No gene fusions were detected. The observed disease prevalence was 43.5%, consistent with the approximately 39% prevalence reported in comparable pediatric cohorts.

Conclusions

This multicentric analysis provides preliminary evidence supporting the feasibility and promising diagnostic performance of the mir-THYpe full molecular test in pediatric patients with indeterminate thyroid nodules. Further validation in larger cohorts is warranted to refine performance estimates and strengthen the evidence for its role in risk stratification and individualized surgical decision-making in pediatric patients.

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PS2-03-08

Analytical validation of a molecular classifier based on MIR-375 expression for preoperative diagnosis of medullary thyroid carcinoma using archived fine-needle aspiration cytology smear slides

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Background

Medullary thyroid carcinoma (MTC) represents approximately 3–5% of thyroid malignancies and is frequently associated with aggressive clinical behavior, rapid progression and early metastatic spread. Although fine-needle aspiration (FNA) cytology is the primary method for evaluating thyroid nodules, the preoperative identification of MTC can be challenging in cases lacking MTC characteristic cytological features. Serum calcitonin measurement may assist in detecting MTC; however, its routine implementation in thyroid nodule evaluation remains controversial and is not consistently performed in clinical practice. In recent years, microRNA-375 (miR-375) has been consistently associated with MTC biology and may provide additional molecular signals in thyroid nodule evaluation. However, its use in routine cytology smear slides and its potential contribution within current diagnostic workflows remain to be better characterized.

Objective

To develop and evaluate a miR-375–based molecular classifier using routine archived FNA cytology smear slides and characterized its expression pattern in medullary thyroid carcinoma.

Methods

FNA smear slides from 621 patients were retrospectively analyzed and categorized according to postsurgical histopathology. The cohort included 52 MTC samples and 569 non-MTC samples, comprising 257 other thyroid carcinomas and 312 benign nodules. RNA was extracted from cytology smear slides and miR-375 expression was quantified using quantitative PCR (qPCR), normalized with miR-103. Expression patterns were analyzed and a classifier threshold was defined using receiver operating characteristic (ROC) curve analysis.

Results

miR-375 expression was undetectable in 169 of 569 (29.70%) non-MTC samples and in only 1 of 52 (1.9%) MTC samples. Using a ROC-derived threshold of 7.54, the classifier signal was observed in 50 of 52 MTC samples, while remaining absent in all 569 non-MTC cases. In this cohort, the analytical performance yielded 96.2% sensitivity and 100% specificity, with an overall classification accuracy of 99.7%. The positive predictive value was 100% and the negative predictive value was 99.7%, based on an MTC prevalence of 8.4%.

Conclusions

The miR-375 expression profile demonstrated a distinct molecular signal associated with MTC when measured in routine FNA smear slides. These findings support the analytical validity of a miR-375–based molecular classifier and suggest its potential relevance within the evaluation of thyroid nodules. Further studies in independent cohorts will be important to determine how this approach may be integrated into existing diagnostic workflows.

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PS2-03-09

Characterisation of somatic genetic alterations in sporadic medullary thyroid carcinoma

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Objectives
Medullary thyroid carcinoma (MTC) is a rare and aggressive tumour that originates from the C cells of the thyroid gland, which produce the hormone calcitonin. MTC accounts for 3–5% of all thyroid cancers. Approximately 25% of cases are hereditary and are associated with pathogenic germline variants in the *RET* (Rearranged During Transfection) proto-oncogene. More commonly, MTC presents as a sporadic disease, and patients do not have a family history of the condition. Somatic *RET* variants are observed in 40–70% of sporadic tumours and are mutually exclusive with the less common *RAS* mutations. In addition, *BRAF* variants have rarely been reported. The literature contains few reports of gene fusions in sporadic MTC (sMTC). The primary objective of this study was to identify somatic variants (including gene rearrangements) in patients diagnosed with sMTC.
Methods
During routine diagnostic work-up, tumour material was collected from 83 patients with sMTC (with no germline *RET* mutations). RNA was isolated from fresh-frozen tissue samples, formalin-fixed paraffin-embedded (FFPE) tissue blocks, fine-needle aspiration biopsies (FNA), and core-needle biopsies (CNB). RNA libraries were prepared using the FusionPlex CTL Kit (Archer), targeting 36 genes and enabling detection of fusions involving 18 genes. Next-generation sequencing (NGS) was performed on an Illumina MiniSeq instrument. Bioinformatics analysis was conducted using Archer Analysis software and an independent pipeline based on publicly available bioinformatics tools.
Results
Oncogenic and likely oncogenic variants in the *RET* ($n = 37$, 45%) and *RAS* ($n = 26$, 31%) genes were predominant in the study cohort. The presence of *BRAF* variants was associated with the co-occurrence of papillary thyroid carcinoma (PTC), as confirmed by histopathological examination. In a subset of the cohort (21%), no variants were identified. Three distinct fusions were detected in samples from six patients: *LOC101929418::ALK* ($n = 4$), *SYN2*::*PPARG* ($n = 1$) and *PPP1CB*::*ALK* ($n = 1$). The first two fusion events were classified as read-through.
Conclusions
Further research is needed to understand the role of the identified fusions in the development and course of sMTC. In addition, the lack of clinically significant variants in part of the cohort indicates the need for further analysis using broader NGS panels.

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PS2-03-10

Antitumor potential of metformin in anaplastic thyroid carcinoma: evidence of mechanisms of action in 2D, 3D models and in patient-derived primary cultures

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Objectives
To evaluate the antitumor effect of metformin in two-dimensional (2D) and 3D models of Anaplastic Thyroid Carcinoma (ATC) and to investigate the involvement of the JAK/STAT3, MAPK, and PI3K/AKT pathways in its mechanism of action.
Methods
ATC cell lines HTH83 and KTC2, including their STAT3-knockout (STAT3-KO) clones and non-tumor cell Nthy-ori 3.1, were evaluated in 2D and 3D models generated using the hanging drop technique. Patient tumor and non-tumor samples were also analyzed. Cell viability was assessed using PrestoBlue. Activation of STAT3, AKT, and ERK was analyzed by Western blot, while epithelial-mesenchymal transition (EMT) gene expression was evaluated by RT-qPCR. Clonogenic survival assays and experiments using patient-derived primary cultures were also performed.
Results
Metformin reduced cell viability in both 2D and 3D models, with HTH83 showing greater sensitivity than KTC2 cells, which were more sensitive than non-tumor cells. In 2D, metformin reduced clonogenic survival of ATC cells. In the 3D model, treatment decreased spheroid cohesion and increased cellular dissemination, following the sensitivity pattern HTH83 > KTC2 > Nthy-ori3.1. Metformin inhibited the activation of p-STAT3, p-ERK, and p-AKT pathways in ATC cell lines and modulated the EMT genes vimentin and E-cadherin. In both 2D and 3D models, metformin did not reduce the viability of STAT3-KO KTC2 cells but reduced the viability of STAT3-KO HTH83 cells, that the JAK/STAT3 pathway mediates metformin's effects in a lineage-dependent manner. Metformin also reduced the viability of patient-derived thyroid tumor cultures.
Conclusion
Metformin demonstrated antitumor action in 2D and 3D models and in primary patient cultures by inhibiting oncogenic pathways involved in ATC, with cell lineage-specific participation of the JAK/STAT3 pathway. These findings highlight the potential of metformin as a safe, accessible therapeutic strategy and support its repositioning as a candidate treatment for anaplastic thyroid carcinoma.

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Clinical Cancer 3

PS2-04-01

Updated cut-offs for basal and calcium-stimulated calcitonin and procalcitonin in the detection of MTC: data obtained in a large monocentric series

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Objectives
Basal and stimulated calcitonin (CT) are widely used in the diagnostic work-up of suspected medullary thyroid carcinoma (MTC), although the diagnostic cut-offs remain matter of debate.
Methods
In this retrospective monocentric study, we analyzed calcium tests performed during the last 10 years (334), including only patients with histological diagnosis. The cohort included 106 patients: 19 RET gene-carriers (12 females, 7 males) were analyzed separately, the remaining wild type (WT) cohort was stratified by sex (55 F, 32 M). CT and proCT were evaluated before and after calcium stimulation (bCT, sCT and b-pCT, s-pCT). Receiver operating characteristic (ROC) curve analysis was used to identify optimal diagnostic cut-offs.
Results
At baseline, the optimal CT or pCT thresholds for sporadic MTC detection were CT > 21.8 ng/L ($P < 0.0001$ sensitivity (SE) 88% specificity (SP) 76%) or proCT > 0.06 µg/L ($P < 0.0001$ SE 92% SP 70%) in females, and bCT > 27.8 ng/L ($P < 0.0001$ SE 93% SP 71%) or b-pCT > 0.13 µg/L ($P < 0.0001$ SE 93% SP 94%) in males. After stimulation, the spCT showed the best diagnostic accuracy in both sexes: s-pCT > 0.12 ($P <$ 0,0001 SE 96% SP 80%) or > 0.2 µg/L ($P <$ 0.0001 SE100% SP 88%) in females or males, respectively. In RET mutated-cohort, the MTC diagnosis was predicted by a bCT > 20.6 ng/L ($P = 0.08$; SE 63%, SP 91%), sCT > 208 ng/L ($P = 0.05$ SE 75%, SP 82%), b-pCT > 0.06 µg/L ($P = 0.03$ SE 63% SP 90%), s-pCT > 0.12 µg/L ($P = 0.07$ SE 63% SP 100%).
Conclusions
We updated sex-specific basal and stimulated CT and pCT thresholds for the detection of MTC and CCH in a large monocentric cohort. These cut-offs are

higher than the ones identified in previous studies, and proCT appears the parameter providing the highest accuracy for MTC diagnosis.

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PS2-04-02

Chronic autoimmune thyroiditis and tall cell variant PTC: a novel association with prognostic impact at 5-year follow-up in a sardinian cohort

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Objective

The relationship between chronic autoimmune thyroiditis (CAT) and papillary thyroid cancer (PTC) remains controversial and the specific impact of CAT across the diverse histological landscape of PTC has yet to be characterized. This study aimed to evaluate: 1) whether CAT is associated with higher prevalence of a specific PTC histological variant; and 2) whether coexisting CAT influences tumor aggressiveness and long-term outcomes in that variant.

Methods

Data from 549 consecutive PTC patients, diagnosed with PTC-CV ($n = 373$), PTC-TCV ($n = 99$), PTC-follicular variant (PTC-FV) ($n = 65$), and other rare PTC variants (PTC-OV) ($n = 12$), and followed for 5 years after total thyroidectomy, were analyzed. CAT was diagnosed based on antibody positivity, ultrasound pattern, and histological findings. Within each variant, patients were stratified by CAT status (CAT+ vs CAT−) and compared for: BRAF V600E mutant protein expression, ATA risk classification, radioiodine (RAI) treatment requirement, and biochemical and structural response at 6–9 months and 5-year follow-up.

Results

CAT prevalence was significantly higher in the PTC-TCV group (65/99, 65.7%), compared to PTC-CV (136/373, 36.5%), PTC-FV (28/65 43.1%) and PTC-OV (2/12, 16.7%) groups (χ^2 30.62, $P < 0.0001$). Uniquely among histological variants, CAT+PTC-TCV patients showed significantly higher rate of BRAF V600E expression (75.4% vs 51.6%; OR 1.555, 95% CI 1.08–2.45; $P = 0.021$), higher ATA intermediate/high risk classification (76.9% vs 24.4%; OR 3.75, 95% CI 1.53–8.81; $P = 0.004$), and greater RAI requirement (69.2% vs 21.1%; OR 3.94, 95% CI 1.65–9.40; $P = 0.002$) compared to patients without CAT. At 6-9 months, CAT+ patients demonstrated a significantly increased risk of biochemical disease persistence compared to the CAT- group (OR 5.44, 95% CI 1.72–15.71; $P = 0.004$). This finding was confirmed using the "decreasing TgAb trend" criterion (OR 6.579, 95% CI 2.461-21.43, $P = 0.0001$). Similarly, at 5-year follow-up, with CAT+ patients showing a higher rate of biochemical disease persistence (56.9% vs 15.2%; OR 7.95, 95% CI 2.67–22.51; $P = 0.0001$). No significant differences in structural persistence were observed between groups. On multivariate logistic regression, CAT was confirmed as independent predictor of biochemical persistence at 5 years (OR 12.97 95%CI 4.05-44, $P < 0.0001$).

Conclusions

CAT is significantly more prevalent in PTC-TCV compared to other histological variants and independently predicts biochemical persistence at 5-year follow-up in our Sardinian Cohort. These findings suggest that coexisting CAT may identify a higher-risk molecular and clinical phenotype within PTC-TCV, with potential clinical implications. Further studies are warranted to elucidate the pathogenetic mechanisms linking thyroid autoimmunity and oncogenesis in PTC-TCV.

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PS2-04-03

Persistent postoperative calcitonin levels stratify long-term outcomes in medullary thyroid carcinoma

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Background

Postoperative calcitonin (POCal) is a key biomarker in medullary thyroid carcinoma (MTC). While undetectable POCal levels are strongly associated with long-term disease-free survival, persistent POCal indicates residual disease after surgery. However, the long-term outcomes of patients with persistent POCal levels remain heterogeneous and incompletely characterized.

Objective and Methods

We retrospectively analyzed clinical and oncological data from patients with MTC treated at two tertiary referral centers in Brazil. Early postoperative calcitonin levels (first measurement after surgery) were evaluated to determine their association with long-term clinical outcomes.

Results

The cohort included 473 patients, of whom 354 had available POCal measurements and final outcome data. The mean age at diagnosis was 41.0 ± 18.7 years, 214 patients (60.5%) were female, and 176 patients (49.7%) had sporadic disease. The median tumor size was 2.0 cm (IQR 1.0–3.5); 173 patients (52.3%) had lymph node metastases and 64 (19.2%) had distant metastases at diagnosis. At the first postoperative evaluation, 152 patients (42.9%) had undetectable POCal, whereas 202 (57.1%) had persistent POCal levels. Among patients with undetectable POCal, after a median follow-up of 7.0 years, 137 (90.1%) remained disease-free and 15 (9.9%) had biochemical disease. No cases of structural disease or disease-specific mortality were observed in this group. Among patients with persistent POCal levels, after a median follow-up of 6.8 years, 20 patients (9.9%) achieved disease-free status, 55 (27.2%) had persistent biochemical disease, 64 (31.7%) developed structural disease, and 63 (31.2%) died from MTC-related causes. Median POCal levels increased progressively across outcome categories, indicating a graded association between calcitonin levels and tumor behavior: 39.0 pg/ml (18.0–71.0) in patients free of disease, 61.0 pg/ml (18.5–206.5) in biochemical disease, 566.5 pg/ml (208.7–1367.7) in structural disease, and 625.0 pg/ml (70.0–5009.7) in patients who died of MTC ($P < 0.01$).

Conclusions

Higher POCal levels are associated with persistent structural disease and increased risk of disease-specific mortality, while patients with lower POCal levels may remain with biochemical disease and may achieve disease-free status during long-term follow-up. These findings highlight the prognostic value of early POCal levels and their use in refining postoperative risk stratification to guide long-term surveillance in patients with MTC.

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PS2-04-04

Transoral thyroidectomy in a cancer-enriched retrospective cohort of 1,000 consecutive cases by a single surgeon: complementary roles of endoscopic and robotic techniques for a tailored surgical approach

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Objectives

Transoral vestibular thyroidectomy—performed using either an endoscopic (transoral endoscopic thyroidectomy via the vestibular approach [TOETVA]) or

robot-assisted (transoral robotic thyroidectomy [TORT]) approach—has emerged as a scar-concealing alternative to conventional open thyroidectomy. However, direct comparisons between these techniques in large, cancer-enriched cohorts from high-volume, single-surgeon experiences remain limited.
Methods
A total of 1,000 consecutive patients who underwent TOETVA ($n = 450$) or TORT ($n = 550$) performed by a single endocrine surgeon between September 2016 and March 2024 were retrospectively reviewed. Baseline characteristics, operative metrics, complication rates, length of hospital stay, and oncologic surrogates were compared.
Results
Of the 1,000 cases, 986 were malignant, predominantly papillary thyroid carcinoma. Patients in the TORT group exhibited more advanced clinicopathologic features, including a larger tumor size, higher prevalence of T1b disease (23.0% vs. 13.7%, $P < 0.001$), and N1a lymph node metastasis (35.6% vs. 25.6%, $P < 0.001$). Despite greater surgical complexity, TORT demonstrated a significantly shorter total operative time (67.7 $\pm$ 23.0 vs. 75.5 $\pm$ 28.0 min, $P < 0.001$) and shorter hospital stay (2.2 vs. 2.4 days, $P < 0.001$). Overall complication rates were low in both groups. Transient nerve injuries occurred infrequently and exclusively in the TOETVA group. Surgical drains were used in only 0.5% of cases.
Conclusions
In this large-scale cancer-enriched cohort, both TOETVA and TORT were safe and feasible, supporting transoral thyroidectomy as a reproducible, scar-concealing option for benign thyroid disease and appropriately staged thyroid cancers. Notably, TORT demonstrated superior operative efficiency and nerve preservation in more advanced cases, whereas TOETVA remained a safe, cost-effective option for early-stage disease. These findings suggest that the two platforms are complementary, facilitating a tailored surgical approach based on disease extent, patient preference, and resource availability.

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PS2-04-05

Surgical extent and the role of adjuvant radioactive iodine in intermediate-risk CN1B papillary thyroid carcinoma: a multicenter cohort study

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Objectives
The optimal extent of thyroidectomy and the role of adjuvant radioactive iodine (RAI) therapy in papillary thyroid carcinoma (PTC) with lateral neck metastasis (cN1b) remain controversial. Although total thyroidectomy followed by RAI is frequently recommended for intermediate-risk disease, evidence supporting this strategy remains limited. This study aimed to examine oncologic outcomes associated with different initial treatment strategies in patients with cN1b PTC.
Methods
We conducted a multicenter retrospective cohort study including patients with cT1–3N1bM0 PTC who underwent thyroidectomy with therapeutic lateral neck dissection between 2010 and 2022 at nine institutions. Patients were categorized into three treatment groups according to initial management: lobectomy, total thyroidectomy alone, and total thyroidectomy followed by adjuvant RAI. Recurrence-free survival (RFS) and disease-specific survival (DSS) were assessed using Kaplan–Meier analysis. Inverse probability of treatment weighting (IPTW) and multivariable Cox proportional hazards models were used to adjust for clinicopathologic differences and identify independent predictors of recurrence.
Results
A total of 593 patients were included, with a median follow-up of 71.5 months. Treatment strategies consisted of lobectomy ($n = 109$), total thyroidectomy alone ($n = 170$), and total thyroidectomy with adjuvant RAI ($n = 279$). Recurrence-free survival and disease-specific survival were comparable across the three groups. IPTW-adjusted analyses also demonstrated no significant improvement in recurrence-free survival with either total thyroidectomy or adjuvant RAI. Multivariable analysis identified older age, larger primary tumor size, larger metastatic lymph node size, and extranodal extension as independent predictors of recurrence.
Conclusions
In patients with cN1b PTC undergoing therapeutic lateral neck dissection, oncologic outcomes were comparable across different initial treatment strategies. Routine total thyroidectomy with adjuvant RAI may not be necessary for all patients with intermediate-risk disease. Individualized treatment strategies based on clinicopathologic risk factors may help optimize management of this heterogeneous population.

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PS2-04-06

Abstract Withdrwn

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PS2-04-07

Development and bidirectional temporal validation of a clinical prediction model for disease progression in thyroglobulin-negative, whole-body scan-positive differentiated thyroid carcinoma

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Objectives
To develop a clinical prediction model for disease progression in thyroglobulin (Tg)-negative but whole-body scan (WBS)-positive differentiated thyroid carcinoma (DTC) patients following radioactive iodine therapy, and to validate its robustness across different time periods (2021-2025).
Methods
Retrospective study of DTC patients treated 2021-2025 who were Tg-negative, TgAb-negative, and WBS-positive post-thyroidectomy and radioactive iodine therapy. The development cohort comprised 130 patients (44 progressors) treated 2022-2024. Bidirectional temporal external validation included historical (2021, $n = 21$) and prospective (2025, $n = 14$) cohorts. A logistic regression model incorporating intraglandular spread, lymph node metastasis count, metastasis ratio, and tumor size was developed with 500-iteration Bootstrap internal validation.
Results
The model demonstrated excellent discrimination in the development cohort (AUC 0.758, 95%CI 0.674-0.852) with optimism-corrected AUC 0.765. Intraglandular spread emerged as the strongest independent predictor (OR 5.32, 95%CI 1.42-25.88, $P = 0.020$). In the combined external validation cohort ($n = 35$, 7 progressors), the model maintained consistent performance (AUC 0.735, ΔAUC = 0.023). At the optimized cutoff of 0.5, sensitivity was 71.4%, specificity 82.1%, and negative predictive value 92.0%.
Conclusions
This bidirectionally validated prediction model demonstrates excellent temporal stability over 5 years with high negative predictive value (92%), enabling reliable risk stratification for Tg-negative, WBS-positive DTC patients. Multicenter prospective validation is warranted before clinical implementation.
Keywords
differentiated thyroid carcinoma, prediction model, temporal validation, intraglandular spread, risk stratification.

Table 1. Model Performance in Development and External Validation Cohorts.

Metric	Development (2022-2024)	External Validation (2021 + 2025)
Total *n*	130	35
Progressors *n* (%)	44 (33.8)	7 (20.0)
AUC (95% CI)	0.758 (0.674-0.852)	0.735 (0.469-1.000)
Optimism-corrected AUC	0.765	—
Sensitivity (%)	—	71.4
Specificity (%)	—	82.1
NPV (%)	—	92

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PS2-04-08

Impact of thyroidectomy extent on quality of life in differentiated thyroid carcinoma patients: a propensity score-matched analysis

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Background
Postoperative quality of life has emerged as a critical consideration. Total thyroidectomy (TT) and thyroid lobectomy (TL) are the predominant surgical strategies for patients with DTC. However, the effects of these surgical interventions on patients' health-related quality of life (HRQOL) remain inadequately understood.
Methods
Patients diagnosed with low- to intermediate-risk DTC between February 2015 and February 2023 were prospectively enrolled in the study. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the thyroid cancer-specific module were employed to evaluate HRQOL at baseline and at 1, 3, 6, and 12 months postoperatively. Propensity score matching (PSM) was utilized to address baseline imbalances between the two groups. A mixed linear model was applied to assess differences in the longitudinal trajectories of HRQOL scores between the groups. The primary endpoint was the Global Health Status (GHS) score at various measurement.
Results
A total of 962 patients were included in the study (TT = 285; TL = 677). Following PSM, baseline characteristics were well-balanced. The incidence of transient hypoparathyroidism was significantly higher in the TT group compared to the TL group (16.2% vs. 2.7%), as was the incidence of hoarseness (6.8% vs. 2.1%). Regarding longitudinal HRQOL trends, the TT group exhibited a poorer trajectory in GHS. At multiple follow-up intervals, the TT group exhibited significantly poorer HRQOL compared to the TL group. This was evidenced by more pronounced symptoms of anxiety, fatigue, voice alterations, and numbness, as well as greater detriments in physical and emotional functioning. By 12 months postoperatively, the majority of HRQOL domains showed no significant differences between the two groups.
Conclusion
TL appears to offer advantages in short-term postoperative HRQOL; however, no such advantage is observed in long-term HRQOL. Given equivalent survival outcomes, TL might be preferred when the objective is to enhance short-term postoperative quality of life.

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PS2-04-09

Clinical outcomes of radioactive iodine therapy prepared with thyroid hormone withdrawal vs recombinant human tsh in metastatic differentiated thyroid cancer: a multicenter retrospective study

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Purpose
This study aimed to compare the clinical outcomes and safety of radioactive iodine (RAI) therapy prepared with thyroid hormone withdrawal (THW) or recombinant human TSH (rhTSH) in patients with distant metastatic differentiated thyroid cancer (DTC, M1) using patient-based and therapy-based analyses.
Methods
A total of 352 patients were included in the patient-based analysis (THW only, $n = 259$; rhTSH only, $n = 40$; mixed, $n = 53$), and 564 RAI therapies were included in the therapy-based analysis (THW, $n = 459$; rhTSH, $n = 105$). Clinical outcomes were evaluated using patient-based analyses for overall survival (OS) and disease-specific survival (DSS) and therapy-based analyses for treatment response (RECIST and ΔTg) and laboratory-based adverse events.
Results
In patient-based analyses comparing THW-only, rhTSH-only, and mixed groups, no significant differences were observed in OS or DSS (all $P > 0.25$). In therapy-based analyses, treatment responses assessed by RECIST and ΔTg did not differ between THW- and rhTSH-prepared RAI therapies (both $P > 0.05$). In multivariate analyses, the TSH stimulation method was not identified as an independent predictor of treatment response. In contrast, laboratory-based adverse events occurred more frequently in RAI therapies prepared with THW than with rhTSH.
Conclusions
RAI therapy prepared with rhTSH and THW achieved comparable clinical outcomes in DTC patients with M1 disease, while THW was associated with a higher frequency of laboratory-based adverse events. These findings suggest that rhTSH represents a viable alternative to THW, particularly when treatment-related safety and subsequent management are important considerations in advanced disease.

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PS2-04-10

Comparison of ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT in detection of site of recurrence in differentiated thyroid carcinoma patients with elevated thyroglobulin and negative iodine-131 scan

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Objective
Frequently recurrent differentiated thyroid cancers(DTC) become Iodine nonavid compelling the use of alternative imaging modality like fluorine-18-fluoro-deoxyglucose (^{18}F-FDG) PET/CT for detection. Recently gallium-68 labelled fibroblast activation protein inhibitor (^{68}Ga-FAPI-04) has emerged as a promising tracer for detection of various malignancies. Aim of this study was to compare the diagnostic performance of ^{68}Ga-FAPI-04-PET/CT with ^{18}F-FDG-PET/CT for detecting site of recurrence in DTC patients with elevated serum thyroglobulin(Tg) and negative iodine scan.
Methods
Twenty-two previously treated of DTC (6 males, 16 females) with mean age of 48.63 ± 11.7 having biochemical recurrence but negative radio-iodine scan, were analyzed. All patients underwent ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT for localization of recurrence site within 4 days of each other in thyroxine withdrawn state. Patients were stratified into two groups: Group A: Tg < 50 ng/ml ($n = 10$) and Group-B Tg ≥ 50 ng/ml($n = 12$).
Results
The mean serum thyroglobulin level was 25.34 ± 13.4 ng/ml in Group-A and 778.73 ± 436.31 ng/ml in Group-B. In Group-A site of recurrence was detected in 3 patients by ^{18}F-FDG PET/CT(accuracy 30%) and in 2 patients using ^{68}Ga-FAPI-04 PET/CT(accuracy 20%). In Group-B site of recurrence was detected in 11 patients by both the modalities (accuracy 91.7%). Diagnostic accuracy of both modalities was significantly higher in Group-B patients. One patient of Group-A showed FDG-positive nodal metastasis with no corresponding FAPI uptake, while no FAPI-positive lesions was observed in FDG-negative cases. The overall mean SUVmax of detected lesions was significantly higher on ^{18}F-FDG compared with ^{68}Ga-FAPI-04 (7.79 ± 4.25 vs 4.20 ± 1.87; $P < 0.001$). Overall diagnostic accuracy for ^{18}F-FDG PET/CT was 63.6% compared to 59.1% for ^{68}Ga-FAPI-04 PET/CT.
Conclusion
In patients with biochemical recurrence of DTC ^{68}Ga-FAPI-04-PET/CT did not demonstrate superiority over ^{18}F-FDG PET/CT in localising the site of recurrence. Lesions were better visualised in FDG PET/CT leading to greater confidence in interpretation.

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Clinical Cancer 4

PS2-05-01

The patterns and risk factors for antidepressant drug prescription in thyroid cancer patients and survivors: analysis based on the korean national health insurance service database

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Objectives
Thyroid cancer is the most common endocrine malignancy and typically carries an excellent prognosis, especially in differentiated thyroid carcinoma (DTC). However, many survivors experience psychological challenges, including depression, which can significantly affect their long-term quality of life (QOL). While thyroid cancer treatment often involves surgery and hormone therapy, the relationship between treatment-related variables and new-onset depression remains poorly understood. Identifying clinical and treatment-related factors associated with depression is critical for improving postoperative survivorship care.
Methods
We conducted a retrospective cohort study using data from the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS), which includes approximately 10% of the South Korean population aged 40–79 years. We included patients diagnosed with thyroid cancer (ICD-10 code C73) between 2002 and 2019 and excluded those with a prior diagnosis of depression or other cancers. Variables analyzed included treatment modality (active surveillance, lobectomy, total thyroidectomy), age, sex, income, smoking, alcohol consumption, physical activity, body mass index (BMI), blood pressure, presence of hypertension or diabetes, radioactive iodine (RAI) dose, and thyroid hormone replacement. The primary outcome was newly diagnosed depression, defined by new prescription of antidepressants and corresponding diagnostic codes.
Results
Among 6,968 thyroid cancer patients included in the analysis, the risk of new-onset depression was significantly elevated in patients who underwent no treatment (HR: 1.33; 95% CI: 1.06–1.66), lobectomy (HR: 1.30; 95% CI: 1.11–1.52), or total thyroidectomy (HR: 1.20; 95% CI: 1.09–1.32) compared to matched controls without thyroid cancer (all $P < 0.05$). There was no significant association between depression risk and cumulative RAI dose or levothyroxine dosage. Antidepressant prescription incidence was significantly higher within the first 5 years post-diagnosis but not beyond 5 years.
Conclusions
Thyroid cancer diagnosis and treatment are associated with an increased risk of prescription of anti-depressants in Korea.

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PS2-05-02

Nodal recurrence in differentiated thyroid carcinoma: a comparative analysis of surgery, radioactive iodine, and combined therapy

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Background
Differentiated thyroid carcinoma (DTC) is the most prevalent thyroid malignancy and despite its generally favourable prognosis, recurrence presents a significant challenge. In current practice, surgery - either alone or in combination with radioactive iodine (RAI)- represents the first line treatment for recurrent DTC. The isolated use of RAI is considered in situations where surgery is not viable. However, comparative evidence evaluating the efficacy of these therapeutic approaches remains limited, hampering optimal clinical decision-making.
Objectives
To compare progression-free survival and disease-specific mortality after recurrence across three therapeutic strategies — surgery alone, RAI alone, and combined surgery plus RAI — in patients with recurrent DTC.
Methods
A retrospective cohort study was conducted including 162 patients with nodal only recurrent DTC treated at a single tertiary centre between 2010 and 2021. Patients were separated in therapeutic groups: surgery alone ($n = 40$), RAI monotherapy ($n = 45$), and combined surgery plus RAI ($n = 77$). Median follow-up was approximately 102 months (IQR 78). Baseline characteristics were compared using appropriate statistical tests. Survival outcomes, including progression-free survival and disease-specific mortality, were assessed using Kaplan-Meier analysis with Cox proportional hazards regression where feasible.
Results
Groups were comparable at baseline for most variables, including age, sex, surgical extent, multifocality, capsular invasion, angioinvasion, positive margins, and T and N stage. The only significant baseline difference was extrathyroidal extension (Chi-square test, $P = 0.041$). No statistically significant differences in second recurrence-free survival were observed (log-rank $P = 0.445$). Cox regression yielded hazard ratios relative to surgery of 1.55 (95% CI: 0.78–3.07) for RAI alone and 1.26 (95% CI: 0.67–2.37) for combined therapy, with overlapping confidence intervals and similar Kaplan-Meier trajectories across groups. Disease-specific mortalityoccurred in 11 patients (6.8%) and 10 of these cases were in the combined therapy group; fatal cases were characterized by high-volume recurrence, rapidly progressive disease, and early radioiodine resistance, pointing to intrinsically aggressive tumour biology as the primary determinant of outcome.
Conclusions
No statistically significant differences in recurrence-free survival were observed among the three therapeutic strategies — surgery alone, RAI monotherapy, and combined therapy. These findings suggest that, within this cohort, the choice of treatment modality did not independently determine the risk of further nodal relapse, supporting the role of individualised, multidisciplinary decision-making rather than a single preferred approach. Regarding mortality, the small numberof events and baseline heterogeneity — notably higher extrathyroidal extension in the surgery group — preclude causal inferences attributable to treatment. The retrospective design limits generalizability; prospective studies withstandardized data collection are warranted.

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PS2-05-03

Differentiated thyroid cancer in children and adolescents: a single-center 60-year experience

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Objectives
Differentiated thyroid cancer (DTC) in pediatric patients is rare and has a distinct biological behavior compared to adult disease. We aimed to describe the clinical features, histopathological characteristics, treatment patterns, and long-term outcomes of pediatric DTC at a single tertiary nuclear medicine center over six decades.
Methods
Retrospective, single-center analysis of 58 consecutive patients aged ≤ 19 years with DTC treated between 1965 and 2025. Clinicopathological data, radioiodine (RAI) therapy records, and follow-up thyroglobulin (Tg) values were retrieved and analysed.
Results
The cohort comprised 50 females and 8 males (F:M 6.25:1), with a median age at diagnosis of 16 years (range, 6–19 years). The predominant histotype was papillary thyroid carcinoma (PTC) in 52 patients (89.7%), followed by follicular thyroid carcinoma in 4 (6.9%) and follicular-variant PTC in 2 (3.4%). Median tumor size was 17,5 mm (range 5–80 mm) and 8 children had a T3 or T4 tumor (13.8%). Lymph node metastases at surgery were documented in 30 of 55 evaluable patients (54.5%) and distant metastases in 8 (13.8%). RAI therapy was administered in 47 patients (81.0%) with the median being 99 mCi (range, 45 – 876 mCi). Disease recurrence occurred in 8 patients (13.8%), predominantly as cervical nodal relapse. At the last follow-up, 49 patients (84.5%) had no evidence of disease or showed an excellent biochemical response (Table 1).
Conclusions
In this six-decade institutional series, pediatric DTC was dominated by the papillary histotype and characterized by high rates of locoregional lymph node involvement. Despite the aggressive nodal presentation at diagnosis, long-term outcomes were favorable in most of the patients following combined surgical and

Table 1. Patient characteristics.

Characteristic	Value
Total patients, *n*	58
Female / Male, *n* (%)	50 (86.2%) / 8 (13.8%)
Median age at diagnosis, years (range)	16 (6–19)
Papillary thyroid carcinoma, *n* (%)	52 (89.7%)
Follicular thyroid carcinoma, *n* (%)	4 (6.9%)
Follicular-variant PTC, *n* (%)	2 (3.4%)
Lymph node metastases at surgery, n/N (%)	30/55 (54.5%)
Distant metastases, *n* (%)	8 (13.8%)
Radioiodine therapy, *n* (%)	47 (81.0%)
Disease recurrence, *n* (%)	8 (13.8%)

RAI treatment, confirming the effectiveness of the current management approach in this age group.

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PS2-05-04

Robotic bilateral total thyroidectomy using the double bipolar method with the DA vinci SP system: a propensity score–matched comparison with the XI system

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Objective
Robotic thyroidectomy has evolved with advances in the da Vinci surgical platform from Si to Xi and more recently to the single-port (SP) system. Although several studies have compared the Xi and SP platforms, most have focused on hemithyroidectomy, and data regarding robotic bilateral total thyroidectomy remain limited. This study aimed to compare surgical outcomes and postoperative complications between the Xi and SP systems in robotic bilateral total thyroidectomy using the Double Bipolar Method.
Methods
We retrospectively reviewed patients with thyroid cancer who underwent robotic bilateral total thyroidectomy between 2010 and 2025 at a high-volume tertiary referral center. All procedures were performed by a single experienced surgeon. A total of 548 patients were included, comprising 396 patients operated using the Xi system and 152 using the SP system. Analyses were stratified according to the extent of neck dissection, including central neck dissection (CCND) and modified radical neck dissection (MRND). To reduce selection bias, 1:1 propensity score matching based on age and sex was performed. Surgical outcomes and postoperative complications were compared between groups. Hypocalcemia was defined as serum calcium <8.5 mg/dl or the need for calcium supplementation, and transient hypocalcemia was defined as recovery within 6 months.
Results
After propensity score matching, 88 matched pairs were identified in the CCND cohort and 64 matched pairs in the MRND cohort. Surgical and pathological outcomes were comparable between the Xi and SP systems. The incidence of most postoperative complications showed no significant difference between the two groups. However, transient hypocalcemia occurred less frequently in the SP group, particularly in patients undergoing central neck dissection. Postoperative calcium and parathyroid hormone levels also demonstrated more favorable postoperative recovery trends in the SP group during the early postoperative period.
Conclusion
Robotic bilateral total thyroidectomy using the SP system demonstrated surgical outcomes comparable to those of the Xi system. The Double Bipolar Method, which utilizes bipolar instruments in both hands during SP robotic surgery, may facilitate precise tissue dissection and improved preservation of parathyroid function. These findings suggest that the SP platform is a safe and effective surgical option for robotic bilateral total thyroidectomy and may offer advantages in reducing postoperative hypocalcemia.

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PS2-05-05

Treatment outcomes of anaplastic thyroid cancer in patients at the national institute of oncology in gliwice, poland between 2008 and 2024

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Anaplastic thyroid cancer (ATC) is an aggressive malignancy associated with high mortality, for which effective therapies are still being sought. Surgical treatment is possible only in a limited number of cases, while palliative radiotherapy, chemotherapy, and molecularly targeted therapies prolong survival in a small group of patients.
Objective
To evaluate the treatment outcomes of ATC in patients treated at the National Institute of Oncology in Gliwice.
Material and methods
A retrospective analysis of patients with ATC diagnosed between 2008 and 2024.
Results
The study included 100 patients (55 women, 46 men) aged 34–91 years (median 68.5). The first symptom in 63% of cases was a rapidly growing neck mass, while 21% presented with symptoms of local invasion (hoarseness, dysphagia, dyspnea). At the time of diagnosis, the cancer was confined to the thyroid gland in 22% of patients, lymph node metastases were present in 43%, and distant metastases in 34%. Surgical treatment was performed in 53 patients, including 13 who underwent radical thyreoidectomy. Radiotherapy at the National Institute of Oncology was administered to 37 patients, 10 received chemoradiotherapy, and 6 chemotherapy. Molecular testing for ATC was introduced in 2022 and was performed in 38 patients: a BRAF V600E mutation was detected in 6 patients and an NTRK fusion in 1 patient, enabling targeted therapy in 6 patients. The median overall survival was 5.8 months (range 0–186), and 16 patients survived longer than 2 years. In this group, 56% had no metastases at diagnosis, 44% underwent radical thyroidectomy followed by radiotherapy (75%) or chemoradiotherapy (25%), and 30% received chemotherapy or targeted therapy. Resection with negative margins (R0), chemotherapy, and targeted therapy had a significant impact on survival longer than 1 year. Survival longer than 2 years was associated only with radical surgical treatment.
Conclusions
Treatment of ATC remains a major challenge. Despite progress, early diagnosis remains crucial, as it may enable radical surgical treatment followed by radiotherapy. In patients receiving palliative treatment, molecular testing of the tumor should be performed as soon as possible. Prospective studies that would allow the selection of the best management strategies are still lacking.

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PS2-05-06

Risk factors for progression in papillary thyroid microcarcinoma: a systematic review and meta-analysis

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Introduction
Since the latest American Thyroid Association guidelines (2025) emphasize the importance of explaining 'unknown' risks to PTMC patients before opting for active surveillance, we investigated different risk factors that could predict worsening outcomes in this heterogeneous patient group.
Methods
Our protocol was registered in PROSPERO (CRD42024603662). We conducted a systematic search of PubMed, Embase, and Cochrane from inception to February 14, 2025. Cohort, case-control, and cross-sectional studies were included. The population consisted of patients with histologically confirmed PTMC with different risk factors, while outcomes were lymph node metastasis (LNM) and extrathyroidal extension (ETE). We used a random-effects model to calculate pooled odds ratios (OR) with 95% confidence intervals (CI).
Results
In total, 274 articles with more than 120.000 patients were included in the study. We found increased odds in case of central lymph node metastasis associated with male sex (OR = 1.86; CI: 1.73–2.00), age (<45 and <55 years old OR = 1.61; CI: 1.42–1.83 and OR = 1.89; CI: 1.71–2.09), tumor size (>5 and >7 mm OR = 2.26; CI: 2.00–2.56 and OR = 1.81; CI: 1.11–2.96), multifocality (OR = 1.96; CI: 1.78–2.16), bilaterality (OR = 1.70; CI: 1.45–2.00) and $BRAF^{V600E}$ mutation (OR = 1.51; CI: 1.25–1.82). Lateral lymph node metastasis was associated with male sex (OR = 1.69; CI: 1.51–1.90), age (<45 and <55 years old OR = 1.5; CI: 1.28–1.76 and CI: 1.31–1.72), tumor size (>5 mm and >7 mm, OR = 2.34; CI: 1.68–3.25 and OR = 3.71; CI: 3.15–4.36), multifocality (OR = 1.98; CI: 1.46–2.70), bilaterality (OR = 1.91; CI: 1.22–3.00) and $BRAF^{V600E}$ mutation (OR = 1.11; CI: 0.69–1.78). For ETE, risk factors were as follows: tumor size (>5 mm OR = 3.00; CI: 2.03–4.45), multifocality (OR = 2.41; CI: 1.99–2.91), bilaterality (OR = 2.58; CI: 1.26–5.27), and $BRAF^{V600E}$ mutation (OR = 2.19; CI: 1.61–2.97).
Conclusion
Male sex, age (<45 and <55 years), tumor size (>5 mm), multifocality, bilaterality, and the $BRAF^{V600E}$ mutation are clinically relevant risk factors for LNM and ETE, tending to promote the progression of PTMC. Our results provide valuable insights into stratifying PTMC patients who are suitable for AS and have a low likelihood of disease progression.

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PS2-05-07

Real-world outcomes of dabrafenib plus trametinib in patients with iodine-refractory/radioactive iodine-refractory thyroid carcinoma: a single-center experience in quality of life and treatment efficacy

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Background
Systemic treatment for thyroid cancer remains challenging due to the modest efficacy and safety concerns associated with multi-targeted kinase inhibitors. The combination of dabrafenib and trametinib (DT) represents a novel therapeutic option for BRAF V600E-mutated thyroid cancer, while real-world data on quality of life (QoL) and effectiveness remain limited. This study aimed to evaluate the efficacy and longitudinal QoL trajectories in patients receiving DT in a real-world setting.
Methods
This retrospective analysis included 20 patients with BRAF V600E-mutated radioactive iodine-refractory (RAI-R) papillary ($n = 15$) or anaplastic ($n = 5$) thyroid carcinoma treated with DT at Fujian Cancer Hospital between 2022 and 2024. Radiologic response was assessed according to RECIST version 1.1. QoL was assessed using the EORTC QLQ-C30 and THY34 questionnaires at baseline and follow-up visits (1, 3, 6, and 12 months), with longitudinal QoL changes quantified as mean individual linear regression slopes.
Results
The median treatment duration was 4.9 months (range 1.0–38.5). Objective response rate (ORR) was 45% (9/20), with a disease control rate (DCR) of 90.0% (18/20). Median progression-free survival (PFS) is not yet reached. Among 12 patients with QoL evaluation, baseline mean global QoL was 64.17 ± 30.94, with preserved physical (90.67 ± 13.03) and role function (86.67 ± 26.99). Over a median follow-up of 3 months (range 1-12), numerical improvements were observed in global QoL (+10.38 ± 8.36 per month), alongside symptom scales in pain (-7.53 ± 6.69) and nausea/vomiting (-11.59 ± 9.61) despite lack of statistical significance. Conversely, tingling/numbness score (+6.89 ± 3.48), body image (+10.67 ± 10.59) and hair problem scores (+12.14 ± 12.10) showed trend of increases, consistent with known adverse effects of targeted therapy.
Conclusions
DT demonstrated clinically meaningful effectiveness in BRAF V600E-mutated thyroid carcinoma, accompanied by a trend toward improved QoL. These findings support the tolerability of DT, though larger studies with extended follow-up are warranted to confirm long-term QoL outcomes.Please copy and paste ONLY the abstract text here into this template.

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PS2-05-08

Impact of obesity on thyroid nodules and cancer risk: a south korean longitudinal cohort study

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Objective
The aim of this study was to investigate the prevalence and incidence of thyroid nodules and and cancer in relation to metabolic and thyroid parameters.
Methods
In this population-based prospective cohort study (Korean Genome and Epidemiology Study - Ansung Cohort, started 2001-2002), a total 3,104 adults aged 50 years and older (mean age 64.9 ± 8.5 years, 56.9% women) underwent thyroid ultrasound (US) every 2 years from 2011-2012 (US-baseline) to 2019-2020. Clinical, anthropometric, and laboratory parameters were collected throughout the study period.
Results
The prevalence of solid thyroid nodules (42.3% in total) was higher in older and women participants, with a greater difference for larger nodules ≥1 cm (20.9% vs. 9.4% in men; $P < .001$). The incidence of nodules ≥1 cm was 2.5/1,000 person-years (48.1/1,000 person-years for all nodules), and it was higher in women but similar across ages. However, nodules <1 cm showed weaker associations with age, sex, and metabolic and thyroid-related parameters. The incidence of thyroid cancer over 6.5 (SD 2.6) years was 1.7% among all participants and 8.3% in those with nodules ≥1 cm. It was higher in women, those with larger or multiple nodules, and in the 50-59 age group; however, it decreased in older participants. Obesity-related metabolic characteristics, but not thyroid-related characteristics, differed among nodular size groups. Particularly, body mass index ≥25 kg/m^2, abdominal obesity, and metabolic syndrome were significantly associated with the presence and occurrence of nodules ≥1 cm and cancer occurrence. Of these, abdominal obesity was consistently significantly associated with the prevalence or incidence of nodule ≥1cm or incidence of cancer (odds ratio (OR) 1.30, 3.20, or 2.04, respectively).
Conclusion
The prevalence and incidence of thyroid nodules ≥1 cm were substantial in adults ≥50 years. Obesity-related factors were strongly linked to the development of thyroid nodules and cancer, with persistent abdominal obesity being a critical risk factor. These findings emphasize the need to integrate metabolic health control in thyroid nodule management.

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PS2-05-09

Patterns and predictors of very late structural recurrence after thyroid lobectomy for papillary thyroid carcinoma

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Background
Late recurrence of papillary thyroid carcinoma (PTC) has been increasingly recognized; however, data focusing on very late structural recurrence after thyroid lobectomy remain limited.
Methods
We retrospectively reviewed patients who underwent thyroid reoperation between 2021 and 2025 at a single tertiary center. Patients who had undergone initial thyroid lobectomy and subsequent reoperation more than 10 years after initial surgery at our institution were included. Clinicopathologic features at initial surgery and patterns of structural recurrence were analyzed. Logistic

regression analysis was performed to identify factors associated with pathologically confirmed cervical lymph node recurrence.
Results
Of 495 patients who underwent initial surgery at our institution, 92 underwent reoperation more than 10 years later. Among these, 54 had undergone thyroid lobectomy, and 48 were confirmed to have PTC at reoperation. The median time to reoperation was 12.8 years. Pathologically confirmed recurrence most commonly involved the contralateral thyroid lobe (85.4%), and cervical lymph node metastasis was identified in 43.8% of patients. Initial lymph node metastasis was significantly associated with cervical lymph node recurrence at reoperation (63.6% vs. 26.9%, $P = 0.011$). In multivariable logistic regression analysis, initial lymph node metastasis remained an independent predictor of cervical lymph node recurrence (OR 4.62, 95% CI 1.34–15.91, $P = 0.015$), whereas levothyroxine therapy status was not independently associated.
Conclusion
A subset of patients treated with thyroid lobectomy for PTC developed very late structural recurrence, most commonly involving the contralateral lobe. Initial lymph node metastasis independently predicted cervical lymph node recurrence, whereas levothyroxine discontinuation was not associated with recurrence patterns. These findings support risk-adapted long-term surveillance after lobectomy.

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PS2-05-10

Complication rate with HEMI-, total, and completion thyroidectomy. systematic review and meta-analysis

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Objective
To synthesize perioperative complication rates (CR) associated with hemithyroidectomy (HT), total thyroidectomy (TT), and completion thyroidectomy (CT) after a previous HT, and to perform a comparative analysis between these procedures.
Methods
The primary endpoint was the CR following HT and CT; the secondary endpoint was a comparison of these rates with TT. PubMed/MEDLINE and Embase were searched for data on perioperative complications including postoperative bleeding, cervical hematoma, transient (t-) and permanent (p-) hypocalcemia (HCA) / hypoparathyroidism (HPTH), t- and p- voice disorders (voice change, hoarseness and vocal cord palsy), seroma, and wound infection. Heterogeneity was addressed through subgroup analyses.
Results
From 3,265 identified records, 243 studies were included, encompassing about 120,000 HTs, 120,000 TTs, and 14,000 CTs. After HT, the less and most frequent complications were p-HCA (0.1%) and t-voice change (5.2%), respectively. Following CT, the less and most frequent complications were wound infection (0.2%) and t-HCA (8%), respectively. In the comparative analysis, cervical hematoma was significantly more frequent in HT (0.6% vs 0.0%), whereas t-HCA (1.2% vs 16.2%) / HPTH (2.1% vs 15.6%) and p-HCA (0.1% vs 2.9%) / HPTH (0.4% vs 2.4%) were significantly higher in TT; t-HCA was significantly more frequent in TT than in CT (6.0% vs 14.5%). Subgroup analyses revealed that: a) in oncological cases, TT yielded higher rates of t-/p- HCA than HT, and higher rates of t-HCA when compared to CT; b) when combined with central neck dissection (CND) , t-HCA was significantly more frequent in TT than in HT. The main limit of this study is represented by the heterogeneous definition of complications reported in the literature.
Conclusion
HT demonstrated a significantly lower CR compared to TT. However, when HT is considered, patients should be adequately counselled regarding the potential need for subsequent surgery (i.e., CT) and the related perioperative risk of complications. Finally, surgical planning should not be reduced to a dichotomous choice between TT and HT because malignancy and CND appears as the major determinants in the CR. These findings merit full consideration in the current era of de-escalation in thyroid cancer management.

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Clinical Cancer 5

PS2-06-01

Investigating the therapeutic potential of antidiabetic drugs metformin and canagliflozin in papillary thyroid carcinoma

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Thyroid cancer (TC) is the most common endocrine malignancy, with its rising incidence largely driven by papillary thyroid carcinoma (PTC), which accounts for ~85% of cases. Although PTC generally has a favourable prognosis, 10–20% of the patients develop aggressive disease characterized by recurrence and metastasis. The mechanisms underlying this phenotypic shift remain unclear, highlighting the need for therapeutic strategies targeting tumour progression. Metformin and canagliflozin, two widely used antidiabetic drugs, have demonstrated antitumour effects in several malignancies, partly through modulation of cellular metabolism; however, their role in PTC remains unclear. This study aimed to evaluate the impact of metformin and canagliflozin on key biological and metabolic processes in PTC cells. Two PTC cell lines, TPC-1 (RET/PTC rearrangement) and BCPAP (BRAFV600E mutation), and a non-neoplastic thyroid cell line (Nthy Ori 3-1) were used as study models. Drug concentrations were optimized using viability assays, and functional, metabolic, and imaging approaches were used to assess proliferation, migration, cell cycle dynamics, mitochondrial alterations, and bioenergetic profiles. Metformin at 20 mM significantly reduced viability in TPC-1 and BCPAP cells, with maximal effects at 48 hours, while no significant changes were detected in Nthy Ori 3-1 cells. This concentration was selected for subsequent analyses. Metformin markedly decreased proliferation in both tumour cell lines and inhibited migration in BCPAP cells, whereas the non-neoplastic cell line remained unaffected. Treatment altered cell cycle progression, cell morphology, and mitochondrial architecture in tumour cells, including increased mitochondrial number and lipid droplet accumulation. Metabolic profiling revealed inhibition of mitochondrial complex I, accompanied by a compensatory increase in glycolysis, supporting a drug-induced bioenergetic shift selectively in malignant cells. Canagliflozin 20 μM similarly reduced viability, with the strongest effect at 48 hours, and significantly decreased proliferation in both PTC cell lines. In contrast, Nthy Ori 3-1 cells exhibited minimal effect. Migration was delayed in tumour cells but remained unchanged in the non-neoplastic line. While canagliflozin altered cell cycle progression and morphology in PTC cells, no major mitochondrial structural changes were observed. Metabolic analyses suggested partial inhibition of glucose transporters and respiratory chain activity predominantly in tumour cells. Overall, these findings support the potential therapeutic use of metformin and canagliflozin in PTC, as they selectively disrupt tumour bioenergetics and impair malignant phenotypes while largely sparing non-neoplastic thyroid cells. Targeting metabolic vulnerabilities may represent a promising strategy for patients with PTC refractory to conventional therapies.

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PS2-06-02

Validation of the 2025 ATA risk stratification system in a cohort of patients with papillary thyroid carcinoma

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Background
The 2025 American Thyroid Association (ATA) guidelines have introduced an updated risk stratification system for patients with papillary thyroid cancer (PTC). Because its impact has not yet been assessed in a real-word setting, we aimed to validate it in a large PTC series and to compare it with the ATA 2015 classification.
Methods
We retrospectively evaluated 670 PTC patients, classified according to both the 2015 and 2025 ATA risk stratification system. The impact of reclassification was assessed by comparing risk classes and examining final disease outcome within each class.
Results
After a median follow up of 53.5 (IQR 21-120) months, 670 PTC patients were evaluated. The majority of patients ($n = 602$, 89.9%) underwent total thyroidectomy, associated with lymph node dissection in 207 (30.9%) cases. Radioiodine treatment was administrated postoperatively in 43.0% ($n = 288$) of patients. According to the ATA-risk 2015, 409 patients (61.0%) were classified as "low-risk" for disease persistence or recurrence, 194 patients (29.0%) as "intermediate-risk", and 67 patients (10.0%) as "high-risk". According to the ATA-risk 2025, 318 patients (47.5%) were classified as "low-risk", 148 patients (22.1%) as "low-intermediate-risk", 127 patients (19.0%) as "intermediate-high-risk", and 77 patients (11.5%) as "high-risk". The reclassification based on the 2025 ATA risk stratification showed that the proportion of "low-risk" PTC decreased by 22.2% (318 vs. 409 patients), while "intermediate-risk" and "high-risk" PTC increased by 41.7 and 14.9% (275 vs. 194 patients and 77 vs. 67 patients), respectively. Cross-comparison between the two stratification systems revealed that structural disease persistence in the 2025 ATA "low-risk" and "high-risk" classes was comparable to the previous version (4.1% vs. 4.9%, $P = 0.606$ and 48.0 vs. 47.8%, $P = 0.972$, respectively). Among "intermediate-risk" PTC, the 2025 "high-intermediate-risk" class was comparable to the former "intermediate-risk" class (22.1% vs. 22.7%, $P = 0.894$), whereas the "low-intermediate-risk" class represents a new class, with a risk of structural disease persistence significantly higher than that of the 2015 "low-risk" class (12.2% vs. 4.9%, $P = 0.003$), but lower than that of the 2015 "intermediate-risk" class (12.2% vs. 22.7%, $P = 0.012$).
Conclusions
In a real-life context, the 2025 risk stratification system resulted in a shift toward higher-risk classes. The newly defined "low-intermediate-risk" class was the only class that significantly diverged from the classes of the 2015 stratification, with a risk of structural recurrence between the prior "low-risk" and "intermediate-risk" classes, highlighting the need for dedicated prospective studies to address proper management of this newly-defined group of patients.

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Clinical outcomes of vandetanib therapy in patients with ret-negative medullary thyroid carcinoma

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Introduction
Recently, the rationale for using vandetanib in patients with RET-negative (RET(-)) medullary thyroid carcinoma (MTC) has been questioned due to insufficient data on its effectiveness. Therefore, a retrospective analysis of vandetanib therapy outcomes in the RET(-) MTC was undertaken.
Material and Methods
The study analyzed the medical charts of 12 patients, including 3 women and 9 men, all diagnosed with RET(-) MTC. The median age at the treatment start was 58.0 years (range: 27.0–79.0). The median time from disease diagnosis to treatment initiation was 62.6 months (range 3.3-302.5). Prior to vandetanib, 11 out of 12 patients (91.7%) underwent total thyroidectomy with lymph node surgery, 8/12 (66.7%) received adjuvant radiotherapy, 2/12 (16.7%) underwent selective internal radiation therapy (SIRT) for liver metastases, 2/12 (16.7%) received ^{131}I-metaiodobenzylguanidine (MIBG) therapy; and one patient (8.3%) had thermal ablation of liver metastases. At the time of vandetanib qualification, 11/12 patients (91.7%) had MTC progression, as determined by the Response Evaluation Criteria in Solid Tumors (RECIST). All but one patient (91.7%) were staged IVc (metastatic disease), while the remaining patient was staged IVb at the start of treatment. Distant metastases were mainly localized in the liver (72.7%), bones (54.5%), mediastinum (36.4%), and lungs (18.2%). Disease stage was evaluated by computer tomography at baseline (treatment initiation) and at 3-month intervals thereafter. The response was assessed according to RECIST.
Results
Treatment efficacy was evaluated in 11 patients. One patient was excluded due to a very short treatment duration (76 days). Seven out of 11 patients (63,6%) achieved disease stabilization (SD) as the best treatment response. The median SD duration was 11.7 months (range 4.5-178.1). Partial response was observed in 2/11 patients (18,2%). Only one patient (9.1%) did not respond to the treatment. The median progression-free survival was 11.3 months (range 3.0-178.1 months), while the median time of treatment response was 16.1 months (range 3.0-224.9 months). The median of treatment duration was 12.3 months (range 2.6-215.5). In 11/12 patients, treatment was discontinued, mainly due to MTC progression (8 patients; 72.7%), whereas in the three remaining patients (27.3%), due to adverse reactions, making treatment continuation impossible. One patient is still on treatment (23,6 months). Nine patients out of 12 (75.0%) died at the time of analysis, eight due to MTC progression.
Conclusions
Vandetanib may represent a therapeutic option for RET(-) MTC patients. However, due to the small sample size, these results require confirmation in a larger cohort.

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PS2-06-04

Clinical outcomes of bilateral total thyroidectomy with and without postoperative radioactive iodine therapy

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Introduction
Radioactive iodine (RAI) therapy is often considered as an adjuvant treatment following bilateral total thyroidectomy (BTT) in patients with differentiated thyroid cancer. However, the benefit of RAI in low- to intermediate-risk patients remains controversial. This study aimed to evaluate the prognostic significance of postoperative RAI therapy in patients who underwent BTT at Gangnam Severance Hospital.
Methods
A retrospective analysis was conducted on 9,997 patients who underwent bilateral total thyroidectomy at Gangnam Severance Hospital. Among them, 8,723 patients received postoperative RAI therapy, while 1,274 did not. Clinical and

pathological variables including sex, age, tumor size, lymph node dissection status, multifocality, margin involvement, capsule invasion, thyroiditis, and recurrence rates were compared between the two groups.
Results
Patients in the RAI (+) group were generally younger (mean age 45.81 vs. 49.47 years, $P < 0.01$) and had larger tumors (1.10 cm vs. 0.83 cm, $P < 0.01$). The RAI (+) group also had a higher rate of multifocality, margin involvement, and capsule invasion ($P < 0.01$ for all). Despite these more aggressive features, recurrence rates were not significantly different between the groups (1.2% in RAI (-) vs. 2.6% in RAI (+), $P < 0.01$), suggesting no significant prognostic benefit of RAI therapy in this cohort.
Conclusion
In patients who underwent bilateral total thyroidectomy at Gangnam Severance Hospital, the use of postoperative RAI therapy did not confer a significant advantage in recurrence prevention when compared to those who did not receive RAI. These findings support the reconsideration of routine RAI therapy in selected low- to intermediate-risk patients.

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PS2-06-05

Evaluation and results of thyroid surgery in day care admission (EVARTS)

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Introduction
Thyroid surgery can be associated with serious and possibly lethal complications, such as postoperative haemorrhaging and airway obstruction. In the past, there has been a reluctancy to perform hemithyroidectomy as a day care procedure due to potential complications. The aim of this non-inferiority study is to establish safety and assess complication rates of hemithyroidectomy in day care setting (post-implementation group) when compared to inpatient hemithyroidectomy (pre-implementation group).
Methods
This is a Dutch single-centre retrospective cohort study including all patients who underwent hemithyroidectomy in our institution between 2018-2024. Since September 2022, day care hemithyroidectomy was been implemented in our institution. The primary outcome measure was to assess safety of the day care procedure. Complication rates, readmission rates, reinterventions and day care protocol violations were analysed. Secondary outcome measures were the identification of patient selection criteria for day care hemithyroidectomy.
Results
A total of 221 patients were included; 102 were treated in the pre implementation group and 119 in the post implementation group. Among the post implementation cohort, 72 patients were deemed eligible for day care admission. Eleven of these patients ultimately required overnight inpatient admission, due to late operative scheduling ($n = 4$), perioperative complications ($n = 1$), postoperative complications during admission ($n = 2$), postoperative complication after admission ($n = 1$) or vulnerability of the patient ($n = 4$). In the day care admission group, postoperative complications during day care admission occurred in one patient (2%), resulting in reintervention. Following discharge, five complications (7%) were reported. No additional adverse outcomes were observed.
Conclusions
Hemithyroidectomy performed in a day care setting was found to be non inferior to inpatient hemithyroidectomy with respect to safety and postoperative outcomes, provided that appropriate patient selection criteria are applied. The low rates of complications, readmissions, and reinterventions observed after implementation indicate that day care hemithyroidectomy is not less safe. These findings support the non inferiority of a structured day care protocol and suggest that outpatient hemithyroidectomy is a safe and feasible alternative to inpatient admission.

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PS2-06-06

Diagnostic accuracy of basal procalcitonin vs stimulated calcitonin in the differential diagnosis of hypercalcitoninemia: a retrospective observational study

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Background
The diagnosis of Medullary Thyroid Carcinoma (MTC) relies on serum calcitonin (CT). However, in patients with moderately elevated basal CT (bCT 10–100 pg/ml, "gray zone"), clinical management is challenging. Calcium stimulation test is often employed to identify MTC-specific hypersecretion (sCT) but lack universally accepted cut-offs, leading to diagnostic uncertainty. Recently, basal procalcitonin (bProCT) has emerged as a promising biomarker for the differential diagnosis of hypercalcitoninemia.
Objectives
To evaluate the diagnostic performance of bProCT compared to sCT and define optimal ProCT cut-offs for identifying pathological CT secretion.
Methods
This retrospective study included adult patients with bCT $\geq$ 10 pg/ml referred to a single tertiary center (2018–2026). Patients were divided into Group A (Pathological CT secretion: 39 MTC, 4 ectopic) and Group B (Non-pathological: 16 non-MTC thyroid diseases, 44 stable hypercarlcitoninemia under surveillance, 2 chronic renal failure) according to histology or clinical workup. ROC curve analysis was used to determine optimal cut-offs for bProCT and stimulated ProCT (sProCT). Diagnostic performance was compared using the Diagnostic Odds Ratio (DOR) in the bCT "gray zone".
Results
A total of 105 consecutive patients (62 F, 43 M) referred for initially elevated CT [median 24.3 (IQR 14.7–91.1) pg/ml] were included; of these, 55 underwent thyroidectomy and two patients underwent surgical resection for pancreatic NET and lung adenocarcinoma. Following the diagnostic workup, median bCT and bProCT levels were significantly higher in Group A vs Group B [139 (54.8–1189) vs 11.9 (6.9–17.88) pg/ml and 0.66 (0.28–6.35) vs 0.05 (0.04–0.07) ng/ml, $P < 0.001$, respectively]. Group B patients under active surveillance showed stable (between 10 and 30 pg/ml) or normalized bCT levels over time. ROC analysis identified an optimal bProCT cut-off of 0.095 ng/ml (AUC 0.965; Sn 93%, Sp 91.9%, $P < 0.001$) and an sProCT cut-off of 0.135 ng/ml (AUC 0.893; Sn 80%, Sp 90.9%, $P < 0.001$). In the 10–100 pg/ml bCT subgroup, bProCT demonstrated significantly superior diagnostic accuracy compared to sCT (DOR 85.5, 95% CI 15.07–485.01 vs DOR 4.62, 95% CI 1.21–17.66). In ectopic secretions, bProCT was often positive (75%), while sCT showed a characteristically flat response.
Conclusions
Basal ProCT is a highly accurate biomarker for identifying pathological hypercalcitoninemia. In the 10–100 pg/ml "gray zone," bProCT provides superior accuracy over sCT. While sCT remains useful for suggesting ectopic secretions via a flat response, bProCT represents a robust complementary and additional diagnostic tool for MTC screening.

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PS2-06-07

Papillary thyroid carcinoma association with high risk of developing luminal a- and b molecular type breast cancer : retrospective study based on 1500 cases

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma is known to be often associated with the risk of developing secondary solid tumors.This is known as secondary malignancies in CLL/SLL. There are several reasons for this: immunodeficiency -CLL (Chronic Lymphocytic Leukemia) causes immune system dysfunction (B-cell dysfunction, T-cell imbalance) Chronic immunosuppression lymphoid cell tumor clone also suppresses immune surveillance. It is noteworthy that immunotherapy/targeted therapy also increases the risk of secondary neoplasia. Genetic predisposition and age are important. As for the most common thyroid tumor, according to literature data, the development of tumors of other localisation and genesis is slightly increased in these cases.

Overall risk on average ~1.2-1.4 times higher than the general population. Thyroid cancer and breast cancer can develop synchronously (simultaneously emerged) or revealed later, which is called metachronous. According to our clinic's cases (women population), this rate is significantly higher and in ten years of retrospective analysis, $n = 1500$ patients with thyroid cancer and 100 patients with breast cancer were revealed synchronously (6.7%). Among them all forms of cancer ER/PR were positive, Luminal Type A (80%) and Luminal Type B (20%), metachronous cancer developed in 255 patients 5-6 years later. There was no case of bilateral cancer. Conclusion: Papillary thyroid cancer is often associated with solid breast malignancies in the Georgian population. In our opinion, Papillary thyroid cancer, like CLL/SLL is associated with an increased risk of secondary cancer. According to our data, patients who developed Papillary thyroid cancer after revealing breast cancer, papillary thyroid cancer forms and disease development did not differ significantly from the patient's clinical outcome, who did not have another secondary solid tumor.

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PS2-06-08

Clinical profile and biochemical-structural discordance in initially non–radioiodine-avid metastatic differentiated thyroid cancer

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Objectives
Radioiodine (RAI) therapy is a standard treatment for metastatic differentiated thyroid cancer (DTC). However, a subset of patients presents with distant metastases that are non–RAI-avid at initial evaluation, challenging disease assessment and management. This study aimed to characterize the clinicopathological features of this population, especially on the relationship between tumor burden and biochemical markers.
Methods
We retrospectively reviewed 38 consecutive DTC patients with distant metastases treated between 2012 and 2025. Patients were classified as non–RAI-avid ($n = 20$) or RAI-avid ($n = 18$) based on initial diagnostic or post-therapeutic whole-body scans. Demographic characteristics, tumor features, metastatic patterns, and stimulated serum thyroglobulin (Tg) levels were compared.
Results
Several aggressive clinicopathological features were significantly more common in the non–RAI-avid group, including male sex (50% vs. 16.7%, $P = 0.04$), classic papillary thyroid carcinoma histology (55% vs. 5.6%, $P = <0.01$), gross extrathyroidal extension (60% vs. 16.7%, $P = <0.01$), and lymph node metastases (85% vs. 27.8%, $P = <0.01$). With respect to tumor burden, patients in the non–RAI-avid group had larger primary tumors (median diameter 3.4 cm vs. 1.8 cm, $P = 0.2$) and more frequent multi-organ distant metastases (60% vs. 38.9%, $P = 0.19$), although these differences did not reach statistical significance. Notably, despite the higher prevalence of aggressive local disease, stimulated serum Tg levels tended to be lower in the non–RAI-avid group compared with the RAI-avid group (median 69 ng/ml vs. 469 ng/ml, $P = 0.136$).
Conclusion
Patients with initially non–RAI-avid metastatic DTC frequently present with aggressive pathological features. The observed discordance between substantial structural disease and relatively lower serum Tg levels may reflect impaired tumor differentiation and reduced Tg-secreting capacity. This potential biochemical–structural mismatch limits the utility of Tg as a surrogate marker of disease burden in non–RAI-avid DTC and supports earlier consideration of alternative, non–RAI-based therapeutic approaches.

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PS2-06-09

Diagnostic accuracy of FNA-TG for metastatic differentiated thyroid carcinoma and correlation with ultrasound lymph node characteristics

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Objectives
Measurement of thyroglobulin in wash-out fluid after fine-needle aspiration biopsy (FNA-Tg) is a recognized method for detecting metastases from differentiated thyroid cancer (DTC). However, internationally accepted cut-off values for clinical use have not yet been established. This study aimed to evaluate the diagnostic accuracy of FNA-Tg and its association with lymph node (LN) characteristics.
Methods
We examined 91 patients (male:female ratio 26:65) who were admitted to our hospital between April 2018 and January 2026 for fine-needle aspiration biopsy (FNA) of thyroid nodules and/or suspicious cervical LNs. Cytological analysis and measurement of FNA-Tg from LNs were performed. The ultrasound characteristics of the LNs were analyzed to assess possible correlations with the FNA-Tg values. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic accuracy of FNA-Tg.
Results
Of the 91 participants, 48 patients had histologically confirmed metastases from papillary thyroid cancer and 43 had negative LNs. As multiple LNs were assessed in some patients, a total of 121 lesions were included in the analysis. FNA-Tg levels were significantly higher in the metastatic group (mean 958.84 ng/ml $\pm$ 1458.29) compared with the non-metastatic group (mean 4.5 ng/ml $\pm$ 15.11). ROC curve analysis identified an optimal cut-off value of FNA-Tg $\geq$100 ng/ml using the Youden index, which yielded a diagnostic accuracy of 95% (115/121 correctly classified LNs), with an area under the curve (AUC) of 0.985 (95% CI 0.964–1.000, $P < 0.001$), sensitivity of 91%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 91%. No statistically significant correlation was found between LN size and FNA-Tg levels. The ultrasound features most strongly associated with positive FNA-Tg were altered LN echogenicity, microcalcifications, absence of the hilum and cystic degeneration ($P < 0.05$). A round shape with a short-to-long axis ratio >0.5, scattered blood flow and macrocalcifications were not statistically significant predictors of metastases.
Conclusions
FNA-Tg has very high diagnostic accuracy, sensitivity and specificity for detecting metastases in DTC, irrespective of LN size and structural characteristics.

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PS2-06-10

Volume reduction after energy-based ablation in bethesda ii thyroid nodules and indeterminate nodules with negative molecular profiling

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Background
Energy-based ablation (EBA) has become an established therapeutic approach for thyroid nodules with a very low risk of malignancy (RoM), particularly those classified as Bethesda II on cytology. Molecular testing can also identify indeterminate thyroid nodules (ITNs; Bethesda III/IV) with similarly low RoM (NPV 96%). However, evidence regarding the safety and effectiveness of EBA in ITNs characterized as benign by molecular profiling remains scarce.
Objective
To compare the performance of EBA in Bethesda II thyroid nodules and indeterminate thyroid nodules with a benign molecular profile (mir-THYpe full negative result), and to evaluate the volume reduction rate (VRR) of these nodules during follow-up.
Method
Two complementary analyses were conducted. In the first analysis, 23 Bethesda II nodules and 31 ITNs with negative mir-THYpe results treated with EBA were assessed at 6 months to compare the VRR. In the second analysis, the cohort of mir-THYpe–negative ITNs was followed for 12, 18 and 24 months to evaluate the longitudinal progression of VRR. Procedure-related complications and the need for reintervention were also documented.
Result
At the 6-month evaluation, the mean VRR was 57.63% in Bethesda II nodules and 64.67% in mir-THYpe full negative ITNs ($P = 0.27$), demonstrating comparable short-term treatment efficacy between the groups. Extended follow-up of the ITN

cohort revealed a sustained reduction in nodule volume, with mean VRRs of 69.0% at 12 months, 71.4% at 18 months, and 72.4% at 24 months. Only one patient required an additional intervention, and no major complications were reported.
Conclusion
These preliminary results suggest that EBA treatment of ITNs with a mir-THYpe full negative result provides a VRR comparable to that achieved in nodules classified as Bethesda II. Furthermore, the findings indicate that volume reduction continues to increase during the 24 months of follow-up.

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Clinical Cancer 6

PS2-07-01

Predictive clinical and ultrasound features of thyroid malignancy in oncology patients with incidental diffuse thyroid uptake on FDG PET/CT

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Objectives
Although the malignancy risk is very low in patients with diffuse thyroid uptake on FDG PET/CT, rare cases of diffuse thyroid metastasis may mimic thyroiditis. However, a standardized approach to managing incidental diffuse thyroid FDG uptake remains unestablished. This study aimed to identify clinical and ultrasound (US) features predictive of thyroid malignancy in oncology patients with incidental diffuse thyroid uptake on FDG PET/CT.
Methods
This retrospective cohort study included 492 consecutive oncology patients with incidental diffuse thyroid FDG uptake and a final diagnosis of thyroid disease from January 2012 to May 2025. The primary outcome was the identification of clinical and US features predictive of malignancy. The secondary outcome was the malignancy risk of incidental diffuse thyroid uptake, determined by pathology or clinical follow-up for at least six months. US features were compared between benign and malignant thyroid disease in 40 patients who underwent thyroid US within three months of PET/CT. The maximum standardized uptake value (SUVmax) was compared between benign and malignant thyroid disease.
Results
Eight (1.6%) patients were diagnosed with thyroid malignancy, including seven diffuse metastases (lung, $n = 5$; gastric, $n = 1$; parotid, $n = 1$) and one thyroid lymphoma. FDG-avid cervical metastatic lymph nodes were present on PET/CT in all patients with thyroid malignancy (100%) but only in 8.3% (40/484) of benign cases ($P < 0.001$). US features of branching hypoechoic strands in the thyroid parenchyma and echogenic changes in the strap muscles were observed exclusively in patients with thyroid malignancy (75.0% [6/8] and 100% [8/8], respectively; $P < 0.001$). At least one of these two US features was present in all cases of thyroid malignancy. The SUVmax values of thyroid malignancies were significantly higher than those of benign thyroid disease (median, 9.7 vs. 2.9, $P < 0.001$).
Conclusions
The absence of FDG-avid cervical lymphadenopathy was highly specific for benign thyroid diseases, while the presence of branching hypoechoic strands or echogenic changes in the strap muscles on US was highly specific for diffuse thyroid metastasis in oncology patients with incidental diffuse thyroid uptake on FDG PET/CT. The absence of FDG-avid cervical lymphadenopathy can effectively rule out malignancy, while the presence of US features of branching hypoechoic strands or echogenic changes in the strap muscles can enable accurate diagnosis of thyroid metastasis.

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When papillary meets medullary: thyroid collision carcinoma - a systematic review of the past 20 years and case report

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Background
Thyroid carcinoma is the most common endocrine malignancy, with papillary thyroid carcinoma (PTC) representing the majority of cases, while medullary thyroid carcinoma (MTC) accounts for a smaller but significant proportion. The coexistence of PTC and MTC may occur either as a mixed tumor or as a thyroid collision tumor (TCT), representing approximately 1-2 % of thyroid malignancies. This study aimed to systematically review the literature on PTC–MTC TCT over the last 20 years and present a clinical case from our center.
Methods
A systematic review identified reports of PTC–MTC TCT published between 2005 and 2025 using PubMed, Google Scholar and SciSpace with relevant keywords. Articles describing coexisting PTC and MTC were included. Data from patient demography and surgical strategy were collected. We also report the case of a 60-year-old man with palpable thyroid nodules. Ultrasound showed a right lobe with a mixed nodule (40.4 mm EU-TIRADS 3) and a solid nodule at the right lobe–isthmus junction (19.8 mm EU-TIRADS 5). Fine-needle aspiration suggested PTC whereas laboratory tests revealed elevated calcitonin (3506 pg/ml) and CEA (279 ng/ml). Immunohistochemistry confirmed MTC. Staging CT showed no suspicious lymph nodes but suggested bone involvement. The patient underwent total thyroidectomy (TT) with bilateral central neck dissection. Histopathological examination revealed coexisting MTC (30 mm), pT2N0, and multifocal PT, pT1bN1a. The patient was referred for radioactive iodine therapy and genetic testing.
Results
The systematic review included 40 studies published between 2005 and 2025 identifying 522 patients. Most reports described single cases although several larger series were also identified. Patients were typically in the fifth to sixth decade of life with female predominance. TT was the preferred surgical approach. However in cases in which MTC was diagnosed postoperatively on histopathological examination, some patients who had initially undergone hemithyroidectomy for PTC were submitted to completion of thyroidectomy. TT was frequently associated with bilateral central neck dissection. The most common genetic alterations in TCT involved RET in MTC and BRAF in PTC although in most reported cases overall genetic testing was negative. In our patient, because MTC was strongly suspected preoperatively, TT with bilateral central neck dissection was performed *ad initium*.
Conclusions
PTC–MTC TCT remain rare and their diagnosis can be challenging because of overlapping features, highlighting the importance of integrating biochemical markers, cytology, imaging and immunohistochemistry. This work emphasizes the need for awareness for TCT and individualized management strategies targeting each tumor.

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PS2-07-03

Predictive value of pre-ablation stimulated thyroglobulin for treatment response in intermediate risk papillary thyroid carcinoma: a retrospective monocentric study

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Objective
This study aims to evaluate the predictive value of pre-ablation stimulated thyroglobulin (sTg) levels in anticipating an "Excellent Response" to radioactive iodine (RAI) therapy in patients with intermediate risk papillary thyroid carcinoma.
Methods
We retrospectively analyzed patients with ATA 2015 intermediate-risk papillary thyroid carcinoma who underwent total thyroidectomy followed by RAI therapy in our institution between 2021 and 2023. 63 patients were included and divided into two groups based on their clinical and biochemical outcome: patients with excellent response and patients who did not have excellent response (encompassing indeterminate, biochemical incomplete, or structural incomplete responses). Pre-ablation sTg levels were compared using the Mann-Whitney U test. A Receiver Operating Characteristic (ROC) curve analysis was conducted to assess predictive accuracy and explore a potential optimal cut-off value.
Results
Out of the 63 included patients, 39 (61.9%) achieved an excellent response, while 24 (38.1%) did not have an excellent response. The median pre-ablation sTg was significantly lower in the excellent response group at 0.79 ng/ml (IQR: 3.84) compared to the not excellent response group, which showed a median of 13.4 ng/ml (IQR: 21.2) ($P < 0.001$). The ROC curve analysis demonstrated strong

predictive performance with an Area Under the Curve (AUC) of 0.80 (95% CI: 0.68–0.92) and an optimal cut-off value of 4.6 ng/ml with a Negative Predictive Value (NPV) of 85.7%.
Conclusion
Pre-ablation stimulated thyroglobulin appears to be an early predictor of therapeutic outcome in patients with ATA intermediate-risk papillary thyroid carcinoma. Utilizing a cut-off of 4.6 ng/ml could provide a threshold to anticipate treatment response due to its high Negative Predictive Value, allowing for a more personalized approach to patient follow-up and disease management.

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PS2-07-04

Highly selective ret inhibitor selpercatinib preserves skeletal muscle in patients with advanced medullary thyroid carcinoma

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Background
In patients with cancer, weight loss is a progressive wasting syndrome mainly characterized by the reduction of fat mass (FM) and skeletal muscle (SM). Marked weight loss with sarcopenia has been reported with several tyrosine kinase inhibitors; conversely, treatment with selpercatinib has been associated with weight gain.
Objectives
The aim of this prospective study was to assess changes in body weight and body composition (FM and SM) in patients with advanced medullary thyroid carcinoma (MTC) treated with selpercatinib.
Methods
We enrolled 12 patients with advanced MTC treated with selpercatinib. All participants underwent clinical assessment and body composition analysis by dual-energy X-ray absorptiometry (DEXA) at baseline and after 12 months of therapy. Changes in body weight, BMI, FM, and SM were evaluated over the study period.
Results
Of the 12 patients, 9 were males and 3 females, with a median age of 62 years at enrollment. All patients continued treatment with selpercatinib throughout the study. Baseline and 12-month values were as follows, respectively: body weight 77.7 $\pm$ 19.4 vs 78.1 $\pm$ 15.4 kg ($P = 0.5$), BMI 25.3 $\pm$ 5.3 vs 25.6 $\pm$ 4.0 kg/m^2 ($P = 0.5$), FM 24.9 $\pm$ 11.8 vs 24.2 $\pm$ 9.4 kg ($P = 0.6$), and SM 49.3 $\pm$ 11.1 vs 50.9 $\pm$ 12.4 kg ($P = 0.1$).
Conclusions
The findings of this study suggest that selpercatinib preserves skeletal muscle to a greater extent than other anticancer therapies. Maintenance of skeletal muscle mass is metabolically relevant and may help sustain functional capacity and performance status in patients with advanced disease undergoing long-term targeted treatment.

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PS2-07-05

Management of biopsy proven lymph node metastases from papillary thyroid cancer under disease monitoring protocols

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Objectives
Cervical lymph node metastases (LNM) from papillary thyroid carcinoma (PTC) often remain stable over time, supporting conservative management in selected patients. Minimally invasive techniques have emerged as alternatives to surgery. However, evidence comparing these strategies and identifying predictors of progression is limited. This study evaluates the safety of monitoring biopsy-proven LNM and aims to identify factors associated with disease progression while exploring the role of minimally invasive treatments.
Methods
We conducted a retrospective bicentric cohort study including patients with PTC and biopsy-proven LNM followed on a monitoring protocol at two Latin American centers. Eligible patients had lymph nodes <2 cm and located away from vital structures. Disease progression and protocol discontinuation were defined as new lymph node disease or enlargement ≥ 3 mm.
Results
The cohort included 72 patients, most were female (82%) with an average age of 40.3 years. After a mean follow-up of 62.8 months, 47 patients (65%) remained under monitoring, while 25 discontinued surveillance and required intervention, due to disease progression ($n = 14$) or patient/surgeoń s preference ($n = 11$). Progressive cases usually happened in male and older patients. No other variables predicted progression. Radiofrequency ablation (RFA) improved ATA response classification, without survival differences.
Conclusions
Monitoring is safe in patients with small, non-threatening LNM. Age and male sex appear to be the most relevant predictors of structural progression. RFA may be considered in patients who decline surgery or in whom surgery carries increased risk, but improvement in ATA response classification after intervention does not improve survival outcomes.

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PS2-07-06

How well do tirads systems detect medullary thyroid carcinoma? a comparison of ACR-tirads and eu-tirads

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Introduction
The American College of Radiology (ACR-TIRADS) and the European Thyroid Association (EU-TIRADS) systems are widely used to stratify malignancy risk in thyroid nodules. However, both were primarily developed for Papillary Thyroid Carcinoma and their accuracy in Medullary Thyroid Carcinoma (MTC) – a rare and biologically distinct entity – remains uncertain. We aimed to assess and compare the performance of ACR-TIRADS and EU-TIRADS in MTC.
Methods
A retrospective study was conducted on patients with histopathologically confirmed MTC and complete preoperative ultrasound reports or images between 2003 and 2025 at a tertiary center. Images were reviewed by an experienced endocrinologist. Nodules were classified according to the two systems, and sensitivity and FNA indication rates were compared.
Results
Thirty-one patients and 32 nodules (68% female; mean age 57$\pm$17 years) were included. Nodules' characteristics: 97% solid, 16% markedly hypoechoic, 78% hypoechoic, 44% irregular borders, 41% microcalcifications, 34% macrocalcifications, 9% taller than wide, 3% extrathyroidal extension; mean largest diameter 2.1$\pm$1.1cm. According to EU-TIRADS, 78% were category 5, 19% category 4, and 3% category 3; under ACR-TIRADS, 56% were TR5, 41% TR4, and 3% TR3. EU-TIRADS demonstrated higher sensitivity (78% vs. 56%, $P = 0.016$), as most nodules had at least one high-suspicion feature and were therefore classified as

category 5. Seven nodules (22%) were categorized as EU-TIRADS 5 but as ACR-TIRADS 4; these were markedly hypoechoic (4/7) or had irregular borders (3/7), but lacked additional suspicious features to reach TR5 in the ACR system. Based on fine-needle aspiration (FNA) criteria, 91% of nodules would be recommended for FNA under EU-TIRADS and 88% under ACR-TIRADS ($P = 0.100$).
Discussion and Conclusions
Both systems classified most MTC nodules (97%) as moderate- or high-risk categories (4-5), indicating good diagnostic performance. EU-TIRADS showed higher likelihood of classifying nodules as high risk than ACR-TIRADS, although this difference had limited clinical relevance, as TR4 nodules were generally large enough to still meet FNA criteria. Interestingly, the inclusion of macrocalcifications in ACR-TIRADS – common in MTC but not considered in EU-TIRADS – did not improve its sensitivity. Both EU-TIRADS and ACR-TIRADS are applicable for the evaluation of MTC nodules, though targeted modifications could further enhance their diagnostic accuracy.

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PS2-07-07

Simulating the impact of the 2025 ATA lobectomy-first recommendations in 1–2 cm papillary thyroid carcinoma: a retrospective counterfactual analysis

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Background
The 2015 American Thyroid Association (ATA) guidelines allowed either lobectomy or total thyroidectomy (TT) for 1–4 cm intrathyroidal cN0M0 papillary thyroid carcinoma (PTC), whereas the 2025 ATA guidelines recommend lobectomy as the initial surgical approach for operation for most cT1b ($\leq$2 cm without gross extrathyroidal extension) cN0M0 tumors to reduce morbidity while maintaining oncologic safety. This study evaluates the potential clinical impact of the updated guidelines on patients who historically underwent TT for 1–2 cm PTC.
Methods
We retrospectively analyzed consecutive patients with 1.0–2.0 cm PTC who underwent TT between 2002 and 2020. Patients with non-papillary histology, gross extrathyroidal extension, distant metastases, or incomplete data were excluded. "Lobectomy-eligible" cases were defined according to anticipated 2025 ATA criteria (cT1bN0M0, no gross ETE). Using a probabilistic Monte Carlo model (10,000 iterations), we simulated a counterfactual "lobectomy-first" strategy based on 2025 ATA criteria. We estimated reductions in surgical complications (hypoparathyroidism, recurrent laryngeal nerve [RLN] injury) and radioactive iodine (RAI) administration, alongside the projected need for completion thyroidectomy.
Results
75 patients (mean age 44 $\pm$ 13 years, 90% female) had tumors 1.4 $\pm$ 0.3 cm; 70% ATA low risk. Hypoparathyroidism occurred in 18% after total thyroidectomy, with no RLN injuries observed. In the counterfactual lobectomy-first model, the expected hypoparathyroidism rate was 11% (95% CI 6–16), corresponding to a relative reduction of 43% (95% CI 34–51). Expected RLN injury was 1% (95% CI 0–3). RAI use would have decreased from 68.9% observed to 24% (95% CI 18–31) under lobectomy-first, a relative reduction of 65%. The projected requirement for completion thyroidectomy was 35% for definite indications (e.g., capsular invasion), rising to 38% in a liberal scenario accounting for contralateral microfoci.
Conclusion
In this cohort of 1–2 cm PTC, adopting a lobectomy-first approach consistent with the 2025 ATA guidelines would be expected to substantially reduce hypoparathyroidism and RAI use, with only about 1/3 of patients ultimately requiring total thyroidectomy and no anticipated compromise in oncologic outcomes based on existing evidence.

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PS2-07-08

Detection and retreatment outcomes of cervical lymph node persistent disease using ultrasonography and F-18 FDG PET/CT in papillary thyroid carcinoma

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Objective
We investigated which modalities were suitable for the detection of persistent disease in cervical lymph node and how the outcome after retreatment of PD differed according to the retreatment methods in patients with papillary thyroid carcinoma (PTC).
Material and Methods
Among 474 PTC patients who underwent initial surgery and radioactive iodine (RAI) therapy, 41 patients had PD on neck ultrasonography (US) or F-18 FDG PET/CT, both of which modalities were performed within two years of initial treatments. Among them, 31 patients underwent retreatment RAI therapy only or reoperation (with or without RAI therapy). Therapeutic outcomes were assessed as whether the patients had no evidence of disease (NED) or residual metastatic lesions after retreatments (subsequent PD, sPD). We evaluated whether the FDG avidity in PD lesions or retreatment methods related to therapeutic outcomes.
Results
In 26 out of 41 patients, PD was located at the single lymph node level of the neck. Diagnostic performance for PD was 6 patients (23.1%) for PET/CT only, 7 patients (26.9%) for neck US only, and 13 patients (50.0%) for both modalities, respectively. Of 31 patients with PD, 10 patients (32.3%) had sPD after retreatments. There was no significant relationship between FDG avidity on PET/CT and NED (65.2% vs. 75.0%, $P = 1.000$). The patients who underwent reoperation regardless of RAI therapy had a higher prevalence of NED than patients who received RAI alone (76.0 % vs. 16.7%, $P = 0.013$).
Conclusions
The diagnostic performance of each modality was complementary in PD located at the single lymph node level. Although the reoperation was significantly related to therapeutic outcomes in patients with PD, therapeutic managements should be further optimized to reduce the rate of retreatment failure.

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PS2-07-09

TSH Suppression after lobectomy for low-risk papillary thyroid cancer: real-world practice under evolving guidelines

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Objectives
Thyroid-stimulating hormone (TSH) suppression has historically been used in differentiated thyroid cancer. In low-risk patients treated with lobectomy, previous American Thyroid Association (ATA) guidelines recommended maintaining TSH at 0.5–2.0 mU/L, while recent updates indicate routine suppression is unnecessary. We evaluated postoperative thyroid function management and levothyroxine use to maintain TSH $<$2.0 mU/L in a real-world cohort of low-risk papillary thyroid carcinoma patients treated with lobectomy.
Methods
We conducted a retrospective observational study including patients with unilateral cT1N0M0/cT2N0M0 papillary thyroid carcinoma who underwent lobectomy between 2016 and 2024. Patients previously treated with levothyroxine or those with incomplete data were excluded. Demographic characteristics, tumor features, postoperative TSH levels, levothyroxine initiation and follow-up thyroid function were analyzed.
Results
A total of 65 patients fulfilled the inclusion criteria: 49 women (75.4%) and 16 men (24.6%). Median age at surgery was 53 years (IQR 41–61). Median tumour size was 9 mm (IQR 5–14.3). Multifocality was present in 8 patients (12.3%) and minimal

extrathyroidal extension in 7 (10.8%). The first postoperative TSH measurement was obtained at a median of 13 weeks (IQR 7–24) after surgery. Only 15 patients (23,1%) had TSH within 0.5–2.0 mU/L, whereas 50 (76,9%) had TSH >2.0 mU/L. Nevertheless, levothyroxine was started in 24 patients (36.9%) after the initial postoperative assessment: 19 due to hypothyroidism and 5 due to TSH >2.0 mU/L. The median follow-up was 43 months (IQR 24–67). During this period, 5 initially untreated patients developed hypothyroidism, resulting in an overall total of 24 patients (36.9%) who developed hypothyroidism. In addition, 2 patients initiated levothyroxine due to persistent TSH >2 mU/L despite remaining within the reference range. Five patients started therapy within the first two years after surgery, whereas two initiated treatment later. No patient experienced recurrence during follow-up. Overall, 34 patients (52,3%) remained untreated throughout follow-up. Among them, only 13 maintained TSH <2 mU/L.
Conclusions
Despite recommendations, a target of TSH <2 mU/L for low-risk patients was often not applied in practice, reflecting emerging evidence. Under the 2015 guidelines, 52 patients (80%) would have met criteria to initiate levothyroxine, vs 24 (37%) under the 2025 recommendations. These findings highlight that updated guidelines allow the reduction of lifelong therapy in a substantial proportion of patients without increasing tumor recurrence risk.
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PS2-07-10

Rhtsh in aiding dynamic assessment of differentiated thyroid cancer patients across different risk-stratification
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Objectives
ZGrhTSH, a novel Chinese rhTSH analog, was shown to be a safe and effective alternative to thyroid hormone withdrawal (THW) for postoperative diagnostic evaluation in patients with differentiated thyroid cancer (DTC). So far no study has ever addressed rhTSH in aiding dynamic assessment of DTC patients from the perspective of different risk of recurrence stratification. We thus did this analysis to evaluate the diagnostic performance of ZGrhTSH across different recurrence risk patients.
Methods
This study was based on a multicenter, open-label, phase 3 trial (ClinicalTrials.gov, NCT04971473) in which each patient underwent TSH-stimulated diagnostic assessments during both the ZGrhTSH and THW phases. Concordance between the two phases was evaluated for three efficacy endpoints: 1) diagnostic whole-body scans (Dx-WBS), 2) stimulated thyroglobulin (Tg) levels, and 3) response to therapy (RTT), stratified by ATA recurrence risk (low, intermediate, or high).
Results
A total of 195 patients were included in the full analysis set. According to ATA recurrence risk stratification, 33 (16.9%), 129 (66.2%), and 32 (16.4%) patients were classified as low-, intermediate-, and high-risk, respectively, while one patient had missing risk classification. The Dx-WBS concordance rates were 84.8% (95% CI, 69.1-93.3%), 89.9% (95% CI, 83.5-94.0%), and 84.4% (95% CI, 68.2-93.1%) in low-, intermediate-, and high-risk groups, respectively. Among 187 patients with negative Tg-antibody (TgAb), using a stimulated Tg cutoff of 1 ng/ml, the concordance rates were 93.8% (95% CI, 79.9-98.3%), 87.8% (95% CI, 80.9-92.5%), and 96.8% (95% CI, 83.8-99.4%) in the respective risk groups. The RTT concordance rates were 81.3% (95% CI, 64.7-91.1%), 78.0% (95% CI, 69.9-84.5%), and 71.0% (95% CI, 53.4-83.9%) across low- to high-risk groups.
Conclusions
ZGrhTSH demonstrated consistently high diagnostic performance across ATA risk strata in Dx-WBS, stimulated Tg, and RTT, supporting its use as a reliable adjuvant assessment alternative to THW.
Keywords
Differentiated thyroid cancer; Recombinant human thyroid-stimulating hormone; ATA risk stratification; Diagnostic whole-body scan; Thyroglobulin.
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Clinical Cases (cancer) 1

PS2-08-01

Papillary thyroid microcarcinoma revealed by skull metastasis: a case supporting aggressive surgical management
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Introduction
Papillary microcarcinoma is most often asymptomatic. It is usually discovered either on histopathological examination of a thyroidectomy specimen performed for benign thyroid disease, or incidentally on imaging carried out for another indication. In some cases, however, it may present more aggressively and be revealed by a bone metastasis. This was the case in a child whom we treated for a papillary microcarcinoma revealed by a metastasis of the cranial vault.
Materials and Methods
A patient currently aged 24 years was initially managed in the neurosurgery department at the age of 16 for a right parietal mass associated with headaches. Brain MRI revealed a solid–cystic tumour with intracranial extension and associated pachymeningitis. Following complete excision with an extended bone flap, a cranioplasty using bone cement was performed at a later stage. Histological and immunophenotypic analysis was consistent with papillary thyroid carcinoma. A total thyroidectomy with central and bilateral jugulocarotid lymph node dissection was subsequently performed.
Results
Histological examination identified a bifocal papillary carcinoma measuring 3 and 4 mm without capsular invasion. All 34 lymph nodes removed during the dissection were reactive, leading to a tumour classification of pT1mN0M1. After radioactive iodine therapy with a dose of 100 mCi, the post-therapeutic whole-body scan showed no other secondary localisation. An ^18F-FDG PET/CT scan was also negative. Four years later, the patient developed a lateral cervical lymphadenopathy. Fine-needle aspiration cytology with analysis of the needle rinse fluid was in favour of nodal recurrence. Revision surgery followed by additional radioactive iodine therapy was therefore performed. After more than eight years of follow-up, regular monitoring has shown no evidence of recurrence, supporting the aggressive surgical approach adopted in this young patient.
Conclusion
Even in the absence of signs of local invasion, some papillary microcarcinomas may behave aggressively and present with distant metastases. Surgical excision should therefore be complete, with extended lymph node dissection when appropriate. An optimal staging work-up is essential.
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PS2-08-02

MACRO-TSH interference in the follow-up of a thyroid carcinoma: a diagnostic challenge
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Introduction
Total thyroidectomy for papillary thyroid carcinoma requires lifelong levothyroxine (LT4) therapy, with TSH suppression tailored to recurrence risk. Analytical interferences may complicate interpretation of thyroid function tests. Macro-TSH, a high-molecular-weight complex formed by TSH bound to immunoglobulins, may lead to falsely elevated TSH levels despite normal thyroid hormone concentrations.
Case Report
A 26-year-old woman with no personal or family history of thyroid or malignant disease, was referred after detection of a left thyroid nodule classified as EU-

TIRADS 5 whose fine-needle aspiration cytology revealed Bethesda VI. Cervical lymph node assessment was unremarkable. She underwent total thyroidectomy and histopathology revealed two synchronous papillary thyroid microcarcinomas in the left lobe (4.5 and 4 mm), without capsular or vascular invasion, with clear margins and no indication for radioiodine therapy (pT1a(m) Nx Mx R0). Postoperatively, LT4 100 mg/day was started. At the first follow-up, she reported fatigue; neck examination was unremarkable and body weight was 87 kg. Thyroid function tests showed TSH >50 µIU/ml, fT4 0.67 ng/dl (reference 0.54–1.54) and fT3 2.81 pg/ml (reference 2.5–4.4), with undetectable thyroglobulin (Tg < 0.04 ng/ml) and negative anti-Tg antibodies. LT4 was increased to ~1.7 mg/kg. After 12 weeks, TSH remained elevated (> 51.9 µIU/ml), with fT4 0.87 ng/dl and fT3 2.76 pg/ml, Tg <0.04 ng/ml and anti-Tg antibodies negative, without malabsorption signs or adherence issues. Neck ultrasound was unremarkable. Further evaluation in a different laboratory showed TSH was 16.65 µIU/ml with elevated fT4 1.40 ng/dl and fT3 3.62 pg/ml. Suspecting macro-TSH, Polyethylene glycol (PEG) precipitation was performed: total TSH 9.58 µIU/ml and free TSH 5.72 µIU/ml (37% recovery), supporting the diagnosis of macro-TSH. The LT4 was titrated to 2.1 µg/kg. At follow-up, TSH was 15.64 µIU/ml (free TSH 5.92 µIU/ml; 41% recovery), with Tg <0.04 ng/ml, anti-Tg 3.4 U/ml (negative), fT4 1.05 ng/dl and fT3 3.13 pg/ml, therefore LT4 was increased to 2.3 µg/kg while evaluation for subtle malabsorption continued.

Conclusions

In thyroidectomized patients with thyroid cancer, macro-TSH may cause persistent TSH elevation despite adequate LT4 therapy. This interference may result in unnecessary investigations and inappropriate dose escalation, increasing the risk of iatrogenic thyrotoxicosis. Macro-TSH should be suspected when TSH levels are discordant with biochemical parameters, including thyroid hormone concentrations, thyroglobulin profile and imaging findings. Recognition of macro-TSH is therefore essential to avoid misinterpretation of biochemical results and to ensure safe long-term management, particularly when overlapping factors, like LT4 absorption issues complicate management.

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PS2-08-03

An unusual thyroid manifestation of cowden syndrome: hyalinizing trabecular tumor associated with a pathogenic pten gene deletion

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Introduction

Cowden syndrome, part of the spectrum of PTEN Hamartoma Tumor Syndrome, is an autosomal dominant disorder caused by germline alterations in the PTEN gene. It is characterized by multiple hamartomas and an increased risk of malignancies, particularly breast, thyroid, and endometrial cancer. Among thyroid tumors, papillary thyroid carcinoma is the most frequently reported histological type. The association with hyalinizing trabecular tumor of the thyroid is uncommon.

Case Presentation

We report a 38-year-old woman with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency, diagnosed in early childhood and followed since then. During adulthood she developed a multinodular goiter with progressive enlargement. Fine-needle aspiration cytology revealed a Bethesda IV lesion and total thyroidectomy was performed. Histopathological examination demonstrated a hyalinizing trabecular tumor of the thyroid. Seven years later, the patient was diagnosed with synchronous endometrial cancer and ovarian cancer. Given the occurrence of multiple tumors suggestive of a hereditary cancer syndrome, germline genetic testing using a multigene panel was performed. Genetic analysis identified a copy number variation consisting of a deletion involving exon 2 of the PTEN gene, confirmed by Multiplex Ligation-dependent Probe Amplification (MLPA). This variant is classified as pathogenic in international databases, establishing the diagnosis of Cowden syndrome.

Conclusion

This case expands the spectrum of thyroid manifestations associated with Cowden syndrome. While papillary thyroid carcinoma is the most frequently reported thyroid malignancy in patients with germline alterations in the PTEN gene, the presence of a hyalinizing trabecular tumor of the thyroid may also represent a manifestation of this syndrome. Recognition of atypical thyroid histologies in this context may facilitate earlier identification of hereditary cancer syndromes and appropriate genetic counseling.

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PS2-08-04

Unexpected iodine-avid hepatic metastasis revealed by iodine-131 whole-body scintigraphy with SPECT/CT in high-grade differentiated thyroid carcinoma: a case report

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Introduction

Distant metastases are uncommon in differentiated thyroid carcinoma (DTC) and most frequently involve the lungs and bones. Hepatic involvement is rare and typically occurs in the context of advanced disease, carrying a poor prognosis. Differentiated high-grade thyroid carcinoma (DHGTC), a recently recognized aggressive entity in the 2022 WHO Classification, is associated with an increased risk of metastatic dissemination. We report a case of DHGTC in which post-therapy iodine-131 whole-body scintigraphy (WBS) with SPECT/CT detected regional lymph node involvement, pulmonary metastases and an unexpected iodine-avid hepatic lesion, leading to disease upstaging and modification of therapeutic management.

Case Report

A 72-year-old woman with a history of right hemithyroidectomy in 2002 for benign nodular disease underwent completion thyroidectomy and right cervical level III lymph node excision in February 2024 after a suspicious nodule was identified on surveillance ultrasound. Histopathological analysis revealed DHGTC with clear cell features, likely arising from transformation of a pre-existing papillary thyroid carcinoma, with lymphovascular invasion, positive surgical margins, and lymph node metastases (pT2 N1b R1, AJCC 8th edition). Initial staging CT in April 2024 showed no locoregional or distant disease. Following thyroid hormone withdrawal, the patient underwent adjuvant radioactive iodine (RAI) therapy in July 2024 (3,700 MBq). Post-therapy WBS with SPECT/CT revealed cervical lymph node involvement, bilateral pulmonary nodules with absent radiotracer uptake, consistent with RAI-refractory metastatic disease, and focal hepatic uptake in the right lobe, suggestive of an iodine-avid metastasis. Stimulated thyroglobulin was markedly elevated at 787.0 ng/ml, consistent with significant metastatic burden. Thoracoabdominal CT confirmed extensive pulmonary and hepatic metastatic disease, which was histologically confirmed by biopsy. Following multidisciplinary tumour board review, the patient was proposed for additional RAI therapy targeting the iodine-avid metastasis, followed by systemic therapy with lenvatinib, a multikinase tyrosine kinase inhibitor, for the management of RAI-refractory disease.

Conclusion

Differentiated high-grade thyroid carcinoma carries a significant risk of distant metastatic dissemination, with hepatic involvement being exceedingly rare and associated with poor prognosis. In this case, post-therapy iodine-131 WBS with SPECT/CT revealed cervical lymph node involvement, pulmonary metastases, and an unexpected iodine-avid hepatic lesion, demonstrating heterogeneous iodine avidity. These findings led to disease upstaging and modification of therapeutic management, highlighting the important role of post-therapy WBS in the evaluation and management of patients with high-risk DTC.

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PS2-08-05

Can one patient have two different advanced thyroid cancers in each of the lobes and contralateral lymph node metastasis?: a role of fine needle aspiration washout

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Introduction

Papillary thyroid cancer (PTC) is the most common thyroid malignancy, while medullary thyroid cancer (MTC) is a rare disease often related to *RET* mutation, especially in young patients. Simultaneous presence of both PTC and MTC in one patients is a very rare finding.

Case Presentation

43-year-old woman presented with thyroid nodules found in both lobes in ultrasound. The lesion in the left lobe was deeply hypoechoic, with blurred margins and thyroid capsule infiltration. A few enlarged pathological left neck lymph nodes were detected. The lesion in the right lobe was heterogenic, normoechoic with internal small hypoechoic areas and rather well-defined

margins. Initially, fine needle aspiration biopsy (FNAB) was performed only of the left-side nodule and a dominant lymph node. The result revealed MTC and a metastatic lymph node. However, in the FNAB needle washout obtained from the metastatic node, both calcitonin and thyroglobulin levels were very high, i.e. calcitonin 728 pg/ml, thyroglobulin > 200 ng/ml, which suggest both MTC and PTC metastasis or only PTC metastasis (serum calcitonin > 2000 pg/ml). Therefore, FNAB of the right lobe nodule was performed and revealed a result typical for PTC. Several lymph nodes were visible on the right side of the neck but none of them was typical for a metastatic one. Before the operation pheochromocytoma was excluded. Due to a presence of MTC, kyphosis and oral mucosa lesions which resembled mucosal neuromas the patient was referred for genetic testing for MEN2B, but we have not obtained the result yet. During surgery, the presence of metastatic lymph nodes was confirmed on the both left and right side of the neck. The postoperative histopathology result is not yet available, but will be included in the final presentation.

Conclusion

Simultaneous presence of MTC and PTC should be taken into account in patients with suspicious thyroid nodules of different ultrasound pattern. Contralateral lymph node metastasis of PTC to the side of MTC-affected lobe is extremely rare and can be preoperatively confirmed by high thyroglobulin in FNAB needle washout. Frequently, lymph node cytology cannot ultimately differentiate the source of malignant cells, especially if the pathologist is aware of the ipsilateral MTC. FNAB washout can be considered the most reliable preoperative method of differential diagnosis between the source of metastases in patients with both MTC and differentiated thyroid cancer.

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PS2-08-06

Bilateral renal metastases from hobnail variant papillary thyroid carcinoma

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Introduction

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid cancer and usually has a favorable prognosis. Distant metastases occur in a small proportion of patients, most frequently involving the lungs and bones. Renal metastases from PTC are extremely rare and may mimic primary renal malignancies, creating a diagnostic challenge.

Case Presentation

A 77-year-old woman without a prior history of thyroid disease presented with vertigo. Clinical examination revealed thyroid enlargement. Ultrasound demonstrated a substernal multinodular goiter with suspicious cervical lymphadenopathy. Fine-needle aspiration cytology was classified as Bethesda V and III. The patient underwent total thyroidectomy with lymph node dissection. Histopathological examination revealed multifocal PTC with a prominent hobnail component, solid and follicular growth patterns, vascular invasion, focal involvement of surgical margins, and extensive lymph node metastases. Postoperative FDG-PET/CT demonstrated suspicious lesions in both kidneys and the left adrenal gland. The patient received radioactive iodine therapy (150 mCi I-131), but serum thyroglobulin levels remained markedly elevated. Magnetic resonance imaging confirmed bilateral renal masses. Biopsy of the right renal lesion demonstrated metastatic PTC with follicular architecture and focal hobnail features (Ki-67: 12%). Systemic therapy with lenvatinib was initiated but required intermittent discontinuation due to adverse effects. Follow-up imaging revealed disease progression with new bone metastases.

Conclusions

Renal metastases from PTC are exceptionally rare and may mimic primary renal tumors. This case highlights the aggressive behavior of the hobnail variant and emphasizes the importance of histological confirmation in atypical metastatic sites, as well as the need for a multidisciplinary approach in advanced disease.

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PS2-08-07

Emergent peripheral vascular disease (PVD) in medullary thyroid carcinoma (MTC) patients treated with pralsetinib: a case series

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Introduction

Pralsetinib, a selective *RET* inhibitor that was evaluated in the phase 1/2 clinical trial (ARROW) for *RET*-altered cancers including MTC, is associated with hypertension. Additionally, a pharmacovigilance study analyzing data from the FDA Adverse Event Reporting System suggested a potential association between pralsetinib and ischemic heart disease; however, peripheral vascular disease (PVD) with pralsetinib use is not described in literature. We present a series of MTC patients who developed severe PVD with pralsetinib use.

Cases

We retrospectively reviewed the records of five patients (3M, 2F) at two institutions with a diagnosis of MTC who developed symptomatic PVD while on therapy with pralsetinib. Four patients had sporadic MTC (3 with *RET* p.M918Tpathogenic variant, 1 with loss of function PDGFR-A only) and one had germline *RET* p.M918T variant associated with MEN2B syndrome. Two patients were previously treated with other systemic therapies before starting pralsetinib (vandetanib and vandetanib followed by cabozantinib). Median time from initiation of pralsetinib to diagnosis of PVD was 4 years (range 1-5) at a median age of 67 years (40-75). Pralsetinib dose immediately prior to intervention for PVD was 200 mg (2 patients), 300 mg (2 patients), 100 mg (1 patient). Four patients had other risk factors/comorbidities including current or prior smoking, chronic kidney disease (stable for many years), well-controlled diabetes, prior myocardial infarction and carotid stenosis while one patient had no risk factors for PVD development. Each patient had symptomatic PVD: claudication symptoms and/or gangrene. Each patient required intervention: 3 patients with below-the-knee amputation (1 bilateral, 2 unilateral), one of whom subsequently required an above-the-knee amputation due to continued poor wound healing; 1 with femoral endarterectomy; and 1 with anterior tibial angioplasty. Three patients had grade 1 hyperphosphatemia, however mean calcium-phosphate product was 36 mg^2/dl^2 (<55). Two patients continued pralsetinib after initial intervention for PVD; 2 discontinued 2-3 months prior to intervention and 1 patient discontinued immediately after intervention for PVD.

Conclusion

Our case highlights a rare but serious adverse effect possibly associated with pralsetinib warranting increased clinical awareness and monitoring. Possible pathogenic mechanisms could be related to inhibition of fibroblast growth factor (FGF) receptor-1 inhibition or other off-target effects on FGF-23 activity leading to hyperphosphatemia. Further studies are needed to better characterize the incidence and mechanism.

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PS2-08-08

Differentiated thyroid carcinoma with bone metastasis and the role of interventional radiology

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Introduction
Bone metastases represent the second most common site of distant spread in differentiated thyroid carcinoma (DTC) and are associated with poorer prognosis. Management is mainly aimed at disease control and symptom relief. Multimodal treatment is often required. Interventional radiology techniques have recently emerged as promising options for local disease control and symptom management. We report the case of a patient with DTC presenting with a large iliac metastasis treated with microwave ablation and cementoplasty.
Case Report
A 67-year-old man presented with an incidental finding on thoracic CT of a large solid nodule in the left thyroid lobe, without cervical compressive symptoms. He also reported progressive left hip pain over several months, impairing mobility. Laboratory evaluation showed normal thyroid function tests and calcitonin levels. Thyroid ultrasound revealed a 46x36x28 mm hypoechoic nodule in the left lobe. Fine-needle aspiration citology was consistent with a follicular neoplasm with oncocytic features (Bethesda IV). Pelvic CT and 99mTc bone scintigraphy with SPECT-CT demonstrated a large lytic lesion in the left iliac wing (55mm) with peripheral osteoblastic reaction and extensive soft-tissue component. Biopsy confirmed metastasis from thyroid carcinoma. Following multidisciplinary discussion, the patient underwent total thyroidectomy with central compartment lymph node dissection. Histopathology revealed a 45mm well-delimitated differentiated follicular carcinoma with extensive vascular invasion, no extrathyroidal extension, negative surgical margins and no lymph node involvement (pT3N0M1). Two months later, he received RAI therapy (150mCi) under recombinant human TSH stimulation. Stimulated thyroglobulin was >50000ng/ml (reference <1.3ng/ml). Post-therapy whole-body scintigraphy demonstrated uptake in the left iliac lesion, a smaller focus in the right iliac bone, and diffuse pulmonary uptake without corresponding chest CT abnormalities. For palliation of the symptomatic iliac metastasis, external-beam radiotherapy was administered, with modest pain relief. Due to persistent pain and bone fragility, four months later he underwent microwave ablation of the lesion combined with acetabular cementoplasty, with significant improvement in pain and mobility. Two additional RAI treatments (100mCi each) were administered at six and eighteen months, eliminating cervical uptake and decreasing pulmonary activity, while the iliac lesions remained stable. Four years after ablation, pelvic MRI showed a slight increase in the left iliac lesion size (68mm), with maintained pain control and preserved mobility.
Conclusions
Bone metastases from DTC are associated with significant morbidity. In this case, microwave ablation combined with cementoplasty provided effective local tumour control, pain relief and functional improvement. These minimally invasive techniques represent valuable palliative options for selected patients.

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PS2-08-09

Abstract Withdrawn

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PS2-08-10

Treatment of a patient with malignant solitary fibrous tumor of the thyroid gland - a case report

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Introduction
Malignant solitary fibrous tumor (MSFT) occurs very rarely in the thyroid gland. MSFT of the thyroid gland is difficult to diagnose and there is little information about its biological behavior.
Case Report
A 67-year-old patient had 18 years ago a bilateral subtotal thyroidectomy for benign goiter. At presentation, she has been experiencing rapid tumor growth on the left side of her neck for two months, dysphagia, hoarseness, and occasional choking. Physical examination revealed that the entire left lobe of the thyroid was occupied by a 7 cm tumor. The cervical lymph nodes were not enlarged. Laboratory tests were within normal limits. Ultrasound showed a hypoechoic nodule measuring 7.5 cm in the left lobe. An ultrasound-guided fine-needle aspiration biopsy was performed and cytological examination revealed a spindle cell tumor of soft tissue origin (Bethesda III). CT showed a markedly enlarged left thyroid lobe, measuring $7.6 \times 6.0 \times 7.7$ cm, extending retrosternally and in close contact with the esophagus and prevertebral fascia. The esophagus and great vessels of the neck and mediastinum were displaced. No pathologically altered lymph nodes were seen. A total thyroidectomy was planned. However, even with intraoperative neuromonitoring, we were unable to identify the recurrent nerve in the altered area of large tumor and scar tissue. Therefore, surgery consisted of R0 tumor resection and a left-sided lobectomy with isthmectomy. Histopathological examination showed that MSFT measured 9 cm in its longest diameter. The tumor had 9 mitoses/10 high-magnification fields. There was no necrosis. There was no infiltration of large vessels or nerves. The tumor was completely surrounded by a very thin connective tissue envelope, which separated it from the resection area. The multidisciplinary thyroid team recommended postoperative external beam radiotherapy (EBRT). The patient was irradiated with TD 56 Gy to the neck and mediastinum. During follow-up, the patient received thyroid hormone replacement therapy and underwent annual CT scans, which did not show any suspicious changes for recurrence 9.3 years after the beginning of treatment.
Conclusions
A patient with MSFT may have a long-term disease-free survival after surgical R0 tumor removal, thyroid lobectomy, and EBRT.

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Histology

PS2-09-01

Unmasking high-grade papillary thyroid carcinoma: lessons from a single-center cohort

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Objectives
The 2022 WHO classification defined differentiated high-grade thyroid carcinoma (DHGTC) as well-differentiated tumors with high-grade features such as necrosis or elevated mitotic activity. This study aimed to evaluate clinical, histopathological, and treatment outcomes of DHGTC and the prognostic value of Ki-67.

Methods
Patients undergoing thyroidectomy (2017–2024) meeting DHGTC criteria (n = 56) were retrospectively reviewed. Data collected included clinical features, imaging, cytology, tumor size, histopathology (mitosis, necrosis, Ki-67), surgery, RAI therapy, and risk stratification. Subgroup analysis compared DTC patients with Ki-67 $<$15% vs $\geq$15%.
Results
Median tumor size was 5.1 cm. Necrosis occurred in 87.5% and mitotic activity $\geq$5/2 mm^2 in 19.6%. Bilateral total thyroidectomy was performed in 56%, lymph-node dissection in 30%. All DHGTC patients were high-risk per ATA 2025. RAI was given in 91%, and 28.6% required additional treatment. At follow-up, 30.4% had excellent biochemical response, 23.2% indeterminate, 7.1% biochemical incomplete, 35.7% structural incomplete. In DTC, Ki-67 $\geq$15% correlated with older age, larger tumors, more lymphovascular and perineural invasion, higher stage, extensive surgery, and worse dynamic response. In DHGTC, Ki-67 $\geq$15% only associated with higher lymphovascular invasion and more extensive surgery.
Conclusions
DHGTC is an aggressive thyroid carcinoma subset despite well-differentiated architecture. High Ki-67 predicts adverse behavior in DTC, but in DHGTC, Ki-67 $>$15% does not worsen prognosis beyond high-grade features. Careful histopathologic evaluation is essential, and Ki-67 alone may not stratify risk.

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PS2-09-02

Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: a systematic review and meta-analysis of real-world studies

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Background
Glucagon-like peptide-1 Receptor Agonists (GLP1-1RAs) are widely prescribed for type 2 Diabetes Mellitus (T2DM) and obesity due to their metabolic and cardiorenal benefits. Concerns about a potential association with thyroid cancer arise mainly from preclinical findings and inconsistent results from randomized trials, in which thyroid cancer was not a primary outcome. Real-world active-comparator new-user studies may help clarify this potential safety signal.
Methods
We conduced a systematic review and meta-analysis in accordance with PRISMA. Observational, active-comparator, new-user cohort studies of adults with T2DM or obesity were eligible if they compared GLP-1RAs initiation with other glucose-lowering or anti-obesity drugs and reported incident thyroid cancer. MEDLINE, Cochrane Library, Scopus and grey literature were searched through 31s December 2025. Two investigators independently screened studies, extracted data, and assessed risk of bias with ROBINS-I. Adjusted hazard ratios (HR) were pooled using a random-effects inverse-variance model. Statistical heterogeneity was quantified with I^2.
Results
Eleven cohort studies met the eligibility criteria and were included in the quantitative synthesis. In T2DM studies, pooled estimates showed no statistically significant association between GLP-1RAs use and incident thyroid cancer. Compared with dipeptidyl peptidase-4 (DPP-4) inhibitors (5 studies), the pooled HR was 0.94 (95% CI 0.80–1.12; I^2 = 26.2%). Compared with sodium–glucose cotransporter-2 (SGLT2) inhibitors (7 studies), the pooled HR was 0.94 (95% CI 0.84–1.05; I^2 = 0%). Compared with sulfonylureas (2 studies), the pooled HR was 1.05 (95% CI 0.90–1.23; I^2 = 0%). In obesity studies (4 studies) the pooled HR was 1.26 (95% CI 0.81–1.97; I^2 = 62.2%).
Conclusions
In this systematic review and meta-analysis of real-world studies employing an active-comparator new-user design, GLP-1 RAs initiation was not associated with an increased risk of thyroid cancer compared with alternative antidiabetic or anti-obesity therapies. These findings provide important real-world evidence supporting the thyroid safety profile of GLP-1RAs. Continued pharmacovigilance and studies with longer follow-up are warranted to further evaluate potential long-term risks.

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PS2-09-03

Immunohistochemical markers KI-67 and P53 as predictors of malignant progression of papillary thyroid cancer in children

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Background
To investigate the immunohistochemical (IHC) expression of Ki-67 and p53 markers in order to assess the malignant potential of paediatric papillary thyroid carcinoma (PTC).
Methods
Twenty children ($\leq$18 years) who underwent surgery for PTC were included in the study. All patients had a tumor category of pT1. According to the metastasis status, patients were divided inti two groups: group 1 - pN0 (n = 10) and group 2 - pN1a-b (n = 10), corresponding to low- and high-risk clinical groups. IHC analysis was performed usisng standard methods with monoclonal mouse antibodies (Agilent).
Results
Ki-67 expression was more frequently detected in high-risk group (40% vs. 10%). The effect size indicated a moderate association (ϕ = 0.33); however, the difference did not reach statistical significance (Fisher's exact test, $P > 0.05$), which may reflect the limited number of cases in this study. p53 expression did not differ between the groups (20% in each group; ϕ = 0). Simultaneous expression of Ki-67 and p53 was observed in 2 cases (10%). The odds ratio for co-expression was 4.33 (95% CI 0.46–41.0), suggesting a possible association between marker expression, with a small-to-moderate effect size (ϕ = 0.29).
Conclusions
Ki-67 expression tended to be more frequent in children with lymph node metastases, suggesting a potential association between proloferative activity and metastatic risk in paediatric PTC. In contrast, p53 expression did not differ between risk groups. Although statistical significance was not reached, the observed trends indicate that Ki-67 may have potential value as a marker of tumor aggressiveness in paediatric PTC and warrant further investigations in larger cohorts.

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PS2-09-04

Association between MIR-146B expression and aggressive clinico-pathological features in differentiated thyroid carcinoma

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Background
Thyroid cancer is the most common endocrine malignancy and generally associated with a favorable prognosis. Nevertheless, a subset of cases presents aggressive biological behavior. Increased expression of microRNA-146b (miR-146b) in differentiated thyroid carcinoma (DTC) has been linked to adverse clinicopathological characteristics, including lymph node metastasis (LNM), extrathyroidal invasion (EI), and the presence of the BRAF V600E mutation. These associations suggest that miR-146b may serve as a molecular marker related to disease progression and poorer clinical outcomes.

Objectives
To investigate miR-146b expression levels as a prognostic biomarker for identifying aggressive clinicopathological phenotypes in DTC, using fine-needle aspiration (FNA) smear slides to support earlier risk stratification and improved clinical management.
Methods
A total of 204 preoperative FNA smear slides from DTC nodules were evaluated for normalized miR-146b expression and for the presence of the BRAF V600E mutation using qPCR with TaqMan assays. Histopathological reports were reviewed to determine the occurrence of lymph node metastasis (LNM), extrathyroidal invasion (EI), vascular invasion (VI), and ATA recurrence risk (RR) classification. Receiver operating characteristic (ROC) curve analysis was used to define miR-146b expression thresholds, establishing three categories of expression: low, moderate, and high.
Results
Higher miR-146b expression levels were progressively associated with aggressive disease features. The probability of lymph node metastasis was 12.0% in the low-expression group, 34.5% in the moderate group, and 75.0% in the high-expression group. The likelihood of classification into ATA intermediate or high recurrence risk categories was 16.0%, 46.2%, and 66.7% for the low, moderate, and high expression groups, respectively. The frequency of BRAF V600E mutation was 6.1% in the low-expression group, 71.4% in the moderate group, and 94.7% in the high-expression group. No association was observed between miR-146b expression and extrathyroidal invasion or vascular invasion, suggesting that these characteristics may be influenced by different molecular mechanisms that warrant further investigation.
Conclusion
Evaluation of miR-146b expression may represent a useful preoperative approach for identifying aggressive features in DTC. This information could contribute to improved risk stratification before surgery and support more individualized treatment planning, as well as more efficient use of healthcare resources.

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PS2-09-05

Diagnostic performance and clinical usefulness of core needle biopsy for thyroid nodules: comparison with fine-needle aspiration in nodules undergoing concurrent FNA and CNB

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Purpose
To evaluate the diagnostic performance and clinical usefulness of core needle biopsy (CNB) and compare them with those of fine-needle aspiration (FNA) performed concurrently in the same thyroid nodules.
Material and Methods
This retrospective study was conducted at a single tertiary institution between January 2016 and August 2023. Among 1027 thyroid nodules from 1004 patients that underwent simultaneous fine-needle aspiration (FNA) and core-needle biopsy (CNB) in the same lesion, 286 nodules (> 5 mm) with a final surgical diagnosis were included. The rates of inconclusive results were compared between CNB and FNA for all nodules and nodules with final diagnoses. For nodules with final diagnosis, the diagnostic performance of FNA and CNB was also compared. FNA and CNB results were each classified into six categories based on the Bethesda System and analogous CNB classification following the Bethesda system, as determined by an experienced endocrine pathologist.
Results
Among the 286 nodules with final diagnoses, 125 (43.7%) were benign and 161 (56.3%) were malignant based on surgical pathology. For all nodules, CNB demonstrated a lower rate of inconclusive results than FNA (34.4% vs. 51.7%, $P < 0.001$), including nondiagnostic (1.1% vs. 6.1%) and AUS/FLUS (32.3% vs. 45.6%) categories. For nodules with final diagnoses, CNB also showed a lower rate of inconclusive results than FNA (26.9% vs. 55.6%, $P < 0.001$), including nondiagnostic (4.5% vs. 0.7%) and AUS/FLUS (26.2% vs. 51.0%) categories. Using Bethesda categories V, and VI as criteria for malignancy, CNB demonstrated significantly higher sensitivity than FNA (65.2% vs. 53.4%, $P < 0.001$), while specificity was comparable between CNB and FNA (100% vs. 99.2%, $P > 0.05$). Among nodules initially diagnosed as AUS/FLUS on FNA, CNB provided conclusive results in approximately 60% of surgically confirmed nodules (88/146), classified as Bethesda categories II, IV, V, or VI. Of the 92 nodules surgically confirmed as follicular or Hurthle cell adenoma/carcinoma, 43 were classified as CNB category IV and only three were classified as FNA category IV (sensitivity: 46.7% vs. 3.3%).
Conclusions
CNB yielded fewer inconclusive results and demonstrated higher sensitivity for malignancy than FNA, when both procedures were performed concurrently on the same thyroid nodules. In particular, CNB appears to be more effective than FNA in the diagnosis of follicular neoplasms.

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PS2-09-06

Superior diagnostic performance of core needle biopsy over fine-needle aspiration in diagnosing follicular-patterned neoplasms

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Objectives
Thyroid follicular-patterned neoplasms present diagnostic challenges, as fine-needle aspiration (FNA) is limited in its ability to distinguish non-neoplastic nodules from follicular-patterned neoplasms. This study aimed to compare the diagnostic performance of FNA and core-needle biopsy (CNB) for diagnosing follicular-patterned neoplasms.
Methods
Between March 2017 and October 2024, we included 261 consecutive follicular-patterned neoplasms (>1 cm) confirmed by surgical pathology (55 malignant tumors, 48 low-risk neoplasms, and 158 benign tumors) and 1254 non-neoplastic benign nodules that underwent both FNA and CNB. CNB subcategories were determined using histologic criteria based on architectural uniformity and nuclear atypia, modified from the CNB pathology guideline. The diagnostic performances of FNA and CNB were evaluated using categories IV–VI as the criteria (test positive) for follicular-patterned neoplasms.
Results
In the 261 follicular-patterned neoplasms, CNB demonstrated significantly lower rates of inconclusive results (category I and III) compared to FNA (10.7% vs. 57.5%, $P < 0.001$), while yielding a substantially higher rate of category IV results (85.1% vs. 11.5%, $P < 0.001$). Notably, while FNA yielded category II (benign) results in 27.3% (15/55) of malignant tumors, CNB resulted in only one such false-negative (1.8%) ($P < 0.001$). For follicular-patterned neoplasms, CNB showed significantly higher sensitivity (86.2% vs. 11.9%, $P < 0.001$) and accuracy (96.7% vs. 84.6%, $P < 0.001$) than FNA, with comparable specificity (98.9% vs. 99.8%) and positive predictive value (94.1% vs. 91.2%). Furthermore, CNB exhibited substantially superior sensitivity for malignancy (94.5% vs. 14.5%, $P < 0.001$).
Conclusions
CNB demonstrated superior diagnostic performance compared to FNA, providing significantly higher sensitivity while maintaining high specificity for follicular-patterned neoplasms, and yielding a significantly lower false-negative (Category II) rate for malignancy. First-line use of CNB for nodules suspicious for follicular-patterned neoplasms may facilitate accurate diagnosis and appropriate management.

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PS2-09-07

Immune cytokines improve prediction of lateral lymph node metastasis in papillary thyroid cancer

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Background
Accurate prediction of lateral lymph node metastasis (LNM) in papillary thyroid cancer (PTC) remains clinically challenging. Although thyroglobulin (TG) is commonly used as a biomarker, its predictive performance for nodal metastasis is

limited. We investigated whether cytokine profiling could identify additional biomarkers associated with LNM and improve predictive performance when combined with conventional markers.
Methods
We analyzed cytokine expression using a 44-plex cytokine array in tumor samples from 40 PTC patients (20 with lateral LNM and 20 without LNM). Differential expression analysis was performed to identify cytokines associated with LNM. Predictive performance was evaluated using receiver operating characteristic (ROC) analysis. Multivariable logistic regression models were constructed to assess whether combining cytokines with thyroid-related biomarkers improves prediction of LNM.
Results
Among the 44 cytokines analyzed, CXCL13, CCL26 and HAVCR1 showed significantly higher expression in patients with lateral LNM compared with those without metastasis. ROC analysis demonstrated moderate predictive performance for CXCL13 (AUC = 0.676) and CCL26 (AUC = 0.681), whereas HAVCR1 showed limited discriminative ability. The conventional biomarker TG demonstrated predictive performance comparable to CXCL13 and CCL26 (AUC = 0.698). Importantly, a combined model integrating TG, CXCL13, and CCL26 significantly improved predictive performance (AUC = 0.834), outperforming each biomarker alone. Multivariable logistic regression further supported the contribution of cytokine markers in predicting lateral LNM.
Conclusion
Our findings suggest that immune-related cytokines, particularly CXCL13 and CCL26, are associated with lateral lymph node metastasis in papillary thyroid cancer. While thyroglobulin alone has limited predictive value, integrating cytokine markers with conventional biomarkers significantly improves the prediction of nodal metastasis. This combined biomarker approach may provide a useful strategy for risk stratification in PTC patients.Our findings suggest that immune-related cytokines, particularly CXCL13 and CCL26, are associated with lateral lymph node metastasis in papillary thyroid cancer. While thyroglobulin alone has limited predictive value, integrating cytokine markers with conventional biomarkers significantly improves the prediction of nodal metastasis. This combined biomarker approach may provide a useful strategy for risk stratification in PTC patients.

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PS2-09-08

Comprehensive assessment of histologically verified follicular thyroid neoplasms: from sonography to intraoperative verification

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Diagnosis of follicular thyroid neoplasms remains a major challenge due to high uncertainty, with malignancy risks ranging from 15% to 30%. The aim of this study – comprehensive analysis of ultrasound, cytological and intraoperative examination and to compare with the data of final histological verification. Materials and methods. The study involved 30 patients with a "follicular neoplasia" cytological conclusion (Bethesda IV). Results from ultrasound, cytology, and intraoperative studies were compared with final histology. Results. Histological verification revealed malignant tumors in 50% of cases and benign tumors in 50%. Among malignancies, papillary carcinomas accounted for 40%, follicular variants of papillary carcinoma 33.3%, follicular carcinoma 20%, and oncocytic carcinoma 6.6%. Benign cases included follicular adenoma (73.3%) and nodular goiter (26.7%). Intraoperative cytological prints identified malignancy in 53.3% of histologically confirmed malignant cases, with a 100% positive predictive value (no false positives in benign cases). Each histological type of tumor had its own ultrasound characteristics: papillary thyroid carcinoma in all cases - decrease in echogenicity of varying degrees of severity, indistinct borders in 80%, tissue homogeneity, fibrosis and/or the presence of small calcifications (TIRADS 5 - 80%, TIRADS 2 - 20%); the follicular variant of papillary carcinoma - definition of a hydrophilic or unevenly hydrophilic border, a regular shape and a decrease in echogenicity in 75% (TIRADS 4 - 50%, TIRADS 5 - 20%, TIRADS 3 - 20%); follicular adenoma - regular shape and a clear hydrophilic or uneven hydrophilic border in all cases, unchanged echogenicity in 56% and decreased in 44% and in 77% a mixed type of vascularization was determined (TIRADS 4 - 56%, TIRADS 3 - 44%); follicular carcinoma in all cases - regular shape with clear hydrophilic borders, decreased echogenicity and a mixed type of vascularization (TIRADS 4 - 100%). Conclusions. In the studied group of follicular neoplasias (Bethesda IV), a high frequency of malignant tumors (50%) was found, among which papillary carcinoma (40%) and follicular variant of papillary carcinoma (33.3%) prevailed. Intraoperative cytological examination showed 53.3% sensitivity and 100% specificity and absence of false-positive results. TIRADS 5 is the most specific indicator of malignancy (sensivity, positive predictive value is 100%). Given the difficulty in sonographic differentiation of follicular cancer, the optimal diagnostic strategy is combining TIRADS classification with intraoperative cytological examination.

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PS2-09-09

The prognostic landscape of anaplastic thyroid carcinoma: a systematic literature review of 190 survival factors

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Objective
Anaplastic thyroid carcinoma (ATC) is an ultra-rare but highly aggressive malignancy. It accounts for $<2\%$ of thyroid cancers but up to 50% of related deaths, with a 6.8 months median survival. However, reported prognostic factors remain heterogeneous, hindering reliable risk stratification. This review aims to map and categorize the prognostic factors in ATC to establish a comprehensive prognostic landscape.
Methods
A systematic literature review was conducted in MEDLINE and Embase (1975-2025) using pre-defined search strategies to identify cohorts of ≥ 20 patients reporting overall survival or cancer-specific survival. Studies were screened using pre-defined eligibility criteria. Overlapping datasets were de-duplicated by retaining the most recent or largest cohorts. Factors were classified into seven domains: biological/molecular, clinical, demographic, histopathological, imaging, performance status, and tumor extension/staging. Data extraction included hazard ratios, p-values, and analysis type (univariate, multivariate). Evidence was synthesized via harvest plots for factors assessed in ≥ 5 studies, while others were summarized in an evidence table.
Results
Among 1,050 records screened, 156 articles were included (90 monocentric cohorts, 10 multicentric, and 56 national registries). Overall, 190 distinct prognostic factors were identified, of which 83% were reported in <5 studies, highlighting the extreme fragmentation of prognostic evidence. Tumor stage emerged as a consistent survival determinant: advanced stage (IVC) was associated with poorer outcomes in 16 cohorts (37.5% from national registries), whereas non-significant (NS) findings ($n = 19$) were primarily reported in smaller monocentric studies (79%). Older age was identified as a prognostic factor in 42 cohorts, remaining significant in 55% of multivariable analyses. A high comorbidity burden was associated with worse survival across 5 national registries ($n = 9$); similarly, poor performance status was significant in 10 cohorts (40%). Distant metastases and larger tumor size were significant in 43 and 33 cohorts, respectively. Conversely, prior or coexisting differentiated thyroid cancer showed a favorable survival trend in 25% of 32 cohorts. Among biomarkers, a high neutrophil-to-lymphocyte ratio showed a relatively consistent association with poor prognosis (67% of 9 cohorts), whereas molecular markers showed limited prognostic value: BRAF and TERT mutations were NS in 90% and 100% of cohorts, respectively.
Conclusion
ATC prognosis is driven by tumor stage and patient fitness, while molecular markers appear to provide limited independent prognostic value. This mapping highlights the urgent need for standardized reporting and identifies the key covariates required for a forthcoming target trial emulation, to generate high-level evidence for treatment strategies in this rare and aggressive disease.

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PS2-09-10

TERT alterations in papillary thyroid carcinoma: correlation with tumor size and prognostic implications

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Background
Mutations in the *TERT* promoter (*TERTp*) are identified in approximately 10% of papillary thyroid carcinomas (PTC). These mutations are considered markers of poor prognosis and exert a synergistic effect with the *BRAF* V600E mutation leading to a more aggressive disease. The single nucleotide rs2853669 *TERT* polymorphism has been reported to contribute to PTC growth, particularly when occurring in combination with *TERTp* and *BRAF* mutations.
Methods
The study group consisted of 256 PTC tumoral tissues: 175 derived from patients who underwent surgical treatment; 81 cases were retrieved from an active surveillance program for low-risk PTC. The mutational status of the *TERTp* and the *BRAF* gene was assessed by Sanger sequencing.
Results
One hundred and thirty of the 256 cases (50.8%) showed only the presence of the *BRAF* mutation, while 3 cases (1.2%) presented only the *TERTp* mutation. Eleven cases (4.2%) exhibited the presence of both mutations, whereas 112 (43.8%) were negative for both. Eighty-six out of 256 cases (33.6%) carried the heterozygous *TERT* SNP rs2853669 (T349C). *TERTp* positive cases ($n = 14$) showed a significantly larger mean tumor size (3.7 ± 1.5 cm; range 0.7–6.5 cm) than *TERTp* negative cases, in fact a statistically significant higher prevalence of *TERTp* mutations was observed in larger tumors. Similarly, cases harboring both *BRAF* and *TERTp* mutations exhibited a significantly larger tumor size. A higher prevalence of patients with advanced disease was found in cases with *TERTp* and/or *BRAF* mutation (10/14, 71%) with respect to patients without the *TERTp* mutation (14/95, 15%) ($P < 0.0001$, Fisher exact test). It is worth nothing that 3 patients died for the disease and were all in the *TERTp/BRAF + TERTp* group. Finally, the mean tumor size of cases carrying the T/C variant of the TERT rs2853669 SNP was significantly greater than that observed in wild-type T/T cases independently from the presence of *TERTp* or *BRAF* mutations. No significant difference was found when correlating the overall presence of the *TERTp* rs2853669 SNP with the outcome.
Conclusions
TERTp mutations are mainly present in larger tumors and in particular in those larger than 2 cm: their presence identifies more aggressive cases. The *TERTp* rs2853669 SNP is also associated with larger tumors but not with a worse outcome.

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Goitre & nodules 1

PS2-10-01

A bayesian approach to personalised radioiodine treatment for benign thyroid disease incorporating patient preferences

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Objectives
Radioiodine is widely used for the treatment of benign thyroid disease, although there are variations in the aim and methods of treatment. The potential to treat according to an individually prescribed radiation dose allows a high degree of personalisation, taking into account patient wishes, clinical experience and scientific expertise. The aim of this study was to develop a multi-disciplinary Bayesian approach toward personalised treatment planning to optimise clinical and cost effectiveness and to minimise treatment-related hypothyroidism.
Methods
A Bayesian network was developed to estimate outcome probabilities conditional on patient demographics and treatment parameters. The model incorporates prior probabilities obtained from retrospective clinical trial data of 300 patients treated with 60 Gy delivered to thyroid. Expert opinion and patient wishes are incorporated as a quantifiable utility scores elicited from patient forums organised by the British Thyroid Foundation patient support organisation. The model was initially tested on 84 patient data sets and investigated for the influence of patient-specific parameters.
Results
At 18 months following treatment, 47% of patients remained hyperthyroid or required further radioiodine. Forty-four per cent of patients were naturally euthyroid without medication, decreasing to 30% at 10 years. Leave-one-out cross-validation (LOOCV) was performed to assess the reliability of per-patient posterior outcome probability from log-volume. This revealed a modest per-patient prediction area under the receiver-operator characteristic curve (AUC). Posterior estimation of AUC had median 0.62 and 94% high density interval of (0.55-0.68), indicating the potential for further treatment personalisation. Initial investigation into quantifiable patient utility has determined relevant factors to include not just potential long term radiation risks, but also potential radiation exposure to family and friends, time spent in isolation, and absence from work.
Conclusions
This study indicates the potential for a highly multi-disciplinary approach to personalised treatment planning, incorporating patient preferences, clinical judgement and scientific analysis. A Bayesian approach can improve clinically feasible outcomes tailored to individual patient wishes. Further work will incorporate increasing levels of patient stratification and will focus on inter-disciplinary communication and information as clinical evidence continues to accumulate.

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PS2-10-02

First-in-human clinical durability study using nanosecond pulsed field ablation: a new paradigm in the treatment of benign thyroid nodules

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Objective
Thyroid nodules are common in the general population and a small percentage of these nodules become locally symptomatic. Thyroidectomy remains the gold standard for treating symptomatic benign thyroid nodules; however, minimally invasive thermal ablation techniques have emerged as safe and effective alternatives to surgery. The nanosecond pulsed field ablation (nsPFA) system applies nonthermal, nanosecond-duration electric pulses to initiate the endogenous pathway of regulated cell death. Early data on minimally invasive, non-thermal, cell-specific therapy for benign thyroid nodules from this group, have demonstrated an 73% volume reduction at 2 year. These findings also provided the first safety and efficacy evidence for the nsPFA electrode system in the treatment of benign thyroid nodules.
Methods
This is a prospective, non-randomized, clinical feasibility study using the nsPFA PE System for the treatment of benign thyroid nodules, conducted at Ospedale del Mare, ASLNA1Centro, Naples, Italy. Twenty-one nodules were previously treated percutaneously using nPulse Vybrance percutaneous electrode under ultrasound guidance. In the final cohort (#3) containing four patients, therapeutic ablation of the entire nodule was performed using multiple applications with the position, pulse, and proceed technique. The nsPFA Console contains a high-voltage pulse generator that produces nanosecond-range pulsed electric fields that are delivered to the patient tissue by the Percutaneous Electrode. The Percutaneous Electrode consists of

a 10 cm shaft, two conductive electrodes with a 5 mm spacer between them. The needle was inserted with a transisthmal technique. Since nsPFA energy is nonthermal, there is no risk of thermal spread with this modality. Previous studies have not reported any adverse effects on tissue for overlapping the ablation zones, so the user can distribute the ablation zones confidently to treat the entire nodule.
Results
In Cohort 3, the overall average volume reduction at 12 months was 68.5%, and at 22 months post-index ablation procedure, it was 73.8%. No cases of transient hoarseness or other serious adverse events occurred in this cohort. Follow-up ultrasound revealed no areas of fibrosis or vascular flow abnormalities. The DAMP molecules attract migrating dendritic cells of the immune system which then bind to the calreticulin on the plasma membrane, stimulating phagocytosis of the treated cells and removing them from the nodule so that no dead cells are left behind. This leaves the nsPFA-treated thyroid nodule soft to the touch without a fibrotic ball, which is often observed with RFA due to necrotic cell death and thermal denaturing of proteins and acellular structures.
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Abstract Withdrawn

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PS2-10-04

Alcohol: a solution for recurrent cystic problems - single centre data from percutaneous ethanol injection in cystic thyroid nodules

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Introduction
Percutaneous Ethanol Injection (PEI) is a treatment option for cystic or predominantly cystic thyroid nodules causing clinical problems.
Objectives
To present data from PEI in pure cystic or predominantly cystic thyroid nodules causing cervical symptoms or cosmetic problems, analysing volume reduction ratios (VRR), clinical benefit and safety.
Methods
We prospectively collected clinical, hormonal and ultrasound data from all patients submitted to PEI in Endocrine and Radiology departments from a southern-western Europe private hospital. Patients with cystic or predominantly cystic thyroid nodules causing cervical symptoms and/or cosmetic problems were selected for PEI, after multidisciplinary discussion. All patients had a previous attempt of volume reduction with simple aspiration of target lesions, performed at the occasion of FNAB. All nodules selected for PEI were nontoxic EU-TIRADS 2, with at least one Bethesda II (benign) FNAB result or a Bethesda I result, with cytological observation suggesting cystic lesion. Procedures were done between 2022-2025. Percutaneous injection of 96% ethanol was performed after local anaesthesia and under ultrasound guidance. Only patients with more than one month of follow-up after PEI were included.
Results
Seventeen patients / nodules were treated with PEI, fulfilling the above criteria. Thirteen (76,5%) patients were females, and the global median age was 47 years. Only two patients received more than one treatment. Follow-up median was 7,6 months. Median nodule volume before PEI was 22,9mL (IQR = 37,7). Pure cysts represented 64,7%, and 35,3% were mixed predominantly cystic nodules. Final median nodular volume was 4,2 mL (IQR = 6,2) and we achieved a median VRR of 85,6% (IQR = 15,6), $P < 0{,}001$ (95% CI). The anterior-posterior nodular axis was the one most reduced by treatment. PEI performed in purely cystic achieved higher VRR than in mixed nodules (median: 93,2% vs 67,8%; $P = 0{,}01$; 95%CI). Clinical benefit regarding compressive or cosmetic complaints was obtained in all but one patient, with 76,5% (13 patients) obtaining complete resolution of complaints. Short-lasting mild to moderate pain during PEI was a common adverse event affecting 70,6% of cases, and one patient reported intense short-lasting pain. No other relevant side effect occurred and euthyroidism was maintained in all cases.
Conclusions
The efficacy of PEI in this group with clinically relevant and recurrent thyroid cystic nodules was similar to other studies in literature. PEI was an efficient and safe treatment in this group of large, growing cystic thyroid nodules, causing symptoms and/or cervical cosmetic defects, with previous unsuccessful aspiration procedures.
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PS2-10-05

Heterogeneity in outcome concepts after percutaneous ethanol injection for cystic thyroid nodules: a systematic review of long-term studies

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Objectives
Percutaneous ethanol injection (PEI) is recommended as first-line treatment for symptomatic benign cystic thyroid nodules (CTNs). Previous meta-analyses pooled volume reduction rates across studies, but the underlying outcome concepts have not been systematically compared. We aimed to assess heterogeneity in outcome concepts and reporting after PEI for CTNs, focusing on volume reduction methods, recurrence terminology, and post-failure management.
Methods
PubMed was searched to March 2025. Studies reporting PEI for $\geq$50 benign CTNs with $\geq$24 months follow-up were included. For each study, we extracted: volume reduction reporting method, outcome classification approach, whether and how recurrence was defined, retreatment criteria, post-failure pathway, and complications.
Results
Three studies (888 cystic nodules; follow-up 36 months to 10 years) met inclusion criteria. Heterogeneity was identified not merely in definitions but in the outcome concepts themselves (Table). Volume reduction was reported as absolute volume without volume reduction rate (VRR), mean VRR $\pm$ SD, or median VRR(IQR). Outcome classification ranged from a binary unsuccessful/responder distinction, to a three-tier system (complete response [CR]/partial response [PR]/no response [NR]), to a morphologic non-responder criterion without VRR cutoff. Only one study defined recurrence as a concept separate from non-response; another had no recurrence concept for cystic nodules; the third used 'recurrence rate,' 'non-responder,' and 'regrowth' without unified definitions, yielding numerically distinct rates whose relationship was unexplained. Post-failure management was reported by only one study: 13 patients (3.6%) underwent surgery, with 2 incidental papillary carcinomas (15.4%) at histology; however, the threshold for surgical referral ('no adequate response to repeated PEI') was not objectively

Table 1. Outcome reporting heterogeneity across studies.

	Del Prete 2002 ($n = 98$)	Lee 2005 ($n = 432$ cysts)	Deandrea 2020 ($n = 358$)
VRR reporting	Volume (mL) only; VRR not calculated	Mean VRR $\pm$ SD at serial timepoints	Median VRR (IQR) at serial timepoints
Outcome classification	'Unsuccessful': <50% after 4 sessions	CR ($\geq$90% + symptoms), PR(50-89%), NR (< 50%/expansion)	Non-responder: cystic reappearance >0.5 mL
Recurrence concept	Defined: >10% vol increase vs previous visit (in responders)	Not defined for complex cyst	'Recurrence rate' in results without definition; distinct from non-responder
Recurrence/ NR rate	Non-response: 6.1% Recurrence: 6.5%	NR: 20.6%	Non-responder: 1.5-7% Recurrence: 14-24% (varied by center/protocol)
Post-failure pathway	Not reported	Not reported	Surgery 13 (3.6%); 'adequate response' undefined; 2 PTC

VRR, volume reduction rate; CR, complete response; PR, partial response; NR, no response; PTC, papillary thyroid carcinoma.

defined. No permanent complications were reported; transient vocal cord paralysis occurred in 0–1.0%.
Conclusions
Long-term PEI studies report fundamentally different outcome concepts, not merely different definitions of the same outcomes. This heterogeneity precludes reliable cross-study comparison and quantitative synthesis. Standardized, PEI-specific consensus definitions—particularly distinguishing non-response from recurrence, and establishing objective retreatment criteria—are needed before meaningful evidence synthesis can be achieved.

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PS2-10-06

Quality of life after laser ablation of thyroid nodules: A 1-year follow-up study

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Objectives
We aimed to evaluate thyroid-related and generic health-related quality of life (HRQoL), using the Thyroid-related Patient-Reported Outcome (ThyPRO)-39 and the Short Form Health Survey (SF)-36, before and 6 and 12 months after laser ablation (LA) for solid thyroid nodules (STNs), respectively.
Methods
We conducted a prospective cohort study on consecutive patients treated with LA for cytologically benign and symptomatic STNs at our university hospital over a period of 4 years. Patients were included if they had the ability to complete self-administered questionnaires in Italian and they had 1-year follow-up.
Results
We included 63 nodules (median volume, 14.8 [10.9 - 39.5] mL) from 63 patients. Six and 12 months after treatment, ThyPRO-39 scores had largely (ie, effect size $>$ 0.5) and significantly (P value adjusted $<$.001) improved across all scales (except for impaired sex life) compared with baseline. Six and 12 months after treatment, SF-36 scores had largely and significantly (P value adjusted $<$.001) improved across all scales (except for role-emotional). Volume reduction ratio (VRR) $>$ 50% did not affect the general quality of life item of ThyPRO-39 at 12-month follow-up (β -0.095, 95% confidence interval [CI] -0.583; 0.394, P value 0.700).
Conclusions
LA of symptomatic and benign STNs is associated with a great improvement of HRQoL scores of ThyPRO and SF-36 at 6-month and 12-month follow-up. Both physical and mental domains of HRQoL are positively affected by LA of STNs. The lack of reaching a VRR $>$ 50% did not preclude the improvement of the general quality of life item of ThyPRO-39 at 12-month follow-up. Risk factors of remaining HRQoL deficits one year after LA need further exploration.

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PS2-10-07

Fine-needle aspiration biopsy of neck lesions: a single-center experience

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Introduction
Ultrasound-guided fine-needle aspiration biopsy (FNAB) remains the gold standard in the diagnostic algorithm for patients with thyroid nodules. The implementation of standardized stratification systems has enhanced diagnostic reproducibility, inter-disciplinary communication and clinical decision-making.
Objective
Analyze the clinical characteristics of the study population and the results of FNAB procedures performed during a pilot implementation phase of this methodology as a routine diagnostic standard in a specialized hospital setting.
Methods
A retrospective, single-center descriptive study was conducted over a two-year period, including hospitalized patients with thyroid nodules who underwent cytological evaluation. Data retrieved from the hospital registry and sonographic characteristics of the nodules (stratified according to the European Thyroid Imaging and Reporting Data System [EU-TIRADS]) were analyzed. Cytological results were classified using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), alongside subsequent therapeutic management strategies.
Results
The study included 451 patients (77 males, 374 females) with a mean age of 55.4 years (range: 18–91). A total of 702 biopsies were performed on thyroid and extrathyroidal lesions. The distribution of nodules by sonographic risk was as follows: EU-TIRADS 2 - 2.9%, EU-TIRADS 3 - 60.9%, EU-TIRADS 4 - 17.8%, and EU-TIRADS 5 - 18.4%. Cytological results according to BSRTC were: BSRTC I - 4.1%, BSRTC II - 88.2%, BSRTC III - 2.9%, BSRTC IV - 0.3%, BSRTC V - 2.6%, and BSRTC VI - 1.8%. The malignancy rates (BSRTC V or VI) across EU-TIRADS categories 2 through 5 were 0%, 0.25%, 0.85%, and 22.1%, respectively. Biopsied suspicious cervical lymph nodes accounted for 3.4% of all lesions. Parathyroid lesions were identified in 2.3% of the cohort. Following multidisciplinary evaluation, surgical intervention was recommended for 17.3% of patients, while conservative management was indicated for 82.7%.
Conclusion
Our findings support the efficacy of an integrated model combining standardized sonographic stratification and cytological classification. This approach serves as a tool for optimized and personalized management of patients with thyroid nodules, in line with European guidelines.

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PS2-10-08

Clinical and pathological correlation of thyroid nodules: insights from a single-center experience

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Objectives
Thyroid nodules affect up to 60% of adults in the general population, making it essential to rule out malignancy (1–15% of cases). Clinical history and cervical ultrasound play a key role in the diagnostic approach and should guide selection for cytological analysis. However, there is no consensus on which clinical and ultrasound features best predict malignancy. This retrospective study aimed to identify these factors.
Methods and Results
A retrospective analysis was performed on patients with nodular thyroid disease submitted to fine-needle aspiration at the Endocrinology Department of a tertiary hospital between December 2024 and January 2025. Clinical variables (sex, age, thyroid function, anthropometry, palpable nodules) and ultrasound variables (number, size, echogenicity, composition, margin, halo, echogenic foci) were analyzed and correlated with cytological classification. The sample included 130 nodules: 81.5% in women, mean age 57.1 $\pm$ 13.9 years. According to ACR-TIRADS, 1.5% were TR1, 3.8% TR2, 31.5% TR3, 57.7% TR4, and 5.4% TR5. Cytology showed 29.2%, 40.0%, 20.8%, 4.6%, 3.1%, and 2.3% classified as Bethesda I–VI, respectively. Among the variables, only echogenicity ($P = 0.007$) and taller-than-wide shape ($P = 0.024$) differed between Bethesda categories. Isoechoic/hyperechoic nodules accounted for 73.1% of benign cases (Bethesda II), while only 25.0% were hypoechoic. Taller-than-wide nodules were overrepresented in Bethesda V (75.0%). Logistic regression showed a significant model ($P = 0.027$; pseudo $R^2 = 0.192$), confirming echogenicity and taller-than-wide shape as predictors of malignancy. Taller-than-wide nodules had OR = 124.65 (95% CI: 1.47–410,563.53; $P = 0.033$) for Bethesda V classification.
Conclusions
Systematic evaluation of thyroid nodules is essential for malignancy risk stratification. Hypoechogenicity and taller-than-wide shape were identified as predictive factors and may help guide selection of nodules for fine-needle aspiration.

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PS2-10-09

Thermal ablation for treatment of amiodarone-induced thyrotoxicosis: a report of two cases

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Patients	Age, sex	Type of AIT	Heart comorbidities	Thermal ablation modality	TH at AIT diagnosis	TH before intervention	TH 2-3 weeks after intervention
Case 1	38, ♂	Mixed	Atypical atrial flutter	RFA	TSH <0,005 FT4 > 100 FT3 :30,6	TSH < 0,005 FT4: 77,8 FT3: 14,7	TSH < 0,005 FT4: 31,7 FT3: 6,78
Case 2	56, ♀	Mixed/Type 2	HFrEF of ischemic, valvular, arythmic etiology	MWA	TSH <0,005 FT4: 56 FT3: 8,36	TSH < 0,005 FT4: 72 FT3: 12,1	TSH: < 0,005 FT4: 36 FT3: 6,8

Table 1. Patient demographics and clinical and hormonal data before and after thermal ablation of the thyroid for AIT.TH: thyroid hormones; TSH reference range: 0.27-4.2 mUI/L; FT4 reference range: 11.2-24.1 pmol/l; FT3 reference range: 3.1-6.8 pmol/l.

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Introduction
Amiodarone-induced thyrotoxicosis (AIT) is an endocrine emergency with a reported incidence of up to 10%; patients are often fragile due to the underlying heart disease. AIT is more resistant to medical therapy than other forms of thyrotoxicosis, and its mortality is non negligible. When rapid control of thyrotoxicosis is required, the decision to perform thyroidectomy represents a major therapeutic dilemma in these patients. Thermal ablation technique has been considered as a potential alternative, and a clinical trial was launched at the Mayo Clinic, but it was closed due to very low recruitment (ClinicalTrials.gov ID NCT03720210).
Case reports
We report two patients diagnosed with AIT and treated with thermal ablation of the thyroid gland. One is a 38-year-old male with atypical atrial flutter who developed AIT several months after stopping amiodarone and remained markedly symptomatic despite prednisone and carbimazole treatment. The other is a 56-year-old female with heart failure with reduced ejection fraction (HFrEF), whose cardiac condition worsened with prednisone and carbimazole treatment of the AIT. Both patients were at high risk for general anesthesia.
Results
One patient was treated using radiofrequency ablation (RFA); the other was treated using microwave ablation (MWA) to avoid potential device interference with implantable defibrillator. In each patient, thermal ablation was performed in two sessions, two weeks apart, resulting in an almost complete devascularization of both lobes and the isthmus. Both patients reported resolution of thyrotoxic symptoms. In both cases, progressive tapering of pharmacological treatment was possible after ablation. Thyroid hormone levels are shown in **Table 1**; the time to FT3 normalization was 19 and 22 days, respectively. There was no recurrence of arrhythmia.
Conclusion
Thermal ablation of almost the entire thyroid gland represents an alternative treatment option for AIT in patients with compromised cardiac function in whom conventional treatment is contraindicated or not tolerated.

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PS2-10-10

Thyroid nodule microwave ablation. first 138 cases in romania

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Background
Microwave ablation (MWA) is a modern minimally-invasive technique using thermal ablation for outpatient treatment of benign and some malignant thyroid nodules, as well as parathyroid adenomas and metastatic lymph nodes. We report our experience with first cases of MWA for thyroid nodules in Romania.
Methods
Retrospective analysis of the first 138 thyroid nodule MWA procedures performed in Romania. All MWA procedures were performed using cooled antenna 16G or 17G. We followed our patients for at least 1 year after the procedure.
Results
Of 138 MWA procedures, 66 were performed for solitary non-functioning nodules, 45 for multinodular goitre, 27 for AFTN (autonomously functioning thyroid nodules) or toxic multinodular goitre. The mean volume of nodules was 16.86cc before ablation. Average ablation time was 6.7 minutes, average power used was 24.8 W. The mean volume reduction rate (VRR) was 42.9% at 1-month, 61.8% at 3-month, 70.5% at 6-month and 79.8% at 12-month follow-up. The VRR of at >90% was seen in 6 patients at 3 months, 13 patients at 6 months and 24 patients at 12 months. Only 2 nodules had VRR less than 50% (mean 47.9%) at 12-month follow-up. Minor complications included some bruising and post-procedural pain or local discomfort, controlled with non-steroidal anti-inflammatory drugs. One patient with AFTN had transient post-procedural thyrotoxicosis, two patients developed transient dysphonia, no other significant complications. Most patients who experienced compressive symptoms before ablation, had significant improvement at 1 month post ablation. All patients with AFTNs had their thyroid function normalized at 1 month, except for the aforementioned patient who developed transient thyrotoxicosis.
Conclusion
Thyroid nodule MWA is a safe and efficient treatment option for thyroid nodules, reducing volume and controlling thyroid function in case of AFTN or toxic multinodular goitre.

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Clinical Cases (non-cancer) 1

PS2-11-01

Levothyroxine malabsorption and macrotsh in a woman with refractory hypothyroidism

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Introduction
MacroTSH is a high molecular weight complex of TSH bound to immunoglobulins that causes spuriously elevated TSH concentrations despite adequate thyroid hormone levels. Malabsorption syndrome further impairs thyroid function control by reducing intestinal levothyroxine uptake.
Case Report
A 41 year old woman with previous radioactive iodine-131 treated hyperthyroidism, type 2 diabetes, hypertension and iron deficiency anaemia was referred for difficult to control hypothyroidism. Regular medication included LT4 275 micrograms daily, metformin plus dapagliflozin, perindopril plus indapamide plus amlodipine, and oral iron. She reported correct LT4 intake 30 minutes before meals and other medications. Symptoms included fatigue, recurrent syncopal episodes, weight gain, menstrual irregularity and nocturnal paraesthesias of the right upper limb. On examination, weight was 81 kilograms (BMI 31.6 kg/m^2), blood pressure 143/101 mmHg, with no exophthalmos and a non palpable thyroid. Initial laboratory evaluation showed microcytic anaemia with Hb 10.5 mg/dl and ferritin 2 ng/ml, with no vitamin B12 or folate deficiency. Thyroid tests revealed TSH 144.2 mIU/L and free T4 0.37 ng/dl, with negative anti thyroglobulin and anti thyroid peroxidase antibodies. Thyroid ultrasound demonstrated a small atrophic gland with heterogeneous echotexture, consistent with chronic thyroid disease and no nodules. After LT4 increase to 288 micrograms daily, TSH showed only a modest decrease (71.23 mIU/L), with free T4 0.41 ng/dl and normal free T3. Polyethylene glycol precipitation showed TSH recovery of 39%, suggesting macroTSH. An LT4 absorption test with an 800 microgram oral dose demonstrated reduced absorption of 25%, with free T4 increment of 0.02 ng/dl, indicating LT4 malabsorption. Coeliac disease screening (total IgA, anti transglutaminase, anti gliadin and anti endomysial antibodies) was negative. LT4 was subsequently increased to 325 micrograms daily, resulting in thyroid function normalization (TSH 12.10 mIU/L, macroTSH 4.81 mIU/L, free TSH 4.96 and free T4 0.73 ng/dl) and marked improvement of symptoms. She was referred to gastroenterology for further evaluation.

Conclusions
Persistent elevation of TSH in patients receiving high dose of LT4 requires systematic evaluation beyond adherence. This case underscores that concomitant LT4 malabsorption and macroTSH can underlie severe hypothyroidism, profoundly distorting biochemical assessment and masking true hormone status. Early consideration of assay interference and absorption defects, coupled with close collaboration between clinicians and the laboratory, is crucial to correctly interpret thyroid function, tailor LT4 dosing and prevent unnecessary or inappropriate investigations.

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PS2-11-02

Immune checkpoint inhibitor related subacute thyroiditis: a rare presentation of pembrolizumab-induced endocrine toxicity

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Introduction
Immune checkpoint inhibitors (ICI) have significant therapeutic benefits and improve clinical outcomes in various types of malignancies. However, these medications are associated with a variety of immune-related adverse events with thyroid dysfunction being among the most prevalent disorders involving up to 22 % of the treated patients. The ICI-induced thyroid dysfunction typically presents as painless destructive thyroiditis with transient thyrotoxic phase eventually leading to permanent hypothyroidism; new onset of primary hypothyroidism and rarely Graves' disease. Recently, several cases of subacute thyroiditis leading to hypothyroidism were described, suggesting a new potential association between ICI therapies and the development of subacute thyroiditis with unclassical clinical outcome.
Case Report
A 65-year-old woman presented in May 2025 with low-grade fever, pain in the neck irradiating towards the right ear, general fatigue and malaise for about a month prior to the visit without history of viral or other form of infection. She was diagnosed with colon cancer and had a surgery in May 2024, two months later because of liver metastasis she started treatment with programmed cell death protein 1 (PD-1) receptor antibody pembrolizumab. On clinical examination painful enlarged thyroid gland with diffuse hypoechogenicity and low blood flow on ultrasound was seen together with several nodules without suspicious features. Laboratory tests revealed clinical thyrotoxicosis with FT4 32.7 pmol/l (11.5-22.7) and markedly increased inflammatory markers. After a two-month treatment course with corticosteroids the disorder resolved with complete restoration of the thyroid morphology and function while the pembrolizumab therapy was not interrupted. 9 months after the episode she was euthyroid with normal sonographic thyroid parenchyma appearance and negative thyroid autoantibody titer.
Conclusion
The described case highlights an uncommon, but distinct manifestation of ICI induced adverse thyroid event. While typically mild and transient, the pain and thyrotoxicosis associated with subacute thyroiditis can mimic infection or other diseases, requiring early recognition and proper management usually without necessity of essential immunotherapy cessation. Close monitoring is recommended since ICI-induced forms of subacute thyroiditis can result in permanent thyroid failure.

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PS2-11-03

Riedel's thyroiditis associated with retroperitoneal fibrosis: a case presentation

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Background
Riedel thyroiditis (RT) is a rare, chronic fibro-inflammatory disorder of the thyroid, with challenging diagnosis and management. Although its exact aetiology is unknown, emerging evidence suggests RT is part of the spectrum of IgG4-related disease. Its coexistence with retroperitoneal fibrosis is uncommon but clinically significant, potentially reflecting multisystem involvement that requires prompt recognition.
Case Presentation
A 34-year-old male with autoimmune hypothyroidism on levothyroxine presented with a painless, progressively enlarging anterior neck mass and low-grade fever. Initial evaluation suggested subacute thyroiditis; however, the patient lacked typical hormonal and ultrasonographic features and did not improve with prolonged glucocorticoid therapy. On examination, he had a hard goiter without compressive symptoms. Ultrasound showed a diffusely enlarged, hypoechoic, hypovascular thyroid. Fine-needle aspiration was nondiagnostic; core needle biopsy revealed fibrous tissue and inflammatory cells without thyroid follicles, raising suspicion for RT, while IgG4 immunohistochemistry was negative. Cross-sectional imaging was performed to assess for extrathyroidal fibrosis. During follow-up, he developed acute lower abdominal pain radiating to the right testicular region. Imaging revealed a large right-sided retroperitoneal fibro-inflammatory mass encasing the distal abdominal aorta, inferior vena cava, iliac vessels, and right ureter, causing hydronephrosis and right renal cortical thinning—findings consistent with retroperitoneal fibrosis, likely IgG4-related. During follow-up, he presented with an acute onset lower abdominal pain radiating to the right testicular region. Following rheumatology assessment, the patient received high-dose intravenous methylprednisolone followed by rituximab and underwent right ureteral stent placement without complete resolution of hydronephrosis.
Conclusion
This case illustrates the rare coexistence of RT and retroperitoneal fibrosis, supporting a systemic fibroinflammatory pathophysiology even in the absence of IgG4 positivity. Early recognition and multidisciplinary management by endocrinologists and rheumatologists are crucial to guide appropriate therapy.

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PS2-11-04

Diffuse lipomatosis of the thyroid : a case report

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Background
Diffuse lipomatosis of the thyroid (DLT) is a rare condition characterized by the diffuse infiltration of mature adipose tissue within the thyroid gland, leading to disruption of its normal architecture and replacement of the thyroid parenchyma. Although uncommon, it typically presents with progressive neck enlargement and may cause compressive symptoms such as dyspnea, dysphagia, and voice changes.
Case Report
We report the case of a 42 years old woman who was referred to our department for evaluation of a large diffuse goiter. Her medical history was notable for chronic renal failure of unknown etiology and obesity (BMI = 33 kg/m^2). On physical examination, a large grade 3 goiter with a soft consistency was palpated, without clinical signs of hypothyroidism or hyperthyroidism. Thyroid function tests were within normal limits (TSH and FT4), and anti-thyroid peroxidase and anti-thyroglobulin antibodies were negative. Thyroid ultrasonography revealed an enlarged, hyperechogenic thyroid gland with a total volume of 60 cc. Due to the progressive enlargement of the goiter and the presence of compressive symptoms, a total thyroidectomy was performed. Intraoperatively, the thyroid gland was friable and had a soft, fatty texture resembling a lipoma. Histopathological examination demonstrated diffuse fatty infiltration of the thyroid gland associated with follicular degeneration and amyloid deposits. A diagnosis of diffuse thyroid lipomatosis was established.
Conclusion
Diffuse lipomatosis of the thyroid is a rare benign condition characterized by adipose tissue infiltration of the thyroid gland, which may lead to the development of a large compressive goiter. Its etiology remains unclear, but it has been associated with obesity and may result from adipose metaplasia or aberrant incorporation of fat during embryogenesis. Recent hypotheses suggest that somatic mutations leading to loss of succinate dehydrogenase subunit B (SDHB) expression may contribute to its pathogenesis. Amyloidosis may either result from or contribute to chronic kidney disease.

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PS2-11-05

Thyroidectomy in the presence of a non-recurrent laryngeal nerve and aberrant right subclavian artery: a case report

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Background
An uncommon but clinically important anatomical variation encountered during thyroid surgery is the non-recurrent laryngeal nerve, a variant of the inferior laryngeal nerve. Its occurrence is strongly linked with an aberrant right subclavian artery (arteria lusoria). The nerve does not follow the usual recurrent course around the subclavian artery, takes a direct path from the cervical vagus to the larynx, predisposing it to injury during cervical procedures. Preoperative awareness and intraoperative assessment are therefore essential to prevent nerve damage.
Case
A 43 year old woman with a multinodular goiter scheduled for total thyroidectomy. Preoperative computed tomography of the chest and neck revealed an aberrant right subclavian artery with a retroesophageal trajectory, suggesting the likelihood of a right-sided NRLN.
Results
During thyroidectomy, the recurrent laryngeal nerve was absent in its expected tracheoesophageal groove. Instead, a nerve branch was identified arising directly from the cervical vagus and coursing transversely to the larynx, consistent with an NRLN. Intraoperative neuromonitoring confirmed the functional integrity of the nerve. The thyroidectomy was completed without complications, and the patient recovered uneventfully, with no postoperative hoarseness or vocal cord dysfunction.
Conclusions
This case illustrates the strong association between arteria lusoria and the presence of an NRLN. It emphasizes the value of preoperative imaging in anticipating such anomalies and demonstrates the importance of intraoperative neuromonitoring in confirming and preserving atypical nerve anatomy. Awareness of these variations and a systematic operative approach are key to minimizing iatrogenic nerve injury in thyroid and neck surgery.

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PS2-11-06

Primary hydatid cyst of the thyroid gland: a rare case report

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Introduction
Echinococcosis is a parasitic zoonosis caused by Echinococcus granulosus, typically affecting the liver and lungs. Thyroid involvement is exceptionally rare, even in endemic regions, and presents a diagnostic challenge due to its nonspecific clinical presentation. We report a rare case of a primary hydatid cyst localized to the thyroid gland, emphasizing the importance of considering this diagnosis in patients from endemic areas with atypical neck swellings.
Case Presentation
A 32-year-old woman, with no significant past medical history, presented with a gradually enlarging, painless left-sided neck swelling for 8 months. Clinical examination revealed a firm, mobile swelling without overlying skin changes or palpable lymphadenopathy. Laboratory investigations were unremarkable. Neck ultrasound identified a 30 mm solid-cystic nodule in the left thyroid lobe. Fine needle aspiration (FNA), performed under ultrasound guidance, revealed multiple scolices consistent with Echinococcus granulosus. The patient underwent total thyroidectomy. Histopathology confirmed the diagnosis of a primary hydatid cyst. Further imaging ruled out other organ involvement. Postoperative recovery was uneventful, and she was discharged on levothyroxine the following day. Follow-up showed no recurrence.
Conclusion
Isolated hydatid disease of the thyroid gland is exceedingly rare. It typically presents as a basal-cervical mass and may mimic other benign thyroid lesions. Diagnosis relies on imaging, cytology, and histopathology, especially in endemic regions. Surgery remains the definitive treatment. Increased awareness and consideration of this entity are essential for timely diagnosis and management.

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PS2-11-07

Persistent unexplained widespread skeletal radioiodine uptake in a patient with benign ectopic thyroid tissue: a 10-year diagnostic challenge

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Introduction
While radioiodine whole-body scintigraphy (WBS) is highly sensitive for detecting metastatic differentiated thyroid cancer, false-positive uptake can occur and lead to diagnostic dilemmas. We report a decade-long follow-up of a patient with widespread *benign* ectopic thyroid tissue and persistently unexplained skeletal radioiodine uptake on WBS.
Case Report
An 85-year-old woman with a history of thyroidectomy for benign multinodular goiter in 1981 was found to have cervical ectopic thyroid tissue (contiguous to the hyoid bone and with lateral cervical thyroid tissue), confirmed as benign on multiple biopsies. Initial WBS unexpectedly revealed multifocal radioiodine uptake in the skull, ribs, pelvis, and spine, highly concerning for metastatic disease. However, serial cross-sectional imaging, including CT, MRI, and FDG-PET/CT, showed no corresponding bone lesions to explain the uptake. Serum thyroglobulin levels remained mildly elevated (25-83 ng/ml) but stable, inconsistent with progressive metastatic disease. A targeted pelvic CT revealed osteoporotic fractures and degenerative changes, but their relation to the longstanding, diffuse uptake pattern remained unclear. A new WBS, eight years later, confirmed the identical, persistent uptake pattern, ruling out transient contamination or artifactual causes.
Conclusions
This case represents a persistent and unexplained false-positive radioiodine extensive uptake pattern, likely related to a benign, chronic process in a patient with widespread benign thyroid tissue. It underscores the critical importance of correlating scintigraphy findings with serum biomarkers and morphological imaging to avoid aggressive and inappropriate treatment for presumed metastatic disease. Despite extensive investigation, the precise mechanism of uptake for this case remains unknown.

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PS2-11-08

Modulation of thyroid function during growth hormone suppression in acromegaly: a case of pituitary macroadenoma treated with somatostatin analogue

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Background
Acromegaly caused by growth hormone (GH)–secreting pituitary adenomas is associated with multisystem complications, including metabolic dysfunction and organomegaly. Thyroid enlargement is frequently observed in patients with chronic GH and insulin-like growth factor-1 (IGF-1) excess; however, the functional consequences of GH signaling on the hypothalamic–pituitary–thyroid axis are not fully understood. Experimental and clinical evidence suggests that IGF-1 may stimulate thyroid follicular proliferation and influence thyroid hormone dynamics. We report a case illustrating changes in thyroid function during pharmacological suppression of the GH/IGF-1 axis.
Case Presentation
A 64-year-old man with type 2 diabetes, hypertension, and osteodystrophy presented with progressive weakness, sleep-disordered breathing, uncontrolled hyperglycemia, and typical acromegalic facial features. Biochemical evaluation showed markedly elevated IGF-1 (690 ng/ml) and GH (32.66 ng/ml; reference 0.03–2.47). Baseline thyroid tests indicated TSH 3.5 mIU/L and FT4 15.6 pmol/l. Thyroid ultrasound revealed a multinodular goiter with a total volume of 60.3 cm^3, and pituitary MRI identified a 1.5-cm macroadenoma. The patient declined surgical and radiotherapeutic options and was started on long-acting somatostatin analogue therapy (Octretide LAR 20 mg monthly).After six months of therapy, IGF-1 decreased to 200 ng/ml, and metabolic control improved (HbA1c from 7.8% to 6.0%). Thyroid hormone levels changed during treatment: TSH became significantly suppressed (0.005 mIU/L) with a transient increase in FT4 (23.5

pmol/l). On follow-up, FT4 decreased toward the normal range (16.7 pmol/l), while TSH remained suppressed (0.003 mIU/L). Macroadenoma size stayed stable, and clinical symptoms, including sleep apnea, improved.
Conclusion
This case highlights the dynamic changes in thyroid hormone regulation during medical suppression of GH excess. The timing of the decrease in GH/IGF-1 activity and the changes in thyroid function parameters suggests a functional link between the GH–IGF-1 axis and thyroid regulation. Recognizing this endocrine interaction may help clinicians interpret thyroid function tests during the treatment of acromegaly.

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PS2-11-09

Managing severe hypothyroidism complicated by nephrotic-range proteinuria in a pregnant patient: a case report

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Background
The coexistence of hypothyroidism and nephrotic-range proteinuria in a pregnant patient presents a complex diagnostic and therapeutic challenge, as proteinuria can exacerbate thyroid dysfunction through urinary loss of protein-bound hormones.
Case Presentation
A 30-year-old pregnant female (Gravida 4, Para 3) presented with fatigue, weakness, and bilateral lower limb swelling during her first trimester. Initial thyroid function tests revealed profoundly elevated TSH (17,300 uIU/ml) and low free thyroid hormones. She subsequently developed bilateral pitting edema, and further investigation confirmed nephrotic-range proteinuria (urine protein/creatinine ratio $>10{,}000$ mg/g). Physical examination was notable for puffy eyelids, dry skin, a diffuse firm goiter.
Investigations
Laboratory findings confirmed severe primary hypothyroidism (TSH >100 uIU/ml) and heavy proteinuria. Immunological workup revealed a positive ANA (1/40) but negative anti-dsDNA and anti-Smith antibodies, making a definitive diagnosis of lupus nephritis uncertain. Renal ultrasound showed mild hydronephrosis.
Management
A multidisciplinary approach involving endocrinology, nephrology, and obstetrics was implemented. The patient was treated with escalating doses of levothyroxine (up to 300 mg/day), intravenous diuretics (frusemide), and was started on prednisolone, low molecular weight heparin (LMWH), and tacrolimus for presumptive management of proteinuric renal disease. A renal biopsy was planned. Obstetric management included fetal monitoring and progesterone support.
Outcome and Follow-up
Follow-up showed gradual improvement in thyroid function (TSH decreased to 4.35 uIU/ml), though significant proteinuria persisted (albumin/creatinine ratio 350). The pregnancy was complicated by preterm premature rupture of membranes (PROM) at 30 weeks of gestation, leading to a Cesarean section and delivery of a 1 kg infant who was admitted to the NICU. The case highlights the intricate relationship between nephrotic-range proteinuria and hypothyroidism, where urinary loss of thyroid hormones complicates management during pregnancy, necessitating close monitoring and a coordinated care plan.

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PS2-11-10

Reversible pituitary hyperplasia secondary to untreated primary hypothyroidism: a case report

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Introduction
Primary hypothyroidism is one of the most common endocrine diseases. Severe untreated primary hypothyroidism can lead to pituitary hyperplasia, resulting in symptoms and signs of intracranial compression and endocrine dysfunction (*Beck-Peccoz et al*, 1996).
Case Report
In March 2024, a 21-year-old female patient was referred to our attention for the evaluation of an incidental pituitary macroadenoma (17 mm), with pituitary stalk dislocation and optic chiasm compression. At biochemical evaluation, we uncovered a severe primary hypothyroidism and hyperprolactinemia (TSH 1295 mIU/L, fT4 <0.5 pmol/l, prolactin 81.2 ng/ml). Macro-TSH and macro-PRL were excluded, and anti-thyroid antibodies and ultrasound findings were consistent with chronic thyroiditis. The patient presented with asthenia, oligomenorrhoea, and a minor impairment of bitemporal visual field. We concluded with a diagnosis of a likely non-secreting pituitary macroadenoma associated with severe primary autoimmune hypothyroidism. The hyperprolactinemia was attributed to enhanced TRH-mediated stimulation associated with longstanding severe primary hypothyroidism, with a possible deafferentation component. After exclusion of central adrenal insufficiency, levothyroxine therapy was started at 50 µg/day and titrated to 125 µg/day, obtaining optimal TSH levels and significant clinical improvement. Follow-up MRI three months after starting levothyroxine showed marked reduction of the pituitary lesion (12 mm) with reversal of stalk displacement. At 10-month follow-up (May 2025), MRI showed further reduction of the lesion to 8 mm with regression of visual field defects and prolactin normalization. The lesion remained stable on the latest MRI (February 2026).
Conclusions
The pituitary lesion decreased in size following TSH normalization. This finding is consistent with pituitary thyrotrope hyperplasia secondary to long-lasting uncontrolled primary hypothyroidism, thus avoiding the need for immediate surgery. The association between pituitary hyperplasia and primary hypothyroidism should be considered when pituitary enlargement is identified on MRI, to avoid unnecessary and potentially invasive treatments.

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Case Presentation

PS2-12-01

Abstract Withdrawn

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PS2-12-02

Clinical response to triac in four patients with RTHβ and autism spectrum disorder

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We report a case series of four pediatric patients with resistance to thyroid hormone beta (RTHβ) and autism spectrum disorder (ASD) treated with TRIAC. Patient 1, a 2-year-old boy (p.K443T in *THRB*), presented with hyperactivity, language delay, limited social interaction, and challenging behaviors. Therapy with the thyroid hormone analogue 3,5,3'-triiodothyroacetic acid (TRIAC) was initiated at 3.5 years and titrated to achieve normal fT4 levels, resulting in marked improvements in attention, communication, adaptive skills, and overall behavior regulation. Twin siblings (p.P453A in *THRB*) demonstrated severe neurodevelopmental outcomes (e.g., low IQ, severe behavioral disorder with ADHD). The sister began TRIAC therapy earlier (at 2.5 years) than her brother (at 7 years), and in combination with structured Applied Behaviour Analysis (ABA) interventions, she showed significant progress in functional language, learning skills, social engagement, and daily living abilities. The brother had a more compromised cognitive profile and showed slower progress during ABA therapy, likely

reflecting the later initiation of TRIAC treatment. Finally, Patient 4 (p.M334R in *THRB*), a 3-year-old boy, presented with global developmental delay and ASD-like behaviors. He started TRIAC therapy three months ago at an initial dose of 0.7 mg, which was titrated up to 1.05 mg based on thyroid function tests (fT4 35.9 → 25.5 pmol/l). He is already noticeably calmer, although longer follow-up is needed to assess sustained neurodevelopmental improvements. TRIAC therapy was well tolerated in all patients and effectively normalized manifestations of hyperthyroidism. This evidence supports the idea that TRIAC treatment can improve functional neurodevelopmental and behavioral outcomes in children with RTHβ and ASD.

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PS2-12-03

Graves' disease impact on the brain: morphometry of hippocampal subfields and amygdalar nuclei

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Introduction
In previous work on automatic brain morphometry in Graves' disease, we found hippocampus and amygdala volumes to be reduced on T1-weighted magnetic resonance (MR) images (full cranial acquisitions) in hyperthyroid patients. With 15 months of anti-thyroid drug or surgical treatment to these patients, the volume reductions were normalized, suggesting a recovery effect. Focused high-resolution acquisitions offer improved visual accessibility of the MTL regions.
Objectives
To determine whether specific hippocampal subfields and/or amygdalar nuclei, when imaged using targeted high-resolution protocols, account for the previously observed volume differences between hyperthyroid patients with Graves' disease and control participants.
Methods
Using a focused MR protocol (Philips Achieva 3T; T2-weighted turbo spin-echo; SENSE-Head-8 coil; 0.35×0.35×2 mm resolution), Medial temporal Lobe (MTL) region images were acquired from 59 patients with Graves' disease in hyperthyroidism and 59 matched controls participating in the CogThy study. The images were processed with FreeSurfer, using modules for segmenting hippocampal subfields (22 per hemisphere) and amygdalar nuclei (10 per hemisphere). A split-sample approach was employed to generate hypotheses in one subset of the data and subsequently test them on an independent subset.
Results
Of 64 segmented subregions, one ("left molecular layer HP head", i.e. a subregion in the anterior hippocampus) showed a notable difference between patients and controls during hypothesis generation ($P = 0.04$). The difference was not evident during hypothesis testing ($P = 0.97$). Total segmented subregion volumes also showed no significant differences, suggesting that the high-resolution anisotropic images, while advantageous for visual diagnostics, may be suboptimal for automatic volumetry using FreeSurfer.
Conclusion
A specialized MR sequence for Hippocampus and Amygdala did not identify any individual subregions that could explain global hippocampus and/or amygdala volume differences. MTL changes appear to be diffuse rather than focal. It is also possible that focused hippocampal sequences have limited utility for automated quantitative imaging.

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PS2-12-04

Significant others' experiences of being close to a person with graves' disease – a phenomenological hermeneutic study

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Background
Graves' disease (GD) is the most common cause of hyperthyroidism in Sweden, affecting approximately 2,000 individuals annually, predominantly women. In its early phase, GD is characterised not only by somatic symptoms but also by pronounced psychological manifestations such as irritability, emotional instability, cognitive difficulties, and impaired well-being. Although thyroid function can be normalised through medical or ablative treatment, more than 30% of patients report persistent mental fatigue and reduced quality of life long after biochemical stabilisation. Coping ability and social support influence recovery in Graves' disease (GD); however, research focusing on significant others remains scarce. No previous studies have explored the lived experience of being a significant other to a person diagnosed with GD. Clinical observations suggest that the fluctuating symptom profile and behavioural changes associated with GD may profoundly affect close relationships and shape how significant others experience everyday life.
Aim
To explore experiences of being a significant other to a person diagnosed with Graves' disease.
Methods
A qualitative interview study was conducted to address the aim. Fourteen adult significant others participated (5 women and 9 men). The data were analysed using a phenomenological hermeneutic approach inspired by Paul Ricoeur's theory of interpretation and further developed for research by Lindseth and Norberg. This approach enables the interpretation of narratives as texts in order to deepen understanding of lived experiences and to generate knowledge about participants' perspectives. Ethical approval was obtained, and written informed consent was secured from all participants.
Expected Results
Preliminary interpretations suggest that being a significant other to a person with Graves' disease involves considerable emotional strain and persistent uncertainty. Participants describe challenges related to altered behaviour and personality expression in the affected person, which influence relational dynamics and everyday life. At the same time, they express a strong sense of commitment and responsibility within the relationship.
Conclusions
This study contributes novel knowledge about what it means to be a significant other to a person with Graves' disease. The findings indicate that the impact of GD extends beyond the individual patient, affecting close relationships and shared everyday life. Greater awareness of this relational dimension may deepen understanding of the broader consequences of Graves' disease within an endocrine context.

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PS2-12-05

Therapeutic plasma exchange for severe thyrotoxicosis: institutional outcomes and development of a management strategy

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Background
In rare and severe cases of thyrotoxicosis, conventional medical therapy may be ineffective, poorly tolerated, or contraindicated. In these situations, therapeutic plasma exchange (TPE) has been reported as a potential supportive intervention to rapidly reduce circulating thyroid hormones. The American Society for Apheresis (ASFA) currently categorizes this indication as Category III with a grade 2C recommendation, reflecting limited and heterogeneous evidence. The present study aimed to review our center's experience with TPE in patients with life-threatening thyrotoxicosis and to evaluate treatment outcomes.
Methods
A retrospective observational study was conducted at a single tertiary institution. All patients diagnosed with thyrotoxic crisis who underwent TPE were included. The diagnosis of thyroid storm was determined using the Burch–Wartofsky Point Scale (BWPS). Demographic data, underlying causes of hyperthyroidism, treatment strategies, number of exchange sessions, and clinical outcomes were analyzed.
Results
Between 2019 and 2024, seven patients with severe thyrotoxicosis received TPE. The cohort consisted of four men and three women, with a median age of 65 years. The underlying cause was Graves' disease in three patients (including one pregnant patient) and amiodarone-associated thyrotoxicosis in four patients. All individuals presented with BWPS scores exceeding 40 and required management in the intensive care unit. Initial treatment included antithyroid drugs,

corticosteroids, and beta-blockers, while Lugol's iodine was administered in five cases. A median of five TPE procedures per patient was performed (range 4–7 sessions). In five patients, a marked reduction in thyroid hormone concentrations was observed following TPE, with free T4 levels decreasing by 47% ($P = 0.016$) and free T3 by 54% ($P = 0.031$). For four patients, plasma exchange served as a stabilizing measure before definitive surgical treatment. One patient did not show clinical improvement and died prior to thyroidectomy.

Conclusion

Despite the small number of cases, our findings suggest that TPE may be an effective adjunctive therapy for reducing thyroid hormone levels in critically ill patients with thyrotoxic crisis. At present, standardized guidelines regarding exchange volume, treatment frequency, and replacement fluids are lacking. Based on our experience, we propose a structured protocol to support clinical decision-making in the management of severe thyrotoxicosis requiring plasma exchange.

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PS2-12-06

Total thyroidectomy for severe amiodarone-induced thyrotoxicos

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Objectives

Amiodarone-induced thyrotoxicosis (AIT) is a well-recognized complication of amiodarone therapy. In some patients, hyperthyroidism persists despite intensive medical management with high-dose antithyroid drugs combined with perchlorate and methylprednisolone, thereby increasing the risk of progressive cardiac deterioration. In such cases, total thyroidectomy may represent a definitive therapeutic option. To date, approximately 300 surgically treated cases of AIT have been described in the literature. The present study aimed to evaluate the outcomes of total thyroidectomy in patients with severe AIT.

Methods

In this retrospective clinical study, we reviewed the medical records of all patients with AIT who underwent total thyroidectomy at our tertiary centre between January 2007 and February 2020. Baseline demographic characteristics and underlying cardiac disease were recorded. Thyroid hormone levels at presentation and at the final preoperative evaluation were documented, together with thyroid ultrasound findings. Data on the duration and regimen of medical therapy were also analysed. Perioperative and postoperative outcomes, including complications and length of postoperative hospital stay, were assessed. Histopathological findings were recorded.

Results

During the study period, 23 patients with AIT (median age 63 years) underwent total thyroidectomy. All patients had severe underlying cardiac disease (in 3 cases the cardiac ejection fraction was below 20%), multiple comorbidities, and severe hyperthyroidism at presentation (median fT_4 57.1 pmol/l, median fT_3 13.99 pmol/l). Treatment with thiamazole, perchlorate, and methylprednisolone was initiated, with a median treatment duration of 2.5 (2.0-3.9) months; however, all patients remained hyperthyroid at the time of surgery (median fT_4 39.6 pmol/l and median fT_3 7.04 pmol/l). The median postoperative stay was 3 (2-9) days. Transient hypocalcemia occurred in 8 patients. Other complications included subcutaneous hematoma ($n = 1$), vocal cord paralysis ($n = 1$), paroxysmal supraventricular tachycardia ($n = 1$), sigmoid diverticular rupture ($n = 1$), and Pneumocystis jirovecii pneumonia with septicemia ($n = 1$). In the latter patient, pre-existing hypoxemia and hypotension worsened intraoperatively. No major perioperative bleeding or anaesthesia-related complications were observed in the remaining patients. Histopathology revealed amiodarone-associated changes in all cases. Notably, incidental papillary thyroid carcinoma was identified in 5 patients (21.7%).

Conclusions

Total thyroidectomy should be considered as a definitive treatment option in patients with severe, medically refractory amiodarone-induced thyrotoxicosis, even in those with advanced cardiac disease, when performed in experienced centres. Early referral for surgical evaluation may reduce prolonged ineffective medical therapy and facilitate faster stabilization of thyroid function and cardiac status.

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PS2-12-07

Evaluation of the efficacy of dose setting in radioactive iodine therapy for graves' disease

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Background

In radioactive iodine therapy (RAIT) for Graves' disease (GD), no standardized method has been established for determining the 131-I dose that reliably induces euthyroidism or hypothyroidism. At our institution, we developed a dose-setting table based on thyroid weight to target euthyroidism, and we increase the expected absorbed dose when hypothyroidism is the intended therapeutic outcome.

Objective

To evaluate the effectiveness of our current dose-setting method in achieving euthyroidism or hypothyroidism.

Methods

Of 2,234 patients with GD who underwent single-dose RAIT at our institution between 2012 and 2013, 1,433 were included after excluding those with <1 year of follow-up or postoperative recurrence. The expected absorbed dose was set at 40 Gy for thyroid weights of 20–30 g, with increments of 10 Gy for every additional 10 g. Dose categories were defined as follows: R (reference dose), RD (decrease from R), R1 (10 Gy increase), R2 (20 Gy increase), and R3 ($\geq$30 Gy increase).

Results

The cohort had a male-to-female ratio of 1:4, a median age of 43 years (interquartile range: 34–52), and a median thyroid weight of 50.2 g (33.1–74.6). The distribution of patients across RD/R/R1/R2/R3 was 254 (18%), 699 (49%), 262 (18%), 170 (12%), and 48 (3%), respectively. The proportions achieving euthyroidism or hypothyroidism at 5 years were 66.4%, 80.2%, 87.8%, 91.2%, and 92.7% for RD/R/R1/R2/R3, respectively ($P < 0.0001$). The median time to hypothyroidism or discontinuation of antithyroid drugs was 1.8, 1.5, 1.0, 0.7, and 0.4 years for RD/R/R1/R2/R3, respectively, with significant differences compared with RD ($P < 0.0001$).

Conclusion

Although some patients remained hyperthyroidism, increasing the expected absorbed dose was associated with a higher and earlier achievement of euthyroidism or hypothyroidism. These findings suggest that dose escalation based on thyroid weight is an effective strategy to some extent.

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PS2-12-08

Semiquantitative 99MTC-MIBI thyroid scintigraphy for differentiation of amiodarone-induced thyrotoxicosis subtypes

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Objectives

Differentiation of amiodarone-induced thyrotoxicosis (AIT) subtypes is essential for appropriate therapy, yet conventional imaging and laboratory parameters often overlap in iodine-replete regions. Subtype AIT-1 often results from iodine-induced thyroid hormone overproduction, AIT-2 from destructive thyroiditis, while mixed AIT (AIT-3) combines both mechanisms. We evaluated the diagnostic performance of semiquantitative 99mTc-methoxyisobutylisonitrile (MIBI) thyroid scintigraphy using a mediastinal background region to differentiate AIT-1, AIT-2 and AIT-3.

Methods

In this prospective study, 55 patients with AIT and 35 euthyroid controls underwent early (~10 min) and delayed (~60 min) MIBI thyroid scintigraphy. Semiquantitative analysis was performed using thyroid-to-mediastinal background ratios (TBR) on both images. Based on percentile distribution of mediastinal TBR values, patients were classified on early images as AIT-1 ($n = 19$), AIT-2 ($n = 20$), AIT-3 ($n = 16$), and on delayed images as AIT-1 ($n = 19$), AIT-2 ($n = 18$), AIT-3 ($n = 18$). Between-group differences were analyzed using non-parametric tests, and ROC analysis determined diagnostic performance.

Results
Early mediastinal TBR differed significantly among AIT subtypes and controls ($P < 0.001$). Median early TBR was highest in AIT-1 (0.74; IQR 0.66–0.85), intermediate in AIT-3 (0.54; IQR 0.48–0.57), and lowest in AIT-2 (0.35; IQR 0.30–0.37); controls had median 0.66 (IQR 0.54–0.77). Post hoc analysis showed significant differences between all AIT groups, while AIT-1 did not differ from controls. ROC analysis demonstrated excellent discrimination (AUC = 1.0) with early cut-offs >0.422 (AIT-1 vs AIT-2), >0.591 (AIT-1 vs AIT-3) and >0.407 (AIT-2 vs AIT-3). Delayed imaging showed lower TBR values but maintained excellent discrimination with cut-offs >0.290, >0.402 and >0.290, respectively.
Conclusions
Semiquantitative MIBI thyroid scintigraphy using a mediastinal background region enables accurate differentiation of AIT subtypes, with early TBR providing the highest diagnostic value and potential support for treatment decisions, particularly in mixed AIT-3 cases.

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PS2-12-09

Case series of amiodarone-induced thyrotoxicosis following semaglutide-induced weight loss

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Introduction
Amiodarone, a lipophilic, iodine-rich antiarrhythmic drug, can induce thyroid dysfunction including thyroxicosis. Amiodarone-induced thyrotoxicosis (AIT) type 1 occurs in patients with pre-existing thyroid disease due to excessive thyroid hormone production by autonomous thyroid tissue exposed to the iodine load, whereas type 2 AIT is a form of destructive thyroiditis usually occurring in previously normal glands. Semaglutide is a glucagon-like peptide-1 (GLP-1) agonist approved as a weight loss treatment. Its use has been increasing globally thanks to its efficacy in glycemic control, weight management and cardiovascular risk reduction. In 2025, we described the association of semaglutide treatment and amiodarone induced thyrotoxicosis (Giordani I. & Sykiotis G.P., *Thyroid* 2025 35:836-837). Following that, Black and colleagues reported an association between AIT and tirzepatide, a dual GIP and GLP-1 agonist. We describe here our updated series of four cases of amiodarone-treated patients who presented with an AIT shortly after initiating semaglutide treatment.
Cases series
The patients' characteristics are resumed in the Table.
Conclusion
In conjunction with previous reports of AIT following bariatric surgery and a recent report following tirzepatide treatment, the case series presented here suggests a possible association between significant weight loss and the development of AIT. The hypothesis is the release of stored amiodarone from adipose tissue during rapid weight reduction. This hypothesis is supported by the pharmacokinetic properties of amiodarone and evidence of lipophilic toxin release during weight loss. These observations underscore the importance of monitoring thyroid function in amiodarone-treated patients undergoing weight loss interventions.

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PS2-12-10

Syndrome of inappropriate secretion of TSH in a RARE coincidence of familial dysalbuminemic hyperthyroxinemia and macro-TSH

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Introduction
Discordant thyroid function tests, specifically the combination of elevated free thyroxine (fT4) and non-suppressed thyroid-stimulating hormone (TSH), present a diagnostic challenge. This pattern typically suggests the syndrome of inappropriate secretion of TSH (SITSH), most commonly caused by either a TSH-secreting pituitary adenoma (TSH-oma) or resistance to thyroid hormone (RTH). We present a case in which this biochemical pattern was caused by a rare coincidence of two distinct laboratory interference phenomena.
Case Report
An asymptomatic female patient was referred for endocrinological evaluation due to persistent elevation of TSH, fT3, and fT4 detected during preventive screening. The patient was clinically euthyroid, with no history of thyroid disease and a normal thyroid ultrasound. The initial workup focused on ruling out analytical error. TSH and fT4 levels were repeatedly confirmed across different laboratories using various immunoassay. All methods consistently showed mildly elevated TSH and fT4 levels. To exclude analytical interference, samples were sent to a reference laboratory for testing of heterophile antibodies, which were ruled out. Concurrently, polyethylene glycol (PEG) precipitation testing identified Macro-TSH (42%), potentially explaining the elevated TSH; however, this did not explain the persistent elevation of fT4. Consequently, pituitary MRI was performed, revealing a slightly enlarged pituitary gland but no distinct adenoma. A TRH stimulation test showed an exaggerated (>3-fold) increase in TSH, a response pattern suggesting RTH rather than a TSH-oma. Ultimately, genetic analysis performed to investigate RTH identified a heterozygous mutation in the ALB gene, confirming familial dysalbuminemic hyperthyroxinemia (FDH) and providing the explanation for the abnormal laboratory findings.
Conclusions
To our knowledge, this is the first reported case of simultaneous familial dysalbuminemic hyperthyroxinemia and Macro-TSH in a single patient. This unique "double interference" highlights the critical importance of stepwise analytical validation in patients with discordant thyroid function tests.
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Pregnancy & Hypothyroidism

PS2-13-01

Lactose free diet for decrease tsh level

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Materials and Method
The study was done at the Armenian-American Wellness Center from January 2022 to January 2022 and involved 450 patients. All pacients have lactose intolerance and hypothyroidism.
Patients were divided into two groups
Groups: 1. patients with lactose intolerance who keep lactose free diet 6 months and take levothyroxine in appropriate dose. Level of TSH was in range 4,5-6 mU/ml, free T4 0.89-1.5 ng/dl. 2. patients with lactose intolerance who doesn't keep lactose free diet, but take levothyroxine in appropriate dose. Level of TSH and Ft4 was in the same range like in the first group. All patients take levothyroxine.
Results
In the first group, range of TSH was decrease from 20 to 30 % and level of free T4 was increase in the same range without any changing in the dose. In the second group, it was less then 15%.

[Abstract PS2-12-09]

Patient (sex, age)	Amiodarone treatment history	Semaglutide treatment & dose	% weight loss at AIT diagnosis	AIT treatment
1 (♂, 71)	From 2.5 y. to 6 mo. before AIT	1.5 months before AIT, 0.5 mg/week	14.7%	carbimazole
2 (♂, 41)	>5 y. before AIT, ongoing	4 months before AIT, 2.4 mg/week	5.6%	prednisone
3 (♀, 57)	From 6 mo. to 1 mo. before AIT	1.5 months before AIT, 0.25 mg/week	6.7%	carbimazole & prednisone
4 (♂, 65)	>10 y. before AIT, ongoing	4 months before AIT, 1 mg/week	6%	carbimazole

Conclusion
Keep lactose free diet can help to decrease level TSH and increase level ft4 from 20 to 30% without changing the dose of levothyroxine.

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PS2-13-02

Hyperthyroidism resulting from hydatidiform mole — a case report

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Hyperthyroidism resulting from hydatidiform mole — a case report We present a case of a hydatidiform mole, a rare entity that presented itself with hyperthyroidism in a 25 years old patient. The patient presented with high levels of human chorionic gonadotropin (HCG) with low thyroid-stimulating hormone (TSH) values and higher free thyroid hormone values in laboratory thyroid function tests. Patient also had signs and symptoms of hyperthyroidism that included sinus tachycardia and hand tremors. The patient then underwent uterine curettage as to avoid risk of developing choriocarcinoma, on histopathological examination a partial hydatidiform mole was diagnosed. After uterine curettage, therapy with methimazole in dose of 10 milligrams was introduced. On follow-up, tremors and tachycardia were resolved but the patient had sensation of tightness in abdominal area. Methimazole was discontinued as thyroid function was shown to be improving. On follow-up a month later, patient reported favorable weight gain, thyroid function tests were normalised and HCG value was in decline. Another procedure was planned as gynecologists suspected a remnant tissue of the hydatidiform mole. Hydatidiform mole is a uncommon entity, but it should be suspected in women of child-bearing age that present with signs, symptoms and thyroid function tests that show hyperthyroidism in conjuction with high HCG values, provided that more common causes of this constellation of laboratory test results and symptoms are excluded and in these cases close cooperation with gynecologists is of the utmost importance.

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PS2-13-03

Factors influencing levothyroxine dose requirements in hypothyroid patients: a cross-sectional study

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Introduction
The standard replacement dose for hypothyroid patients is typically 1.6μg/kg of levothyroxine per day. However, individual requirements may differ between patients and between theoretical posology. The aim of our study was to determine the factors associated with variations of levothyroxine dose per body weight.
Methods
We conducted a cross-sectional study including well-controlled (TSH :0.4-4.5μUI/ml) hypothyroid patients with stable levothyroxine requirements for at least six months. We determined the levothyroxine dose per body weight and analyzed its relation with TSH levels, age and etiology of hypothyroidism. We also compared differences between hypothyroidsm secondary to total thyroidectomy, radioactive iodine therapy and Hashimoto's thyroiditis.
Results
We included 198 patients (mean age of 52 $\pm$ 10.7 years, and only 8% men). Hypothyroidism was secondary to Hashimoto's thyroiditis in 67.3%, secondary to radioactive iodine therapy in 18.4% and secondary to surgery in 14.3% of patients. Mean TSH was 2.09 $\pm$ 1.09μUI/ml, with no significant difference between etiological groups. However, dose of levothyroxine per body weight differed significantly across etiologies ($P < 0.001$), with dose per body weight in Hashimoto's thyroiditis, post iodine therapy and post thyroidectomy respectively at 1.11 $\pm$0.5 μUI/ml, 1.53 $\pm$ 0.41μUI/ml and 1.29 $\pm$ 0.41μUI/ml. A significant and negative correlation was found between TSH and dose of levothyroxine per body weight ($P = 0.008$, r=-0.189) and between dose per body weight and age ($P = 0.039$, r=-0.149). We found no correlation between TSH and age.
Conclusion
Although the standard dose of levothyroxine is 1.6μg/kg, requirements are significantly influenced by the etiology of hypothyroidism, with age and TSH levels also acting as independent factors. These findings suggest that levothyroxine initiation and adjustment should be taking into account the cause of thyroid deficiency and patient age to achieve optimal control.

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PS2-13-04

Variability of tsh and levothyroxine requirements after sleeve gastrectomy in patients with autoimmune thyroiditis in ajara, georgia

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Objectives
Bariatric surgery may alter the pharmacokinetics and gastrointestinal absorption of levothyroxine, potentially leading to instability in thyroid function. Patients with autoimmune thyroiditis who require lifelong hormone replacement may be particularly susceptible to such changes. This study aimed to evaluate postoperative variability in thyroid-stimulating hormone (TSH) levels and levothyroxine management strategies in patients with autoimmune thyroiditis following sleeve gastrectomy.
Methods
A retrospective observational study was conducted in 12 patients (mean age 38 $\pm$ 5 years), including 3 men and 9 women, with a history of autoimmune thyroiditis who underwent sleeve gastrectomy. Before surgery, all patients were receiving levothyroxine replacement therapy administered in the morning on an empty stomach. Postoperatively, TSH levels were monitored, and patients were assessed for clinical symptoms of hypo- and hyperthyroidism. Management strategies included levothyroxine dose adjustment and/or modification of the timing of administration.
Results
Postoperative follow-up revealed TSH variability in 100% of patients, with levels ranging from 0.15 to 5.8 mIU/L, accompanied by alternating symptoms of hypo- and hyperthyroidism. Euthyroidism was achieved through levothyroxine dose adjustment in 3 patients (25%; 2 men, 1 woman). In 5 patients (41.7%; 1 man, 4 women), stabilization of thyroid function was achieved by changing the timing of levothyroxine administration from morning to evening without increasing the dose. However, 4 patients (33.3%; all women) required an increase in levothyroxine dosage despite switching to evening administration to maintain biochemical euthyroidism. These findings suggest that postoperative changes in gastrointestinal physiology and drug absorption significantly influence levothyroxine requirements.
Conclusions
Sleeve gastrectomy is associated with clinically significant variability in TSH levels and levothyroxine requirements in patients with autoimmune thyroiditis. Individualized therapeutic strategies, including dose adjustment and modification of administration timing, may improve the achievement of euthyroidism. Close postoperative monitoring of thyroid function is essential in this patient population. Further prospective studies with larger cohorts are warranted to better elucidate the mechanisms underlying altered levothyroxine pharmacokinetics following bariatric surgery.

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PS2-13-05

Iron and vitamin B12 status in autoimmune thyroid disease: observations from adjara, georgia

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Background
Autoimmune thyroid diseases (AITD), including Hashimoto thyroiditis and Graves disease, are among the most prevalent endocrine disorders. In addition to

thyroid dysfunction, these conditions may be associated with systemic metabolic alterations and micronutrient deficiencies. Disturbances in iron metabolism and vitamin B12 deficiency have been reported in patients with autoimmune disorders and may be influenced by increased metabolic demand, autoimmune gastritis, or gastrointestinal factors such as *Helicobacter pylori* infection. Data exploring these associations in the South Caucasus region remain limited.
Objective
To evaluate vitamin B12, ferritin, and hemoglobin levels in patients with autoimmune thyroid disease and explore their relationship with thyroid antibody levels and *Helicobacter pylori* infection in a regional cohort from Adjara, Georgia.
Methods
This cross-sectional observational study included 47 patients aged 18–60 years referred for endocrinology evaluation in Batumi, Adjara. Clinical and laboratory data were collected, including thyroid function tests (TSH, FT4) and thyroid antibodies (anti-TPO, anti-TG). TRAb levels were assessed in patients with Graves disease. Serum vitamin B12, ferritin, and hemoglobin levels were measured in all participants. *Helicobacter pylori* infection was evaluated using the urea breath test. Breast ultrasound findings were additionally recorded in female patients when available as part of routine clinical care. Patients with vegetarian or vegan diets, prior gastric surgery, active bleeding, or ongoing iron or vitamin B12 supplementation were excluded. Statistical analysis included Spearman correlation and Mann–Whitney tests.
Results
The cohort included 47 patients (mean age 42 $\pm$ 11 years), with women comprising 74% of the study population. Hashimoto thyroiditis was diagnosed in 37 patients and Graves disease in 10 patients. Vitamin B12 deficiency was observed in 34% of participants, while reduced ferritin levels were detected in 40%. *Helicobacter pylori* infection was present in 43% of patients and was associated with lower ferritin concentrations (Mann–Whitney $P = 0.041$). Patients with Graves disease demonstrated lower ferritin and hemoglobin levels compared with those with Hashimoto thyroiditis. In the Graves subgroup, TRAb levels showed a modest inverse correlation with ferritin (Spearman $\rho = -0.32$, $P = 0.038$). Breast ultrasound, available in a subset of female patients, revealed simple cystic changes in several cases, with a tendency toward higher anti-TPO titers in this subgroup.
Conclusion
These observations suggest that micronutrient imbalance may represent an underrecognized aspect of autoimmune thyroid disease. Consideration of iron status and vitamin B12 levels may contribute to a more comprehensive clinical assessment of patients with thyroid autoimmunity.

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PS2-13-06

Shear wave elastography differentiates healthy subjects from euthyroid hashimoto's thyroiditis

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Objectives
Distinguishing between healthy subjects (HS) with a normal thyroid and patients with euthyroid Hashimoto's thyroiditis (EHT) can be challenging. Thyroid elastography has demonstrated increased tissue stiffness in Hashimoto's thyroiditis and may detect structural changes before biochemical abnormalities become apparent. However, its diagnostic criteria and clinical utility remain to be established. Our study aimed to evaluate differences in thyroid stiffness between HS and EHT using ultrasound shear wave elastography (SWE).
Methods
In this prospective study, 72 subjects were enrolled, including 58 HS (46 females and 12 males) and 14 EHT patients (11 females and 3 males). HS had normal thyroid stimulating hormone (TSH) levels, negative thyroid autoantibodies, and an isoechoic, homogeneous thyroid ultrasound pattern. EHT patients also had normal TSH levels but tested positive for antibodies against thyroid peroxidase (TPOAb) and/or thyroglobulin (TgAb), along with a hypoechoic non-homogeneous thyroid ultrasound pattern. Demographic data, including age and body mass index (BMI), were recorded, and thyroid volume was measured. SWE was performed in all subjects to measure the thyroid elasticity index (EI). Subjects' characteristics were analysed using non-parametric tests; a p-value < 0.05 was considered statistically significant. ROC analysis was used to evaluate the diagnostic performance of SWE, with accuracy assessed by the area under the curve (AUC).
Results
HS and EHT patients did not differ significantly in median age (46.5 vs 40.5 years), BMI (25.7 vs 24.5), TSH levels (1.53 vs 2.16 mIU/L), or thyroid volume (8.9 vs 8.4 mL). Compared with HS, EHT patients had significantly higher median concentrations of TPOAb (49.5 vs 31.5 kU/L, $P = 0.004$) and TgAb (1.3 vs 1.3 kU/L, $P < 0.001$), as well as a significantly higher median EI (17.92 vs 12.97 kPa, $P = 0.002$). The optimal EI cut-off value for distinguishing HS from EHT was 14.03 kPa, yielding a specificity of 85.7%, sensitivity of 63.8%, and an AUC of 0.766. In the overall cohort, EI showed a significant correlation with TPOAb ($P = 0.013$) but not with TgAb. In HS, EI correlated significantly with TgAb ($P = 0.001$) but not with TPOAb, whereas no significant correlation was observed in the EHT group.
Conclusions
In euthyroid subjects, EI significantly differentiates between HS and patients with EHT. Our findings suggest that SWE may serve as a valuable additional non-invasive tool for the detection of thyroid autoimmunity in euthyroid subjects.

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PS2-13-07

Levothyroxine prescription and administration in the intensive care unit: a retrospective cohort study

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Background and Objectives
Dysregulated hypothyroidism results in poor healing, increased infections and cardiovascular complications. NICE guidance recommends Levothyroxine should be administered on an empty stomach, at least 30-60 minutes before food and separated from interacting medications. In the Intensive Care Unit (ICU) , continuous enteral feeding, complex medication regimes and competing clinical priorities often make adherence to these recommendations challenging. This study aimed to assess the accuracy of Levothyroxine prescribing and administration in ICU patients.
Methods
We conducted a retrospective review of all ICU patients prescribed Levothyroxine between 01/01/2020 and 31/12/2024. Data were collected on prescribing instructions and administration practices during the first seven days of ICU admission. Secondary outcomes included thyroid function testing, mortality and ICU length of stay.
Results
A total of 163 patients over five years received Levothyroxine during ICU admission, accounting for 763 individual administration episodes. The cohort was predominantly female (58.9%) with a mean age of 64 years. Indications included primary hypothyroidism (84.7%), prior total thyroidectomy (2.8%) and hypopituitarism (2.8%). Levothyroxine was appropriately prescribed in 2.1% of episodes and correctly administered in 1.4%. Incorrect administration most commonly involved concurrent enteral nutrition and administration of other medications (70.6%), while 22.5% of doses were omitted entirely. Administration routes were nasogastric (54.9%), oral (16.1%) and percutaneous endoscopic gastrostomy (4.6%). Thyroid function tests were performed in 58.2%, with results within the reference range in 54.5% of those tested. In-hospital mortality was significant, at 87% during a period that included the COVID-19 pandemic, with a median length of ICU stay of 5 days (IQR 4). Major complications occurred in 27.2% of patients, including infections (15.8%), cardiovascular events (7.3%) and seizures (1.6%).
Conclusion
These findings highlight substantial variability in practice and identify a potentially modifiable aspect of endocrine care in critical illness. Pragmatic interventions, including coordinated feeding schedules, clear prescribing instructions, staff education and intravenous Levothyroxine, may improve treatment delivery.

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PS2-13-08

Chronic hashimotòs thyroiditis in pregnancy and postpartum period

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Introduction
Chronic thyroiditis can be present during pregnancy and the postpartum period in full spectrum of potential variations.The reason for this is the hormonal changes during pregnancy that affect thyroid function, as well as favorable influence on the autoimmune events that can significantly worsen and vary after childbirth.
Case Report
Prior the pregnancy at the age of 35, the patient was monitored for compensated chronic thyroiditis wich was diagnosed based on elevated A-TPO antibodies-736IU/ml, TSH until 2.5mIU/l and caharcteristic ultrasound finding of non-homogeneus, hypoehoechoic, small goitre. Following pregnancy confirmation, TSH level were 3.49 mIU, and thyroxine therapy (T4) 25 mg was initiated due to subclinical hypothyreoidism in pregnancy (TSH > 2.5 mIU/ml). During pregnancy, TSH levels remained was adequate. One mounth after a normal delivery, thyroxin (T4) therapy was discontinued, and TSH levels were approximately 1.8mIU/L. Three mounts postpartum TSH was 0.03 mIU/L with elevated FT4 levels in high (25pmol/l) and rise in A-TPO antibodies. Folloving the hypothiroide phase of postpartum tiroiditis hipothyreoidism developed over the next two months;however, TSH subsequently rose to 78mIU/ml, leading to the initiation of full substitution therapy with 100 mg T4. In the second pregnancy nine month later, there was no need to incrase the T4 dosage..Three months postpartum, a tendency for recurrence of PPT is observed, regardless of the pre-existing hypothyroidism. An increase in FT4 levels was recorded due the destruction of remaining thyroid tissue, necessitating a dose reduction to 25 mg. Two mounth later TSH increased to 12mIU/L followed by dosage adjustment back to the pre-pregnancy dose of 100 mg.
Conclusion
Chronic thyroiditis can present as subclinic hypothyroidism during pregnancy. As postpartum thyreoiditis PPT it can lead to persistent hypothyroidism in 30% of cases. Even in cases of hyperthyroidism, PPT can recur with lower extent of destruction, witch overall indicates the need for frequent monitoring of thyroid function over a longer follow-up period.

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PS2-13-09

Maternal graves' disease (GD) and effects on children's cognition, functioning, and well being: a systematic literature review

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Thyroid hormones play a critical role in fetal brain development, particularly during early gestation when the fetus relies largely on maternal thyroxine supply. Disturbances in maternal thyroid function during pregnancy have been associated with adverse neurodevelopmental outcomes in offspring. While maternal hypothyroidism has been extensively studied, considerably less attention has been given to maternal hyperthyroidis, particularly Graves' disease. Graves' disease is characterized by elevated thyroid hormone levels and circulating TSH receptor antibodies (TRAb) both of which can cross the placenta and influence fetal thyroid regulation. Existing studies suggest potential associations between maternal thyroid disorders and offspring cognitive outcomes as well as neurodevelopmental conditions such as ADHD and autism spectrum disorder. However, findings remain inconsistent and the underlying biological and psychosocial mechanisms are not well understood. The aim of this study is to systematically synthesize current evidence on the relationship between maternal Graves' disease or hyperthyroidism during pregnancy and offspring cognitive and neurodevelopmental outcomes. A systematic literature review is being conducted in accordance with PRISMA guidelines. Searches are performed in major biomedical databases in collaboration with a medical librarian. Eligible studies include registry-based studies, cohort studies, and clinical studies examining prenatal exposure to maternal Graves' disease or hyperthyroidism and subsequent child outcomes. Outcomes of interest include cognitive functioning (e.g., IQ), neurodevelopmental disorders such as ADHD and autism spectrum conditions, neurological outcomes including epilepsy, and broader indicators of child functioning and wellbeing. Data extraction includes study design, exposure operationalizations, timing of exposure during pregnancy, maternal thyroid hormone levels and autoantibodies (e.g., TRAb), pharmacological treatment during pregnancy, and psychosocial factors such as maternal mental health and stress. Where appropriate, quantitative synthesis and meta-analysis will be conducted. Preliminary screening suggests substantial heterogeneity in exposure definitions, timing of measurement, and outcome assessment across studies. The review will therefore not only summarize current evidence but also identify methodological limitations and potential mechanistic pathways linking maternal thyroid dysfunction and offspring neurodevelopment. Improved understanding of these associations may support earlier identification of children at increased developmental risk and contribute to more informed clinical monitoring during and after pregnancy.

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PS2-13-10

Thyroid dysfunction in one twin born to a mother with hyperthyroidism

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Maternal hyperthyroidism may influence fetal thyroid function via transplacental transfer of thyroid-stimulating antibodies (TRAb). Neonatal thyroid dysfunction is rare but clinically significant due to potential complications if unrecognized. In multiple pregnancies, variations in placental circulation may lead to unequal antibody exposure. We report a case of twin neonates born to a mother with hyperthyroidism in which only one twin developed neonatal hyperthyroidism.
Case Report
A woman with a history of hyperthyroidism was followed closely during pregnancy. She was treated with propylthiouracil, and thyroid function was monitored. In the third trimester, maternal TSH was **0.02 mIU/L**, FT4 **2.5 ng/dl**, and TRAb **5.8 IU/L**. Twin gestation progressed without other complications, and cesarean delivery occurred at **36 weeks**.Twin E S was delivered with Apgar scores of **8 and 9**. Vital signs were stable, and physical examination was unremarkable. Laboratory evaluation on day two showed **TSH 2.8 mIU/L** and **FT4 1.3 ng/dl**, within the normal neonatal range. The infant remained clinically stable with routine care.Twin A S initially appeared stable but developed irritability, tachycardia (**180 bpm**), and feeding difficulties within 24 hours. Laboratory evaluation revealed **TSH < 0.01 mIU/L** and **FT4 4.6 ng/dl**, consistent with neonatal hyperthyroidism. The infant was admitted for monitoring and treated with antithyroid therapy. Thyroid hormone levels gradually normalized, and clinical status improved with supportive care.
Conclusion
Discordant thyroid dysfunction may occur in twin pregnancies, underscoring the need for careful clinical and biochemical evaluation of all neonates exposed to maternal TRAb.

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Hypothyroidism 2

PS2-14-01

GLP-1 receptor agonists and thyroid function in euthyroid obese patients: a comparison between autoimmune and non-autoimmune thyroid disease

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Objectives
Obesity can influence thyroid function through adipokine-mediated cytokines, insulin resistance, and chronic inflammation affecting the hypothalamic–pituitary–thyroid axis. GLP-1 receptor agonists are effective anti-obesity therapies and may also exert direct effects on thyroid cells. However, evidence on whether their impact on thyroid function differs according to autoimmune status is limited. This study evaluated changes in TSH, free T4 (fT4), and free T3 (fT3) in euthyroid obese patients receiving GLP-1 receptor agonists and compared outcomes between autoimmune and non-autoimmune groups.

Methods
Patients who initiated GLP-1 receptor agonist therapy for obesity at the Endocrinology Clinic of Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between June and December 2025 were retrospectively reviewed. Patients using levothyroxine, thyroid-suppressive medications, insulin therapy, or with baseline TSH outside the reference range were excluded. A total of 73 euthyroid patients were included; 24 had autoimmune and 49 non-autoimmune thyroid disease. TSH, fT4, and fT3 were measured at baseline and three months, and insulin resistance was assessed using HOMA-IR. Statistical analyses were performed using the Wilcoxon signed-rank and Mann–Whitney U tests ($P < 0.05$).
Results
The mean age was 43.5 ± 11.0 years and baseline BMI was 36.8 ± 5.4 kg/m^2; 64.4% were female. After three months of GLP-1 receptor agonist therapy, TSH levels decreased significantly (1.929 ± 0.824 vs 1.770 ± 1.141 mIU/L; $P = 0.016$) and fT4 increased (1.328 ± 0.445 vs 1.382 ± 0.392 ng/dl; $P < 0.001$), while fT3 remained unchanged ($P = 0.602$). Metabolic parameters improved, with significant reductions in HOMA-IR, BMI, and fasting glucose (all $P < 0.001$). When analyzed by subgroup, TSH reduction was significant only in the non-autoimmune group ($P = 0.020$) but not in the autoimmune group ($P = 0.290$). The increase in fT4 was significant in the non-autoimmune group but not in the autoimmune group ($P = 0.627$), with borderline significance for between-group differences ($P = 0.064$). Changes in fT3 were not significant in either group. Improvements in metabolic parameters were comparable between groups. Correlation analysis showed no significant association between ΔTSH and BMI change, baseline HOMA-IR, or fasting glucose.
Conclusion
GLP-1 receptor agonist therapy was associated with a modest decrease in TSH and an increase in fT4 levels in euthyroid obese patients over three months, remaining within reference ranges. The lack of correlation between TSH change and metabolic improvement suggests a potential effect on the hypothalamic–pituitary–thyroid axis independent of weight loss. Thyroid responses were similar between autoimmune and non-autoimmune groups. Further prospective studies are needed to clarify the underlying mechanisms.
Keywords
Incretin-based therapy.
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PS2-14-02

Ultrasound-derived predictors of thyroid functional trajectory in hashimoto's thyroiditis

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Objectives
Hashimoto's thyroiditis (HT) is a progressive autoimmune disorder that may lead to thyroid functional decline over time. While biochemical assessment is essential, thyroid ultrasound (US) may identify early structural and hemodynamic changes preceding overt dysfunction. This study aimed to evaluate longitudinal changes in thyroid function and ultrasonographic characteristics in euthyroid patients with HT and to identify US-derived predictors of functional progression.
Methods
In this prospective study, 20 euthyroid patients with confirmed HT underwent two assessments 6–18 months apart. Each visit included thyroid function tests and comprehensive thyroid US evaluation, including gland volume, vascularity assessment using color Doppler, Doppler-derived flow indices, and strain elastography. The elastography ratio was calculated as the ratio of thyroid parenchymal strain to sternocleidomastoid muscle strain. Longitudinal changes were analyzed, and regression models were applied to identify predictors of thyroid volume progression and changes in thyroid-stimulating hormone (TSH).
Results
During follow-up, thyroid volume increased significantly (7.96 ± 2.32 vs. 9.09 ± 2.75 ml, $P = 0.007$), despite preserved euthyroidism. A trend toward increased TSH and anti-thyroglobulin antibody levels was observed but did not reach statistical significance. Thyroid vascularity patterns and elastographic parameters remained unchanged. Multivariable regression analysis demonstrated that changes in end-diastolic velocity (EDV) of thyroid arteries independently predicted thyroid volume progression ($r = 0.5$, $R^2 = 0.22$, $P = 0.03$). Additionally, the baseline elastography ratio was independently associated with the percentage increase in TSH over time ($r = 0.5$, $R^2 = 0.20$, $P = 0.03$).
Conclusions
In euthyroid patients with Hashimoto's thyroiditis, subtle but measurable longitudinal changes in thyroid structure and blood flow occur before overt functional deterioration. Doppler-derived EDV and strain elastography may serve as non-invasive imaging markers for early prediction of disease progression and functional decline.
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PS2-14-03

Levothyroxine therapy in autoimmune thyroiditis with subclinical hypothyroidism: impact on insulin sensitivity and cardiometabolic risk

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Objectives
Subclinical hypothyroidism (SCH) is associated with increased cardiovascular risk and insulin resistance. The impact of levothyroxine therapy on lipid profile and insulin sensitivity in patients with SCH due to autoimmune thyroiditis remains incompletely characterised.
Methods
We evaluated the effects of levothyroxine therapy in 120 patients (mean age 45.7 ± 12.2 years; 80 women) with SCH secondary to autoimmune thyroiditis, with no prior treatment for thyroid or cardiovascular disease. Levothyroxine was titrated to achieve TSH levels between 0.4 and 4.0 mIU/L. Laboratory assessments were performed before and at least 6 months after thyroid function normalisation, and included thyroid function tests, antithyroid antibodies, lipid profile (total cholesterol [TC], LDL, HDL, triglycerides [TG], Apo A1, Apo B, Lp(a)), C-reactive protein, homocysteine, fasting insulin, C-peptide and insulin resistance indices (HOMA-IR, HISI, IGI, WBISI). Statistical analysis used the Mann-Whitney test and Spearman's correlation coefficient.
Results
After levothyroxine treatment, TSH decreased significantly (6.43 ± 0.53 to 1.23 ± 0.42 mIU/L; $P = 0.03$), while fT4 and fT3 increased (0.74 ± 0.12 to 1.25 ± 0.14 ng/ml, $P < 0.05$; 1.75 ± 0.14 to 3.21 ± 0.54 pg/ml, $P < 0.05$). TC and LDL decreased significantly (199.3 ± 20.4 to 152.3 ± 19.1 mg/dl, $P < 0.01$; 116.1 ± 34.2 to 91.2 ± 16.3 mg/dl, $P < 0.01$). Apo B and Lp(a) also decreased (128.3 ± 97.8 to 44.1 ± 29.3 mg/dl, $P < 0.01$; 32.0 ± 19.1 to 21.4 ± 18.1 mg/dl, $P < 0.01$). HDL and Apo A1 improved significantly (45.2 ± 15.2 to 58.5 ± 18.1 mg/dl, $P < 0.01$; 124.5 ± 43.3 to 136.5 ± 56.4 mg/dl, $P < 0.01$). No significant changes were observed in CRP, homocysteine, folic acid, or vitamin B12. Treatment significantly reduced fasting insulin (67.6 ± 41.0 to 51.1 ± 24.0 mU/ml, $P = 0.01$), C-peptide (9.4 ± 3.1 to 8.2 ± 2.4 ng/ml, $P = 0.02$), HOMA-IR (0.24 ± 0.17 to 0.17 ± 0.10, $P = 0.03$) and increased HISI (334.9 ± 92.9 to 703.8 ± 97.1, $P = 0.02$). At baseline, TSH correlated positively with TC, LDL, TG, Apo B and IGI; fT3 correlated negatively with Apo B and Lp(a); CRP correlated positively with TG and homocysteine and negatively with HDL.
Conclusions
Treatment of SCH in patients with autoimmune thyroiditis significantly improves insulin resistance indices and cardiovascular risk profile, including reduction of atherogenic lipoproteins and improvement of insulin sensitivity markers.
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PS2-14-04

Impact of incretin-based therapy on levothyroxine dose requirements in euthyroid obese patients

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Objective
Levothyroxine (LT4) is primarily absorbed in the duodenum and proximal jejunum, and its bioavailability can be influenced by gastrointestinal motility. Incretin-based therapies, including GLP-1 receptor agonists such as semaglutide and dual GIP/GLP-1 receptor agonists such as tirzepatide, delay gastric emptying and may alter LT4 absorption. Additionally, weight loss associated with these therapies may modify LT4 requirements. This study aimed to evaluate changes in LT4 dose requirements and TSH levels during the first three months after initiation of incretin-based therapy in euthyroid obese patients receiving LT4 treatment.
Methods
This retrospective study included obese patients who initiated incretin-based therapy at the Endocrinology Clinic of Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between June and December 2025. Patients receiving levothyroxine with baseline TSH within the reference range (0.35–4.50 mIU/L) were included if euthyroid at treatment initiation, while those receiving TSH-suppressive therapy were excluded. Baseline and three-month data included weekly LT4 dose, TSH, fT4, fT3, BMI, waist circumference, fasting glucose, and insulin. Weight-adjusted LT4 requirement was calculated. Comparisons were performed using the Wilcoxon signed-rank test and correlations with Spearman analysis.
Results
A total of 26 patients were included (mean age 45.7 ± 11.5 years; 84.6% female). Most patients received semaglutide (92.3%), while 7.7% received tirzepatide. The etiology of thyroid disease was predominantly autoimmune thyroid disease (84.6%). The mean weekly LT4 dose decreased significantly from 892.3 ± 260.5 µg/week to 819.2 ± 229.2 µg/week at three months (−8.2%; $P < 0.001$). Dose reduction occurred in 61.5% of patients, while no patient required dose escalation. TSH levels did not change significantly (2.224 ± 1.646 → 1.727 ± 2.197 mIU/L; $P = 0.096$), and free T4 ($P = 0.567$) and free T3 ($P = 0.269$) remained stable. Waist circumference, fasting glucose, and insulin levels decreased significantly, whereas the reduction in BMI was not statistically significant ($P = 0.101$). Weight-adjusted LT4 requirement remained unchanged (13.8 ± 4.4 vs 13.6 ± 3.2 µg/kg/week; $P = 0.889$), and no correlation was observed between ΔTSH and ΔBMI ($P = 0.583$).
Conclusion
In obese patients with hypothyroidism receiving levothyroxine therapy, initiation of incretin-based treatment was associated with a reduction in total LT4 dose while TSH levels remained stable. The lack of change in weight-adjusted LT4 requirement suggests that this effect may not be explained solely by weight loss. These findings raise the possibility that incretin-based therapies may influence levothyroxine pharmacokinetics through delayed gastric emptying and prolonged intestinal exposure, potentially enhancing LT4 bioavailability. Our results highlight the need for closer monitoring of thyroid function after initiation of incretin-based therapy.
Keywords
Levothyroxine; Incretin-based therapy; Hypothyroidism.
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PS2-14-05

GUT microbiota alterations in patients with autoimmune thyroid diseases

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Objectives
The study of the gut microbiota is one of the key areas of medical research. Currently, there is limited data on changes in gut microbiota composition in patients with autoimmune thyroid diseases (AITD) — autoimmune thyroiditis (AIT) and Graves' disease (GD).
Methods
72 patients aged 18 to 65 years were enrolled: 21 patients with AIT, 21 patients with GD, 30 healthy volunteers. The criteria for exclusion were previous hospitalizations or surgical interventions for any reason during the last 6 months, usage of antibiotics, prebiotics, probiotics or synbiotics within the last month, diabetes mellitus, history of thyroidectomy or radioiodine therapy, severe concomitant diseases. Thyroid status was assessed, stool samples were collected, and the gut microbiota composition was analyzed by 16S rRNA sequencing. Statistical analyses were performed using the IBM SPSS Statistics 27.
Results
Patients with AITD were predominantly euthyroid (81% in the AIT group and 57% in the GD group). Changes in the gut microbiota composition were observed at different taxonomic levels. Thus, at the phylum level, patients with GD have a reduced the relative abundance of Firmicutes compared with the control ($P = 0.007$) and with AIT patients ($P = 0.038$), but an increased relative abundance of Bacteroidota compared with the control ($P = 0.006$) and with AIT group ($P = 0.036$). At the family level, a Prevotellaceae relative abundance was increased in patients with GD ($P < 0.001$), and Eubacterium coprostanoligenes group was decreased ($P < 0.001$). In AIT patients, the families Erysipelatoclostridiaceae ($P = 0.007$) and Butyricicoccaceae ($P = 0.007$) were decreased compared with healthy volunteers. At the species level, patients with AITD have reduced relative abundance of Blautia and Dorea compared to the control group ($P < 0.05$). The Anaerostipes and Sutterella relative abundances in GD patients are higher than in the controls ($P = 0.013$ and $P = 0.002$, respectively).
Conclusions
For the first time, changes in gut microbiota composition in patients with autoimmune thyroid diseases have been demonstrated in the Eastern European population. These data indicate a potential role for gut microbiota in the pathogenesis of autoimmune thyroid diseases.
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PS2-14-06

Expanding the phenotype of SLC26A7-related thyroid disease: a family with late-onset hypothyroidism and goitre

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Introduction
SLC26A7 is an anion transporter belonging to the SLC26 family, initially described in the kidney and later identified in thyroid follicular cells, where it contributes to iodide transport involved in thyroid hormone synthesis. Pathogenic variants in *SLC26A7* have recently been recognized as a rare cause of congenital hypothyroidism. In 2022, we reported a novel homozygous frameshift variant of the *SLC26A7* gene (p.Pro628Glnfs*11), identified by next-generation sequencing and confirmed by Sanger sequencing, in a patient presenting with late-onset hypothyroidism associated with dyshormonogenic goitre. This variant results in a frameshift leading to premature truncation of the encoded protein. Here, we describe additional members of the proband's family who developed a similar clinical phenotype characterized by goitre and hypothyroidism with onset during late adolescence, in whom the same *SLC26A7* variant was subsequently identified.
Case Report
The proband, an 18-year-old Tunisian male, was referred to our centre in 2021 because of the recent appearance of a rapidly enlarging goitre associated with myxoedema. Thyroid function tests revealed marked hypothyroidism. Genetic analysis subsequently identified the homozygous frameshift variant in the *SLC26A7* gene. At that time, no similar abnormalities had been reported among first-degree relatives. In 2023, his younger brother (17 years old) presented with rapidly developing cervical swelling. Thyroid ultrasound revealed a large goitre, and laboratory evaluation documented overt hypothyroidism. In 2024, a third brother presented with a similar clinical picture, also at the age of 17, characterized by goitre and thyroid function abnormalities consistent with hypothyroidism. None of the affected individuals had a history of growth retardation, neurodevelopmental delay, or other clinical manifestations suggestive of untreated congenital hypothyroidism. Genetic testing confirmed the presence of the same homozygous *SLC26A7* variant in both affected brothers. In both patients, levothyroxine replacement therapy was initiated, leading to normalization of thyroid function tests and progressive reduction in goitre volume. A fourth brother was found to be heterozygous for the variant and currently shows normal thyroid morphology and preserved thyroid function. The parents and another sister could not be evaluated as they currently reside abroad.
Conclusions
This familial observation supports the hypothesis that the *SLC26A7* pathogenic variant identified in this family may be associated with a late clinical presentation. These findings expand the phenotypic spectrum of *SLC26A7*-related thyroid disorders and highlight the importance of considering genetic causes of goitre and hypothyroidism even in adolescents or young adults without a history suggestive of congenital hypothyroidism.
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PS2-14-07

Identification of a novel truncating variant P.GLN896TER in IGSF1 gene in two cousins with central hypothyroidism

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Introduction
Central hypothyroidism (CeH) is a rare disorder characterized by insufficient thyroid hormone production due to impaired thyroid gland stimulation by thyroid-stimulating hormone (TSH). Unlike primary hypothyroidism, serum TSH levels are low or normal despite low circulating free thyroxine (fT4). The estimated prevalence of CeH is 1 in 80,000 to 120,000 individuals. Diagnosis is often challenging because symptoms may be mild, nonspecific, or absent in early life. Genetic causes account for a substantial proportion of isolated CeH cases, with pathogenic variants in genes like *TSHB, IGSF1*, and *IRS4*. Variants in IGSF1 gene are associated with X-linked disorder primarily characterized by CeH and macroorchidism.
Case Report
A 3.7-year-old boy (1A) of Finnish origin presented with severe constipation and abnormal thyroid function tests showing borderline low fT4 with normal TSH (fT4 8.6pmol/l, ref: 11-21; TSH 1.2mU/L, ref: 0.5-4.2). Birth history was uneventful, and early growth and development was normal. Endocrine evaluation including pituitary stimulation test, demonstrated adequate growth hormone and cortisol responses with low prolactin level (64mU/L, ref: 86-324). TSH response to thyrotropin-releasing hormone was modest, suggesting impaired TSH secretion due to pituitary gland defect. Pituitary magnetic resonance imaging (MRI) was normal. CeH was diagnosed and levothyroxine therapy was initiated. During adolescence, he exhibited delayed pubertal progression and a bone age 3 years behind chronological age. The second patient, a 19-year-old boy (1B), a maternal cousin of 1A, presented with fatigue, impaired concentration, decreased motivation and constipation. Laboratory evaluation revealed low fT4 with normal TSH levels (fT4 9.1pmol/l, ref: 11-21; TSH 1.5mU/L, ref: 0.5-4.2). Endocrine evaluation for pituitary hormones were normal except prolactin (<21 mU/L, ref: 86-324). Delayed pubertal development was reported (age 15 years) with normal testicular measurement. Pituitary MRI showed a small non-enhancing cystic lesion in pars intermedia region, suggestive of a Rathke's cleft cyst without adenoma. CeH was diagnosed and levothyroxine therapy was initiated resulting in biochemical improvement and resolution of symptoms. Whole exome-sequencing revealed a novel hemizygous *IGSF1* variant p.Gln896Ter in both the patients. This variant has not been reported in literature and is not present in population databases. It is a nonsense variant causing premature termination of the protein and is classified as pathogenic.
Conclusion
This is a first report from the Finnish population, describing two related CeH patients with a previously unreported pathogenic *IGSF1* gene variant. Identification of novel variants and the associated phenotypes contribute to improved understanding of disease mechanisms, facilitating diagnosis and disease management.

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PS2-14-08

Autoimmune gastritis as an overlooked cause of persistent hypothyroidism

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Introduction
Hypothyroidism is a very common pathological condition that is caused by a deficiency of the thyroxine hormone. In the thyroid gland, thyroxin is transformed into an active form of triiodothyronine through the enzyme deiodinase. Deiodinases are selenium-containing enzymes. Their activity may be influenced by the following factors: inflammatory processes, long-term diet and starvation, selenium deficiency, insulin resistance;.
Clinical case
A 64-year-old male patient visited us (06.01.2025) with the following complaints: general weakness, tendency to sleepiness, swelling of the eyelids (periorbital), dizziness and nausea.
Anamnesis
Autoimmune thyroiditis with ongoing severe auto-aggression and severe hypothyroidism, Stomach ulcer, Anemia, also, according to the medical history, the patient has a cardiac pacemaker. The patient is under the supervision of a cardiologist and periodically takes a proton pump inhibitor. The laboratory test results revealed –TSH >100 mIU/L (0.34-3.5 mIU/L); FT4 - 0.0388 ng/dl (0.8-2.0 ng/dl); FT3-0.391 pg/ml (2.15-6.45 pg/ml), Anti-TPO ->600 IU/ml (<40 IU/ml), Anti-TG- 1295 IU/ml (<115 IU/ml) Iron-4.32 mkrmol/l (5.83-34.5 mkrmol/l), Ferritin -24.3 ng/ml (30-400 ng/ml), Vitamin B12-175 pkg/ml (197-771 pkg/ml); HGB-8.2 g/dl (13.5-17.5 g/dl) HCT-27.0% (39-53%), RBC-2.91 g/dl (4.6-5.9 g/dl);.
Diagnosis
Autoimmune thyroiditis with ongoing severe auto-aggression and severe hypothyroidism. The patient was being treated with levothyroxine 200 mg for 5 years without any results, (Decompensated hypothyroidism was permanently noted); Suspicion was Autoimmune Gastritis; patient was referred to a gastroenterologist; autoimmune gastritis was confirmed, Histopathology report: Chronic atrophic gastritis, compatible with autoimmune gastritis, serology revealed anti-parietal cell antibodies and anti-intrinsic antibodies, appropriate treatment was initiated. The proton pump inhibitor was rescheduled to be taken in the evening before bedtime. Also added to the current treatment: levothyroxine (T4) 25 mg (225 mg), also added Lyothyronine (T3) 12.5 mg twice a week. Monitoring the levels of FT4 and FT3 after 2 weeks. After two week, laboratory findings were as follows: FT4-1.13 ng/dl, FT3-1.88 pg/ml (2.15-6.45 pg/ml) Iron-8.32 mkrmol/l (5.83-34.5 mkrmol/l), Ferritin 50.3 ng/ml (30-400 ng/ml), B12 319 pkg/ml (197-771 pkg/ml); After one month laboratory findings were as follows: FT4-1.24 ng/dl, FT3-2.88 pg/ml. After three month, laboratory findings were as follows: TSH-10.28 mIU/L, FT4-1.34 ng/dl, FT3-3.4 pg/ml; According to the laboratory test results in dynamics complete laboratory and clinical euthyroidism was achieved.
Conclusion
In patients with chronic autoimmune thyroiditis and persistent or decompensated hypothyroidism despite adequate levothyroxine therapy, clinicians should consider the presence of other autoimmune disorders, particularly autoimmune gastritis, which may impair hormone absorption and contribute to treatment resistance.

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PS2-14-09

Prevalence of subclinical hypothyroidism in patients with kidney disease: a 10-year retrospective cross-sectional study

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Background
Subclinical hypothyroidism (SCH) is a biochemical diagnosis with uncertain clinical consequences. Growing evidence suggests that SCH may represent a risk factor for the development of chronic kidney disease (CKD), though data regarding the prevalence of SCH in patients with CKD remain scarce.
Aim
To investigate the prevalence of SCH in patients with kidney disease.
Materials and Methods
A retrospective cross-sectional study of thyroid function tests was conducted at the University Hospital of Patras, Greece (2014-2024). Measurements were retrieved from our laboratory analyzer database. Data included nephrology inpatients (KG) and outpatients attending the phlebotomy unit for routine testing, served as controls (CG). The KG shared three main diagnoses: chronic renal failure (50%), acute renal failure (20%), and kidney transplant complications (30%). Thyroid testing (TSH and FT4 measurements, with or without T3 or thyroid peroxidase antibodies (TPOAb)) was routinely performed within the first day of admission, regardless of prior thyroid disease. SCH was defined as TSH >4.2 mIU/L with normal FT4 and positive anti-TPO as >34 IU/ml.
Results
The KG included 6,271 individuals (median age 60.3 years; 56.5% male) and the CG 7,072 individuals (median age 46.9 years; 28.2% male). Median TSH levels

were higher in the KG compared with the CG [1.77 mIU/L (IQR 1.11–2.81) vs 1.69 mIU/L (IQR 1.04–2.57), $P < 0.001$], whereas median FT4 levels were lower in the KG [1.23 ng/dl (IQR 1.08–1.41) vs 1.25 ng/dl (IQR 1.12–1.40), $P < 0.01$]. The prevalence of SCH was higher in the KG than in the CG (9.7% vs 7.0%, $P < 0.001$). The prevalence of positive anti-TPO antibodies was similar between the two groups (KG 16.1% vs CG 17%). Binary multivariable logistic regression analysis showed that KG patients had 1.46-fold higher odds of being diagnosed with SCH compared with controls (95% CI: 1.274–1.672). Age had a statistically significant effect (OR = 1.005, 95% CI: 1.002–1.009). Additionally, women were 30.7% more prone (95% CI: 14.5–49.2) to develop SCH.
Conclusions
Our findings indicated higher TSH levels in patients with kidney disease, linked to a greater prevalence of SCH. It remains unclear whether SCH contributes to kidney disease or is an adaptive response to renal dysfunction, suggesting a bidirectional relationship between thyroid function and kidney health.

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PS2-14-10

Multicenter rct of LT4/LT3 combination therapy in autoimmune hypothyroid patients

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Rationale
Hypothyroidism affects ~5% of the general population. Levothyroxine (LT4) monotherapy is standard treatment, yet ~15% of biochemically euthyroid patients report persistent complaints, particularly tiredness. This may be due to the inability of LT4 monotherapy to restore physiological T4/T3 ratios, as T3 in healthy individuals is also directly secreted by the thyroid. Previous trials on LT4/LT3 combination therapy have shown conflicting results. Genetic variation in DIO2 (rs225014) and MCT10 (rs17606253) may influence treatment response.
Objective
To evaluate whether LT4/LT3 combination therapy reduces tiredness in patients with autoimmune hypothyroidism who remain symptomatic despite LT4 monotherapy and biochemical euthyroidism.
Study design
This is a national, randomized, placebo-controlled, double-blind, multicentre trial.
Study population
600 adults ($\geq$ 18 years) with autoimmune hypothyroidism and persistent tiredness despite biochemical euthyroidism on LT4, negatively impacting daily life.
Intervention
Participants are switched to a generic LT4 preparation to eliminate pharmacokinetic variability. The intervention group receives once-daily LT4 and twice-daily LT3 tablets (LT4:LT3 ratio 16:1), while the control group receives once-daily LT4 and twice-daily placebo tablets. Treatment duration is 52 weeks.
Primary outcome
The primary endpoint is the change in tiredness scores on the ThyPRO tiredness subscale at 52 weeks. The study also aims to assess whether treatment effects are modified by genetic variation in DIO2 and MCT10, controlling the study-wise type I error (5%, two-sided) across these three primary hypotheses.
Secondary outcomes
Effects of LT4/LT3 combination therapy compared to LT4 therapy on non-tiredness ThyPRO subscales, composite quality of life scores, bone mineral density (measured using DEXA scans), objective neurocognitive performance, and a cost-effectiveness analysis of LT4/LT3 combination therapy vs LT4 monotherapy.
Current status
As of now, 498 patients have been included, with inclusion expected to finish by the end of 2026. Participants who complete the 52-week follow-up are given access to the study medication as part of an open-label study.

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Surgery

PS2-15-01

Evaluation of surgical outcomes andpostoperative complications followingthyroidectomy: a retrospective study

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Background
Thyroidectomy is a widely performed surgical intervention for benign and malignant thyroid disorders. Despite its routine nature, it carries the risk of postoperative complications that may impact patient recovery and long-term outcomes.
Methods
This was a retrospective descriptive study conducted at JPMC, karachi, Pakistan from May 2022 to May 2025. A total of 215 patients who underwent thyroidectomy were included in the study. Data were extracted retrospectively from hospital records, operative notes, and discharge summaries.
Results
Out of the 215 patients included, 176 (81.9%) were female and 39 (18.1%) were male, with a mean age of 42.8 $\pm$ 11.3 years. Total thyroidectomy was performed in 129 (60.0%) patients, hemithyroidectomy in 54 (25.1%), and subtotal thyroidectomy in 32 (14.9%). Histopathology revealed benign lesions in 135 (62.8%) and malignant in 80 (37.2%) cases. Postoperative complications were observed in 59 (27.4%) patients. The most frequent complication was transient hypocalcemia (18.1%), followed by recurrent laryngeal nerve injury (6.5%) and wound-related issues. Complication rates were significantly higher in patients undergoing total thyroidectomy ($P < 0.05$) and those with malignant pathology ($P = 0.031$). The mean hospital stay was 3.1 $\pm$ 1.4 days, with longer stays noted in patients experiencing complications ($P < 0.001$).
Conclusion
Thyroidectomy remains a safe procedure with acceptable complication rates when performed with appropriate surgical expertise. However, patients undergoing total thyroidectomy and those with thyroid malignancies are at greater risk of postoperative complications.

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PS2-15-02

Thyroid surgery in an island population: a five-year experience from the autonomous region of madeira

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Background
Thyroid surgery outcomes vary depending on healthcare resources, population characteristics, and geographic constraints. Evidence from island regions remains limited. This study aims to describe our department's experience with thyroid

surgery in the Autonomous Region of Madeira, Portugal, and analyze surgical outcomes over a five-year period.
Methods
A retrospective observational study was conducted including all patients undergoing thyroid surgery at Hospital Dr. Nélio Mendonça (Madeira, Portugal) between January 2020 and December 2025. Patients with incomplete clinical data, under 16 years of age, procedures limited to biopsy, or reoperations related to complications of surgeries performed outside the study period were not included. Demographic, surgical, histopathological, and postoperative outcomes were analyzed. Postoperative complications were classified according to the Modified Clavien–Dindo system. Minor complications were defined as grade $\leq$IIIa and major complications as $\geq$IIIb.
Results
A total of 461 patients were included in the study. Mean age was 53.8 years (range 16–86), with a female predominance (82.7%; F:M ratio 4.78:1). Most procedures were elective (99.8%). The common procedure was total thyroidectomy (73.8%), followed by hemithyroidectomy (19.1%). Histopathologically, benign diseases accounted for the majority of cases, with colloid goiter (23.8%) and nodular hyperplasia (20.4%) being the most frequent diagnoses. Among malignant tumors, papillary thyroid carcinoma was the most common (29.5%). Overall, 55.1% of patients had no postoperative complications. According to the Clavien–Dindo classification, complications were grade I in 3.5%, grade II in 31.5%, grade IIIa in 1.1%, grade IIIb in 1.5%, grade IVa in 0.4%, and grade V in 0.2% of cases. Minor complications accounted for 91.1% of all events, whereas major complications occurred in 8.9%. The most frequent complications were asymptomatic hypocalcemia (18.2%), symptomatic hypocalcemia (8.9%), and transient dysphonia (7.6%). Cervical hematoma occurred in 2.8% of patients, with 1.1% of cases requiring surgical drainage.
Conclusion
These results suggest that thyroid surgery performed in a geographically isolated island population can achieve outcomes comparable to those reported in larger mainland centers with low postoperative morbidity and few major complications. These findings highlight the feasibility and safety of specialized endocrine surgery in regional island hospitals and contribute valuable data on thyroid surgery outcomes in underrepresented populations.

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PS2-15-03

Risk factors for permanent post-surgical hypoparathyroidism among a large cohort of thyroidectomized patients

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Objective
Permanent postsurgical hypoparathyroidism (POSH) is a major complication of bilateral thyroidectomy, with a reported prevalence of around 2-10% of cases. Chronic Autoimmune Thyroiditis (CAT) has been reported as a risk factor for post-surgery hypoparathyroidism, although most reports refer only to transient hypoparathyroidism and definition of CAT varies across studies. The aim of the present study was to assess whether CAT was a risk factor for POSH in a large series of patients undergoing total thyroidectomy for both benign and malignant conditions.
Methods
Patients who underwent a total thyroidectomy for both benign and malignant conditions from 2018 to 2024 were enrolled. Data regarding gender, age, BMI, positivity for anti-thyroglobulin and anti-thyroperoxidase antibias, thyroiditis at ultrasound and presence of an immune cell infiltrate at histology were collected.
Results
the study group included a total of 554 patients who underwent thyroidectomy (277 for a benign and 277 for malignant thyroid conditions). Sixteen patients (2.9%) developed POSH, with only 4 having a complete loss of PTH secretion. No differences in terms of age, gender was observed between patients with and without POSH. A higher rate of patients with a BMI$\geq$35 kg/m2 was observed among patients with POSH (25% vs 5%, $P = 0.006$). Patients with POSH had a significantly higher rate of AbTg/AbTPO positivity (5.4% vs 1.4%, $P = 0.006$) and of Thyroiditis at ultrasound (6.9% vs 1.2%, $P < 0.001$), while the rates of immune infiltrate at ultrasound were similar between the two groups. In a logistic regression model, presence of TgAb/TPOAb positivity (O.R: 9.376, C.I:1.914-45.920, $P = 0.006$) AND A BMI$\geq$35 kg/m2 significantly increased the risk of POSH, independently form the presence of malignancy at histology, age and gender.
Conclusions
The presence of CAT and obesity constituted significant risk factors in a large group of thyroidectomized patients. These risk factors should be taken into account for a personalized approach to thyroid surgery.

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PS2-15-04

Delayed hypoparathyroidism presenting nine years after subtotal thyroidectomy- case report

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Introduction
Post-surgical hypoparathyroidism is a known complication of total thyroidectomy. In most of the cases it's a transient finding but in approximately 1.5% of the patients resulted in permanent hypoparathyroidism. The following case is that of a 64-years old patient presenting in the emergency department with symptoms of hypocalcemia.
Case presentation
A 64-year old male patient presented in the emergency department with hand contractures, muscle cramps in lower limbs, paraesthesia and dizziness. These symptoms started in the early hours of the morning and worsened. His medical history included chronic anemia due to hematochezia, for which, a colonoscopy was planned to determine the cause. Nine years ago, he underwent subtotal thyroidectomy for multinodular goiter and took no hormonal replacement therapy. On physical examination, Chvostek sign was positive and his vitals were stable. Electrocardiography showed normal sinus rhythm with elongated QT interval. Laboratory investigation revealed low total calcium 3.5 mg/dl (8.4-10.2), low ionized calcium 0.61 mmol/l (1.1-1.3), normal magnesium 1.69 mg/dl (1.6-2.6) and high phosphorus 5.3 mg/dl. Vitamin D was below the normal range 10 ng/ml ($<$ 12), with a PTH in the low-normal range 12.7 pg/ml (9.2-44). TSH was high 13.415 mUI/l (0.35-4.94), with normal ft3 1.85 pg/ml (1.58-3.91) and low ft4 0.66 ng/dl (0.7-1.48). The patient was started on intravenous calcium gluconate, oral calcitriol 0.75 mg/day and oral calcium carbonate 1500 mg. His symptoms improved and the dosage of calcium carbonate was gradually tapered. Patient was released on 1500 mg calcium carbonate, calcitriol 0.5 mg/day, vitamin D 2000 UI/day and Levothyroxine 50 mg/day.
Conclusion
Delayed hypoparathyroidism is a rare postsurgical complication, possibly caused by scar tissue formation and progressive ischemia of parathyroid glands. Due to non-specific symptoms, this diagnosis is often overlooked. It's important to take this diagnosis into consideration in every patient with symptoms of hypocalcemia, even years after thyroid surgery. A careful long-term follow-up is recommended in high-risk population.

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PS2-15-05

Safety of hemithyroidectomy in day care surgery – a delphi study

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Background
Hemithyroidectomy is an important diagnostic procedure for thyroid tumours or a therapeutic intervention for symptomatic thyroid nodules. Hemithyroidectomy is associated with low complication rates and is suitable for treatment in day care. Although studies have shown promising results for outpatient hemithyroidectomy, no national guidelines in the Netherlands have been established for performing hemithyroidectomy in day care setting. The aim of this study is to acquire national consensus regarding selection criteria for hemithyroidectomy in day care and identify patient-related risk factors and potential concerns regarding patient safety.
Materials and methods
This study is a modified Delhi-process among registered thyroid surgeons in the Netherlands. Consecutive questionnaires were distributed among registered

participants. Consensus was reached when ≥ 75% of participants have a corresponding opinion, in which they either agree, do not agree or give neutral replies to certain statements.
Results
A total of 112 thyroid surgeons participated in the first Delphi round, representing 36/54 Dutch hospitals. At the time of the survey, 27% of respondents reported performing hemithyroidectomy as a day care procedure. Consensus was reached on the routine use of intraoperative nerve monitoring during identification of the recurrent laryngeal nerve and on omitting the use of surgical drains. Reported postoperative observation times following day care surgery varied widely, ranging from two to twelve hours. Opinions regarding the need for a national guideline for day care thyroid surgery were evenly divided among participants.
Conclusions
Hemithyroidectomy is considered a safe procedure to perform in day care setting. Routine early discharge does not lead to increased complication rates or readmissions. This study aims to acquire consensus on patient selection criteria in order to establish a national guideline for hemithyroidectomy in day care. We look forward to presenting final results including round 2 at the ETA 2026.

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PS2-15-06

Role of intraoperative nerve monitoring (IONM) in identifying unrecognized recurrent laryngeal nerve dysfunction during thyroid surgery: a prospective study

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Objectives
Recurrent laryngeal nerve (RLN) palsy is one of the most common complications following thyroidectomy and may occur even without gross nerve injury. This injury can lead to voice change, aspiration, and dysphagia, significantly affecting patients' quality of life. Intraoperative nerve monitoring (IONM) provides real-time functional assessment of the RLN and may facilitate early detection of nerve dysfunction during surgery. This study aimed to evaluate the incidence and clinical course of unrecognized RLN dysfunction during thyroidectomy using IONM.
Methods
This study included patients undergoing thyroidectomy at Samsung Medical Center (Seoul, Korea). Intraoperative nerve monitoring was used to identify the RLN and assess nerve function during surgery. Signal loss events were recorded intraoperatively, and postoperative vocal cord function was evaluated by laryngoscopy.
Results
A total of 191 patients were included in the study. Intraoperative signal loss (LOS) occurred in 30 cases (15.7%). Postoperative transient vocal cord palsy developed in 7 patients; all recovered within 6 months. Among patients who underwent central neck dissection (CND), signal loss occurred in 2 cases, but no transient or permanent vocal cord palsy was observed. In patients with thyroiditis, LOS occurred in 8 cases and transient vocal cord palsy developed in 3 patients; however, all patients recovered without permanent dysfunction.
Conclusions
Unrecognized RLN dysfunction may occur during thyroidectomy even without apparent nerve injury. Intraoperative nerve monitoring may facilitate early detection of nerve dysfunction and contribute to safer thyroid surgery. Early identification of RLN dysfunction using IONM may also allow surgeons to modify surgical strategies and reduce the risk of bilateral nerve injury.

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PS2-15-07

A comparative analysis of quality of life by period of patients undergoing between robotic and open MRND

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Objectives
Advances in surgical techniques have increased attention not only to operative safety but also to cosmetic outcomes and postoperative quality of life. In thyroid cancer, which generally shows excellent long-term survival after surgery, postoperative quality of life has become an important concern for patients. Persistent impairment may lead to long-term emotional and psychological stress. Therefore, evaluating patient-reported outcomes according to surgical approach is clinically meaningful. This study aimed to compare postoperative quality of life and cosmetic satisfaction between different surgical techniques and to observe the recovery trajectory experienced by patients during the postoperative period.
Methods
A retrospective analysis was conducted on 40 patients who underwent thyroid cancer surgery at S Medical Center between January 2021 and March 2026. Twenty patients underwent da Vinci robotic surgery, while twenty patients underwent open surgery. Postoperative outcomes including pain, sensory changes, cosmetic satisfaction, voice changes, swallowing function, and neck mobility were assessed. Data were collected at postoperative day 1, day 3, day 5, 2 weeks, 3 months, and 6 months using a 5-point Likert scale. Statistical analyses were performed using SPSS version 26. Baseline characteristics and post-operative quality-of-life parameters according to surgical method and follow-up period were analyzed using cross-tabulation and chi-square tests. Mean scores for pain, sensory change, cosmetic satisfaction, voice change, swallowing function, and mobility were calculated at each time point and compared between the two surgical groups. Additional binary logistic regression analysis was performed within the robotic surgery group.
Results
Among the study population, most patients were female, and the largest age group was in their twenties. The most prominent postoperative symptom observed in both surgical groups was voice change on postoperative day 3. Logistic regression analysis showed a statistically significant association between robotic surgery and postoperative outcomes.
Conclusions
Compared with conventional cervical incision surgery, robotic thyroidectomy using the BABA approach demonstrated potential benefits in long-term postoperative quality of life in addition to its established cosmetic advantages. Robotic surgery may therefore represent a favorable option, particularly for patients who prioritize cosmetic outcomes or require complex surgical procedures. However, overall differences in postoperative pain and quality of life between the two approaches were not substantial. Further studies including patients who have experienced both surgical methods may provide additional insight through comparative patient-reported evaluations.

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PS2-15-08

What makes thyroidectomy difficult? the role of sex and thyroid volume in predicting surgical complexity

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Background
Identifying factors that predict a Difficult Thyroidectomy (DT) is crucial for optimizing surgical planning, reducing operative time, and minimizing complication risk. This study aimed to identify independent preoperative predictors of DT using operative time as a surrogate marker.
Methods
A retrospective analysis was conducted on 251 patients who underwent total cervicotomic thyroidectomy between January 2021 and June 2023. DT was defined as an operative time above the 75th percentile of the cohort. Univariate analyses were performed using appropriate statistical tests ($\chi 2$, Mann-Whitney U, Student's T). Variables with $P < 0.10$ or high clinical relevance were then included in a multivariate logistic regression model to estimate independent predictors (Odds Ratio, OR) and assess model discrimination (Area Under the Curve, AUC).
Results
The median operative time for DT patients ($n = 58$) was 118.50 minutes, significantly longer than the 87 minutes observed in Non-Difficult Thyroidectomy (NDT) patients ($n = 193$) ($P < 0.001$). Univariate analysis showed a significant association between DT and male sex, BMI, cervico-mediastinal goiter, tracheal stenosis, thyroid mass, and thyroid volume ($P < 0.05$). The multivariate logistic regression model (AUC 0.766) identified only two independent predictors: Male Sex (OR 2.96, 95% CI 1.51–5.81, $P = 0.002$) and Thyroid Volume (OR 1.013 per mL, 95% CI 1.006–1.020, $P < 0.001$). DT was associated with significantly higher rates of transient hypoparathyroidism (15.5% vs 6.2%; $P = 0.031$) and total complications (24% vs 9.8%; $P = 0.005$).

Conclusion
In our cohort male sex and thyroid volume are the most significant independent preoperative factors predicting difficult thyroidectomy, which in turn is associated with increased postoperative morbidity, specifically transient hypoparathyroidism. Preoperative assessment of these variables is vital for risk stratification and surgical resource planning.

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PS2-15-09

10 Cases of failure to respond to laser thermal ablation from a series of 284 patients: histological outcomes after surgery and related evaluations

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Thermal ablation techniques have been developed as an alternative to surgery for the treatment of symptomatic benign nodules, with the inherent advantage of being minimally invasive, repeatable, with a low complication rate, and allowing to avoid perioperative risks and acquired hypothyroidism. On the other hand, thyroid surgery represents the radical therapeutic solution in the case of sometimes unrecognized neoplasms. A series of patients who underwent laser thermal ablation by the same team of endocrinologists from 05/2016 to 02/2026 is presented. The indication for the procedure was given for compressive symptoms caused by a thyroid nodule classified as TIR2 or TIR3, (repeated twice) with refusal of the option surgical treatment by the patients themselves. Cases that subsequently required surgical intervention due to persistent compressive symptoms or due to lack of reduction or further increase in the volume of the treated nodular lesion were analyzed.319 thermoablative procedures were performed in 284 patients. For 35 patients (12%), a single ablative session was not resolutive, and therefore there was an indication to repeat the thermoablation or to perform surgical intervention. Among patients unresponsive to the first treatment:nodules withTIR3A cytology was significantly higher (21.4% vs 7.0%).The volume reduction already at 6 months after the procedure was 5.7% vs 50%. 10 of 35 patients who did not respond to two thermoablation sessions (4%) were underwent surgical intervention, and the histological outcome showed a malignant neoplasm in 50% of the cases; in particular, one case of carcinoma was observed anaplastic, with an unfavorable outcome, and a poorly differentiated carcinoma.Analysis of this case series highlights the importance of achieving accurate selection of those patients who would not benefit from ablative procedures and should therefore be directed straight to surgical intervention.These data emphasize the importance of a timely reassessment with referral to surgical treatment for patients who, six months after thermoablation, show a volume reduction of less than 20%, in order to ensure effective treatment of overlooked malignant neoplasms, especially those with aggressive behavior.

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PS2-15-10

Comprehensive evaluation of medtronic's butterfly platform, a new audiovisual information material for patient education and shared decision-making in surgical thyroid disease

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Background
To support shared decision-making around surgical thyroid disease, patients increasingly use online health information, but the quality of thyroid-related resources varies. This study evaluated a new audiovisual information material co-created by Medtronic with physician-experts and patient representatives.
Methods
Patients were assessed at baseline (t1), after accessing the French Butterfly platform but before surgery (t2), and 3 weeks post-surgery (t3). They rated usefulness (USE), impact (eHIQ) and quality (Brief DISCERN), completed a custom debriefing questionnaire, and self-reported anxiety (GAD-7), depression (PHQ-9) and stress (PSS-14). Both language versions were evaluated for readability (FRES, FKGL, SMOG, GFI, Scolarius), understandability and actionability (PEMAT-A/V), linguistic characteristics (LIWC-22) and tone (YesChat Tone Analyzer). Quantitative and qualitative findings were triangulated.
Results
Of 26 enrolled patients, 24 participated at t2 and 22 at t3; both benign and malignant or potentially malignant indications were represented. Usefulness and impact scores at t2 exceeded predefined thresholds, and qualitative analysis showed that most participants found the material useful or very useful. Anxiety and depression scores were low across t1–t3, whereas stress remained high; PSS-14 scores at t1 correlated positively with eHIQ-Part 2 scores at t3, suggesting that more stressed patients may experience greater impact. Readability indices for both languages indicated higher complexity than the generally recommended 6th–8th grade level, yet neither quantitative nor qualitative feedback suggested language-related difficulties. Investigator ratings showed very good understandability and excellent actionability. Linguistic analysis indicated slightly greater complexity in the French version; tone analysis for both versions indicated a clear, approachable, professional style with direct, informative content and generally simple language. Participants suggested minor improvements, mainly regarding online navigation.
Conclusions
This study provides initial evidence that Medtronic's Butterfly platform is a good-quality, reliable information source that supports shared decision-making in surgical thyroid disease.

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TED Clinical 2

PS2-16-01

When time is sight: diagnostic delay leading to sight-threatening thyroid eye disease- a case report

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Introduction
Thyroid eye disease (TED), the most common extrathyroidal manifestation of Graves' disease, is yet known for its clinical anonymity, where its subtle and misleading ocular symptoms often lead to a pattern of misdiagnosis or delayed recognition, resulting in diagnostic delay. Such delay may allow progression to life-threatening stages, ultimately derailing patients' quality of life. We present a patient with known thyroid disease who discontinued therapy; worsening systemic and ocular symptoms were misattributed, and delayed recognition allowed TED to progress to corneal perforation and evisceration.
Case Report
A 74-year-old woman known to have thyroid disease since 2018 was under endocrine follow-up but soon discontinued therapy. Her condition deteriorated in November 2021 with weakness, weight loss, diarrhoea, vertigo, and diplopia. She underwent repeated consultations with ophthalmologists, clinicians, and neurologists and was misdiagnosed with Myasthenia Gravis, undergoing multiple investigations and treatments without improvement. In March 2022, endocrinology evaluation revealed suppressed TSH (0.1 μIU/ml) and thyroid ultrasound was recommended but not performed; meanwhile ocular symptoms and systemic manifestations continued to worsen. In July 2022, diffuse toxic goitre with early thyroid eye disease was diagnosed and treatment with methimazole and low-dose prednisolone was initiated. Disease was classified as EUGOGO sight-threatening TED with maximal activity (CAS 7/7) and TRAb 5.99 IU/L. Ophthalmology consultation in December 2022 recognised active TED when vision in the left eye declined drastically. In January 2023, active TED with severe visual deterioration was recognised and treated with intravenous methylprednisolone pulses. The course was complicated by corneal infection requiring multiple ocular procedures including blepharorrhaphy and conjunctival flap. A second pulse course (500–500–750 mg) on the following month was followed by tarsorrhaphy. Despite partial improvement of the right eye, the left eye progressed to endophthalmitis and corneal perforation requiring orbital decompression and eventual evisceration. Following treatment, the remaining eye stabilised with resolution of inflammatory activity (Clinical Activity Score 0/7).
Conclusions
Delayed recognition of thyrotoxicosis and active TED permitted progression to a severely destructive phase with irreversible corneal damage. The fourteen month interval between symptom onset and appropriate treatment allowed the disease to advance despite aggressive corticosteroid therapy and surgery. Early diagnosis of

Graves disease, prompt immunosuppression and timely referral to specialised centres are essential to preserve vision and avoid disfiguring surgery. Greater awareness of TED among general practitioners and neurologists may prevent similar devastating outcomes.

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PS2-16-02

Clinical predictors of response to intravenous glucocorticoid treatment in thyroid eye disease: a retrospective study

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Objectives
Thyroid Eye Disease (TED) is an autoimmune inflammatory condition associated with Graves' disease. Intravenous glucocorticoids remain the first-line treatment for active TED, however, the response to therapy varies between patients. The aim of this study was to identify clinical and biochemical factors associated with treatment response and ocular manifestations in patients with TED.
Methods
We performed a retrospective analysis of patients with TED treated with glucocorticoids at our center. Baseline data included age, sex, smoking status, Clinical Activity Score (CAS), thyroid-stimulating hormone receptor antibodies (TRAb), hormone concentrations (TSH, FT3 and FT4), LDL cholesterol concentration and radioiodine treatment during TED therapy. Treatment response was defined as a reduction in CAS and/or improvement in diplopia or proptosis between baseline and the last available follow-up visit. Associations between laboratory parameters and disease activity were assessed using Spearman correlation analysis. Multivariable logistic regression models were used to evaluate predictors of treatment response and ocular manifestations. Receiver operating characteristic (ROC) analysis was performed to assess the predictive value of baseline CAS.
Results
59 patients were included in the analysis. Overall, 52 patients (88,1%) met the criteria for treatment response. The mean reduction in CAS between baseline and the last follow-up visit was 2,08 points. In the multivariable logistic regression model only baseline CAS was independently associated with treatment response (OR 2,24, 95% CI 1,14–4,41, $P = 0{,}020$). Smoking, age and sex were not significant predictors. Baseline TRAb levels showed a moderate positive correlation with CAS (rs = 0,318, $P = 0{,}015$). Hormone concentrations (TSH, FT3 and FT4) measured at baseline were not associated with treatment response and did not correlate with disease activity. Similarly, changes in thyroid hormone concentrations between baseline and follow-up were not related to improvement in CAS. Higher baseline CAS was also associated with the presence of diplopia or motility impairment (OR 1,77, 95% CI 1,11–2,83, $P = 0{,}017$). Smoking was more frequently observed among patients with ocular motility disturbances, although it was not an independent predictor. Radioiodine therapy during TED management was not associated with treatment response or ocular manifestations. ROC analysis demonstrated moderate predictive performance of baseline CAS for treatment response (AUC = 0,69).
Conclusions
Baseline inflammatory activity measured by CAS appears to be the strongest clinical predictor of response to glucocorticoid therapy in this cohort. TRAb levels are associated with disease activity, whereas thyroid hormone concentrations do not predict treatment response. Early treatment during the active inflammatory phase of TED may improve therapeutic outcomes.

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PS2-16-03

Safety of intravenous and subcutaneous efgartigimod reported from multiple global clinical trials in immunoglobulin g-mediated autoimmune diseases

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Objectives
Efgartigimod safety has been investigated in multiple IgG-mediated autoimmune diseases, including generalised myasthenia gravis (gMG), primary immune thrombocytopenia (ITP), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), for which it has received regulatory approval in multiple regions. We report the long-term safety of efgartigimod in gMG, ITP, and CIDP, administered via varying dosing regimens.
Methods
Data were pooled per disease from global clinical trials investigating varying efgartigimod dosing regimens and administration routes (intravenous 10 mg/kg; subcutaneous 1000 mg PH20 [coformulated with recombinant human hyaluronidase PH20]). Event rates (ER) were reported per participant year of follow-up (PYFU).
Results
The analysis includes data from at least 874 patients representing ~1350 PYFU. Treatment-emergent adverse events (TEAE) were mostly mild-to-moderate in severity. During controlled trials, severe infection ERs were comparable between placebo- and efgartigimod-treated participants. Reported TEAE-related treatment discontinuation rates were consistently low. Rates of discontinuation and severe and serious TEAEs did not increase with additional treatment cycles (gMG) or prolonged exposure to weekly administration (ITP, CIDP). Further analyses of participant population subgroups are ongoing. No albumin reduction or increases in low-density lipoprotein cholesterol levels were reported in efgartigimod-treated participants. No vaccinations, laboratory value monitoring, or pretreatment medications are required to receive efgartigimod. Efgartigimod was consistently well tolerated across trials in autoimmune diseases, including those with subcutaneous administration of efgartigimod.
Conclusions
Efgartigimod was well tolerated and demonstrated a similar safety profile regardless of disease state, dosing regimen, and length of exposure.

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PS2-16-04

Tocilizumab in refractory pretibial myxedema: new therapeutic frontiers?

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Introduction
Pretibial myxedema (PTM), is a rare extrathyroidal manifestation of Graves' disease (GD), occurring in approximately 1–4% of patients and with concomitant Graves' Orbitopathy (GO) present in nearly all reported cases. It presents as bilateral non-pitting edema of the pretibial region, occasionally accompanied by hyperkeratotic and hyperpigmented papules and plaques.
Case Report
We report the case of a GD female patient treated with total thyroidectomy in 2022. In November 2024, following the development of moderate-to-severe active GO, first-line therapy with high-dose intravenous glucocorticoids (ivGCs) was initiated. At baseline, the patient presented with bilateral proptosis of 25 mm, eyelid aperture of 18 mm, intermittent diplopia and CAS 6/7. Six months after ending treatment, partial response was observed: CAS improved to 4/7 and eyelid aperture reduced to 16 mm, while proptosis remained unchanged at 25 mm.

However, at one-year follow-up, disease worsening was documented, with CAS returning to 5/7, persistent proptosis of 25 mm, eyelid aperture of 16 mm and inconstant diplopia in supraversion and lateroversion. Concurrently, the patient had developed bilateral PTM approximately 18 months after thyroidectomy, refractory to topical corticosteroids and occlusive bandaging. Given the inadequate and non-sustained response of GO to first-line therapy, tocilizumab (8 mg/kg monthly infusion for 6 months) was initiated in July 2025. After 6 months of treatment, marked improvement in GO was observed: proptosis reduced to 23 mm (OD) and 22 mm (OS), eyelid aperture decreased to 13 mm, diplopia became intermittent, and CAS improved to 2/7. Notably, the patient reported rapid and significant improvement of PTM following the first infusion, with progressive marked reduction of edema and local symptoms confirmed at subsequent visits. No significant adverse events were recorded.

Discussion

The pathogenesis of PTM remains incompletely understood, but it is considered an autoimmune condition likely sharing key immunomediated mechanisms with GO. Interleukin-6 (IL-6) is a key pro-inflammatory cytokine implicated in GO pathogenesis, and tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has demonstrated efficacy in moderate-to-severe active GO refractory to ivGCs. To our knowledge, this is the first reported case of PTM successfully treated with tocilizumab. Given the shared pathogenetic background of GO and PTM, IL-6 inhibition may represent an effective therapeutic option not only for ivGC-refractory GO but also for refractory PTM, by targeting fibroblast activation and underlying autoimmune inflammatory cascade. Further studies are warranted to confirm the therapeutic role of tocilizumab in PTM and to define optimal treatment protocols.

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PS2-16-05

Longitudinal orbital MRI characteristics of fast vs slow progressors in thyroid eye disease

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Objectives

To characterize the clinical and magnetic resonance imaging (MRI) features distinguishing fast from slow disease progression in patients with thyroid eye disease (TED) using the interval between serial orbital MRI examinations as a temporal classifier.

Methods

This retrospective study included a total of 27 consecutive patients with TED (mean age 47.9 $\pm$ 9.6 years; 77.8% female) who underwent two orbital MRI examinations between September 2019 and February 2026 at a tertiary referral hospital. Patients were dichotomized into a "Fast" group (inter-scan interval $\leq$250 days, $n = 13$) and a "Slow" group (>250 days, $n = 14$) based on the median interval. MRI parameters included the signal intensity ratio (SIR), water fraction (WF), and fat fraction (FF) of the right inferior rectus muscle (IR) and orbital fat (F). Clinical variables included the Clinical Activity Score (CAS), diplopia status, exophthalmometry, and thyroid-stimulating hormone receptor antibody (TSHR-Ab) levels. Between-group comparisons were performed using the Mann–Whitney U test and Fisher exact test. Within-group longitudinal changes were assessed using the Wilcoxon signed-rank test.

Results

The Fast group had a significantly higher disease progression rate than the Slow group (100% vs. 57%, $P = 0.016$). New-onset diplopia during the observation period was significantly more frequent in the Fast group (53.8% vs. 14.3%, $P = 0.046$). While the change in SIR showed a medium effect size (rank-biserial r = 0.40) with a trend toward a greater increase in the Slow group ($P = 0.085$), within-group analysis revealed a significant longitudinal decrease in SIR only in the Slow group (1.194 to 0.893, $P = 0.002$). In contrast, the Fast group maintained stable SIR levels (1.123 to 1.079, $P = 0.787$). Baseline demographics, CAS, TSHR-Ab levels, and MRI parameters were comparable between groups (all $P > 0.10$).

Conclusions

Fast progressors, defined by an inter-scan interval of $\leq$250 days, showed consistent disease progression and a higher incidence of new-onset diplopia, despite having baseline characteristics comparable to slow progressors. The significant SIR reduction in the Slow group likely reflects tissue remodeling over a protracted disease course. These findings suggest that the temporal pattern of progression serves as a clinically meaningful classifier for identifying aggressive TED phenotypes, independent of baseline parameters.

Keywords
thyroid eye disease; Graves' orbitopathy; orbital MRI; signal intensity ratio.
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PS2-16-06

Impact of total thyroidectomy on TSH receptor antibody levels and ocular manifestations in graves' disease

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Introduction

Graves' disease (GD) is an autoimmune disorder characterized by stimulating antibodies against the thyrotropin receptor (TRAb), an important biomarker for disease activity and follow-up. In addition to thyroid dysfunction, GD may be complicated by Graves' orbitopathy (GO), which can lead to impaired ocular motility and diplopia. Total thyroidectomy can be considered a treatment option for GD and may influence autoimmune activity. However, the relationship between postoperative TRAb dynamic and ocular manifestations remains incompletely understood. This study aimed to evaluate the impact of total thyroidectomy on TRAb levels and to explore possible associations between it and ocular motility impairment and diplopia.

Patients and Methods

We conducted a retrospective observational study (2020-2025) including 74 patients diagnosed with GD who underwent total thyroidectomy in a tertiary endocrine center in Bucharest, Romania. Serum TRAb levels were measured preoperatively and during postoperative follow-up using electrochemiluminescence immunoassay (ECLIA). Inclusion criteria encompassed euthyroid status preoperatively, TRAb positivity (>1.75IU/L), and minimum 12-month follow-up. Ocular evaluation included presence or absence of diplopia and assessment of extraocular motility, categorized as normal or reduced. Descriptive statistics were used to summarize the data.

Results

Normality tests (Shapiro–Wilk) indicated that preoperative and postoperative TRab values were not normally distributed ($P < 0.05$). Therefore, the Wilcoxon signed-rank test was applied, revealing a significant reduction in TRAb levels after thyroidectomy ($Z = -6.715$, $P < 0.001$). These results support the potential role of thyroidectomy in reducing circulating TRAb levels. Similarly, preoperative TRab were not normally distributed in either the diplopia or non-diplopia groups ($P < 0.05$). Therefore, the Mann–Whitney U test was used for group comparisons. Preoperatively, TRAb levels did not differ significantly between patients with and without diplopia (U=537.00, Z= −0.839, $P = 0.402$). The same, postoperative TRAb levels were not significantly different between the two groups (U=405.00, Z= −1.340, $P = 0.180$). Taking into consideration motility status, McNemar's test showed no statistically significant change between the pre- and post-thyroidectomy evaluations ($P = 0.441$).

Conclusions

Total thyroidectomy in patients with Graves' disease is associated with a reduction in TRAb levels, supporting its beneficial effect on autoimmune activity. However, TRAb levels were not significantly associated with impaired ocular motility or diplopia. These findings suggest that ocular manifestations in Graves' disease are likely multifactorial and not dependent on antibody levels. Further studies with controlled designs and longer follow-up periods are warranted to confirm these results and assess long-term clinical outcomes.

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PS2-16-07

A case of orbitopathy with suspected mixed etiology: graves' orbitopathy and IGG4-related disease

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Introduction
IgG4-related disease (IgG4-RD) is a systemic inflammatory condition characterized by IgG4-positive lymphoplasmacytic infiltration and fibrosis, which can also involve orbital structures. Its clinical and radiological features may mimic those of Graves' orbitopathy (GO). As a result, the differential diagnosis may be challenging.
Case Report
We report the case of a 52-year-old man with GO and Graves' disease (GD). In February 2023, he developed irritative symptoms and exophthalmos. In October 2023, he was referred to our center with severe and active GO: clinical activity score (CAS) 6/7, proptosis of the right eye (RE) 27 mm and left eye (LE) 24 mm, with signs of optic nerve involvement (visual acuity RE 2/10). Intravenous glucocorticoid therapy (IVGC) (cumulative dose of methylprednisolone 8 g) was promptly administered, but the response was insufficient.The patient underwent right orbital decompression, resulting in a complete recovery of visual acuity and a reduction of proptosis (RE 23 mm). In June 2024, definitive treatment of hyperthyroidism with radioiodine was performed, followed by an additional course of IVGC (cumulative dose 2 g), leading to further improvement in proptosis (RE 22 mm, LE 21 mm), although CAS remained 5/7. Due to the persistence of active disease despite treatment, total IgG and IgG subclasses were measured, revealing elevated IgG4 levels (240 and 289 mg/dl). Orbital CT showed thickening of the extraocular muscles and hypertrophy of the lacrimal glands. 18F-FDG PET demonstrated increased orbital uptake in the absence of systemic hypermetabolic sites. These findings, together with the atypical phenotype and persistent IgG4 elevation, suggested a mixed pathogenesis (GO + IgG4-RD) and clinical, laboratory, and imaging follow-up was initiated.
Conclusions
This case meets two of the three diagnostic criteria for IgG4-RD (serological and radiological), without histological confirmation, representing a possible but not definitive diagnosis according to current guidelines. The literature indicates that GO and IgG4-RD may coexist without a shared etiopathogenesis, and that isolated IgG4 elevation alone is not diagnostic. In atypical, treatment-resistant orbitopathies, an accurate differential diagnosis between GO and IgG4-RD is essential to guide optimal management. Clinical, laboratory, and imaging monitoring is therefore crucial to clarify the nature of IgG4 alterations and to detect any signs of local or systemic progression.

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PS2-16-08

Changes in diplopia after teprotumumab therapy in patients with active thyroid eye disease

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Objectives
Diplopia is one of the most common functional impairments in thyroid eye disease (TED). However, the degree of improvement in diplopia after treatment may vary depending on the severity and pattern of ocular motility disturbance. This study evaluated changes in diplopia after teprotumumab (TEP) therapy in patients with active TED and examined whether treatment response differed according to the severity of diplopia in a real-world clinical setting.
Methods
We retrospectively analyzed 16 consecutive patients with active TED who had subjective diplopia and completed eight infusions of TEP between December 2024 and December 2025. The cohort included 4 men and 12 women with a mean age of 55.9 years (range 44–82). Previous treatment included intravenous steroid pulse therapy in 11 patients, of whom 5 had also undergone orbital radiotherapy, while TEP was used as the initial therapy in 5 patients. Clinical evaluation included measurement of proptosis and assessment of diplopia severity using the Gorman score. Orbital MRI using a 1.5-T scanner was performed to evaluate extraocular muscle enlargement and inflammatory findings before treatment and 3–4 weeks after completion of TEP therapy.
Results
Mean proptosis improved from 20.8 mm (range 18–24) before treatment to 18.1 mm (range 14–22) after treatment. On orbital MRI, extraocular muscle enlargement was bilateral in 12 patients and unilateral in 4, and improvement of muscle enlargement and inflammatory findings was observed in all patients. Before treatment, 6 patients had diplopia in primary gaze and 10 had diplopia only in non-primary gaze positions. Improvement of at least one grade in the Gorman score was observed in 8 patients (50%), and complete resolution of diplopia occurred in 3 patients (18.8%). All 3 patients with complete resolution of diplopia had enlargement of more than three extraocular muscles bilaterally. In contrast, persistent primary gaze diplopia was observed in 2 patients with unilateral enlargement of the inferior and medial rectus muscles.
Conclusions
Teprotumumab therapy improved proptosis and orbital inflammatory findings in patients with active TED. Improvement in diplopia was observed in 50% of patients, although complete resolution was limited. Patients with unilateral extraocular muscle involvement and primary gaze diplopia appeared less likely to achieve full resolution, suggesting that residual ocular deviation may persist despite improvement of orbital inflammation.

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PS2-16-09

Thyroid-associated orbitopathy in a patient with severe autoimmune hypothyroidism and positive tsh receptor antibodies

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Introduction
Thyroid eye disease (TED) is an organ-specific autoimmune disorder that usually accompanies Graves' hyperthyroidism. However, orbitopathy may rarely occur in approximately 3% of patients with Hashimoto's thyroiditis, where it can be overlooked or misattributed to other causes of diplopia and extraocular muscle enlargement. We report a patient with severe autoimmune hypothyroidism, marked TSH receptor antibody positivity, and active thyroid-associated orbitopathy.
Case Report
A 63-year-old man from Armenia presented with a one-year history of diplopia, more prominent on the right, together with generalized dry/scaly skin, fatigue, periorbital edema, and lower-extremity swelling. Initial laboratory testing showed severe primary hypothyroidism with TSH >100 mIU/L (reference 0.25–4.2) and FT4 3 pmol/l (reference 12-22 pmol/l). Autoimmune testing revealed anti-thyroid peroxidase antibodies 736.6 mIU/ml (reference <9) and TSH receptor antibodies 20.8 IU/L (reference <1.5). Levothyroxine was started at 100 μg/day and gradually increased according to thyroid function. After sequential titration to 200 μg/day, TSH normalized to 3.93 mIU/L. Because of persistent diplopia, MRI of the brain and orbits was performed. Imaging demonstrated bilateral asymmetric fusiform enlargement of the extraocular muscles with mild edema of the adjacent retrobulbar fat. The right medial rectus measured up to 0.9 cm, the right superior rectus 1.2 cm, the left superior rectus 1.0 cm, and the left inferior rectus 1.1 cm. Radiological exophthalmos was present, with cornea-to-interzygomatic-line distances of 2.6 cm on the right and 2.5 cm on the left. Targeted CISS images showed close contact between the right medial rectus and the right optic nerve, raising concern for orbital apex crowding. According to EUGOGO criteria, the patient had active moderate-to-severe thyroid-associated orbitopathy due to clinically significant diplopia and a Clinical Activity Score of 3/7 (eyelid erythema, conjunctival redness, mild eyelid swelling). Treatment was initiated with intravenous methylprednisolone, 500 mg weekly for 6 weeks followed by 250 mg weekly for 6 weeks.
Conclusions
This case shows that thyroid-associated orbitopathy may occur in severe autoimmune hypothyroidism with marked TSH receptor antibody positivity. In such patients, TED should be considered in the differential diagnosis of diplopia and extraocular muscle enlargement. Early recognition, restoration of euthyroidism, orbital imaging, and guideline-based treatment are essential to reduce the risk of vision-threatening complications.

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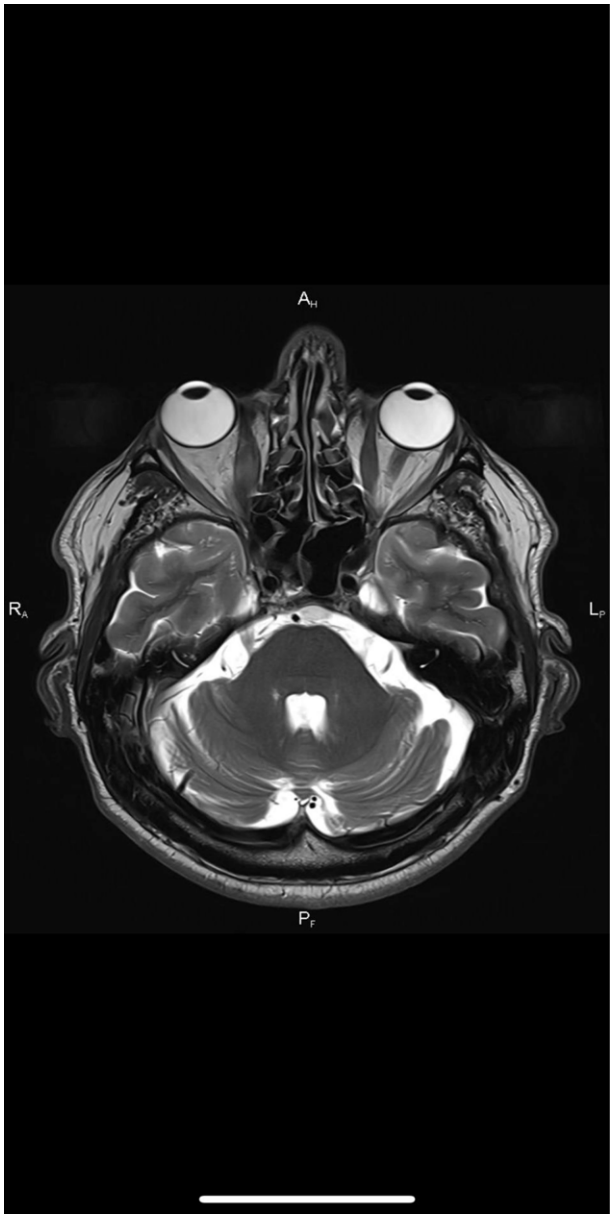
[Abstract PS2-16-09]



Poster Session 3 EDC / Graves' Orbitopathy

PS3-01-01

Perinatal exposure to TBBPA alters hypothalamic plasticity and adult responses to a western diet

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Tetrabromobisphenol A (TBBPA) is a widely-used flame retardant, classified as an endocrine-disrupting chemical that interferes with the hypothalamo-pituitary-thyroid axis. TBBPA is suspected to act as an obesogen, particularly when combined with a Western-style high-fat, high-sucrose (HFHS) diet. Disruption of thyroid hormone signalling during critical perinatal windows may induce long-lasting alterations in metabolic regulation and brain plasticity. This study aimed to determine whether perinatal TBBPA exposure alters hypothalamic plasticity and responses to an HFHS diet in adulthood, focusing on glial reactivity and neurogenesis. C57BL/6J dam mice were orally exposed to TBBPA (10 mg/kg bw/day) during late gestation and lactation (E14–P21), and offspring were fed a control or HFHS diet for 16 weeks starting at 2 months of age. TBBPA exposure abolished the transient postnatal surge in thyroid hormones that normally occurs shortly after birth. In adult males, perinatal TBBPA exposure induced persistent alterations of hypothalamic glial and neurogenic markers. In the arcuate nucleus, TBBPA reduced astrocyte and microglial densities under control diet condition. While HFHS feeding increased astrocyte density, it fully restored microglial density in TBBPA-exposed mice. In parallel, TBBPA markedly impaired hypothalamic neurogenesis, reducing both cell proliferation and neuroblast density independently of adult diet. In the median eminence, TBBPA increased progenitor density specifically in HFHS-fed mice, suggesting region-specific and diet-dependent modulation of hypothalamic neurogenic niches. Altogether, these findings indicate that perinatal TBBPA exposure durably alters hypothalamic plasticity and responses to a Western diet in adulthood. TBBPA combined with an HFHS diet also impaired adult cognitive performance. Ongoing analyses will test whether this phenotype is associated with altered hippocampal neurogenesis during the perinatal period.

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PS3-01-02

Low-dose roundup® exposure triggers cancer-related transcriptomic changes in thyroid cells

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Objectives
To evaluate the transcriptomic alterations induced by Roundup® Original DI in thyroid cells exposed to regulatory doses using RNA sequencing (RNA-seq).
Methods
The non-tumorigenic thyroid cell line Nthy-ori 3-1 and the papillary thyroid carcinoma cell line TPC-1 were exposed to Roundup® at concentrations of 65, 160 (acceptable occupational exposure level [AOEL]), and 830 µg/l (acceptable daily intake [ADI]) for 24 and 48h. All experiments were performed in triplicate. RNA sequencing was performed to identify differentially expressed genes (DEGs) compared to untreated controls. Functional enrichment analyses were performed to identify the modulated molecular pathways ($P < 0.05$).
Results
In Nthy-ori 3-1 cells, 24-h exposure resulted in 169, 138, and 203 DEGs at 65, 160, and 830 µg/l, respectively, predominantly downregulated. After 48h, fewer DEGs were observed (71, 97, and 99), with a relative increase in the number of upregulated genes. The enriched pathways included Gα12/13 signaling, IL-17 signaling, and NF1-dependent RAS signaling. In TPC-1 cells, 254, 310, and 215 DEGs were identified after 24-h exposure at 65, 160, and 830 µg/l, respectively, predominantly upregulated. After 48h, 72, 245, and 98 DEGs were observed. Functional enrichment analyses revealed pathways related to the molecular mechanisms of cancer, STAT3 signaling, IL-6 signaling, wound healing, and p38 MAPK signaling. The 160 µg/l concentration induced the highest number of unique genes and modulated several cancer-related pathways.
Conclusions
Roundup® exposure induced significant transcriptomic alterations in both thyroid cell lines, affecting pathways associated with inflammation, proliferation, and oncogenic signaling. Notably, the AOEL concentration promoted the most pronounced transcriptional changes in malignant cells, suggesting that exposure levels currently considered safe may influence the molecular mechanisms involved in thyroid tumor progression.

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PS3-01-03

Transcriptomic analysis reveals that bisphenol a triggers mitochondrial stress and metabolic rewiring in BRAF-mutant thyroid cancer cells

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Objectives
Bisphenol A (BPA) is a ubiquitous endocrine-disrupting chemical associated with thyroid dysfunction. However, the molecular mechanisms by which BPA affects thyroid cells with different oncogenic backgrounds remain poorly understood. This study aimed to investigate the temporal and dose-dependent transcriptomic alterations induced by BPA in normal and neoplastic thyroid cell lines to identify molecular pathways involved in the cellular response to environmental BPA exposure.
Methods
RNA sequencing (RNA-seq) was performed in the non-tumoral thyroid cell line Nthy-ori 3-1 and papillary thyroid carcinoma (PTC) cell lines TPC-1 (RET/PTC1 rearrangement) and BCPAP (BRAF V600E mutation). Cells were exposed to BPA at human-relevant concentrations (0.8 and 1.0 μg/mL) for 24h and 48h. Differentially expressed genes (DEGs) were identified using an adjusted p-value < 0.05 and $|\log2 \text{ fold change}| \geq 1$. Functional enrichment analyses were conducted using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome databases, followed by transcription factor analysis.
Results
Transcriptomic responses varied markedly according to genotype. BRAF-mutant BCPAP cells showed the greatest sensitivity to BPA exposure, with 6,048 DEGs identified. In these cells, BPA predominantly affected pathways related to mitochondrial respiration, protein translation, and nucleocytoplasmic transport. At 48h, the Cellular Response to Chemical Stress pathway was significantly enriched, with strong induction of CHAC1, LAMP3, and EBI3 and marked downregulation of RGPD6 and MYCT1. These alterations, together with the modulation of FAM156B, suggest disruption of cellular homeostasis and impaired redox balance, consistent with adaptive responses to environmental stress. In contrast, TPC-1 and Nthy-ori 3-1 cells exhibited more restricted transcriptomic responses. A shared alteration involved MT-ATP8, which showed divergent regulation, being upregulated in Nthy-ori 3-1 and TPC-1 but downregulated in BCPAP cells. TPC-1 cells additionally displayed enrichment of immune signaling pathways, including IL-4 and IL-13 signaling, as well as extracellular matrix remodeling involving MMP1. The stress-response gene MTRNR2L12 (Humanin) was strongly induced in both normal and TPC-1 cells, suggesting a protective mechanism that appeared absent or bypassed in BCPAP cells.
Conclusions
BPA exposure perturbs the thyroid transcriptome in a dose-, time-, and genotype-dependent manner. The increased vulnerability of BRAF-mutant cells to mitochondrial stress and metabolic rewiring suggests that BPA may contribute to the progression of aggressive PTC subtypes. These findings provide mechanistic insight into how environmental endocrine disruptors may influence thyroid cancer biology and highlight the importance of regulating exposure to such compounds.

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PS3-01-04

Longitudinal plasma proteomics identifies biomarkers of disease severity and recurrence during antithyroid drug treatment in graves' disease

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Background
Graves' disease (GD) is the leading cause of hyperthyroidism. In Europe, antithyroid drugs (ATD) represent first-line therapy, yet recurrence occurs in a substantial proportion of patients after treatment withdrawal. Current clinical predictors capture only part of the biological heterogeneity of GD, highlighting the need for novel biomarkers reflecting disease activity and recurrence risk.
Methods
This study is part of the IMAG study (Identification of New Markers for Activity of Graves' disease). Plasma samples from 63 patients with GD (new onset or recurrence after $\geq$2 years of remission) were analyzed using high-throughput proteomics. Longitudinal plasma proteomic profiling was performed at baseline and at 3 and 12 months after initiation of ATD treatment.
Results
Restoration of euthyroidism during ATD therapy was accompanied by coherent proteomic remodeling. Proteins involved in lipoprotein and thyroid hormone transport, including APOD, SERPINA7, and TTR, increased over time, whereas proteins related to endothelial integrity, complement activation, and coagulation (including CDH5, FHR5, and F13B) decreased. Among baseline biomarkers, MMRN1 (Multimerin-1), an endothelial- and platelet-derived glycoprotein, was significantly lower in patients with severe GD and negatively correlated with TRAb levels, indicating an association with disease severity. In contrast, FCGBP (IgG Fc-binding protein), a mucin-like immune protein expressed in epithelial tissues, was strongly associated with recurrence risk. Baseline FCGBP levels were higher in patients who subsequently developed GD recurrence and correlated with TRAb and FT3 concentrations. Combining MMRN1 and FCGBP with the GREAT score improved prediction of GD recurrence (AUC 0.922) suggesting that proteomic biomarkers capture biological pathways not reflected by clinical parameters alone.
Conclusions
Longitudinal plasma proteomics reveals distinct biomarker profiles linked to disease severity, recurrence risk, and treatment response in GD. MMRN1 and FCGBP emerge as complementary biomarkers reflecting vascular and immune pathways and may improve risk stratification beyond current clinical tools. These findings highlight the potential of plasma proteomics to support personalized treatment strategies in Graves' disease.

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PS3-01-05

Thyrotropin receptor-stimulating autoantibodies in pediatric graves' disease assessed by an ultra-rapid turbo bioassay

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Background
Thyrotropin receptor-stimulating autoantibodies (TSAb) are detected in 95–99% of patients with Graves' disease (GD) and play a central pathogenic role by directly driving thyroid hormone overproduction. As functional biomarkers, TSAb are highly relevant for both diagnosis and disease monitoring. We evaluated TSAb in pediatric patients with different phases of autoimmune thyroid disease (AITD), including GD before and during methimazole therapy, using a novel ultra-rapid bioassay.
Methods
Serum samples from pediatric patients with AITD and healthy controls were analyzed at the accredited, certified, academic JGU Molecular Thyroid Lab, using the novel Turbo™ TSAb cell-based bioassay (Thyretain®, QuidelOrtho, NJ, USA), with a cyclic AMP readout that correlates with luciferase gene activity. TSAb samples $<$0.024 IU/l were considered negative. Eighty AITD samples and 35 control samples were included. Median age was 12 and 10.5 years in patient and controls, respectively with a female-to-male ratio of 1.65.

Results
All healthy control samples were TSAb negative. Among the 80 pediatric samples with AITD at various serological stages, 43 (52.5%) were collected during a hyperthyroid phenotype with pathologically increased serum free thyroid hormone levels, 30 (36.5%) during biochemical hypothyroidism, and 7 (11.0%) during euthyroidism. The Turbo™ cAMP bioassay detected TSAb in all 36 untreated pediatric GD patients (sensitivity 100%) and in five samples obtained from children on methimazole. Overall, 41 of 80 pediatric AITD samples were TSAb-positive. TSAb correlated with thyroid functional status ($P = 0.028$). Dual TSH-R-Ab positivity (positive TSH-R blocking activity) was identified in three of 80 AITD samples (3.75%).
Conclusions
This is the largest reported pediatric series of TSAb-positive GD samples assessed using a rapid and reliable TSAb bioassay. TSAb significantly correlated with thyroid functional status, underscoring their biological and clinical relevance. These novel findings support the potential utility of the Turbo™ stimulating bioassay as a valuable tool for the diagnosis and monitoring of pediatric AITD.

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Development of integrative models predicting the clinical phenotype of graves' orbitopathy

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Background
Graves' orbitopathy (GO) is an autoimmune-induced inflammatory disorder of the orbit and the most common extrathyroidal manifestation of Graves' disease (GD). This disabling disease bears the risk of irreversible visual impairment that remains a unique pathophysiological and clinical challenge. In this study, we investigated potential single and multimarker models for predicting the clinical course of GO.
Material and methods
The study enrolled 91 consecutive patients with GO of various activity and severity. Stimulating thyrotropin receptor antibodies (TSAb) were measured using a cell-based bioassay (Thyretain®, Quidelortho). Serum lipid parameters (TC, HDL, HDL, ApoB and ApoAI) were assessed with the Olympus AU400 analyzer. Various serum interleukin levels were measured with Quantikine® ELISA kits. Total oxidant (TOS) and total antioxidant status (TAS) were quantified using spectrophotometric assays (Rel Assay Diagnostics) on Olympus AU400. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) concentrations were measured using an ELISA kit (Boster Biological Technology).
Results
Single and multi-marker predictive models were created from different sets of serological biomarkers combined with demographic data. We evaluated the ability of the developed models to predict clinical activity and severity of GO using Receiver Operating Characteristics (ROC) curves, based on their area under the curve (AUC). The AUC values of the obtained predictive models of activity ranged from 0.717 to 0.918, while the AUC values of the severity prediction models ranged from 0.749 to 0.960 (**Table**). The proportional increase in the AUC values of the obtained models was observed with the gradual addition of different markers to the models. Single models including TSAb serum levels had the lowest AUC values, while models encompassing demographic factors (sex, age, BMI), TSAb serum levels, interleukin concentrations (IL-1β, IL-1RA, IL-6, IL-8), oxidative stress markers (TOS, TAS, 8OHdG), and lipid concentrations (TC, HDL, HDL, ApoB/ApoAI) expressed the best discriminatory performance for both clinical activity and severity of GO.
Conclusion
Integration of specific thyroid autoantibodies, lipid, inflammatory, and oxidative stress biomarkers can substantially enhance prediction of the clinical phenotype of GO, hence facilitating the establishment of robust biomarker panels.

Table 1. Areas under the curve for single- and multi-marker predictive models of the clinical activity and severity of GO

Predictive models of GO activity	AUC	p	CI
TSAb	0.717	<0.001	0,611-0,823
TSAb, IL-6, IL-8, IL-1β, IL-1RA, TAS, TOS, 8OHdG, TC, HDL-C, LDL-C, apoB/apoA1	0.838	<0.001	0.714-0.961
TSAb, age, sex, BMI, IL-6, IL-8, IL-1β, IL-1RA, TAS, TOS, 8OHdG, TC, HDL-C, LDL-C, apoB/apoA1	**0.918**	<**0.001**	0.838-0.998
Predictive models of GO severity	**AUC**	**p**	**CI**
TSAb	0.749	<0.001	0.644-0.853
TSAb, IL-6, IL-8, IL-1β, IL-1RA, TAS, TOS, 8OHdG, TC, HDL-C, LDL-C, apoB/apoA1	0.868	<0.001	0.760-0.976
TSAb, age, sex, BMI, IL-6, IL-8, IL-1β, IL-1RA, TAS, TOS, 8OHdG, TC, HDL-C, LDL-C, apoB/apoA1	**0.960**	<**0.001**	**0.907-1.000**

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Metabolomic signature in graves' pediatric patients and its association with dendritic and regulatory B cells

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Plasma metabolomic profiling revealed a distinct metabolic signature distinguishing pediatric Graves' disease patients (GB) from healthy controls (HC). Metabolites contributing most strongly to the separation were predominantly lipid-related species, including multiple phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins. Differential analysis showed that the majority of altered metabolites were reduced in Graves' disease compared with healthy controls. The most pronounced decreases were observed among phosphatidylcholine acyl-alkyl species, phosphatidylcholine diacyl species, hydroxysphingomyelins, lysophosphatidylcholines. In contrast, a smaller subset of metabolites showed higher concentrations in Graves' disease, including glutamine, asymmetric dimethylarginine (ADMA), serotonin, aminoadipic acid, and hydroxyproline. In addition, enrichment was observed for pathways associated with mannose-type O-glycan or glycosaminoglycan biosynthesis, indicating that metabolites contributing to glycan-related metabolic processes were also represented among the altered features. In accordance, metabolomic differences observed between groups involve multiple interconnected metabolic pathways, encompassing nucleotide metabolism, nitrogen-related metabolic processes, lipid metabolism, and glycan-associated pathways. To investigate potential relationships between systemic metabolism and immune regulation, plasma metabolite levels were analyzed in relation to selected regulatory B cell (Breg) and dendritic cell (DC) phenotypes measured in peripheral blood mononuclear cells obtained from the same individuals. Correlation analyses identified associations between several metabolites and defined immune cell subsets. Because these immune populations have previously been shown to correlate with thyroid-related clinical parameters in the same cohort, the observed metabolite-immune cell relationships may suggest a potential link between systemic metabolic alterations and immunological features associated with disease activity.

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Basic Cancer 4

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Trascriptional profiling reveals lncrna hererogeneity among tumor FOCI in multifocal papillary thyroid cancer

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Background and Objectives
Papillary thyroid cancer (PTC), the most common endocrine malignancy, is multifocal disease in 30-40% of cases. However, clinical impact of multifocality remain undetermined. Similarly, studies on molecular characterization of distinct tumor foci within the same patient are limited. Although it has been well established that lncRNAs (long non-coding RNAs) play a fundamental role in cancer biology, their specific involvement in PTC multifocality is poorly understood. The aim of this study is to investigate whether different foci of multinodular PTC are characterized by a distinct lncRNAs and mutational signature.
Methods
Patients undergoing surgery for PTC at the Endocrinology Unit of University of Pisa (Italy) were enrolled ($n = 17$, 11 classical and 6 follicular subtypes). Material from different foci within the same patient was collected from FFPE tissue blocks and DNA/RNA extracted for molecular analyses. Mutational pattern was identified using targeted sequencing on Ion S5 platform. LncRNA transcriptional profile was assessed using lncRNA qPCR Array (QIAGEN) evaluating 84 lncRNAs involved in key biological pathways. Data analysis was performed using QIAGEN online platform.
Results
Initially, the expression of four selected lncRNAs (MALAT1, PVT1, H19, and HOTAIR) was evaluated by qPCR (10 nodules from 5 PTC) revealing that a gene expression profile by PCR approach can be obtained from FFPE samples of multinodular PTC. Next, we optimized a protocol for cDNA, DNAsi digestion and preAmp step capable to obtain a robust and reproducible detection rate (about 95%) of lncRNAs by using qPCR Array starting from 100 ng of total RNA from FFPE tissues. LncRNA expression analysis was then performed in 11 patients with 2–4 nodules/each (total $n = 28$). Notably, different tumor foci showed distinct lncRNA profile, highlighting both intratumoral and intertumoral heterogeneity. A subset of 25 lncRNAs showed the highest variability across samples, particularly in the follicular compared to the classical subtype. Moreover, some lncRNAs displayed subtype-specific expression patterns: PTCSC1, MRPL23-AS1, NAMA, NRON, GNAS-AS1, and PTCSC3 were overexpressed in follicular subtype, whereas MIAT and TMEM161B-AS1 in the classical variant. In addition, DIO3OS was enriched in BRAF-mutated nodules, while MEG9 expression was reduced in BRAF-mutated samples.
Conclusion
Our preliminary results identify distinct lncRNA transcriptional profiles across different tumor foci in multifocal PTC, indicating a significant molecular heterogeneity. Further analyses are ongoing to clarify the relationship between lncRNA signatures, mutational profiles, and clinical features.

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Genetic landscape of thyroid neoplasms: deciphering recurrent RAS-like mutations and evolution of multifocal tumorigenesis

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Thyroid neoplasms display wide genomic and histopathological heterogeneity, ranging from benign lesions to highly aggressive undifferentiated carcinomas. We sought to characterize their molecular landscape to identify novel genetic drivers and clinically relevant prognostic biomarkers in thyroid cancer (TC). Whole-exome sequencing (WES) was performed on DNA from frozen tissues of 34 thyroid lesions from 30 patients: 13 follicular thyroid adenomas (FTA), 12 papillary thyroid carcinomas (PTC) of different subtypes, 5 invasive encapsulated follicular variant PTC (IEFV-PTC), 1 follicular thyroid carcinoma (FTC), 2 oncocytic thyroid carcinomas (OCA), and 1 poorly differentiated thyroid carcinoma (PDTC). Four multifocal cases were included, each contributing two independent tumoral samples (2 IEFV-PTC with matched PTC; 1 FTA with matched PTC; 1 case with 2 FTA). Somatic mutations and copy number alterations (CNAs) were identified using state-of-the-art bioinformatics. In multifocal cases, mutation clonality and mutational signatures were assessed to investigate tumor evolution. Only alterations in cancer-related genes were considered. *HRAS* Q61K/R hotspot mutations were the most frequent (15%) somatic genetic alterations. In PTC, recurrent mutations were identified in *AGAP6* (33%) and *BRAF* V600E (17%), absent in other histotypes. Tumor evolution analysis of multiple samples from the same patients identified a shared *EIF1AX* hotspot mutation (R13C) between one FTA and its matched PTC, while the remaining multifocal cases showed no shared mutations. CNA analysis further indicated independent tumor evolution, with mainly private alterations even in the presence of shared CNAs. Overall, *RAS*-like alterations (*HRAS* and *EIF1AX*) were the most prevalent, consistent with the predominance of follicular-patterned lesions in this cohort. The absence of conventional driver mutations in most tumors suggests that thyroid neoplasms may be driven by rare or subtle genomic events rather than recurrent pathogenic mutations, or other genetic alteration not depicted by WES (e.g., structural variants). The presence of a shared *EIF1AX* hotspot mutation in one multifocal case supports a common ancestral clone, whereas the lack of shared alterations in the remaining cases indicates genetically independent tumors.

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Effects of BRAF-targeted therapy on telomerase expression in thyroid cancer

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Background & Aim
Thyroid cancer (TC) is the most common malignancy of the endocrine system. Over the past decades, specific somatic mutations have been associated with tumorigenesis in TC. *TERT* promoter mutations are primarily described in more aggressive thyroid cancers and lead to telomerase reactivation, conferring replicative immortality, one of the cancer hallmarks. In addition, the *BRAF* V600E mutation, one of the most prevalent alterations in papillary thyroid carcinoma (PTC), has been shown to be correlated with the upregulation of ETS transcription factors, which can bind to mutant *TERT* promoters in TC cells, thereby enhancing *TERT* transcription. Given the limited availability of therapies targeting *TERT* expression, this study aims to evaluate the effect of using a BRAF inhibitor (Vemurafenib) on *TERT* expression.
Methods
We used an immortalized normal thyroid cell line (Nthy-Ori 3-1) alongside two TC-derived cell lines (TPC-1 and B-CPAP). TPC-1 harbours the *RET/PTC1* rearrangement, whereas B-CPAP has the *BRAF* V600E mutation, with both presenting the *TERT* promoter mutation (-124 G>A). Vemurafenib's effect on cell viability was evaluated using the Presto Blue assay, followed by the assessment of cell proliferation via the EdU assay and apoptosis using the TUNEL assay. To investigate the impact of Vemurafenib on BRAF signalling, BRAF protein expression and ERK phosphorylation levels were quantified by Western blot. Finally, RT-qPCR was used to evaluate the effects of Vemurafenib on *TERT* transcription.
Results
Vemurafenib exerted a pronounced effect on cell viability and proliferation in B-CPAP cells, for which the IC^{50} value was reached. In TPC-1 cells, *TERT* expression remained unchanged, and Western blot suggested that the MAPK pathway was not modulated after Vemurafenib treatment.

Conclusion
Vemurafenib's effect on cell proliferation and viability seems to depend on cell genotype, being stronger in the B-CPAP cell line, which harbours the *BRAF* V600E mutation.

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Deciphering ubiquitin and HIPPO pathways interplay in familial thyroid cancer

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Background
Thyroid cancer (TC) is the most common endocrine malignancy, with its incidence rising significantly. About 10% of all TC cases are familial forms, which remain largely underexplored. Non-syndromic familial non-medullary thyroid carcinoma (NSFNMTC) is a rare, poorly understood condition with a highly heterogeneous presentation. Our team identified for the first time a germline variant in the USP42 gene (p.Gly486Arg) in a NSFNMTC family. USP42 is a ubiquitin-specific protease (USP) that stabilizes proteins by removing ubiquitin chains, preventing proteasomal degradation. We previously demonstrated that USP42 gene silencing led to significant changes in cell morphology, proliferation, apoptosis, and cell cycle regulation, suggesting a pivotal role of USP42 in thyroid cell biology. However, the mechanisms by which USP42 and other USPs cause cancer remain largely unknown. The Hippo signaling pathway has garnered increasing interest over recent decades, particularly for its regulation by USPs through key components (e.g. YAP/TAZ, LATS). In TC, Hippo signaling pathway research is largely underexplored, leaving significant gaps in understanding of its mechanisms and clinical applications.
Aim
This project aims to investigate how USP42 and other USPs may modulate thyroid tumor biology through modulation of the Hippo Signaling pathway, as shown in other tumors models.
Methodology
Immunohistochemistry (IHC) was conducted in FFPE of familial and sporadic cases in order to determine the expression of YAP and phosphorylated-YAP. Nthy-ori 3-1, TPC-1 and BCPAP cell lines were platted and analyzed by RT-PCR to access YAP1 and LATS2 expression at 48h. Western blot for protein expression analysis is being conducted. In Nthy-ori cells, USP42 will be silenced and expression of YAP1 and LATS2 will be accessed by RT-PCR and Western blot.
Results
IHC slides are currently being analyzed by an experienced pathologist. Preliminary IHC results show that staining appeared to be stronger in tumor tissue than adjacent tissue, and more intense in familial cases than sporadic cases. Tumoral cell lines present lower mRNA expression of YAP1 and LATS2 when comparing to Nthy-ori 3-1 cells at 48h. USP42 silencing is currently being performed to access the effects of this gene in the HSP.
Conclusions
USP42 may have an impact in the Hippo signaling pathway. We expect with this work to advance our understanding of TC biology and identify novel molecular targets for therapeutic strategies in NSFNMTC.

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Identification of additional fusion events potentially cooperate with PAX8::PPARG in thyroid carcinoma

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Objective
Follicular thyroid carcinoma (FTC) commonly develops through activating mutations in *RAS* family genes or through the *PAX8::PPARG* fusion. However, these alterations are also frequently observed in benign follicular thyroid lesions, suggesting that additional molecular events may be required for malignant transformation and tumor progression. This study aimed to identify additional genetic alterations that may cooperate with *PAX8::PPARG* in thyroid tumorigenesis.
Methods
A cohort of 120 fresh-frozen thyroid tumor samples from patients undergoing thyroidectomy at Hospital São Paulo (Universidade Federal de São Paulo) and Hospital das Clínicas (Universidade de São Paulo) was screened. None of the patients had received prior treatment. Three tumors harboring the *PAX8::PPARG* fusion were identified, including two follicular subtypes of papillary thyroid carcinoma (FV-PTC) and one FTC. Bulk RNA sequencing data were analyzed to identify additional fusion events using Arriba (v2.1.0) and STAR-Fusion (v1.15.0) with predefined filtering criteria, and only events supported by both algorithms were prioritized for further evaluation.
Results and Conclusion
The *PAX8::PPARG* fusion was confirmed in all three tumors. Additional fusion events were identified, suggesting the presence of potential cooperative molecular alterations. One candidate fusion involved a gene reported as a tumor suppressor in glioblastoma and highly expressed in thyroid tissue; however, discrepancies between the detection algorithms indicate that further validation is required. Two additional fusion events were consistently detected by both programs and involved genes previously implicated in tumor suppressor pathways across multiple cancer types. Notably, one of these fusions included a gene associated with the Hippo signaling pathway, a key regulator of cell proliferation and tumor progression that has also been implicated in thyroid tumor biology. Our findings suggest that additional fusion events may coexist with *PAX8::PPARG* in thyroid carcinomas and could potentially contribute to tumor initiation or progression. Identification of cooperative genetic alterations may provide new insights into the molecular mechanisms underlying follicular-patterned thyroid tumors and improve the understanding of *PAX8::PPARG*-driven thyroid tumorigenesis.

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When diploidy deceives: copy-neutral loh unmasks ret homozygosity in aggressive medullary thyroid carcinoma

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Introduction
Sporadic cancer is a complex disease characterized by accumulation of somatic genetic alterations. Somatic copy number alterations (SCNAs) may also occur and contribute to disease progression although some alterations, particularly copy-neutral

events, may remain undetected with common techniques due to the presence of apparently diploid genomes. Copy-neutral loss of heterozygosity (CN-LOH) is a distinct genomic abnormality in which duplication of a chromosomal segment is accompanied by loss of the corresponding homologous region, resulting in two copies derived from the same parental origin. The main genetic driver events characterizing sporadic medullary thyroid cancer (sMTC) are mutations in the *RET*, *RAS*, and *NF1* genes. SCNAs have also been described, whereas CN-LOH has not yet been reported.
Case report
In 2013, a 49-year-old patient was diagnosed with sMTC. Distant metastases were already present at diagnosis, and the tumour showed a high aggressiveness with the involvement of bone. As germline analysis of the *RET* gene was negative, NGS somatic analysis the mutation *RET* M918T as apparently homozygous with an allele frequency of 92.4%. NGS analysis revealed discordance in the zygosity of common *RET* SNPs, homozygous in tumour tissue and heterozygous in germline DNA. This finding raised the hypothesis of allelic loss of the wild-type allele; however, MLPA analysis of *RET* demonstrated a diploid copy number status, which was confirmed by array-CGH analysis. The SNP analysis revealed CN-LOH affecting the entire chromosome 10 where *RET* gene maps with no evidence of SCNA loss. Instead, the observed LOH occurred in the absence of copy number variation, which is consistent with either a mitotic recombination event or somatic uniparental disomy.
Conclusions
CN-LOH may contribute to tumorigenesis through multiple mechanisms, including oncogene activation, unmasking of recessive mutations in tumour suppressor genes and altered gene expression resulting from disruption to genomic imprinting patterns. Several studies reported an association between CN-LOH and aggressive features in cancer. In this case, the presence of homozygous double *RET* mutations may underlie the aggressiveness of the disease. This study was supported by AIRC (IG-2024, cod.30526).

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Interaction of SIGLEC-15 with thyroid cancer cells

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Siglec-15 is emerging as an important immunomodulatory receptor expressed on tumor-associated myeloid cells present in a wide range of tumors. Upon engagement with its ligands, Siglec-15 can modulate tumor progression and metastasis[4–6]. Thyroid cancer in general, andanaplastic thyroid cancerin particular, is characterized by strong infiltration of TAMs, making Siglec-15 an attractive target for studying potential therapeutic interventions.
Objective
The classically described ligand of Siglec-15 issialyl-Tn (STn)(Sia-α2,6-GalNAc-α1-O-Ser/Thr), an antigen that is highly expressed on many cancer cells.[7,8] However, recent studies have also reportedSTn-independent bindingof Siglec-15 to tumor cells, suggesting that additional glycans or glycoproteins may contribute to this interaction.[4,9]
Methods
In this study, we specifically investigated the binding of Siglec-15 to thyroid cancer cells. To dissect the molecular basis of this interaction, we used recombinant humanSiglec-15-Fc chimera proteinsand examined their binding to a panel of thyroid cancer cell lines. These experiments were combined with the use ofbroad metabolic inhibitors of glycosylation, genetic engineering approaches, andtranscriptomic analysesto elucidate the glycan structures and protein context responsible for rSiglec-15 binding.
Results
Our results demonstrate that recombinant Siglec-15 can bind to several thyroid cancer cell lines both in the presence and absence of STn expression. Using metabolic glycosylation inhibitors, we further show that rSiglec-15 binding depends onO-GalNAc–type glycans, indicating that specific mucin-type glycosylation patterns may be critical for this interaction.
Conclusions
Understanding the potential binding partners of Siglec-15 on cancer cells may provide opportunities tointerfere with Siglec-15–mediated signaling in the tumor microenvironment. Such insights could contribute to the development ofimmunotherapeutic strategies targeting Siglec-15 in thyroid cancer, with the ultimate goal of improving clinical outcomes for patients.

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Basic Cancer 5

PS3-03-01

Modulation of ICAM1 by mirnas and its effects in aggressive thyroid cancer

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Objectives
Intercellular adhesion molecule-1 (ICAM1) has been associated with more aggressive tumor phenotypes, including increased invasive capacity and metastatic potential. MicroRNAs (miRNAs), small non-coding RNAs that act as post-transcriptional regulators of gene expression, have been described as important mediators of intercellular communication mediated by small extracellular vesicles (sEVs). In this context, the regulation of *ICAM1* by miRNAs encapsulated in sEVs emerges as a promising strategy for the targeted transfer of these small RNAs to tumor cells.
Methods
Candidate miRNAs were selected through bioinformatic analyses based on predicted interaction and negative correlation with the *ICAM1* transcript levels. Expression of *ICAM1* was evaluated in the normal follicular cell line NThy-ORI and in the tumor cell lines TPC-1, BCPAP, KTC-2, and 8305C. Commercial mimics for the candidate miRNAs identified in the bioinformatic analyses, *miR-204-3p* and *miR-873-5p* were transfected in selected cell lines and. In parallel, small extracellular vesicles were isolated from the NThy-ORI cell line and characterized in terms of morphology, size, and concentration.
Results
ICAM1 expression was higher in tumor cell lines compared with the normal cell line. Transfection with *miR-204-3p* and *miR-873-5p* mimics resulted in reduced ICAM1 expression in the KTC-2 tumor cell line.
Conclusions
Although additional analyses are required, our results indicate that *miR-204-3p* and *miR-873-5p* may be involved in the modulation of *ICAM1* expression in thyroid tumor cells. Furthermore, the isolation and characterization of small extracellular vesicles establish an experimental basis for their use as a delivery system.

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PS3-03-02

Analytical validation of a customized DNA-based NGS panel for molecular profiling of thyroid samples

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Objective
Next-generation sequencing (NGS)-based molecular testing has become an important component of thyroid nodule and cancer management. According to the ACCE framework for genetic test evaluation, analytical validation is the first essential step to ensure reliable assay performance prior to clinical implementation. This study aimed to develop and analytically validate a customized DNA-based targeted NGS panel designed to detect molecular alterations relevant to both adult and pediatric thyroid cancers.
Methods
A targeted DNA-based NGS panel was designed to detect single nucleotide variants (SNVs), small insertions/deletions (indels) and copy number alterations (CNAs). Analytical validation was performed using formalin-fixed paraffin-

embedded (FFPE) and fresh-frozen (FF) thyroid samples. The validation set included samples harboring genetic alterations commonly observed in thyroid cancer as well as mutation-negative specimens. DNA quantity and quality were assessed using Qubit dsDNA High Sensitivity and Illumina Infinium HD FFPE QC assays; library quality control was assessed using the TapeStation D1000 ScreenTape assay. Libraries were prepared from 100-300 ng DNA using Illumina DNA Prep with Enrichment and sequenced on a NextSeq 2000 platform. Sequencing data were processed using DRAGEN Enrichment v4.3.6 for variant calling and CNA analysis. Performance metrics included positive percent agreement with previously characterized variants, sequencing depth and coverage, and assay reproducibility.
Results and Conclusion
The customized panel targets 48 genomic regions across 35 genes implicated in thyroid tumorigenesis, comprising 3,813 probes and covering 0.45 Mb. Sequencing generated 120 million reads passing filter, with a mean of 9.4 $\pm$ 4.2 million aligned reads per sample and an average depth of 415$\times$, providing robust coverage. The assay detected all 13 distinct SNVs previously characterized in the validation samples (100% agreement), including key driver alterations such as BRAF p.V600E, *RAS* and *TERT* promoter mutations. Mutant allele frequency analysis confirmed reliable detection across a broad allelic spectrum, including low-frequency variants consistent with low tumor cellularity. The panel also identified SNVs and CNAs in samples without prior molecular testing and detected co-occurring alterations in tumors with known driver mutations, demonstrating the ability to capture complex mutation profiles. Less common alterations are under investigation in samples lacking the most prevalent alterations found in thyroid nodules. In conclusion, this customized panel demonstrated robust analytical performance for detecting SNVs, indels and CNAs in thyroid samples, supporting its potential application in molecular testing across clinically relevant thyroid specimen types to improve risk stratification of indeterminate nodules, identify actionable alterations, and enable disease monitoring.

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PS3-03-03

RT-QPCR quantification of aromatase expression in follicular cell-derived differentiated thyroid carcinoma

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Introduction
Cytochrome P450 aromatase (CYP19A1) converts androgenic precursors into estrogens. In humans, aromatase is expressed in several tissues, including the gonads, placenta, breast, prostate, brain, bone, adipose tissue, and endometriotic lesions. Follicular cell-derived differentiated thyroid carcinoma (DTC) shows a marked female predominance, with differentiated thyroid carcinoma (DTC) presenting a higher female-to-male ratio. Estrogens have been implicated in DTC growth through genomic and non-genomic signaling pathways and through modulation of the tumor microenvironment. Local estrogen synthesis within thyroid tumors has been proposed as a potential autocrine or paracrine tumorigenic mechanism; however, this hypothesis remains insufficiently explored. We therefore investigated aromatase expression in DTC tissue samples.
Objectives
To quantify aromatase expression in DTC using quantitative real-time polymerase chain reaction (RT-qPCR).
Methods
We used formalin-fixed, paraffin-embedded DTC tissue samples, as well as lymph node and distant metastases, from a single center. Total RNA samples were extracted and aromatase expression was quantified using SYBR Green-based RT-qPCR. Relative mRNA expression was calculated using an efficiency-corrected $2-\Delta\Delta Ct$ model. TBP was used as the endogenous control gene. Expression levels were normalized to TBP and normal human thyroid tissue.
Results
The sample included 5 papillary thyroid carcinomas (PTC), 2 cribriform-morular thyroid carcinomas (CMTC), 1 follicular thyroid carcinoma, 1 follicular variant of PTC, and 1 diffuse sclerosing variant of PTC. Additionally, 2 lymph node metastases of PTC and 1 laryngotracheal metastasis of CMTC were analyzed. All DTC samples showed higher aromatase expression than normal thyroid tissue, with fold differences ranging from 1.63 to 25.95 relative to the normal thyroid sample.
Conclusions
Aromatase expression was higher in the analyzed DTC samples than in normal thyroid tissue. Further studies with larger cohorts are required to confirm these findings and to explore potential associations with histological subtype, clinical characteristics, and prognostic factors.

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PS3-03-04

RNA sequencing reveals novel genetic alterations in sporadic medullary thyroid carcinoma

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Objective
Sporadic medullary thyroid carcinoma (MTC) is primarily driven by activating alterations in the RET and RAS oncogenes. However, the molecular landscape underlying disease pathogenesis and progression remains incompletely characterized. This study aimed to analyze RNA sequencing (RNA-seq) data from sporadic MTC tumors to identify gene fusions, single-nucleotide variants (SNVs), and small insertions/deletions (Indels) potentially associated with disease pathogenesis and molecular heterogeneity.
Methods
Formalin-fixed paraffin-embedded tumor samples from three patients with sporadic MTC who underwent thyroidectomy at Hospital São Paulo, UNIFESP, Brazil, were analyzed. Raw sequencing data underwent quality control and alignment to the GRCh38 reference genome. SNVs and indels were identified using GATK v4.2 with Mutect2 and annotated with Variant Effect Predictor (VEP). Variants were filtered to retain predicted high- or moderate-impact alterations and subsequently analyzed using the Maftools package in R. Variant occurrence was assessed through comparison with publicly available datasets, including The Cancer Genome Atlas (TCGA) and COSMIC. Gene fusion detection was performed using STAR-Fusion (v1.15.0) and Arriba (v2.1.0), considering only events classified as high- or medium-confidence. Pathway enrichment analysis was conducted using TCGA-based reference cohorts.
Results
No gene fusions were detected in any of the tumors by either STAR-Fusion or Arriba. SNV and indel analysis revealed heterogeneous mutational profiles. Case 1 exhibited a single SNV, classified as tolerated, indicating a relatively low mutational burden. Case 2 harbored 34 variants, including alterations in genes previously implicated in tumorigenesis, as well as two variants affecting a gene critical for calcitonin production, an important biomarker for MTC. Case 3, harboring RET p.M918T (exon 11) and p.G548V (exon 8) variants, showed a higher mutational burden, including two additional RET exon 8 variants not previously reported. Cases 2 and 3 also presented alterations in genes related to DNA damage response previously implicated in MTC, including one variant present in both tumors. Among all detected variants, four had been previously reported in TCGA and eleven in the COSMIC database. Pathway analysis highlighted enrichment of tumorigenesis-related pathways, including TP53-associated networks, in cases 2 and 3.
Conclusion
These findings expand the molecular characterization of sporadic MTC and suggest that more aggressive tumors may harbor a higher mutational burden and broader pathway involvement. Further studies in larger cohorts are warranted to clarify the role of these alterations in MTC biology and clinical behavior.

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PS3-03-05

Detection and quantification of braf v600e in thyroid lesions by droplet digital pcr: comparison with ngs

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PS3-03-06

Association of BRAF V600E allele frequency with aggressive clinicopathological features in papillary thyroid carcinoma

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Background
Papillary thyroid carcinoma (PTC) is typically associated with an indolent clinical course and favorable prognosis. However, a subset of tumors presents aggressive clinicopathological features that may be associated with less favorable outcomes. The allele frequency (AF) of the BRAF V600E mutation has recently been explored as a quantitative parameter potentially related to tumor aggressiveness, including intermediate/high American Thyroid Association recurrence risk (ATA RR), lymph node metastasis (LNM), extrathyroidal invasion (EI), and angiolymphatic invasion (AI).
Objectives
To evaluate the association between BRAF V600E mutation allele frequency and aggressive clinicopathological characteristics in papillary thyroid carcinoma.
Methods
A total of 116 PTC samples with previously documented histopathological data regarding ATA recurrence risk (RR), lymph node metastasis (LNM), extrathyroidal invasion (EI), and angiolymphatic invasion (AI) were included in this study. BRAF V600E mutation status and allele frequency were determined by quantitative PCR (qPCR). Receiver operating characteristic (ROC) curve analysis was applied to determine an optimal AF threshold, allowing stratification of cases into three groups: BRAF-negative, BRAF-positive with AF below the cut-off, and BRAF-positive with AF above the cut-off.
Results
Among the 116 PTC cases analyzed, 46 (46/116 – 39.6%) were positive for the BRAF V600E mutation. For these 46 cases both the presence of the mutation and increasing allele frequency showed significant associations with intermediate/-high ATA RR ($P < 0.001$), lymph node metastasis ($P < 0.001$), and extrathyroidal invasion ($P = 0.030$). ROC curve analysis identified 16.90% as the optimal AF cut-off. The proportion of cases classified as intermediate/high ATA RR increased across the three groups, reaching 10.0%, 38.5%, and 63.6%, respectively. A similar trend was observed for lymph node metastasis, with rates of 13.0%, 27.3%, and 61.9%. Regarding extrathyroidal invasion, frequencies increased from 3.6% in BRAF-negative cases or those with AF below the cut-off to 18.2% in tumors with AF above the cut-off.
Conclusion
Quantitative assessment of BRAF V600E allele frequency may provide additional information regarding aggressive clinicopathological characteristics in papillary thyroid carcinoma. Considering allele frequency alongside mutation status may contribute to improved risk stratification and support more individualized clinical management.

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PS3-03-07

High prevalence of suspected hereditary cancer predisposition in radioiodine-refractory differentiated thyroid carcinoma: implications for genetic counseling and cascade screening

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Background
Radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC) represents the most aggressive subset of thyroid cancer. While somatic driver mutations are well-characterized, the contribution of germline variants in cancer predisposition genes remains underexplored. Detection of such variants has direct implications for family screening, surveillance strategies, and therapeutic decision-making.
Methods
We performed comprehensive genomic profiling on formalin-fixed paraffin-embedded tumor tissue from 35 patients with RAIR-DTC enrolled in the Hellenic Network of Molecular Oncology (EDIMO). Next-generation sequencing using Ion AmpliSeq technology interrogated >500 genes for single-nucleotide variants, insertions/deletions, and copy number variants (CNVs). Variants with variant allele frequency (VAF) >40% were classified as potentially germline in origin.
Results
Suspected germline variants VAF >40% were detected in 21/35 patients (60%). Among these, 6 metastatic patients carried variants in established cancer predisposition genes: *TERT* promoter ($n = 4$; VAF 44–53%; including 2 patients with concomitant breast/ovarian cancer, one carrying *RAD51D* variant VAF 44%); *TSHR* ($n = 1$, VAF 43%); *ATM* ($n = 1$, VAF 50%); and co-occurring *APC* (VAF 49%) and *TP53* (VAF 56%) in one patient. Clinically significant CNVs were identified in 6 patients (5 metastatic), involving *CHEK2* ($n = 2$), *BRCA2* ($n = 2$), *RAD54L* ($n = 1$), *ATM* ($n = 2$), and *CHEK1* ($n = 2$). Additionally, 15/21 patients harbored variants in pharmacogenomic genes (*DPYD, NQO1, CYP2D6*; VAF 42–99%) with implications for drug metabolism and toxicity.
Conclusion
Comprehensive tumor-based genomic profiling in RAIR-DTC reveals a remarkably high rate of suspected hereditary cancer predisposition, particularly in metastatic disease. Confirmatory germline testing and cascade family screening are warranted to identify at-risk relatives, guide surveillance for secondary malignancies, and inform precision oncology approaches in both probands and family members.

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PS3-03-08

Functional characterization of a non-canonical SDHD splice-site variant (c.314+4A>G) in a family with thyroid and carotid paragangliomas

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Background
Thyroid paragangliomas (TPGL) are exceptionally rare (<0.1% of thyroid neoplasms, ~0.5% of paragangliomas) and often occur within hereditary head and neck paraganglioma syndromes. While hereditary paragangliomas are frequently linked to *SDHD* germline variants, intronic splice-site alterations are scarcely reported in TPGL. We describe the clinical and novel functional characterization of a TPGL associated with a novel intronic *SDHD* variant.
Methods
We investigated a family of a 36-year-old woman with intrathyroidal TPGL and bilateral carotid body paragangliomas in her father and brother, all carrying a heterozygous intronic *SDHD* variant, c.314+4A>G (NM_003002.5). Germline testing was performed by next-generation sequencing, followed by in-depth RNA sequencing on whole blood. RNA-seq libraries were prepared with a directional protocol and sequenced on an Illumina NextSeq 2000 (~80M 150-bp paired-end reads/sample), aligned with HISAT2, quantified with HTSeq, and analyzed with DESeq2; splice junctions were visualized by sashimi plots in IGV.
Results
The *SDHD* c.314+4A>G variant lies within the intron 3 donor site and is absent from gnomAD and the Leiden University Medical Center SDHD gene variant database; SpliceAI predicts splice disruption (Δ score 0.81). RNA-seq demonstrated two competing exon 3→4 junctions in both carriers: a canonical junction from the wild-type allele and a cryptic junction 4 bp downstream, attributable to the mutant allele. In the proband and her brother, aberrant junctions accounted for approximately half of all exon 3→4 splice events, consistent with a "leaky" splice-site defect and predicted frameshift with premature termination. Overall *SDHD* expression was reduced in the proband compared with her brother, suggesting allele-specific transcript instability and possible haploinsufficiency.
Conclusion
This study provides direct RNA-level evidence that the intronic *SDHD* c.314+4A>G variant causes aberrant splicing and supports reclassification from VUS to likely pathogenic under ACMG/AMP criteria (PS3, PM2, PP3, segregation). Our findings expand the spectrum of splice-disrupting *SDHD* c.314 variants implicated in hereditary head and neck paragangliomas and underscore the value of RNA-based assays in interpreting non-canonical splice-site changes.
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Abstract Withdrawn

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Clinical Cancer 7

PS3-04-01

Predictors of malignancy in bethesda IV thyroid nodules: a retrospective cohort study
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Introduction
Bethesda category IV thyroid cytology (follicular neoplasm/suspicious for follicular neoplasm) remains associated with significant diagnostic uncertainty, as the distinction between benign and malignant lesions requires histological demonstration of capsular and/or vascular invasion. Consequently, many patients undergo diagnostic surgery despite a substantial proportion presenting benign histology. This study aimed to identify clinical, laboratory and ultrasound predictors of malignancy in Bethesda IV thyroid nodules and to compare malignancy rates with surgical morbidity.
Methods
A retrospective observational study was conducted including adult patients with Bethesda IV thyroid cytology who underwent diagnostic thyroid surgery between January 2019 and December 2025. Demographic, clinical, laboratory and ultrasound variables were collected. The primary outcome was malignancy in the target nodule on final histopathology. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was classified as non-malignant according to current WHO criteria. Comparative analysis and multivariable logistic regression were performed to identify independent predictors of malignancy.
Results
A total of 175 patients were included. The overall malignancy rate was 12.6% (22/175), while 12.0% of nodules were classified as NIFTP. Most malignant lesions corresponded to papillary thyroid carcinoma (86.4%). In multivariable analysis, ACR TI-RADS ≥4 was independently associated with a higher risk of malignancy (OR 5.66; 95% CI 1.25–25.58; $P = 0.024$). Age was inversely associated with malignancy risk, with an approximate 4% reduction in odds of carcinoma per additional year of age (OR 0.96; 95% CI 0.93–0.99; $P = 0.017$). Other variables, including sex, TSH, multinodularity, and cytological subtype, were not associated with malignancy. The overall postoperative complication rate was 17.1%, exceeding the observed malignancy rate.
Conclusions
In this cohort of Bethesda IV thyroid nodules, malignancy rates were lower than historically reported and inferior to the observed surgical morbidity. ACR TI-RADS ≥4 and younger age were independent predictors of malignancy and may contribute to improved preoperative risk stratification. These findings support an individualized risk-based approach integrating ultrasound and clinical parameters to optimize the proportionality of diagnostic surgery in Bethesda IV nodules.
Keywords:
Bethesda IV, ACR TI-RADS, thyroid nodules, follicular neoplasm, malignancy prediction.
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PS3-04-02

Perioperative risk factors predicting long-term outcomes in sporadic and hereditary medullary thyroid carcinoma
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Objectives
Medullary thyroid carcinoma (MTC) may occur sporadically or as part of hereditary syndromes and can be associated with significant morbidity and mortality in advanced stages. This study aimed to evaluate perioperative clinicopathological risk factors associated with long-term outcomes and to compare clinical characteristics of sporadic and hereditary MTC.
Methods
We conducted a retrospective study of patients with MTC diagnosed between January 2004 and October 2025. Median follow-up was 157 months. Risk factors evaluated included age >55, male sex, lateral lymph node metastases, advanced tumor stage, vascular invasion and elevated postoperative calcitonin levels. Tumor stage was categorized as early (I–II) or advanced (III–IV) according to the TNM/AJCC 8th edition. Biochemical cure was defined as normal or undetectable postoperative calcitonin and CEA levels. Outcomes included biochemical cure, locoregional recurrence or persistence, metastatic disease and death. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher's exact test.
Results
Twenty-seven patients with MTC were included: 40.7% had hereditary disease (diagnosed through screening) and 37% were male. Median age at diagnosis was 44 (18–62). Total thyroidectomy was performed in all patients, with at least central lymph node dissection in 77.8%. Advanced stage disease was present in 42.3% and lateral lymph node metastases in 25.9%. Biochemical cure was achieved in 37,5%; recurrence occurred in two patients, metastatic disease in two, and one patient had both locoregional and metastatic disease. Mortality was 11.1% ($n = 3$). Four patients required treatment with tyrosine kinase inhibitors. Advanced tumor stage was associated with higher recurrence rates ($P = 0.007$) but not with metastatic disease. Lateral lymph node metastases ($P = 0.022$), vascular invasion ($P = 0.009$) and elevated postoperative calcitonin levels ($P = 0.006$) were associated with lower rates of biochemical cure. No association was found between demographic factors and long-term outcomes. Hereditary MTC was diagnosed at a younger age than sporadic cases (median 29 vs 60.5 years, $P = 0.003$) and more frequently showed multifocal tumors (81.8% vs 31.3%, $P = 0.018$). No significant differences in long-term outcomes were observed between hereditary and sporadic MTC.
Conclusions
Hereditary MTC was diagnosed at a younger age and more frequently presented multifocal disease compared with sporadic MTC. The high prevalence of hereditary

cases likely reflects intensive screening practices. Advanced tumor stage, lateral lymph node metastases and vascular invasion were associated with worse outcomes. Elevated postoperative calcitonin levels strongly predicted recurrent or persistent disease, highlighting the importance of perioperative risk assessment in prognostic stratification of MTC.

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PS3-04-03

Tumor size and recurrence in T3B papillary thyroid carcinoma: implications for surgical extent

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Background
Papillary thyroid carcinoma (PTC) with gross invasion of the strap muscles is classified as T3b stage. However, the optimal extent of thyroid surgery (lobectomy vs total thyroidectomy) for patients with T3b PTC remains unclear. This study aimed to identify predictive factors for recurrence in patients with T3b PTC and to evaluate the role of tumor size in determining surgical extent.
Methods
We retrospectively reviewed patients with T3b PTC without contralateral thyroid involvement who underwent thyroid surgery at our institution. Recurrence-free survival (RFS) was evaluated using the Kaplan–Meier method and predictive factors for recurrence were assessed using Cox proportional hazards regression analysis.
Results
During a median follow-up of 59.5 months (range, 9–131 months), structural recurrence was observed in nine patients with T3b PTC. In Cox proportional hazards regression analysis of the entire T3b cohort, tumor size greater than 2 cm was significantly associated with an increased risk of recurrence (*vs.* ≤ 2 cm; hazard ratio, 7.60; 95% confidence interval, 1.39–41.68; $P = 0.019$). Subgroup analysis excluding patients with lateral neck node metastasis (N1b) was performed. Among these patients, recurrence occurred in two of 85 patients (2.4%) with tumors ≤ 2 cm and in four of 23 patients (17.4%) with tumors > 2 cm. Kaplan–Meier analysis demonstrated that tumors larger than 2 cm were associated with significantly worse recurrence-free survival (log-rank $P = 0.006$) .
Conclusions
In patients with T3b papillary thyroid carcinoma without contralateral thyroid involvement, tumor size was significantly associated with recurrence risk. Particularly in patients without lateral neck node metastasis, tumors larger than 2 cm were associated with worse recurrence outcomes. These findings suggest that patients with T3b PTC with tumors ≤ 2 cm without lateral neck node metastasis or contralateral thyroid involvement may be considered candidates for lobectomy.

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PS3-04-04

Feasibility and safety of robotic and endoscopic transoral vestibular completion thyroidectomy after diverse previous thyroid surgery: a preliminary retrospective cohort study

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Objectives
Transoral thyroidectomy has demonstrated acceptable safety and efficacy with favorable surgical and cosmetic outcomes. However, its role in completion thyroidectomy—particularly after diverse prior surgical approaches—remains to be established. We aimed to evaluate the feasibility and safety of transoral completion thyroidectomy (robotic and endoscopic) in patients with diverse surgical histories.
Methods
This retrospective study included 10 patients who underwent transoral completion thyroidectomy between July 2022 and November 2025, including 8 transoral robotic thyroidectomy (TORT) and 2 transoral endoscopic thyroidectomy vestibular approach (TOETVA) procedures.
Results
All patients were female (mean age 42.3 ± 10.3 years). Index approaches were diverse, including open ($n = 3$), transaxillary ($n = 2$), bilateral axillo-breast approach ($n = 1$), TOETVA ($n = 1$), and TORT ($n = 3$). Indications were metachronous papillary thyroid carcinoma (PTC) in the remnant lobe ($n = 9$) and newly developed PTC ($n = 1$). All procedures were completed without conversion, with negligible blood loss, and no drain placement. The mean total operative time was 54.8 ± 5.3 min (TOETVA: 48.0 min, TORT: 56.5 min); notably, the TORT group achieved a short mean console time of 17.6 ± 2.8 min. The only complication was transient hypoparathyroidism in one patient (10%). During short-term follow-up (6.0 ± 5.3 months), no structural recurrence was detected.
Conclusions
Transoral completion thyroidectomy is a feasible and safe option using either robotic or endoscopic vestibular platforms in selected patients, even after diverse prior surgical approaches. Both techniques provided sufficient access and a favorable short-term safety profile, serving as a valuable alternative for patients desiring scar-minimizing reoperation.

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Comparison of the 2015 and 2025 ATA risk stratification systems for structural recurrence in papillary thyroid carcinoma

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Objectives
The 2025 American Thyroid Association (ATA) guidelines introduced revised risk stratification systems for differentiated thyroid cancer, including histology-specific models for papillary, follicular, and oncocytic carcinoma and a four-tier risk classification. However, the clinical performance of the updated system in papillary thyroid carcinoma (PTC) remains insufficiently validated. We aimed to compare the predictive performance of the 2025 ATA risk stratification system with the 2015 ATA system for structural recurrence in patients with PTC.
Methods
We retrospectively analyzed 284 patients who underwent surgery for PTC between 2019 and 2021. Patients were classified according to the 2015 ATA three-tier system (low, intermediate, high) and the 2025 ATA four-tier system (low, low-intermediate, intermediate-high, high). The primary outcome was structural recurrence. Predictive performance was evaluated using the integrated area under the ROC curve.
Results
During a median follow-up of 46.5 months, structural recurrence occurred in 23 patients (8.1%). According to the 2015 ATA system, recurrence occurred in 0 of 119 low-risk, 8 of 106 intermediate-risk, and 15 of 59 high-risk patients. Using the 2025 ATA classification, recurrence occurred in 0 of 86 low-risk, 1 of 56 low-intermediate, 2 of 53 intermediate-high, and 20 of 89 high-risk patients. Predictive performance was comparable between the two systems, with integrated AUC values of 0.873 for the 2015 system and 0.852 for the 2025 system.
Conclusion
The updated 2025 ATA risk stratification system demonstrated similar predictive performance to the 2015 system for predicting structural recurrence in papillary

thyroid carcinoma, supporting the clinical utility of both systems for risk stratification.

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PS3-04-06

Autoimmune thyroiditis and NIFTP: a possible link

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Objectives
Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) is a thyroid neoplasm of uncertain malignant potential. Autoimmune thyroiditis (AT), particularly Hashimoto's thyroiditis, has been associated with papillary thyroid carcinoma (PTC). Proposed mechanisms involve chronic inflammation and immune-mediated modulation of the thyroid microenvironment. However, the relationship between AT and NIFTP remains poorly explored in the current medical literature. This study aimed to assess the prevalence of AT and other tumors in patients with NIFTP.
Methods
Histopathology reports of thyroid specimens with a NIFTP diagnosis recorded between January 2017 and December 2023 at a tertiary referral center were reviewed. Histological features of AT, and the presence of antithyroid antibodies, namely thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), were assessed. Concomitant malignant thyroid neoplasms were also recorded. Follow-up data were reviewed for tumor recurrence.
Results
Forty patients with NIFTP were included. Participants were predominantly female ($n = 35$, 87.5%) and had a mean age of 52.3 $\pm$ 13.1 years. Hemithyroidectomy was performed in 21 patients (52.5%) and total thyroidectomy in 15 (37.5%). Histological features of AT were identified in 14 cases (35.0%). Preoperative antithyroid antibodies were frequently unavailable; postoperative TgAb were elevated in only 1 of 14 evaluated patients, 6 of whom had undergone total thyroidectomy. Prior to surgery, only 4 (10.0%) were medicated with levothyroxine, and another 2 had clinical or subclinical hypothyroidism. Overall, synchronous malignant neoplasms were identified in 21 patients (52.5%). Half of the participants had PTCs ($n = 20$, 50.0%), mostly microcarcinomas ($n = 14$, 35.0%), while medullary thyroid carcinoma (MTC) coexisted in 2 patients (5.0%). Globally, synchronous malignancies occurred in 78.6% of patients with histological AT, compared with 40.0% without AT (RR = 1.96, 95% CI 1.13 – 3.41, Pearson's chi-square test $P = 0.020$, $n = 39$). Mean NIFTP size was 20.4 $\pm$ 11.5 mm. Surgical indication was driven by other nodules in 12 cases. Nodal metastases were found in 4 cases: 3 associated with PTC and 1 with MTC. All patients achieved complete biochemical and structural response during a median follow-up of 3.3 (2.4 – 5.2) years.
Conclusion
In this NIFTP cohort study, histological features suggestive of AT were observed in approximately one-third of participants. The observed coexistence of NIFTP with AT and synchronous PTC may suggest a relationship between AT and the biological microenvironment in which both these tumors arise. Larger studies are needed to further investigate this possible association.

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PS3-04-07

Advanced medullary thyroid cancer: is there a chance for chemotherapy?

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Advanced medullary thyroid carcinoma (MTC) represents a clinical challenge, especially in RET wild-type tumours, not amenable to target therapies. Moreover, chemotherapy has been always considered scarcely or completely ineffective in the treatment of metastatic MTC. We report the case of a 45-year-old man who underwent total thyroidectomy and central + right lateral compartment lymphadenectomy in May 2023 for bilateral MTC (max diameter 50 mm) with extrathyroidal extension to the strap muscles and macroscopic involvement in 2/23 lymph nodes. After surgery, laboratory tests showed Ctn 0.8 ng/l, CEA 3.3 µg/l (<5), CA19.9 46 kU/l (<40). RET genetic analysis was negative. From July 2023 to February 2024 Ctn, CEA and CA19.9 progressively increased (peak CA19.9 275 kU/l, CEA 9.4 µg/l). A 18F-DOPA PET/CT revealed increased uptake consistent with metastatic lymphadenopathy in the cervical region and mediastinal inlet. Therefore, in February 2024, the patient started cabozantinib 80 mg/day. After an initial decline in serum Ctn, CEA, and CA 19-9 and a partial response at PET/CT, in January 2025 CEA and CA 19.9 were significantly elevated (6 µg/l and 259 kU/l, respectively), and 18F-DOPA PET/CT documented disease progression at the cervicomediastinal level; thus, cabozantinib was increased to 120 mg/day. In March 2025 cabozantinib was discontinued due to progression, and off-label treatment with lenvatinib was started at a dose of 20 mg/day. Lenvatinib allowed to achieve transient stabilization but, in October 2025, biochemical testing and imaging confirmed a further disease progression. Therefore, the patient started off-label chemotherapy consisting of 5-fluorouracil (5-FU) 400 mg/m^2 intravenous (IV) bolus, followed by 5-FU 2400 mg/m^2 as a 48-h infusion, combined with dacarbazine 800 mg/m^2 IV in 30 minutes, every 14 days (Nocera *et al*., BJC 2000). At the last follow-up visit, after 8 cycles, tumour markers returned to the normal range (CA 19-9 29.1 kU/l, CEA 2.5 µg/l) and PET/CT scanning showed a significant reduction of the lymph node metastases. In conclusion, this case shows that, although conventional chemotherapy has been replaced in favour of TKI treatment, there are anecdotal cases in which it may be effective. Therefore, in case of failure of other approaches, chemotherapy should always be considered.

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PS3-04-08

Development and validation of a short-form thyroid cancer–specific quality of life questionnaire (KT-QOL-12)

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Background
The Korean Thyroid Cancer–Specific Quality of Life questionnaire (KT-QoL-49) is a validated instrument for assessing the multidimensional quality of life of thyroid cancer survivors. Its length limits feasibility in routine clinical practice and longitudinal studies. We aimed to develop and validate a concise short-form version (KT-QoL-12) while preserving the original multidimensional structure.
Methods
Item reduction was performed by selecting three representative items from each of the four domains (physical, psychological, social, spiritual), resulting in a 12-item questionnaire. Construct validity was evaluated using confirmatory factor analysis (CFA). Internal consistency was assessed using Cronbach's alpha. Concurrent validity was examined by correlating KT-QoL-12 scores with KT-QoL-49 total scores. Responsiveness was evaluated by comparing 6-month change scores.
Results
The KT-QoL-12 showed strong correlation with KT-QoL-49 at baseline (r = 0.89) and in 6-month change scores (r = 0.88), indicating high concurrent validity and preserved responsiveness. CFA supported the four-factor structure (RMSEA = 0.086, CFI = 0.950, TLI = 0.931, SRMR = 0.070). Internal consistency was acceptable to excellent across domains (Cronbach's $\alpha = 0.79$–0.91). Mixed-effects modeling showed no significant temporal effect ($P = 0.549$), consistent with the original instrument.
Conclusions
KT-QoL-12 maintains the multidimensional structure, reliability, and responsiveness of KT-QoL-49 while substantially reducing respondent burden. This brief instrument provides a practical and psychometrically sound tool for clinical assessment and research in thyroid cancer survivorship.

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PS3-04-09

Single-port robotic areolar (SPRA) surgery for thyroid, parathyroid, and mrnd: a 500-case experience

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Background
Single-port robotic areolar approach (SPRA) is a novel remote-access thyroid surgery technique using the da Vinci SP (Single Port) platform. It provides either excellent cosmesis and convenient approach to both thyroid glands and lateral cervical lymph nodes. Herein, I'd like to report cumulative 500 clinical results of SPRA surgeries.
Methods
Retrospectively analyzed a cohort of 500 consecutive SPRA procedures, performed by single endocrine surgeon. Vocal cord function was assessed by routine pre- and postoperative laryngoscopy, based on 6 months as permanent. Hypoparathyroidism was defined as PTH $\leq$5 at postoperative day 1 as transient, and PTH $\leq$10 at the outpatient visit after 6 months as permanent.
Results
Patients' age was 43.1$\pm$11.3 years and 94.8% were female. Lobectomy was 76.8% and total thyroidectomy was 15.8%. Total thyroidectomy with modified radical neck dissection (MRND) was 3.0% and re-do surgery was 2.2%. Parathyroidectomy for hyperparathyroidism performed in 10 cases. Vocal cord palsy occurred in 0.6% in transient and 0.2% in permanent. Transient and permanent hypoparathyroidism occurred in 19.8% and 6.6%. MRND yielded 31.16$\pm$12.71 retrieved and 8.74$\pm$5.43 metastatic nodes. Postoperative 3-month thyroglobulin under the $<$1.0 ng/m was 90.7%.
Conclusions
SPRA showed promising robotic neck surgery technique using da-Vinci SP platform, with favorable surgical and oncologic safety and minimally invasiveness.

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Clinical Cancer 8

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Ultrasound features can predict thyroid cancer histotypes and subtypes

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Objectives
Based on current knowledge, clinicians cannot reliably identify the most aggressive thyroid tumors using ultrasound (US) features and fine-needle aspiration biopsy (FNAB). This shortcoming hampers clinical decisions, particularly for subcentimeter nodules, for which total thyroidectomy, lobectomy, or active surveillance may be considered. This study aims to identify specific ultrasound patterns for differentiated thyroid cancer histotypes, mainly papillary thyroid carcinoma (PTC) subtypes.
Methods
We retrospectively correlated histological characteristics with US features suspicious for malignancy (hypoechogenicity, microcalcifications, irregular margins) in nodules from patients who underwent thyroidectomy between 2015 and 2018 due to cytology suspicious for follicular neoplasia, malignancy, or malignant results.
Results
Hypoechogenicity was observed in 50.9% of benign nodules (BN), 77.8% of PTC, 64.7% of follicular carcinomas (FTC), 66.7% of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), and 90.0% of poorly differentiated thyroid carcinomas (PDTC) ($P < 0.001$). Microcalcifications were present in 12.7% of BN, 44.4% of PTC, 5.9% of FTC, 11.1% of NIFTP, and 30.0% of PDTC ($P < 0.001$). Irregular margins were detected in 7.3% of BN, 37.4% of PTC, 5.9% of FTC, none in NIFTP, and 30.0% of PDTC ($P < 0.001$). Among PTC subtypes, hypoechogenicity was more common in tall cell PTC (TC-PTC) (95.5%), followed by classic PTC (C-PTC) (76.7%), solid PTC (S-PTC) (87.1%), and follicular PTC (F-PTC) (63.5%) ($P < 0.001$). Microcalcifications were more frequent in C-PTC (52.1%) and less common in TC-PTC (30.7%), F-PTC (21.2%), and S-PTC (32.3%) ($P < 0.001$). Irregular margins were observed in 39.1% of C-PTC, 59.1% of TC-PTC, 7.1% of F-PTC, and 35.4% of S-PTC ($P < 0.001$). The US pattern lacking all three suspicious features was seen in 41.8% of BN, 35.3% of FTC, 33.3% of NIFTP, and 10.8% of C-PTC. Conversely, the combination of hypoechogenicity and irregular margins without microcalcifications was identified in 1.8% of BN, 5.9% of FTC, 20.0% of PDTC, and 42.1% of TC-PTC ($P < 0.001$).
Conclusions
US features associated with malignancy mainly correlated with the PTC histotype. FTC, NIFTP, and F-PTC often showed benign US patterns (variable echogenicity, regular margins, no microcalcifications). Microcalcifications correlated with C-PTC, especially with hypoechogenicity and regular margins. Hypoechogenicity and irregular margins were linked to more aggressive tumors, including PDTC, TC-PTC, and S-PTC, with higher specificity when microcalcifications were absent, particularly in TC-PTC. Overall, US features of nodules suspicious at FNAB provide insights into tumor histotypes and PTC subtypes, supporting tailored management strategies

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PS3-05-02

Is lobectomy enough for medullary thyroid carcinoma? a tertiary center experience

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Introduction
Medullary thyroid carcinoma (MTC) accounts for 2–5% of thyroid cancers. Surgery is the only curative treatment; guidelines generally recommend total thyroidectomy (TT) ($\pm$ central neck dissection) to reduce recurrence and improve outcomes. Complications of thyroid surgery can severely impair quality of life. In selected unilateral, sporadic, early-stage MTC, lobectomy may achieve outcomes comparable to TT with fewer complications. We aim to assess the long-term oncologic and surgical outcomes of lobectomy as initial MTC treatment.
Methods
Retrospective review of MTC patients treated with lobectomy at our institution. Clinical and pathological data were assessed: tumour stage, histopathological features, recurrence, time to recurrence, current status, completion thyroidectomy and postoperative complications.
Results
Nine patients (66.7% female) were included, median age 60 years (IQR 56–69). All were diagnosed postoperatively after surgery for nodular thyroid disease. Initial stage was I ($n = 5$) or II ($n = 3$). No lymphovascular invasion, extrathyroidal extension, or multifocality; all resections were R0. Median tumour size was 1.3 cm (IQR 0.6–2.2). Postoperative calcitonin was 0.40 pg/mL (IQR 0.00–3.42) and carcinoembryonic antigen (CEA) was 2.64 ng/mL (IQR 2.11–3.42). No pathogenic germline *RET* variants were detected. One patient had completion thyroidectomy 41 months after lobectomy due to rising calcitonin (no contralateral MTC) and later developed cervical nodal recurrence after 9.24 years, treated with bilateral central and left lateral neck dissection. No distant metastatic disease occurred. After medium follow-up of 66.7 months (IQR 48,3-91,4), 8 patients had no evidence of disease and 1 had biochemical disease (doubling times: CEA 2.58 yrs; calcitonin 7.57 yrs). Recurrent laryngeal nerve injury occurred in one patient after initial surgery and in one after reoperation.
Conclusions
Our findings suggest lobectomy may be a feasible and safe option for carefully selected early-stage MTC patients, with strict postoperative surveillance. Small cohort size limits interpretation of the results. Notably, initial surgery was not based on a preoperative MTC diagnosis. Large collaborative studies are needed to clarify the role of lobectomy as a risk-adapted strategy.

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PS3-05-03

10 years active surveillance in a patient with low-risk papillary thyroid micro carcinoma

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Objectives
The purpose of this study is to present long term active surveillance in a patient with FNAB diagnosed papillary thyroid carcinoma.
Methods
A 50-year-old female patient came to our clinic in 2014. year, with a FNAB diagnosed papillary carcinoma of the right lobe of the thyroid. The patient was recommended for surgical treatment but was not inclined to it. The patient wanted to be included in active surveillance protocol.
Results
Findings before the start of active monitoring in 2014.: Ultrasound: Solid nodule in the right thyroid lobe measuring 9x8x8mm, with normal vascularization. No pathological lymph nodes in the remaining parts of the neck. Thyroid scintigraphy with Tc-99m pertechnetate: Scintigraphic "hot" nodule in the middle third of the right thyroid lobe with a tendency to develop autonomy. Repeated FNAB: small clusters of atypical thyrocytes, most likely papillary carcinoma. Laboratory: TSH 1.27; FT4 14.9; FT3 4.22; ATG 18.5; ATPO 17.9. We put the patient on supportive therapy with 100 mg l-thyroxin and regular 6 months checkup. Findings from 2022.: Thyroid scintigraphy with Tc-99m MIBI: The nodule in the right thyroid lobe is only discretely more metabolically active than the remaining thyroid tissue. There are no signs of metabolically active lesions in the remaining parts of the thyroid gland and neck, nor in the upper mediastinum. Findings from 2025.: Ultrasound: Solid nodule in the right thyroid lobe measuring 8x6x6mm, with normal vascularization. No pathological lymph nodes in the remaining parts of the neck. Laboratory: TSH 1.326; FT4 18.33; FT3 4.83; anti-TPO $<$ 28.0; anti-TG $<$ 1.3; The patient was not inclined to repeat FNAB, since the nodule did not grow.
Conclusion
Although most patients in the area served by our clinic prefer surgical treatment, this case shows that active monitoring is a valuable alternative model. Our personal opinion is that supportive therapy with l-thyroxine in such situations is very useful.

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Initial experience with modified baba robotic thyroidectomy using a three-port system

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Background
Robotic thyroidectomy using the bilateral axillo-breast approach (BABA) has been widely adopted due to its excellent cosmetic outcomes and stable surgical visualization. Although single-port surgery has been introduced to decrease invasiveness, it may be associated with limited instrument triangulation and restricted operative exposure. In contrast, the BABA approach provides a wide working space and symmetric surgical view, allowing safe dissection around critical structures. Therefore, we applied a reduced-port technique to the conventional BABA approach to minimize invasiveness while maintaining surgical stability evaluated the feasibility and safety of reduced-port robotic BABA thyroid lobectomy using a three-arm configuration.
Methods
This retrospective single-center study included patients who underwent surgery performed by a single experienced endocrine surgeon using the da Vinci Xi robotic system. All patients received reduced-port robotic thyroid lobectomy via the BABA approach. Unlike the conventional BABA technique, which utilizes four robotic arms, this modified approach employed a three-arm configuration to reduce working space. Specifically, the axillary port on the side of the resected lobe was omitted, and the procedure was carried out using the three remaining robotic arms. To maintain adequate operative exposure, the strap muscles were retracted with 3-0 Vicryl sutures. To ensure procedural safety during the initial implementation, patient selection was restricted to relatively young individuals with non-obese body habitus and clinically simple thyroid disease. Perioperative outcomes including operative time, estimated blood loss, hospital stay and postoperative pain score were evaluated
Results
Nine patients underwent reduced-port robotic thyroid lobectomy using the BABA approach. The cohort included 2 males and 7 females, with a mean age of 40.7 $\pm$ 8.5 years and a mean BMI of 23.2 $\pm$ 3.0 kg/m^2. The mean tumor size was 7.8 $\pm$ 2.9 mm (range 4–15), while 2 patients had extrathyroidal extension. The mean number of retrieved lymph nodes was 2.78 $\pm$ 2.3. All procedures were successfully completed using the three-arm reduced-port robotic technique without conversion to open surgery or the need for additional ports. The mean operative time was 110.2 $\pm$ 22.3 minutes, and the estimated blood loss was minimal (22.2 $\pm$ 10.9 mL). The mean hospital stay was 3.8 $\pm$ 0.4 days, and postoperative pain scores averaged 3.6 $\pm$ 0.5. There were no cases of recurrent laryngeal nerve palsy or other postoperative complications.
Conclusion
Reduced-port robotic thyroid lobectomy using a three-arm BABA technique appears to be technically feasible and safe in carefully selected patients.

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Prognosis of synchronous follicular and papillary thyroid cancer compared with follicular thyroid cancer

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Objective
Synchronous follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC) within the same thyroid lobe is rare, complicating diagnostic and therapeutic strategies. This study aims to enhance understanding of the clinical management and outcomes of these synchronous thyroid malignancies.
Methods
A retrospective study was performed to analyze the medical records of patients who underwent thyroidectomy for thyroid cancer at Gangnam Severance Hospital between March 2003 and December 2021. Of these, 258 cases were reviewed, including 44 patients with synchronous FTC and PTC (Group1) and 214 patients with FTC only (Group2). Clinical and pathological characteristics were analyzed.
Results
Group1 had a higher female proportion (84.1% vs. 74.6% in Group2) and a greater rate of total thyroidectomy (77.3% vs. 40.4%, $p<0.001$) and lateral neck dissection (9.1% vs. 0.9%, $p=0.008$). The extrathyroidal extension was more prevalent in Group1 (43.2% vs. 22.1%, $p=0.006$). Group2 had eight cases of recurrence, while Group1 showed superior disease-free survival.
Conclusion
The synchronous occurrence of FTC and PTC is rare but increasingly recognized. While patients with synchronous FTC and PTC had lower recurrence and metastasis rates, their long-term prognosis was similar to those with FTC only, as reflected by comparable disease-free survival curves.
Keywords
synchronous thyroid carcinoma, follicular thyroid carcinoma, papillary thyroid carcinoma

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PS3-05-06

The effect of thyroid ultrasound screening: analysis of 100 papillary thyroid cancer cases

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Objectives
The aim of our study was to evaluate the influence of the indication of neck ultrasound examination (US), on age, gender, treatment selection, and post-surgical stages according to the 2025 American Thyroid Association (ATA2025) and TNM classifications, in papillary thyroid cancer patients (PTC).
Methods
One hundred consecutively operated PTCs $\geq$10 mm in maximal diameter measured on US have been divided into three groups based on the reason for US. In 55 patients, US has been performed per protocol (palpable nodule, neck complaint, a nodule revealed by other imaging techniques, neck irradiation, familial/genetic background) (PR1); in 19 patients US was performed first, but they had palpable nodules (PR2); while in 26 cases no indication for US existed (screening in endocrine visit or other ultrasound screening, including carotid Doppler) (PR3).
Results
The mean age was 46.3$\pm$13.3, 44.6$\pm$14.1 and 37.4$\pm$11.8 years, PR1, PR2 and PR3, respectively. The mean nodule' volume was 7.14$\pm$10.0, 2.09$\pm$1.76 and 0.78$\pm$0.48 mL, PR1, PR2 and PR3, respectively. Compared to PR1+PR2, PR3 patients were younger and had smaller nodules ($P < 0.05$ for both features). Total thyroidectomy was performed in 43 (78.2%) PR1, in 15 (78.9%) PR2 and in 22 (84,6%) PR3 patients. RAI followed the surgical procedure in 36 (65.5%) PR1, in 13 (59.1%) PR2 and in 14 (53.8%) PR3 cases. There was no significant difference between the groups regarding treatment modalities. In group PR1 21 (38%) stage T1, 26 (47%) T2, 6 (11%) T3, and 2 (4%) T4 cases, in group PR2 14 (74%) T1 and 5 (26%) T2, while in group PR3 26 cases (100%) T1 cases were found. Regarding the ATA2025 classification, the ratio of low plus low-intermediate to intermediate-high plus high risk patients was 22:33, 11:8 and 18:8 for groups PR1, PR2 and PR3, respectively ($P < 0.05$ PR1+PR2 vs. PR3).
Conclusion
A quarter of patients operated on with PTC would have remained unrecognized if "off-protocol" screening had not been performed. Patients in PR3 were significantly younger and presented with smaller nodules. In 19% of all PTCs, ultrasound screening corrected the shortcomings of the system. Although all PR3 cases were stage T1 and had lower risk for recurrence, these patients were treated the same way as the PR1 and PR2 patients with significantly more advanced disease. The discrepancy may be partly explained by the fact that people with more anxious personalities are more likely to present for screening and find it harder to accept a more conservative approach for treatment.

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PS3-05-07

Comparing baba and gosta for robotic thyroidectomy: a beginner robotic surgeon's experience

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Introduction
Thyroidectomy leaves a visible scar on the anterior neck, which raises patient and surgeon interest in minimally invasive surgery. As a result, robotic thyroidectomy is increasingly performed. This study compares the Robotic Bilateral Axillo-Breast Approach (BABA) and Gas-Insufflation One-Step Transaxillary Approach (GOSTA) from the perspective of a beginner robotic surgeon.
Method
Between July 2023 and February 2025, patients who underwent robotic thyroidectomy by a single novice surgeon at Chonnam National University Hwasun Hospital were retrospectively reviewed. Operative approaches included BABA and GOSTA.
Result
A total of 17 BABA and 42 GOSTA cases were enrolled. While most demographic characteristics were similar between groups, operative time was significantly shorter in the GOSTA group. However, as the number of BABA cases was limited, the first 17 GOSTA cases were selected to match and compared with BABA. In this matched comparison, there were no significant differences in univariate or multivariate analysis. For more accurate assessment of the learning curve, Cumulative Summation (CUSUM) analysis was performed on GOSTA lobectomy cases. The CUSUM curve began to decline after 25 cases, suggesting that the learning curve was overcome. Comparison of operative time before and after this cutoff showed a significant difference ($\beta = 39.10$, 95% CI: 19.46 to 58.73, $P < 0.001$).
Conclusion
Both BABA and GOSTA can be safely performed by beginner surgeons. As no approach showed clear superiority, surgeons may choose the method based on institutional resources and personal preference.

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PS3-05-08

Thyroid core-needle biopsy. 879 biopsies in romania

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Background
Core-needle biopsy (CNB) is a valuable option to investigate a thyroid nodule, offering possibility of histological rather than cytological evaluation. However, it is still seen as a sophisticated and potentially dangerous investigation. We report our data regarding results, complications and patient satisfaction with CNB.
Methods
Retrospective analysis of the first 879 thyroid nodule CNBs performed in Romania. All CNBs were performed using 18G semi-automatic biopsy instruments. We used the Korean Thyroid Association reporting system (KTA-CNB) for histology reports.
Results
Of 879 CNBs, there were only 7 non-diagnostic results (0.8%). Among nodules which previously underwent FNA (fine-needle aspiration), CNB offered a conclusive result (either benign or malignant, KTA II, V and VI categories) in 71% of Bethesda 1, 74% of Bethesda 3, 54% of Bethesda 4 nodules. There were no non-diagnostic results in these nodules. We performed on average 2.1 passes per lesion. There were no major complications (none of complications required hospitalisation), some minor adverse events were limited to bruising, perithyroidal hematoma (1.5%), anxiety and panic attacks (1%) and pain during or after procedure (1.2%). Five patients (0.6%) developed transitory hoarseness which resolved spontaneously in 20-90 minutes. 200 patients completed a questionnaire at the end of procedure. Based responses, the anxiety level decreased from 4.9 (out of 10) to 0.8, pain level at the time of introduction of local anaesthesia was 2.1 (out of 10), during sampling was 0.8 and decreased to 0.6 after finishing procedure. 83% of patients declared CNB to be better or much better than they were expecting. 68% of patients who previously underwent FNA, also declared CNB to be better or much better. All patients declared they would recommend or strongly recommend CNB to someone who got recommendation for thyroid biopsy.
Conclusion
The CNB is a safe and reliable diagnostic procedure for thyroid nodules. It offers very low chance of non-diagnostic results, as well as clarification of diagnosis in case of non-diagnostic or inconclusive FNA. CNB is a procedure which improves patient experience by reducing the number of procedures needed to make a clinical decision. CNB is well-tolerated and recommended by the patients who underwent this procedure.

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PS3-05-09

How often is hemithyroidectomy enough? predicting the need for completion thyroidectomy in differentiated thyroid carcinoma

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Background
Surgical management of differentiated thyroid carcinoma (DTC) has shifted from routine total thyroidectomy (TT) to hemithyroidectomy (HT) in selected patients. This study evaluates how often patients meeting preoperative criteria for HT ultimately require completion thyroidectomy based on postoperative histopathology.
Methods
We conducted a retrospective review of 518 patients treated for DTC at King Abdulaziz University Hospital, Saudi Arabia (2015–2025). Patients with incomplete histopathology or preoperative imaging were excluded. Eligibility for HT was defined as tumor size $\leq$4 cm, absence of gross extrathyroidal extension or suspicious lymph nodes or bilateral nodules on imaging, and no distant metastasis. We determined the proportion of patients requiring completion thyroidectomy based on: lymph node (LN) metastasis (>2 mm), vascular invasion (VI), distant metastasis (DM), or aggressive histological variants (AHV).
Results
Fifty-six patients met the inclusion criteria. Of these, 41 (73.2%) underwent TT and 15 (26.8%) underwent HT; 22 (39.3%) had compartmental LN dissection. Overall, 22 patients (39.3%) met criteria for completion thyroidectomy. Indications included central LN metastasis alone in 14/22 (63.6%), VI alone in 3/22 (13.6%), AHV alone in 2/22 (9.0%), combined DM and VI in 1/22 (4.5%), and combined LN metastasis and AHV in 1/22 (4.5%).

Conclusion
Nearly 40% of patients considered eligible for HT preoperatively required completion TT, most commonly due to central lymph node metastasis, followed by vascular invasion.

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PS3-05-10

Hormone-producing distant metastases in HRAS-mutated high-grade differentiated thyroid carcinoma arising from follicular thyroid carcinoma

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Introduction
Hyperfunctioning distant metastases from differentiated thyroid carcinoma (DTC) are uncommon, although an increasing number of cases have been described. We report a case of hormone-secreting pulmonary and skeletal metastases from HRAS-mutated high-grade differentiated thyroid carcinoma (HGDTC) derived from follicular thyroid carcinoma (FTC), which demonstrated a marked response to radioactive iodine (RAI) therapy.
Case presentation
A 68-year-old woman was referred for a evaluation of an enlarging thyroid mass and multiple pulmonary nodules that were detected after initiation of antithyroid medication for Graves' disease. Surgical pathology following total thyroidectomy revealed HGDTC originating from FTC. Molecular analysis using next-generation sequencing identified an HRAS Gln61Arg mutation. Despite thyroidectomy, biochemical thyrotoxicosis persisted. A post-therapeutic whole-body radioiodine scan demonstrated intense iodine uptake in multiple lung nodules and a lesion of the left iliac bone lesion, indicating hyperfunctioning distant metastases. The patient underwent two courses of RAI treatment. Following therapy, thyroid function transitioned from thyrotoxicosis to hypothyroidism. In addition, follow-up chest computed tomography revealed a marked decreased in the size and number of pulmonary metastatic lesions.
Conclusion
Hyperfunctioning distant metastases from DTC represent a rare but clinically significant cause of persistent thyrotoxicosis after thyroidectomy. This case underscores the importance of considering hormone-producing metastases when thyrotoxicosis persists despite removal of the thyroid gland. It also illustrates that RAI therapy can be highly effective when metastatic lesions retain iodine avidity. Furthermore, oncogenic alterations such as HRAS mutations may play a role in the development of hormone-producing metastatic disease and may provide insights into tumor differentiation status as well as potential therapeutic responsiveness.

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Clinical Cases (cancer) 2

PS3-06-01

Prolonged survival in anaplastic thyroid carcinoma following multimodal treatment: a case report

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Introduction
Anaplastic thyroid carcinoma (ATC) is one of the most aggressive human malignancies and is historically associated with extremely poor prognosis. Median survival is approximately 5-6 months, and therapeutic options remain limited, particularly in patients without the BRAFV600E mutation. We report a case of a patient with ATC treated with multiple therapeutic approaches, with survival of more than three years after diagnosis.
Case report
A 56-year-old man with a 20-year history of multinodular goiter was referred to our Endocrinology Department in December 2022 due to rapid enlargement of a cervical mass over two months. Computed tomography (CT) revealed a heterogeneous solid lesion arising from the left thyroid lobe (116 × 101 × 106 mm) extending to the supraclavicular region and thoracic inlet, with suspected invasion of internal jugular vein and contact with the trachea. Fine needle aspiration and core needle biopsy confirmed ATC. Next-generation sequencing did not identify pathogenic mutations or gene fusions. The patient underwent total thyroidectomy with tumor resection on December 21, 2022. Histopathology confirmed ATC. Seventeen days later, systemic chemotherapy with carboplatin and paclitaxel was initiated. After two cycles, imaging revealed a left supraclavicular lesion, which was surgically excised in April 2023. Weekly paclitaxel was continued until June 2023, combined with radiotherapy (66 Gy/ 33 fractions). Subsequent FDG-PET demonstrated new suspicious lesions involving cervical lymph nodes, subcutaneous tissue, and bone. Lenvatinib (24 mg/day) was started in July 2023 but discontinued in August due to an infected malignant cervical wound. Two months later, CT showed no evidence of disease, however, subsequent imaging demonstrated the appearance of a new mediastinal lymph node, leading to further surgical resection. In November 2024, recurrence in the anterior mediastinum was identified. Lenvatinib was restarted in December 2024 but disease progression occurred. The patient subsequently received four cycles of carboplatin plus paclitaxel, again followed by progression. Immunotherapy with pembrolizumab was initiated in June 2025. Due to continued progression of the mediastinal lesion, palliative radiotherapy (20 Gy/ 5 fractions) was delivered in January 2026 with continuation of pembrolizumab The patient is currently awaiting imaging reassessment and remains alive 3 years after de diagnosis.
Conclusion
The management of ATC remains highly challenging and prognosis is generally poor. However, multimodal treatment strategies, combining surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, may provide meaningful clinical benefit in selected patients. This case illustrates how sequential and combined therapeutic approaches may contribute to prolonged survival in ATC.

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PS3-06-02

Papillary thyroid carcinoma presenting with renal metastasis: a rare case report

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Introduction
Papillary carcinoma is the most common thyroid malignancy and is usually associated with good outcome. However, some variants of papillary carcinoma behave aggressively and have a poor prognosis. Usual sites of metastasis include lungs and, less frequently, bone. Renal metastasis is rare and may mimic a primary renal malignancy. This clinical case reports an aggressive papillary thyroid carcinoma (PTC) with synchronous renal and pulmonary metastasis at presentation.
Case report
A 66-year-old woman with longstanding thyroid nodules was referred after an ultrasound identified a high-suspicion right thyroid nodule (EU-TIRADS 5) and a partially necrotic ipsilateral level III lymph node. Initial FNA of the thyroid nodule showed atypia of undetermined significance. Repeated FNAs of both thyroid and lymph node were non-diagnostic due to extensive necrosis, with limited immunocytochemistry. Thyroglobulin (Tg) needle-washout from the lymph-node aspirate was markedly elevated, suggesting metastatic thyroid carcinoma. CT staging showed multiple bilateral pulmonary nodules and a hypervascular left renal mass, initially suspicious for primary renal neoplasm. During the investigation, she developed hoarseness. The patient underwenttotal thyroidectomy with right modified radical and central neck dissection (levels II–IV and VI–VII) with neuromonitoring. Invasion of

the trachea and right NLR was detected. Histology revealed extensively invasive and angioinvasive papillary thyroid carcinoma with a classic component and an exuberant diffuse multinodular follicular-variant component. Biopsies of lung and renal lesions confirmed metastases of thyroid origin (TTF-1, thyroglobulin, PAX8 positive) - pT4aN1b(7/39)R1M1, AJCC 8th Edition. The postoperative course was complicated by tracheal fistula requiringcervical drainage with tracheal suture and muscle patch repair, followed bytracheostomy. After recovery, radioiodine therapy (200mCi I-131) was administered. Post-therapy scintigraphy imaging demonstrated iodine-avid pulmonary and renal metastases. Next-Generation Sequencingpanel test of the thyroid tumour tissue identified actionable NRAS and PIK3CA pathogenic variants. The tracheostomy was successfully closed, and the patient regained full oral intake following speech and swallowing therapy.

Conclusions

This case underscores a rare presentation of an aggressive metastatic PTC with renal and lung involvement, which is associated with an unfavourable prognosis. Renal metastasis should be considered in patients with thyroid cancer and a renal mass. Tg needle-washout can be decisive in confirming metastatic differentiated thyroid carcinoma when FNA cytology is repeatedly non-diagnostic. Management requires multidisciplinary planning, including surgery, radioiodine, and consideration of local and/or systemic therapies.

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PS3-06-03

When the effect persists: a rare case of sustained response to lenvatinib two years after discontinuation in papillary thyroid carcinoma

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Introduction

Differentiated thyroid cancer usually has a favourable prognosis; however, some patients develop progressive disease refractory to radioactive iodine (RAI). In this setting, tyrosine kinase inhibitors, particularly lenvatinib, are effective treatments. Although lenvatinib improves progression-free survival, long-term use may be limited by clinically relevant toxicities, often requiring dose reduction or temporary interruption.

Case Report

A 90-year-old independent and cognitively intact woman underwent total thyroidectomy with central neck dissection in 2013 for a 2-cm infiltrative multifocal papillary thyroid carcinoma with minimal extrathyroidal extension. She received multiple RAI treatment between 2013 and 2021 (cumulative dose 306 mCi). Post-therapy scintigraphy after the last treatment showed minimal uptake in the anterior cervical region. Over time, thyroglobulin levels progressively increased under thyroid-stimulating hormone suppression (anti-thyroglobulin antibodies negative), reaching 48 ng/mL. In 2021, computed tomography (CT) identified a small lesion adjacent to the trachea. In 2022, she developed dyspnoea and stridor. CT showed a 3.5 cm mass invading the trachea with critically airway compromise, as well as millimetric pulmonary nodules suspicious for metastases. A tracheal stent was placed, followed by external beam radiotherapy (30 Gy in 10 fractions). Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) demonstrated intense uptake in the peritracheal lesion (SUVmax 29.9). Lenvatinib 20 mg/day was initiated in January 2023, and subsequent molecular testing revealed a BRAF V600E mutation. A partial response was achieved, with complete resolution of the peritracheal lesion and stability of the pulmonary nodules. Lenvatinib was discontinued in February 2024 because of progressive non-healing venous ulcers, which resolved completely after 10 months of supportive care. Given the patient's good clinical condition and the absence of disease progression, a strategy of close surveillance was adopted without resuming lenvatinib. Nearly two years later, she remains clinically, biochemically, and radiologically stable. CT in February 2026 showed no cervical recurrence and stable pulmonary nodules. ^{18}FDG-PET revealed no metabolically active disease. The most recent thyroglobulin level was 4.98 ng/mL.

Conclusions

We report an elderly patient with a sustained partial response persisting two years after lenvatinib discontinuation. Disease control is usually maintained only during therapy, and withdrawal may increase the risk of progression. Short treatment interruptions have been associated with better outcomes, whereas abrupt discontinuation may trigger rapid progression ("flare phenomenon"). Data on sustained responses after long-term discontinuation are rarely reported. This case suggests that durable tumour control after lenvatinib discontinuation may occur in selected patients, highlighting the need for further investigation of treatment duration and discontinuation strategies.

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PS3-06-04

Management of advanced medullary thyroid carcinoma with inoperable metastases - the role of somatic ret mutation testing and systemic therapy

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Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignant tumor derived from the calcitonin-producing parafollicular C-cells, either sporadic or hereditary, in which comprehensive biochemical screening is mandatory for multiple endocrine neoplasia (MEN)-associated endocrinopathies, as well as testing for the RET proto-oncogene mutation, germline or somatic. Complete surgical resection is the cornerstone of curative treatment; however, in case of metastases, persistent disease or recurrence, systemic treatments are required.

Case report

We present the case of a 33-year-old female who initially presented with a multinodular goitre and markedly elevated serum calcitonin (416 times higher than the upper normal limit (UNL)). The imaging revealed bilateral thyroid nodules and suspicious thoracic lymph nodes, while the biochemical screening for MEN was negative. She underwent total thyroidectomy with bilateral cervical lymphadenectomy – the pathology report confirmed multicentric MTC with lymph node metastases. Immunohistochemistry showed positivity for chromogranin A and somatostatin receptors (SSTR 2 and SSTR5), with a Ki67 of 3%. Germline RET mutation testing was negative. Two months post-surgery, calcitonin remained elevated (256 × UNL) and carcinoembryonic antigen (CEA) was slightly increased (2 × UNL). Extensive imaging evaluation (neck ultrasonography, cervical, thoracic and cranial CT, FDG PET-CT and bone scintigraphy) didn't identify structural disease. For 6 years, biochemical markers were gradually decreased and imaging studies remained negative. During the follow-up evaluation, calcitonin had a sudden increase (810 × UNL) and imaging revealed multiple bilateral cervical and mediastinal lymphadenopaties, while octreotide scintigraphy showed somatostatin receptor-positive lesions. She underwent cervical surgery with extensive bilateral lymphadenectomy – multiple MTC metastases – while the cardiothoracic surgical team deemed the mediastinal metastases inoperable due to the intimate contact with the large vessels. Two months postoperatively, calcitonin increased (1013 × UNL) and she developed symptoms suggestive of carcinoid syndrome, with persistent diarrhoea – somatostatin analogue and systemic tyrosine kinase inhibitor were initiated. Six months later, somatic RET mutation testing was positive, while calcitonin remained stable under systemic treatment. Follow-up imaging with neck ultrasonography and head MRI were negative, with the chest CT showing no evidence of lesion progression. The patient remains clinically stable, with good tolerance to treatment and regular follow-up every six months.

Conclusions

This case highlights the clinical course of advanced sporadic MTC with a positive somatic RET mutation and illustrates the role of systemic therapy in controlling unresectable metastatic disease. Targeted treatments may achieve sustained biochemical stabilization and prevent structural disease progression, thereby improving long-term disease control and patient quality of life.

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PS3-06-05

Rapid recovery of recurrent laryngeal nerve palsy after lenvatinib plus pembrolizumab in anaplastic thyroid cancer: a case report

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Introduction
Recurrent laryngeal nerve (RLN) palsy is a common presenting feature of anaplastic thyroid cancer (ATC), reflecting locally invasive disease. Recent advances in targeted therapy combined with immunotherapy have shown promising anti-tumor activity and may lead to rapid functional recovery. We report a case of ATC with early reversal of vocal cord palsy after treatment with lenvatinib plus pembrolizumab.
Case Presentation
A 56-year-old man presented with hoarseness, dyspnea, and a rapidly enlarging right supraclavicular mass. Initial core needle biopsy at another hospital suggested poorly differentiated adenocarcinoma. Thyroid ultrasonography revealed multifocal hypoechoic nodules in both lobes (right mid-lobe, 1.8 cm; left mid-lobe, 0.5 cm). Repeat fine-needle aspiration of the solid portion of a 5-cm right supraclavicular lymph node demonstrated metastatic papillary thyroid carcinoma (PTC). Given the rapid clinical progression, the disease was diagnosed as ATC dedifferentiated from PTC. Next-generation sequencing of the metastatic lymph node identified a*BRAF*mutation and a tumor mutational burden of 18.8 muts/Mb. FDG-PET and chest CT revealed multiple small pulmonary metastases and an L3 vertebral metastasis. Treatment with lenvatinib 20 mg daily and pembrolizumab 200 mg every 2 weeks was initiated. Remarkably, the patient reported voice normalization merely 11 days after treatment initiation. Follow-up otolaryngologic examination confirmed the recovery of right vocal cord mobility, which had initially been impaired. After 7 months of combination therapy, marked reduction of the primary tumor and metastatic lymphadenopathy was observed, with an ongoing radiologic response.
Conclusion
This case suggests that lenvatinib plus pembrolizumab may induce rapid recovery of RLN palsy together with substantial tumor regression in advanced ATC. Early improvement in vocal cord mobility may serve as a clinically meaningful indicator of a prompt response to systemic therapy

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PS3-06-06

A challenging triad in thyroid evaluation: low free T4 with normal TSH, a giant thyroid nodule, and vascular ehlers–danlos syndrome

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Introduction
Discordant thyroid function tests may pose diagnostic challenges. Persistently low free thyroxine (FT4) with normal thyroid-stimulating hormone (TSH) is unusual and may suggest central hypothyroidism. The presence of a large thyroid nodule may further complicate evaluation. Additionally, Vascular Ehlers–Danlos syndrome is a rare connective tissue disorder associated with vascular fragility by vascular fragility and abnormal connective tissue architecture, which may increase surgical complexity and perioperative risk.
Case Report
A 38-year-old woman with multinodular goiter was referred for reassessment of thyroid nodules. Her medical history included type 2 diabetes mellitus, hypertension, dyslipidemia, polycystic ovary syndrome, and vascular Ehlers–Danlos syndrome (COL3A1 mutation). Thyroid ultrasound showed a dominant left nodule measuring 42 × 22 × 55 mm, solid, isoechoic, with regular margins (EU-TIRADS 3), with additional smaller nodules in the right lobe and isthmus. Fine-needle aspiration cytology reported a follicular neoplasm. Thyroid function tests showed persistently low FT4 with normal TSH over several years (TSH 1.7–2.7 mIU/l; FT4 0.53–0.87 ng/dL), without clinical hypothyroidism. Thyroid autoantibodies were negative and pituitary MRI was normal. Due to the nodule size and indeterminate cytology, left hemithyroidectomy was performed. Histopathology revealed a minimally invasive follicular thyroid carcinoma with capsular invasion and no angioinvasion. The case was discussed in a multidisciplinary oncologic meeting and completion thyroidectomy was recommended, but has not yet been performed.
Conclusion
This case highlights the diagnostic challenge of persistently low FT4 with normal TSH and the management of large thyroid nodules with indeterminate cytology. Vascular Ehlers–Danlos syndrome also raises important surgical considerations due to vascular fragility.

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PS3-06-07

Thyroglobulin, the lifesaver in a case of papillary thyroid carcinoma

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Introduction
Papillary carcinoma is the most common type of thyroid gland cancer, representing about 80 to 85% of cases. It originates in the follicular cells of the thyroid. The most common symptom is the presence of a nodule in the anterior region of the neck. Regional lymph node metastases are common and may be present in up to 50% of cases. Diagnosis is mainly made through imaging tests and cytological confirmation.
Objective
To present and reveal the uncommon diagnosis of a very common pathology.
Materials and methods
Clinical case of a 27-year-old male patient with no personal history. Admitted to the Endocrine and Cervical Surgery consultation due to alterations in thyroid ultrasound. Asymptomatic. No history of cervical irradiation. No family history of thyroid pathology.
Results
Cervical ultrasound with a polylobulated nodule measuring 31mm, multiple focus of calcification and microcalcifications (EU-TIRADS 5). Analytically euthyroid. Aspiration biopsy of a thyroid nodule and level 2 lymphadenopathy was performed, resulting in findings consistent with lymphocytic thyroiditis and insufficient material in the lymph node. Simultaneous tissue thyroglobulin and calcitonin levels were measured in the lymph node, yielding a positive result for thyroglobulin of 359.68 ng/ml. The patient underwent total thyroidectomy with left central and lateral cervical lymph node dissection (levels 2-4 and 6-7) due to a biochemical diagnosis of papillary thyroid carcinoma with lateral cervical metastases, confirmed by the pathological anatomy of the surgical specimen (pT3aN1b(1/34)R0). The postoperative period was uneventful, and the patient was discharged on postoperative day 3. Ablative therapy (150 mCi of Iodine-131) was proposed. No evidence of recurrence to date.
Discussion and Conclusion
Generally, the prognosis for papillary thyroid carcinoma is good, especially in early stages and in younger patients. In young people, however, timely diagnosis is crucial, and biopsies are not always positive; in particular, tissue samples from needle flushes are a diagnostic tool.

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PS3-06-08

The odd couple: collision nodal metastasis in concurrent medullary and papillary thyroid carcinoma

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The synchronous occurrence of Medullary (MTC) and Papillary Thyroid Carcinoma (PTC) is reported in up to 19% of MTC cases, most frequently representing incidental papillary thyroid microcarcinomas. Current literature suggests that this association is largely coincidental, with no evidence of reciprocal influence on biological behavior or synergistic impact on patient prognosis. While the coexistence of these two distinct malignancies is well-documented, the presence of "collision" metastases, where both MTC and PTC components reside within the same lymph node, remains an exceedingly rare phenomenon with limited reporting in clinical series. A 59-year-old male was

referred for a multinodular goiter. Physical examination revealed a 2cm nodule in the right lobe. Laboratory evaluation showed elevated CEA (6.6ng/mL N<) and calcitonin (189pg/mL; N <) with normal TSH. Ultrasonography identified two nodules in right thyroid lobe: a TI-RADS 3 with 37mm and a TI-RADS 5 with 11mm. Fine-needle aspiration cytology of the 11mm nodule revealed MTC. There was no evidence of lymphadenopathy in the lateral cervical compartments. The patient underwent total thyroidectomy with central neck dissection. Histopathology revealed two distinct primary malignancies: an 11mm low-grade medullary thyroid carcinoma (pT1b) in the right lobe, and a 1mm classic variant papillary microcarcinoma (pT1a) in the isthmus with an inframillimetric focus in the left lobe, indicating intrathyroidal dissemination. The lymph node status (N1a) was particularly noteworthy: out of 10 retrieved nodes, 6 were metastatic. The distribution showed independent and combined spread: 1 node contained only MTC metastasis, 4 nodes contained only PTC metastasis, and 1 node exhibited concomitant metastasis from both MTC and PTC (confirmed by immunohistochemistry/calcitonin expression). Postoperative calcitonin decreased to 25.4pg/mL. The patient is currently undergoing further investigation: CT scan and bone scintigraphy identified a lytic lesion in the 6th left rib and indeterminate hepatic nodules, raising suspicion for distant metastasis. A liver MRI and PET-CT were requested to complete staging. This case illustrates the rarity of mixed lymphatic spread in dual thyroid carcinomas. While concurrent MTC and PTC are relatively frequent, their clinical course and prognosis are usually dictated by the MTC component, which carries the higher biological risk. While the identification of 'collision' metastases is pathologically striking, it does not fundamentally mandate a departure from standard therapeutic protocols or necessarily imply more aggressive biological behavior. It does, however, provide a compelling scientific rationale for investigating the tumor microenvironment and the mechanisms that facilitate synchronous metastatic spread.

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PS3-06-09

Thyroid lymphoma in a young patient, a rare entity

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Introduction
Diffuse large B-cell lymphoma (DLBCL) of the thyroid is a rare and aggressive malignancy, frequently associated with Hashimoto's thyroiditis and most frequently affecting women over 60 years of age. It arises from malignant transformation and uncontrolled proliferation of B lymphocytes. Clinically, it typically presents as a rapidly enlarging cervical mass, often accompanied by compressive symptoms such as dysphagia, dyspnea and hoarseness.
Case report
A 34-year-old male with non-relevant past medical history, went to his primary care facility, presenting with cough, odynophagia, dysphagia and progressive cervical mass. He also reported fatigue, night sweats and an unintentional weight loss of 4 kg. Physical examination revealed thyroid enlargement with limited mobility and palpable cervical lymphadenopathy. Cervical ultrasound demonstrated heterogeneous parenchyma to the right of the isthmus and in the inferior portion of the right thyroid lobe, showing hypervascularization and a heterogeneous hypoechoic nodular lesion with irregular lobulated margins measuring 25 × 21 mm, classified as TIRADS 5. Bilateral cervical lymphadenopathy was also identified, including a right-sided nodal conglomerate measuring 35 × 28 × 15 mm. These findings raised suspicion of thyroid malignancy with cervical nodal metastasis, although Hashimoto's thyroiditis with reactive lymphadenopathy could not be excluded. Thyroid function tests were normal and anti-thyroid antibodies were negative. Fine-needle aspiration cytology of both the thyroid lesion and cervical lymph nodes showed morphological features that raised suspicions for a proliferative disorder. Staging CT of the neck, chest, abdomen, and pelvis revealed mediastinal lymphadenopathy and a right paramediastinal pulmonary lesion measuring 39 × 26 mm. Differential diagnosis included a lymphoproliferative process or primary pulmonary malignancy with nodal dissemination. Following multidisciplinary discussion, an incisional surgical biopsy of the pulmonary lesion was performed, revealing pulmonary tissue infiltration by diffuse large B-cell lymphoma. Bone marrow examination showed no evidence of lymphoma infiltration. The patient subsequently started chemotherapy with the R-CHOP regimen. After six cycles, PET imaging demonstrated no metabolically active disease, indicating complete remission.
Conclusions
Thyroid lymphoma represents a rare, diagnostically challenging malignancy. Although this patient presented mainly with compressive cervical symptoms without associating respiratory manifestations, the concomitant involvement of two organs may difficult the identification of the primary tumor site. Prompt recognition and early systemic chemotherapy, typically with R-CHOP, are critical to improving prognosis.

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PS3-06-10

Synchronous presentation of three distinct thyroid carcinoma subtypes: a case report

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Among all diagnoses of thyroid nodules, 5% to 15% are malignant. The simultaneous presence of two or more carcinoma subtypes in a single organ is an extremely rare event, occurring in less than 1% of cases. This study aims to report a rare case of the simultaneous presence of three thyroid carcinoma subtypes. Furthermore, it emphasizes the relevance of defining a specific subtype to guide clinical follow-up and therapeutic strategies. The patient is a 71-year-old female with an incidental finding of five thyroid nodules during a carotid Doppler ultrasound (USG). One of the nodules was classified as TI-RADS 5, located in the lower pole of the left lobe (volume = 2.3 cc). Fine-needle aspiration biopsy (FNAB) was indicated and performed, resulting in Bethesda IV, and the immunohistochemical panel was positive for Thyroglobulin (2H11 + 6E1). Other markers were negative. Total thyroidectomy was indicated and performed. The histopathological examination confirmed nodular multifocality, with emphasis on the lesions located in the lower and upper poles of the left lobe, both characterized by firm consistency and superficial opacity. Antibody panels were performed on both nodules. Three distinct histological types were identified in the analyzed sample, comprising follicular variant papillary microcarcinoma, oncocytic variant papillary carcinoma, and medullary microcarcinoma. A multidisciplinary review of the case was conducted for diagnostic stratification according to current guidelines and planning of relevant adjuvant therapy. After the thyroidectomy, the patient underwent TSH suppression at levels of 0.1 to 0.5 mUI/l. Radioactive iodine remnant ablation at a dose of 30 mCi was also indicated. Clinical follow-up showed normalization of laboratory markers. Ultrasound demonstrated no remnant thyroid tissue. Currently, the patient is asymptomatic, stable, and undergoing periodic follow-up. The concomitance of three distinct histological subtypes of thyroid carcinoma in a single patient represents a clinical scenario of extreme rarity and diagnostic complexity. This report reiterates the importance of thorough histopathological and immunohistochemical analysis, combined with a multidisciplinary therapeutic strategy, to ensure oncological control and long-term clinical stability.

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Clinical Cases (cancer) 3

PS3-07-01

Lobectomy for sporadic medullary thyroid carcinoma (SPMTC): first reported case in greece

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Introduction
In spMTC without ultrasonographic indications of lymph node involvement, total thyroidectomy with prophylactic lymph node dissection (LND) of the central

neck compartment (CNC) is recommended, while controversy exists when calcitonin levels are ≥200 pg/mL regarding the need for additional bilateral lateral LND. Intraoperatively documented stromal desmoplasia (DSR) is being studied as a new independent predictive factor for the presence of infiltrated cervical lymph nodes.
Case report
A 25-year-old male, following sudden swelling in the right cervical region, reffered for thyroid-neck ultrasound which revealed a hypoechoic nodule on the right thyroid lobe measuring 2.09x1.51 cm surrounded by thin hypoechoic halo, without calcifications, and high elasticity index; 2 indeterminate LNs of the ipsilateral CNC measuring up to 1.76 cm were revealed, as well. Serum calcitonin levels: 477 pg/mL. Fine needle aspiration biopsy (FNAB) of the suspected nodule was indicative of MTC with calcitonin levels in the washout fluid measuring up to 293,429 pg/mL, while FNAB of the largest indeterminate LN was negative for malignancy (calcitonin washout: 2 pg/mL). Patient's family history was negative for hereditary MTC and related genetic syndromes, which was confirmed by *RET* germline sequencing (exons: 5,8,10,11,13,14,15,16) where no pathologenic mutation was detected. Serum CEA levels: 21 ng/mL, while plasma metanephrines-normetanephrines were within normal limits. After patient's informed consent, a right thyroid lobectomy and removal of 7 LNs of the ipsilateral CNC was performed. Intraoperative frozen sections were evaluated via real-time teleconsultation by expert pathologists, in collaboration with Essen University Hospital. DSR was absent thus, the surgery was completed without removal of the left thyroid lobe. Calcitonin levels, 3rd day postoperatively: 5.65 pg/mL. Histopathological examination revealed low-grade non-invasive MTC (mitoses: 2/2 mm^2, Ki67: 3-4%, no tumor necrosis) with 7 benign lymph nodes. 3 months after surgery, Calcitonin: 1.99 pg/mL, CEA: 0.77 ng/mL.
Conclusions
This is the first reported case in Greece of spMTC treated by lobectomy. Classification of the neoplasm as low-grade combined with the immediate fall of calcitonin levels, as well as the absence of highly suspicious ultrasonographic features, is consistent with the literature and the accumulating data towards a personalized surgical approach to MTC, with the absence of DSR serving as one of the prognostic factors that should be taken into account.

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PS3-07-02

Primary thyroid lymphoma - case report

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Introduction
Primary thyroid lymphoma (PTL) is an uncommon pathological entity, accounting for approximately 5% of all thyroid malignancies. To be classified as PTL, the disease must be confined to the thyroid gland and neck lymph nodes, without evidence of contiguous extension or distant metastasis at the time of diagnosis. Patients typically present with a rapidly growing painless mass in the thyroid gland in their sixth-seventh decades. Pressure symptoms are often present. Classic B-type symptoms of fever, night sweats and weight loss are less common. Clinical examination can detect diffuse or nodular thyroid enlargement. Preexisting Hashimoto's thyroiditis is a recognized risk factor for PTL. The diagnosis of PTL remains challenging, and surgical intervention is frequently required to establish a definitive diagnosis. Treatment selection and prognosis in thyroid lymphoma are determined by both the histological subtype and the stage of the disease. Positron emission tomography (PET) is the most convenient method for staging, with the detection of regional-distant disease and monitoring the treatment response. Treatment options include surgery, radiotherapy, chemotherapy and their combination.
Case report
A 60-year-old woman was referred to the endocrine surgery unit presenting with compressive cervical symptoms associated with a rapid and painless thyroid enlargement. Her medical history was unremarkable, with no reported history of cervical irradiation, familial thyroid cancer, or Hashimoto's thyroiditis. Laboratory evaluation revealed only a mild elevation of thyroid-stimulating hormone (TSH). Thyroid ultrasound revealed a well-defined solid nodule in the right lobe extending into the isthmus, measuring 32×30×20 mm, with predominantly isoechoic echotexture and hypoechoic areas. There were no pathologic lymph nodes. Fine Needle Aspiration of the thyroid nodule was benign (Bethesda II). The patient underwent right lobectomy, with an uneventful postoperative recovery. Histopathological analysis confirmed the diagnosis of diffuse large B-cell lymphoma of the thyroid. Postoperative staging with computed tomography (CT) and PET showed no evidence of additional lesions, supporting the diagnosis of PTL, stage IE according to the Ann Arbor classification. The patient subsequently received chemotherapy.
Conclusions
Primary thyroid lymphoma, despite its rarity, requires early identification because management and prognosis differ substantially from other thyroid malignancies. Given the inconsistent diagnostic accuracy of fine-needle aspiration, each case warrants careful and individualized assessment.

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PS3-07-03

Cribriform-morular variant of thyroid carcinoma with aggressive behavior: new successful therapeutic approaches

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Introduction
Cribriform-morular variant of thyroid carcinoma (CMV-TC) occurs predominantly in young women. It frequently presents in patients with familial adenomatous polyposis, which results from germline mutations in the *APC* gene. Although these tumors often show indolent behavior, some cases have been associated with aggressive features. CMV-TC shows elevated expression of estrogen and progesterone receptors, which have been considered potential therapeutic targets in the literature. We report the case of a male patient with an aggressive CMV-TC.
Case Report
A 41-year-old man with a 139 months (M) follow-up (FU) after total thyroidectomy for a 8 cm CMV-TC nodule with extrathyroidal extension and angioinvasion. No regional lymph node or distant metastases were found. A de novo germline mutation in the *APC* gene (c.1690C>T, p.Arg564Ter) was detected. A germline mutation in the *MUTYH* gene was found. No somatic mutations, including *BRAF*, *NRAS* or *TERT* promoter mutations, were detected. Prophylactic total colectomy was performed for extensive polyposis without oncological disease. Serum thyroglobulin levels remained undetectable since the first radioiodine therapy (2 M FU) despite persistent disease adhering to the trachea. External beam radiotherapy (66 Gy, 8 M FU) proved to be ineffective, and a second radioiodine therapy confirmed radioiodine-refractory disease. Multiple pulmonary metastases were detected (43 M FU) and progressed in size and number. Due to progression of the cervical lesion, radiofrequency ablation (52 M FU) and laryngectomy (63 M FU) were performed. Histological findings were similar. Therapy with 24 mg of lenvatinib was initiated (94 M FU), but was suspended due to the development of a tracheoesophageal fistula (103 M FU). A 70% reduction in metastatic volume was observed according to RECIST criteria. Since these tumours are characterized by high expression of estrogen and progesterone receptors, a study of sex hormone levels (96 M FU) was conducted, which revealed a sustained serum pattern of low testosterone, elevated estradiol, and low-normal gonadotrophins, compatible with aromatase increased activity, albeit in the absence of gynecomastia. Testicular, adrenal, or pituitary pathology was not found. Letrozole 2,5 mg was initiated (105 M FU), and goserelin (3,6 mg monthly) added (110 M FU). This treatment resulted in sustained reductions in estrone and estradiol levels and > 70% reduction in metastatic volume according to RECIST criteria, with disappearance of several lesions.
Conclusions
The use of lenvatinib followed by letrozole combined with goserelin yielded a reduction in pulmonary metastases in aggressive CMV-TC. The underlying molecular mechanisms are currently under investigation.

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PS3-07-04

Primary thyroid paraganglioma with synchronous retroperitoneal paragangliomas: a rare case of multifocal disease

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Introduction
Primary thyroid paraganglioma is an exceptionally rare neuroendocrine tumor, with fewer than 70 cases reported. These tumors likely arise from inferior laryngeal paraganglia and can mimic medullary thyroid carcinoma morphologically, creating diagnostic challenges. Approximately 80% are associated with germline succinate dehydrogenase mutations. Multifocal disease with concurrent retroperitoneal paragangliomas is extremely rare and raises concern for hereditary paraganglioma syndromes.
Case Report
A 54-year-old woman presented with an 18-month history of progressive dysphonia, dyspnea, and cervical prominence. Her medical history included asthma and hypercholesterolemia. Physical examination revealed a hard palpable thyroid mass with audible stridor. The patient was urgently admitted for multidisciplinary evaluation given the locally invasive thyroid tumor with critical airway compromise. Cervical CT showed marked enlargement of the left thyroid lobe with heterogeneous density causing severe tracheal deviation and approximately 90% airway narrowing. The mass appeared contiguous with the posterior tracheal wall, suggesting invasion, and contacted the esophagus. Chest–abdomen–pelvis CT revealed small pulmonary nodules and two retroperitoneal masses anterior to the great vessels, all with hypervascular enhancement. A pericardiophrenic lymph node was noted. Fine-needle aspiration supported the diagnosis of paraganglioma. Laboratory evaluation showed thyroid function tests were normal, and an elevated chromogranin A with normal calcitonin.
Conclusions
This case represents a rare presentation of primary thyroid paraganglioma with concurrent retroperitoneal paragangliomas. Functional imaging with 68Ga-DOTATATE PET-CT would aid comprehensive staging and treatment planning. Management may include surgical resection when feasible, radiotherapy for local control, or emerging systemic therapies such as belzutifan for advanced disease. This case underscores the need for heightened awareness of this rare entity and systematic evaluation for multifocal disease in all patients diagnosed with thyroid paraganglioma.

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PS3-07-05

Life-threatening airway obstruction in isolated hras-mutated papillary thyroid carcinoma: an unexpected clinical phenotype

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Introduction
Aggressive papillary thyroid carcinoma (PTC) with rapid local invasion is frequently associated with BRAF V600E and TERT promoter co-mutations. In contrast, activating RAS mutations – including HRAS – represent an alternative MAPK-pathway oncogenic driver, are typically linked to follicular-patterned tumours, indolent clinical course, and favourable prognosis. Rapidly progressive airway compromise from histologically differentiated PTC is exceedingly rare and typically associated with poorly differentiated or anaplastic variants. We report a case of isolated HRAS-mutated, histologically differentiated PTC exhibiting rapidly progressive local invasion with critical airway obstruction within 6 months, highlighting a previously underrecognised aggressive phenotype in RAS-driven thyroid carcinoma.
Case Report
A 71-year-old man with no thyroid disease history developed progressive dyspnoea and odynophagia over 6 months. He presented with acute type 2 respiratory failure, marked inspiratory stridor and hypoxaemia requiring emergency orotracheal intubation. Videolaryngoscopy revealed extrinsic supraglottic compression with infiltrative mucosal changes. Cervico-thoracic CT scan demonstrated a calcified right thyroid nodule with critical tracheal stenosis, and a hypodense "horseshoe-shaped" mass (48×40 mm) circumferentially encasing the hypopharynx and proximal trachea with paratracheal mediastinal lymphadenopathy – radiological features consistent with highly aggressive locoregional invasion. No distant metastases were identified. Biochemistry revealed markedly elevated thyroglobulin (>10,000 ng/mL), low-normal TSH and negative thyroid antibodies. Thyroid FNA confirmed malignancy with features consistent with differentiated thyroid carcinoma. Notably, despite clear radiological evidence of transmural airway invasion, multiple endoscopic samplings – including microlaryngoscopic biopsies, bronchial aspirate, bronchoalveolar lavage and endobronchial biopsies – were uniformly negative for malignancy, revealing profound sampling-imaging discordance. Emergency tracheostomy was performed; intra-operative findings confirmed tracheal fixation with suspected transmural tumour invasion. Disease was deemed unresectable. Molecular profiling revealed isolated HRAS mutation with negative BRAF V600E – situating this exceptionally aggressive tumour within a RAS-driven subset typically associated with indolent disease. Lenvatinib 24 mg daily was initiated, achieving partial radiological response (48×40 mm to 43×38 mm at one month). The patient died shortly thereafter from complications related to locally advanced airway-invasive disease.
Conclusions
This case demonstrates that isolated HRAS-mutated PTC, despite histologically differentiated morphology, can present with rapidly progressive, life-threatening airway invasion clinically indistinguishable from anaplastic carcinoma, highlighting that RAS mutations do not invariably predict indolent disease behaviour. Rapidly progressive upper airway symptoms in thyroid malignancy warrant urgent cross-sectional imaging and early airway protection. Timely referral to specialist centres enables molecular profiling and consideration of targeted therapy for unresectable disease.

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PS3-07-06

Primary small cell neuroendocrine carcinoma of the thyroid: a rare and aggressive tumor

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Introduction
Primary small cell neuroendocrine carcinoma (SCNEC) of the thyroid is an extremely rare malignancy, with only a few well-documented cases reported and highly aggressive behavior. The differential diagnosis is challenging and must include medullary thyroid carcinoma, primary thyroid lymphoma, and metastatic small cell carcinoma, particularly from pulmonary origin, and its management requires a multidisciplinary approach.
Case Report
A 54-year-old patient with a history of chronic obstructive pulmonary disease (COPD) and HIV infection presented with a 1.5-month history of a rapidly enlarging cervical mass, progressive dysphonia, and dyspnea. Physical examination revealed a firm 7 cm mass in the anterior cervical region. Neck ultrasound demonstrated an irregular hypoechoic infiltrative lesion involving both thyroid lobes and bilateral suspicious cervical lymph nodes. Fine-needle aspiration cytology with immunocytochemistry revealed a small cell neuroendocrine tumor with bilateral lymph node metastases. Staging studies including cervicothoracoabdominopelvic computed tomography, FDG-PET, PET-DOTA-NOC, brain magnetic resonance imaging, and bronchoscopy excluded another primary tumor but demonstrated locally advanced unresectable disease, with more than 50% of the brachiocephalic arterial trunk involvement and tracheal invasion, causing approximately 50% luminal obstruction. Following multidisciplinary discussion, urgent chemotherapy with cisplatin and etoposide was initiated. After four cycles, restaging imaging showed a near-complete response. The patient subsequently underwent total thyroidectomy with bilateral radical cervical lymph node dissection. Two weeks later, a second-stage procedure with mini-sternotomy and mediastinal lymph node dissection was performed due to suspected mediastinal lymph node involvement. The postoperative period was complicated by right vocal cord paresis, COPD exacerbation, tracheal fistula and Enterococcus faecium bacteremia requiring intensive care admission. Histology report confirmed diagnosis and adjuvant radiotherapy was proposed but could not be completed due to treatment intolerance and repeated COPD exacerbations. Next-generation sequencing revealed an EGFR mutation without available targeted therapeutic option. Eight weeks after surgery, restaging showed rapid disease recurrence with a 12 cm cervicomediastinal mass and liver metastases. Chemotherapy was restarted, but disease progression occurred three months later, leading to treatment with topotecan. The patient died approximately 11 months after diagnosis.

Conclusion
Primary thyroid SCNEC is a highly aggressive tumor with poor prognosis. Multidisciplinary management is mandatory and induction chemotherapy may enable surgical resection in selected patients. However, rapid recurrence despite aggressive treatment emphasizes the need for further research and the development of more effective therapeutic strategies.

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PS3-07-07

Metastatic hepatocellular carcinoma to the thyroid gland

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Background
Metastasis of hepatocellular carcinoma (HCC) to the thyroid gland is extremely rare, with fewer than a dozen cases reported in the literature. Despite the thyroid's rich vascularity, clinically apparent metastases are uncommon. These lesions can mimic primary thyroid neoplasms, complicating diagnosis and treatment.
Case Presentation
A 73-year-old male with a history of HCC presented with an asymptomatic thyroid nodule detected on surveillance 18F-FDG PET/CT. Imaging revealed a hypermetabolic lesion in the right thyroid lobe. Neck ultrasonography showed a suspicious hypoechoic mass (K-TIRADS 4). Fine-needle aspiration was inconclusive. Hemithyroidectomy was performed for definitive diagnosis. Histopathology showed features consistent with HCC, and immunohistochemical staining confirmed hepatocellular origin (HepPar-1+, ARG1+, AFP+, TTF-1–, PAX8–, thyroglobulin–). No evidence of primary thyroid carcinoma was found. The patient was managed with active surveillance, and follow-up at 6 months showed no recurrence.
Discussion
Thyroid metastasis from HCC is rare and often discovered incidentally or during evaluation for a thyroid mass. In many cases, fine-needle aspiration may be insufficient to establish a diagnosis. Immunohistochemistry plays a critical role in differentiating metastatic HCC from primary thyroid malignancies. Despite the advanced nature of metastatic disease, isolated thyroid involvement may have a relatively indolent course. Surgical resection can aid in diagnosis and symptom control, and in select patients, may contribute to prolonged survival. Clinicians should maintain a high index of suspicion for metastatic disease in patients with a history of HCC who present with new thyroid lesions.
Conclusion
This case highlights the importance of considering metastatic HCC in the differential diagnosis of thyroid nodules in patients with liver cancer history. Multimodal imaging and immunohistochemistry are essential for accurate diagnosis. Early recognition of thyroid metastasis may allow for effective surgical intervention and tailored management strategies.

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PS3-07-08

When rising thyroglobulin does not mean cancer recurrence: the impact of graves' disease on thyroid remnants

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Introduction
Serum thyroglobulin (Tg) is a key biomarker used in the follow-up of patients with papillary thyroid carcinoma (PTC). However, its interpretation can be challenging in the setting of Graves' disease (GD) since residual thyroid tissue growth can be stimulated by TRAb, potentially increasing Tg levels.
Case presentation
A 52-year-old woman was referred to the Thyroid Cancer Clinic. She had previously undergone right hemithyroidectomy at the age of 45 for a >4cm nodule (benign). At the age of 51, she developed GD and failed to achieve remission with methimazole (MM), leading to left hemithyroidectomy. Histology revealed a 4mm follicular-subtype PTC. Her medical history included rheumatoid arthritis and fibromyalgia. Medication included levothyroxine 100µg od, methotrexate, folic acid, cyclobenzaprine and omeprazole. Two months after surgery, laboratory tests showed: TSH 0.41µIU/mL; fT4 13.3pmol/l (7.9–14.4); Tg 2.56ng/mL; undetectable thyroglobulin antibodies (TgAb). Neck ultrasound (US) revealed a 16 mm hypoechoic nodular formation in the right thyroid bed. Ten months post-operatively evaluation showed TSH 0.01µIU/mL; fT4 15.2pmol/l; Tg 5.12ng/mL; TgAb 4.4U/mL (<4.0); TSH receptor antibodies (TRAb) 4.6U/l (<1.5) and US demonstrated growth of the right-sided hypoechoic nodule to 20 mm. Levothyroxine was progressively reduced and eventually discontinued. Three months later, the patient remained thyrotoxic with Tg rising to 24.62 ng/mL and MM was initiated, gradually tapered and stopped. Whole-body scintigraphy showed increased uptake in the lower right thyroid bed and mild uptake in the remaining bed. She initially remained euthyroid, but after 12 months developed overt hyperthyroidism with progressive Tg elevation (19.75 ng/mL to 41.07 ng/mL). She subsequently underwent radioactive iodine therapy (I-131, 10.12 mCi) and started levothyroxine replacement. At the last follow-up, 16 months after I-131, she was euthyroid (TSH 0.47µIU/mL; fT4 13.8pmol/l; fT3 5.9pmol/l), with Tg 0.91ng/mL, negative TgAb, and ultrasound showing a 15 mm thyroid remnant in the right thyroid bed.
Conclusion
In this case, considering the low risk of PTC recurrence, autoimmune stimulated growth of residual thyroid tissue causing Tg increasing levels was the most likely diagnosis. However, it illustrates the diagnostic challenge of interpreting laboratory and sonography findings in patients with differentiated follicular cell-derived thyroid cancer and concomitant GD. Awareness of the described pitfalls is essential to prevent misinterpretation and avoid unnecessary interventions.

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PS3-07-09

Vertebral metastasis as initial presentation of differentiated thyroid cancer: two case reports and literature review

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Introduction
Vertebral metastasis is rarely the initial presenting symptom leading to a diagnosis of thyroid cancer. Clear cell morphology observed in a diagnostic bone biopsy can further complicate the identification of the primary tumor. We report two cases highlighting different clinical presentations, diagnostic challenges, and management strategies.
Case Presentations
Case 1 describes a 68-year-old man with progressive paraparesis due to T4–T6 vertebral metastasis, revealing a high-grade papillary thyroid carcinoma. **Case 2** involves an 89-year-old man with incidental L4 vertebral metastasis, ultimately diagnosed as clear-cell follicular thyroid carcinoma. Both patients underwent total thyroidectomy, targeted vertebral interventions, and adjuvant therapy.
Conclusions
Vertebral metastasis may be the first manifestation leading to thyroid carcinoma diagnosis. Multimodal imaging, histopathology, immunohistochemistry, and molecular profiling are essential for accurate diagnosis. Early recognition and combined surgical and adjuvant management optimize short-term neurological outcomes.

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PS3-07-10

Radioembolization for liver-dominant progression in medullary thyroid carcinoma: a case report

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy arising from parafollicular C cells, frequently metastatic at presentation. Although systemic therapies have improved outcomes, liver dominant progression remains a major therapeutic challenge. Radioembolization has emerged as a promising liver directed treatment modality in selected patients. We report the case of an 18 year old male diagnosed with MTC in 2022, who underwent total thyroidectomy with central and bilateral selective neck dissection. A local recurrence in January 2023 required a repeat bilateral cervical lymphadenectomy. Persistent and rapidly progressive disease was confirmed 3 months after this surgery, with a calcitonin doubling time of 20 days, carcinoembryonic antigen (CEA) of 13.1 ng/mL, and extensive cervical involvement, supradiaphragmatic lymph node, hepatic, and bone metastases (confirmed in FDG-PET/CT). After vandetanib failed, selpercatinib was initiated, yielding a marked biochemical response, resulting in a favorable therapeutic response with marked biochemical improvement (calcitonin - 3532 to 2.24 pg/mL) and radiological regression. By June 2025, the patient developed hepatic progression despite maintained systemic control prompting referral for radioembolization with Yttrium-90 resin microspheres. All right lobe approached was performed, resulting in a tumor mean absorbed dose of 117.1 Gy. Following the procedure, the patient demonstrated a marked biochemical response (calcitonin - 7956 to 1718 pg/mL) and radiological improvement. This case illustrates the complexity of managing metastatic medullary carcinoma, where no structured treatment algorithm exists and it is sometimes necessary to employ multiple approaches simultaneously to achieve the best efficacy, highlighting the importance of a multimodal treatment strategy. Radioembolization represents a valuable therapeutic option in selected patients, with the potential to control hepatic disease, improve symptoms, stabilize tumor markers, and extend progression free survival, while maintaining a favorable safety profile and low toxicity rates. Thus, this clinical case reinforces the role of radioembolization as a complementary strategy for patients with MTC and predominant hepatic involvement.

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Miscellaneous (cancer) 2

PS3-08-01

Distinct multifocal papillary thyroid carcinomas with different lymph node metastases: a case report

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Introduction
Papillary thyroid carcinoma is the most common cancer of the thyroid gland, accounting for almost 80% of all cases. It typically has an indolent clinical course and a good prognosis. However, it frequently presents as multifocal disease that is characterized by the presence of two or more histologically distinct tumor foci within the thyroid gland, which may occur in a single lobe or bilaterally. These lesions may arise either from intrathyroidal spread of a single primary tumor or from independent clonal events.
Case report
We report the case of a 64-year-old female patient with no significant personal or family medical history. The patient was evaluated for a right cervical mass measuring approximately 2cm. The cervical ultrasound revealed, in the right thyroid lobe, a hypoechoic nodule, with irregular margins, measuring approximately 15 mm in its largest dimension (EU-TIRADS 5). At right level III, a lymph node measuring approximately 2.5 cm in its largest axis was identified. It was rounded, with irregular borders and heterogeneous, suspicious for metastatic involvement. Fine needle aspiration of both the thyroid nodule and the lymph node was performed, giving the diagnosis of metastatic papillary thyroid carcinoma. The was submitted to total thyroidectomy with right cervical lymph node dissection (levels II–IV, VI, and VII) without complications. Histopathological evaluation of the surgical specimen revealed two distinct classical papillary thyroid carcinomas within the thyroid gland (pT2(m)N1bR1). Both tumors demonstrated metastatic involvement of lymph nodes in the central compartment. The case was discussed at a multidisciplinary group, and adjuvant treatment with radioactive iodine was decided. Given the presence of two morphologically distinct primary tumors, next-generation sequencing analysis was requested for both lesions in order to further characterize their molecular profiles and assess potential genetic differences between the tumor foci.
Conclusion
Genetic heterogeneity represents a challenge in cancers such as multifocal papillary thyroid carcinoma, in which multiple synchronous but separated tumors may coexist. Although multifocality is relatively common in papillary thyroid carcinoma, the presence of metastases arising from genetically distinct tumor foci is rare. In the era of personalized medicine, treatment decisions often rely on the molecular analysis of the tumor. This case highlights the importance of evaluating multifocal tumors individually, especially when there are morphological differences between tumor foci. Identifying such cases is clinically relevant, as genetically distinct tumors within the same patient may require different therapeutic approaches, particularly when lymph node metastases are present, as in this case.

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PS3-08-02

Papillary thyroid carcinoma presenting with follicular cytology and lateral neck metastasis: a case report

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Introduction
Thyroid nodules with indeterminate cytology may present diagnostic challenges, particularly when associated with suspicious cervical lymphadenopathies. Follicular-pattern cytology cannot reliably distinguish benign from malignant lesions without histological evaluation.
Case report
A previously healthy 20-year-old caucasian woman presented with a painless right cervical mass noticed in February 2025. Cervical ultrasound revealed a 17 mm heterogeneous thyroid nodule in the right lobe (EU-TIRADS 4) and a 35–38 mm heterogeneous right laterocervical mass with cystic areas and calcifications, suspicious for malignant disease. Fine-needle aspiration cytology of the thyroid nodule was reported as follicular neoplasm (Bethesda IV). Cytology of the cervical lesion was non-diagnostic, raising differential diagnoses of ectopic thyroid tissue vs nodal metastasis. Given the suspicious cervical adenopathy, the patient underwent total thyroidectomy with central and right lateral cervical lymph node dissection. Histopathology revealed multifocal bilateral papillary thyroid carcinoma (largest focus 15 mm) with lymph node metastases. Metastatic disease was found in the central compartment and right lateral neck compartment (3/21 nodes in the lateral compartment; largest with 32 mm), corresponding to pT1b(m) pN1b disease. Postoperatively, the patient had no surgical complications and subsequently underwent radioiodine therapy (30 mCi I-131). Post-therapy whole-body scintigraphy demonstrated residual thyroid tissue in the cervical region without distant uptake.
Conclusions
This case highlights that papillary thyroid carcinoma may initially present with follicular-pattern cytology, emphasizing the importance of correlating cytology with imaging and clinical findings. The presence of suspicious cervical lymphadenopathies should raise concern for metastatic disease and influence the surgical approach.

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PS3-08-03

Elevated thyroid autoantibodies as a potential risk factor for papillary thyroid carcinoma: a case report

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Background
Papillary carcinoma is the most common form of thyroid cancer that originates from follicular cells and has an excellent prognosis. Its pathogenesis is multifactorial, involving genetic mutations, environmental factors, family history, and chronic inflammation of the thyroid gland. Among the various risk factors, autoimmune thyroid disease has been increasingly recognized as a

potential contributor to the development of PTC. Several studies have reported that positive Anti-thyroglobulin antibodies (TgAb) are associated with an increased risk of PTC and may also correlate with tumor characteristics such as multifocality and capsular invasion. Persistent inflammation may promote oxidative stress, DNA damage, and repeated cycles of follicular cell injury and regeneration, which can increase the risk of malignant transformation. Autoimmune-related hypothyroidism is associated with elevated TSH levels, which may lead to increased stimulation of thyroid follicular cells. In this case, we are highlighting the potential role of high anti-TG antibodies as a risk factor for papillary thyroid carcinoma.
Case Report
A 32-year-old Caucasian male presented with complaints of weight gain, increased appetite, discomfort in the neck area, and severe weakness. The family history is negative for malignancy. Initial laboratory assessment demonstrated subclinical hypothyroidism and impaired fasting glucose, while thyroid ultrasonography revealed multiple suspicious nodules with cervical lymph node enlargement. Further investigations demonstrated severely elevated Anti-TPO and Anti-TG antibody titers, and calcitonin was negative. Fine-needle aspiration (FNA) of two suspicious thyroid nodules and cervical lymph nodes confirmed papillary thyroid carcinoma with lymph node metastases. Chest CT showed no distant metastatic lesions. The patient underwent total thyroidectomy with lymphadenectomy, followed by radioactive iodine therapy (150 mCi). Histopathological evaluation demonstrated multifocal papillary thyroid carcinoma with metastasis to regional lymph nodes (N9). Postoperatively, the patient developed transient hypoparathyroidism accompanied by hypocalcemia, along with progressively decreasing thyroid antibody titers and thyroglobulin levels. Levothyroxine was started on suppressive dosage. Treatment comprised suppressive levothyroxine therapy in addition to metformin with lifestyle changes, calcitriol, and calcium supplementation.
Conclusion
This case illustrates how markedly elevated thyroid antibody titers may affect thyroid structure and potentially contribute to the development of PTC. Chronic autoimmune inflammation of the thyroid gland may create a microenvironment that promotes cellular damage and malignant transformation of thyroid follicular cells. This case underscores the importance of careful and further monitoring of biochemical markers that may play a role in the development of papillary thyroid carcinoma. Further research is needed to better clarify the role of thyroid autoimmunity in thyroid carcinogenesis.

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PS3-08-04

Role of potassium channel tetramerization domain (KCTD) containing protein 14 in papillary thyroid cancer

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Objectives
KCTD14 is a member of Potassium Channel Tetramerization Domain (KCTD) protein family, involved in oligomerization, protein-protein interactions and various biological processes. Many KCTD proteins have been linked to the development and to the progression of various types of cancer. However, several members of this family remain poorly characterized, including KCTD14. Thyroid cancer (TC) is the most common endocrine malignancy, characterized by a rapidly increasing incidence worldwide and heterogeneous clinical behavior. This study aims to explore the expression and the functional role of KCTD14 in TC.
Methods
The Cancer Genome Atlas-Thyroid Cancer (TCGA-THCA) dataset was interrogated to evaluate KCTD14 expression levels in thyroid tumor tissues compared to healthy thyroid tissues. Western blot and qRT-PCR were carried out to evaluate KCTD14 expression levels across a panel of thyroid cancer cell lines. Stable transfections were performed in cultured cells to modulate KCTD14 protein expression. Immunofluorescence was performed to uncover the localization of the protein. Proteomic profiling was conducted to identify pathways altered by KCTD14 modulation.
Results
In silico analyses revealed increased mRNA expression of KCTD14 in tumor tissues compared to normal thyroid tissues. Immunofluorescence analysis revealed that KCTD14 is predominantly localized in the cytoplasm. Proteomic analysis indicated that pathways modulated by KCTD14 are mainly involved in metabolism.
Conclusions
Our preliminary results suggest a potential role of KCTD14 in thyroid tumor progression.

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PS3-08-05

Coexistence of BRAF V600E–mutated papillary thyroid carcinoma and pleomorphic xanthoastrocytoma in a young patient: a case report

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Background
The BRAF V600E mutation is a common oncogenic driver in papillary thyroid carcinoma (PTC) and is associated with activation of the MAPK signaling pathway and more aggressive clinicopathological features. The same mutation is also detected in a substantial proportion of pleomorphic xanthoastrocytomas (PXA), a rare astrocytic tumor typically occurring in young individuals. However, the coexistence of these two BRAF-mutated neoplasms in the same patient has rarely been described.
Case Presentation
A 28-year-old male was incidentally found to have a thyroid nodule during cardiac echocardiography in October 2025. Subsequent thyroid ultrasound revealed a suspicious 19.8 mm subcapsular nodule in the left thyroid lobe with possible minimal extrathyroidal extension and suspicious central compartment lymph nodes. Fine-needle aspiration cytology confirmed papillary thyroid carcinoma (Bethesda VI). The patient underwent total thyroidectomy with central neck dissection in November 2025. Histopathology demonstrated a 2.2 cm oncocytic variant of PTC with capsular invasion and metastases in 12 of 28 central compartment lymph nodes. Surgical margins were negative. Molecular analysis identified a heterozygous BRAF V600E mutation. Postoperative ultrasound showed no residual thyroid tissue or pathological lymph nodes. Given the extent of nodal involvement (>5 lymph nodes) and molecular findings, adjuvant radioactive iodine therapy (150 mCi) was administered under recombinant human TSH stimulation. Stimulated thyroglobulin prior to treatment was 0.3 ng/ml with negative anti-thyroglobulin antibodies. Post-therapy scintigraphy demonstrated focal uptake in the upper thyroid bed and left lateral cervical region. The patient also has a history of BRAF V600E–positive pleomorphic xanthoastrocytoma (WHO grade 2), treated with three surgical resections (2017, 2020, 2020), with no recurrence on recent brain MRI.
Conclusion
This case highlights the coexistence of two rare BRAF V600E–mutated neoplasms in a young patient. Although BRAF V600E is typically a somatic mutation, the presence of distinct MAPK-driven tumors raises questions regarding potential shared molecular susceptibility and underscores the importance of long-term multidisciplinary follow-up.

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PS3-08-06

IODINE-131 therapy >1 Ci in high-risk differentiated thyroid cancer: clinical profile and patient outcomesiodine-131 therapy >1 Ci in high-risk differentiated thyroid cancer: clinical profile and patient outcomes

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Introduction

Radioactive iodine therapy (RAI) is a cornerstone in the management of high-risk differentiated thyroid cancer (DTC). Some patients demonstrate incomplete responses, requiring repeated treatments. Exceeding the 1 Ci threshold raises concerns regarding the benefit-risk balance. The objective of this study is to describe the clinical characteristics, therapeutic course, and outcomes of DTC patients who received a cumulative dose of >1 Ci of I-131.

Materials and Methods

We conducted a retrospective study including 6 patients followed at the Endocrinology Department of the Central Army Hospital of Algiers. All patients had metastatic DTC with persistent iodine-avid lesions and had received a cumulative I-131 activity of at least 1 Ci.

Results

Among the 6 patients, 5 were female and 1 male, with a mean age of 64.5 years. All were initially classified as high risk according to ATA 2015. Metastatic sites included bone (6/6), lung (2/6), lymph nodes (3/6), and brain (1/6). Baseline thyroglobulin levels were >500 ng/mL in 5 patients. All patients received between 1 and 1.4 Ci of I-131, delivered over 6 to 8 treatment cycles. Biological evolution showed a progressive decrease in thyroglobulin to <100 ng/mL in 4 patients, associated with reduced uptake on post-therapy scintigraphy. RAI-refractory disease was identified in 4 patients. No significant adverse events related to I-131 were reported.

Discussion

The continuation of RAI beyond 600 mCi remains controversial. Our series demonstrates a partial response, with decreased thyroglobulin levels, but no patient achieved complete remission. Clinical tolerance to cumulative high-dose therapy was acceptable; however, the oncologic benefit appears limited, highlighting the need to carefully assess the risk-benefit ratio before exceeding 1 Ci.

Conclusion

Early detection of RAI-refractory status, access to targeted therapies, and a multidisciplinary management approach are crucial to optimize outcomes in high-risk patients. This study emphasizes the importance of individualized evaluation prior to administering very high cumulative doses of I-131 and integrating modern therapeutic options for refractory DTC.

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PS3-08-07

Role of locoregional therapy in thyroid carcinoma metastases: a case series

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Introduction

Locoregional therapies (LTs) are considered part of the multimodal treatment of oligometastatic and radioiodine-refractory advanced thyroid carcinoma (TC), in carefully selected patients.

Case Reports

Case 1. Patient #1, diagnosed with a pT2Nx tall-cell variant papillary thyroid carcinoma (PTC), underwent total thyroidectomy (TX) and radioiodine therapy (RAI) (250 mCi) in 2019. During follow-up, a biochemical incomplete response was observed with stable thyroglobulin (Tg) levels (8–10 µg/l) until March 2023, when a FDG-PET positive painful osteolytic metastasis (MET) in the pubic bone was found and then treated with CT-guided cryoablation, resulting in Tg drop (412→20 µg/l) and symptoms improvement. **Case 2.** Patient #2, affected by oncocytic poorly differentiated thyroid carcinoma (PDTC) harboring a PTEN mutation, underwent TX followed by RAI (150 mCi) in 2019. Nodal recurrence required right supraclavicular and laterocervical lymph node (LN) dissections (2022-2024). Thereafter, an incomplete biochemical and structural response was observed, with Tg increase (15.3→106 µg/l) and multiple FDG-PET avid metastatic LNs. In 2025, CT-guided cryoablation of the largest metastatic LN was performed, with Tg reduction (106→23 µg/l) and disappearance of FDG-uptake. **Case 3.** Patient #3, affected by a pT4aN1 PTC, harboring BRAF V600E mutation, underwent TX with lymphadenectomy, RAI, and external beam radiotherapy due to tracheal and esophageal invasion. Distant METs led to treatment with Dabrafenib and Trametinib, achieving partial response. Later, a symptomatic MET developed in the right iliac bone and was treated with CT-guided cryoablation, resulting in pain resolution. **Case 4.** Patient #4, affected by a pT3a oncocytic follicular PDTC, underwent TX and RAI (550 mCi). Follow-up imaging revealed a progressive painful osteolytic MET in the T11vertebral soma with focal FDG uptake. In December 2025 the lesion was treated with CT-guided radiofrequency thermal-ablation, with consequent absent residual FDG uptake and symptom relief.

Conclusions

LTs represent a valuable option for oligometastatic radioiodine-refractory TC improving symptoms and biochemical and radiological response. These approaches may be complementary to systemic therapies and/or delay their submination.

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PS3-08-08

Secondary thyroid malignancy in patients with history of craniospinal irradiation and acquired GHD under growth hormone therapy

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Introduction

Radiotherapy exercises therapeutic effect through DNA damage into cancerous cells but is associated with malignant transformation via damage to double stranded DNA strands (1), chromosomal translocation (2), and incorrect DNA repair. The brain tumour itself, surgery to head and neck area, and craniospinal irradiation causes damage to the hypothalamic- pituitary region and is a known risk factor for growth hormone deficiency (GHD) in cancer survivors. We report two patients with secondary thyroid malignancy detected by long term survivor surveillance programme whilst on growth hormone (GH) for acquired GHD.

Case reports

Patient 1 underwent surgery and craniospinal radiotherapy for anaplastic ependymoma at two years of age. Post operative magnetic resonance imaging (MRI) showed no recurrence. He had GHD and was started on GH since the age of 10 years. Thyroid ultrasound done 2 years later as part of the survivorship surveillance program revealed a 1.1cm mixed solid and cystic nodule which turned out to be a classic papillary carcinoma (PTC). Total thyroidectomy was performed. GH was stopped in view of thyroid malignancy and he is now in remission. Patient 2 suffered from medulloblastoma at the age of 5 years, treated with surgery and craniospinal irradiation. MRI showed no recurrence and he was started on GH at eight years of age. A right thyroid nodule was detected on surveillance ultrasound when he was 10 years old which turned out to be follicular variant of PTC. Thyroidectomy was performed and growth hormone was stopped for one year in view of thyroid malignancy.

Conclusion

We have presented two young cancer survivors, who had received craniospinal irradiation and developed asymptomatic thyroid malignancy which was detected by our survivorship surveillance program. GH was stopped at diagnosis of thyroid malignancy since GH may permit for oncogenic transformation, proliferation, although GH is not believed to be causative (3). Regular thyroid ultrasound is informative and future prospective studies are required to inform the timing to restarting growth hormone in these survivors who experience secondary malignancy.

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PS3-08-09

Expression of SGLT2 in papillary thyroid carcinoma

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Introduction

Papillary Thyroid Carcinoma (PTC) is the most prevalent endocrine malignancy, accounting for over 85% of all thyroid cancers. The growing evidence shows diabetes mellitus (DM) and obesity increase the risk of thyroid neoplasms, suggesting a pivotal role for metabolic dysregulation in thyroid oncogenesis. Metabolic reprogramming, characterized by the Warburg effect, is a hallmark of PTC progression. Beyond the upregulation of glucose transporters (GLUTs), the aberrant expression of the Sodium-Glucose Cotransporter 2 (SGLT2) has been demonstrated in several types of cancer, including thyroid cancer cells. It suggests an additional active transport mechanism that may be involved in tumor metabolism and progression. Our study aims to analyze SGLT2 expression in a retrospective cohort of patients with PTC and to correlate it with clinical, molecular, and pathological characteristics.

Methods

A sample of 40 patients with PTC who underwent thyroidectomy between 2014 and 2015 and were screened for mutations in the *BRAF*, *RAS*, and *pTERT* genes was characterized for the prevalence of metabolic and cardiovascular comorbidities at the time of PTC diagnosis. Expression of SGLT2 was evaluated by immunohistochemistry.

Results

At diagnosis of PTC, the sample composed of 37 women and 3 men, presented an average age of 55,8 ($\pm$13.9) years; 23% of the patients were diagnosed with diabetes; 50% with arterial hypertension; 50% with dyslipidemia; with 33.3% overweight; 5.9% with obesity, and 15% with hypothyroidism. The prevalence of insulin resistance, estimated by the Triglyceride-Glucose Index $>$4.68, was 40%. Regarding the tumor, 67,5% of PTC were classic variants, 20% were follicular, and 5% were tall cell variants. *BRAF* mutation was present in 62,5% of the sample, *RAS* in 10% *pTERT* in 5%. The expression of SGLT2 was observed in 70% of the samples (30% weak, 27.5% moderate, and 12.5% strong), and its extension was greater than 10% in 85% of cases. SGLT2 expression in non-tumoral thyroid tissue was observed in only two cases, both associated with an adjacent inflammatory infiltrate.

Discussion

Despite the limitations of this study, such as its retrospective nature and the small sample size, our study confirms the presence of SGLT2 in PTC. Besides, preclinical studies have suggested that SGLT2 inhibition is a potential therapeutic for thyroid cancer; its role remains unclear.

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PS3-08-10

"From imaging to histopathology: predictive value and limitations of tirads and bethesda in thyroid cancer—a 14-year surgical cohort"

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Introduction

The incidence of thyroid cancer has increased, largely due to incidental detection of thyroid nodules. Current guidelines support conservative surgery in selected patients, making preoperative risk stratification essential. Imaging systems (TIRADS) and cytology (Bethesda) guide clinical decision-making, but their predictive value is variable.

Objective

To analyze patient characteristics, surgical management, and outcomes of thyroid cancer over 14 years, and to evaluate correlations between TIRADS, Bethesda, and final histopathology.

Materials and Methods

A retrospective descriptive and analytical study included 230 patients treated at the ENT Department of Hospital Perpetuo Socorro between 2010 and the present. Variables analyzed included age, sex, thyroid disease history, TIRADS, Bethesda, histopathology, papillary carcinoma subtype, TNM staging, ATA risk stratification, surgery type, complications, hospital stay, adjuvant treatments, and outcomes.

Results

80% of patients were female, mean age 55.17 years. Half had prior thyroid disease. Papillary carcinoma was most frequent (80%), mainly classic (58.6%), followed by follicular variant (22.2%). Initial treatment was total thyroidectomy in 67.7%, conservative surgery in 32.7%, with 16.2% requiring completion thyroidectomy. Spearman's rho showed weak correlation between TIRADS and Bethesda (ρ= 0.307). 17.1% of papillary carcinomas had TIRADS 3, and 22.5% of papillary and 25% of follicular carcinomas had Bethesda II–III. Over 20% of malignant tumors were non-suspicious preoperatively, but combining TIRADS and Bethesda reduced this proportion below 5%. Most frequent complications were hypocalcemia (39.4% transient, 25.3% permanent) and vocal cord paralysis (16.2% transient, 10% permanent).

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PS3-08-11

2 Cases of solitary thyroid metastasis of clear cell renal cell carcinoma

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Introduction

Metastatic thyroid gland tumors are rare, accounting for only 2–3% of thyroid malignancies. Renal cell carcinoma (RCC) is a highly aggressive tumor capable of systemic spread; however, isolated solitary metastases to the thyroid are clinically uncommon. We report two cases of solitary thyroid metastasis from clear cell RCC (ccRCC) that were successfully managed with surgical intervention.

Case Report

Case 1: An 81-year-old woman presented with a palpable anterior neck mass. CT revealed a 50 mm, heterogeneously enhancing tumor in the left thyroid lobe extending into the superior mediastinum. Although FNAC suggested malignancy, the histological type remained undetermined. The patient underwent a left hemithyroidectomy. Histopathological examination revealed nested cells with clear cytoplasm and prominent nucleoli. Negative immunohistochemical staining for thyroglobulin and thyroid transcription factor-1 (TTF-1) confirmed the diagnosis of metastatic ccRCC. Remarkably, the patient remains recurrence-free 10 years postoperatively without any further adjuvant treatment. **Case 2:** A 79-year-old male underwent retroperitoneoscopic left radical nephrectomy for ccRCC. During routine follow-up four years later, a 35 mm mass was detected in the left thyroid lobe via ultrasound. FNAC was consistent with metastatic RCC. A left thyroid lobectomy was performed. Intraoperatively, the tumor was soft and lacked adhesions to the recurrent laryngeal nerve or surrounding tissues. Histopathology confirmed metastatic ccRCC. One year after thyroidectomy, the patient is being followed up with no signs of complications or systemic recurrence.

Conclusions

The metastatic pathway for RCC often bypasses the lungs via the "renal-thyroid route" through the paravertebral venous plexus (Batson's plexus), particularly in left-sided primary tumors. Our cases underscore that thyroid metastasis must be considered during long-term follow-up, even a decade after the primary surgery. Clinical data indicate that aggressive surgical resection of solitary metastases leads to a favorable prognosis, with reported 5-year survival rates reaching 55–90% following complete excision. Surgical intervention remains the treatment of choice for long-term, recurrence-free survival.

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PS3-08-12

The clinical pathway for postoperative nuclear medicine management of differentiated thyroid cancer (2026 edition)

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The Clinical Pathway for Postoperative Nuclear Medicine Management of Differentiated Thyroid Cancer (DTC) is developed based on the latest evidence-based research and clinical guidelines. The expert panel included multi-disciplinary specialists in thyroid cancer care in China, supported by a methodology expert in systematic reviews, meta-analyses, and guidelines. Unlike the "Expert Consensus on the Clinical Pathway for Postoperative 131I Therapy of DTC (2017 Edition)," which was solely developed for managing the 131I treatment process in hospitalized patients, this updated pathway highlights the role of nuclear medicine as a comprehensive diagnostic and therapeutic platform across the patient's entire clinical journey. Based on current clinical issues and underlying evidence, this pathway leverages the advantages of nuclear medicine theranostics in the dynamic assessment of postoperative DTC patients. Consequently, management is tailored so patients receive either specific 131I treatments (remnant ablation, adjuvant therapy, or treatment for known disease), transition directly to thyroid-stimulating hormone (TSH) suppression therapy, or are identified as having radioactive iodine-refractory DTC (RAIR-DTC). This pathway emphasizes visualized evidence-based management by integrating patient risk stratification with nuclear medicine theranostics. It advocates for active surveillance and management throughout the entire course of DTC care for patients who have undergone 131I treatment, those who do not require 131I treatment after assessment, and those with RAIR-DTC. Ultimately, this pathway is expected to play a proactive role in guiding and standardizing the postoperative management of DTC.

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PS3-08-13

Medullary thyroid carcinoma in clinical practice: a single-center retrospective study

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Introduction
Medullary thyroid carcinoma (MTC) is a rare tumor of parafollicular cells, mostly sporadic but 25% associated with germline RET mutations. Prognosis highly depends on tumor staging and biological behavior.
Objectives
To describe cases of MTC, assessing course of diagnosis, treatment and follow-up.
Methods
Retrospective analysis of adult patients with a histological diagnosis of MTC, followed in the Endocrinology department of a non-oncological tertiary center between January 2015 and December 2025. Data included demographic, clinical, biochemical, genetic, histopathological, treatment and outcome features.
Results
The cohort included 32 patients, mostly female ($n = 18$, 56,3%). Mean age at diagnosis was 58,5 ± 17,8 years. Median follow-up was 54 months (28,3-105,3). Preoperatively, calcitonin was assessed in 24 patients (75%), with median value of 776 pg/mL (107,7-1958). Of these, 21 underwent fine needle aspiration cytology (FNAC), with MTC in 12 (57,1%). Cervical lymph node involvement was reported in 7 patients and distant metastasis in 2. Genetic testing was performed in 26 patients. Seven (26,9%) had a germline RET mutation - 1 in exon 16 (MEN2B), 4 in exon 11, 1 in exon 14 and 1 in exon 8 (Cys531Arg). All patients underwent total thyroidectomy. Central neck dissection was performed in 13 (40,6%) and lateral in 8 (25%). Regarding histology, mean tumor dimension was 20,7 ± 17,6mm. Most patients had unifocal disease ($n = 22$, 73,3%). Of the six with bilateral and multicentric disease, 4 were MEN2 cases (66,7%). Nodal involvement was present in 11 patients (37,9%). Six months after first surgery, 2 patients were lost to follow-up, 5 had no available data and 1 died. Of the remaining, 12 (50%) had no evidence of disease (NED), 8 (33,3%) biochemical disease (BD), 2 (8,3%) cervical structural disease (SD) and 2 (8,3%) distant metastasis. As of December 2025, 9 patients remained with NED (3 lost to follow-up). Of the 8 BD patients, 2 progressed to cervical SD. Regarding the 2 cervical SD cases, 1 has metastatic disease (MEN2B patient). Two patients are under therapy with selpercatinib and 1 patient with vandetanib. Deaths due to MTC occurred in 2 patients (6,3%), both stage IV at presentation.
Conclusions
MTC affected mostly middle-aged female patients and was hereditary in 26,9% of cases. Calcitonin was a reliable marker of MTC, unlike FNAC, which showed an inferior diagnostic yield. A significant rate of biochemical cure was attained post-operatively, while latest data showed an increase in locoregional and metastatic disease. This underscores the importance of long-term follow-up, in order to identify and treat recurrence.

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Miscellaneous (clinical)

PS3-09-01

Potential metabolic risks of excessive supplementation

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Background
Selenium is an essential trace element for thyroid function, as it is incorporated into deiodinases and glutathione peroxidases, which regulate thyroid hormone metabolism and protect thyrocytes from oxidative stress. Selenium supplementation is widely discussed in the management of autoimmune thyroid diseases, particularly Hashimoto's thyroiditis. However, emerging evidence suggests that excessive selenium intake may adversely affect glucose metabolism.
Objective.
To review current evidence on the association between high selenium exposure and the risk of hyperglycemia and type 2 diabetes mellitus, particularly in patients receiving selenium in thyroid clinical practice.
Methods
A narrative review of randomized controlled trials, meta-analyses, and large observational studies evaluating selenium status, supplementation, insulin resistance, and incident T2DM was conducted.
Results
Several epidemiological studies demonstrate a relationship between serum selenium levels and T2DM risk. Higher selenium concentrations (> 120–130 µg/l) have been associated with elevated fasting glucose levels and increased insulin resistance. In the Nutritional Prevention of Cancer (NPC) trial, long-term supplementation with 200 µg/day of selenium was linked to a higher incidence of newly diagnosed T2DM, particularly among individuals with adequate or high baseline selenium status. Proposed mechanisms include overexpression of glutathione peroxidase-1, leading to excessive suppression of reactive oxygen species that are physiologically required for insulin signaling, thereby contributing to impaired insulin sensitivity.
Conclusions
While selenium plays a critical role in maintaining thyroid homeostasis, indiscriminate supplementation—especially at doses ≥200 µg/day and in selenium-replete populations—may carry potential metabolic risks. In thyroid practice, selenium prescription should be individualized, taking into account baseline selenium status, regional selenium sufficiency, and the patient's metabolic profile. Further studies are required to define optimal therapeutic ranges that balance thyroid benefits with metabolic safety.

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PS3-09-02

Iodine status in romanian schoolchildren and neonates before and after COVID-19 pandemics

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Objective
Romania has geographical iodine deficiency (ID) in up to 2/3 of the country. Universal salt iodization was introduced for human consumption and bakery industry in 2002. The aim of this study was to compare the iodine status in Romanian schoolchildren and neonates before and after COVID 19 pandemics.
Subjects and Methods
Median urinary iodine concentration (mUIC) was evaluated and compared in 2 national representative samples of 1352 schoolchildren (6-12 years) in 2024 and 624 schoolchildren in 2016. The percentage of neonatal TSH >5 mIU/l was evaluated in 18349 neonates from 2024 and 7863 neonates from 2017 registered in the MEDILOG program for TSH screening. The use of iodized salt in households was evaluated through questionnaires in 1352 families in 2024 and in 629 pregnant women in 2016-2017.
Results
Median UIC in schoolchildren was 141 μg/l in 2024, compared to 255 μg/l in 2016, showing decreased but still adequate iodine intake (i.e., $>$ 100 μg/l); in 2024 mUIC was similar in historical endemic and non-endemic counties (140 μg/l and 143 ug/l, respectively) and in urban and rural areas (140 μg/l and 142 μg/l, respectively), while in 2016 was 251 μg/l in endemic counties and 255 μg/l in non-endemic counties. Iodized salt was used in 61.7% of households in 2024, compared to 84.9% of pregnant women in 2015-2016. In children using iodized salt mUIC was higher than in those using non-iodized salt (24.6%): 150 *vs.* 121 μg/l ($P < 0.001$). The percentage of neonatal TSH>5 mIU/l in 2024 was 14.7% (3.2-27.3%), compared to 22.9% (6.3-46.3%) in 2016, suggesting persistence of mild to moderate iodine deficiency in neonates. Interestingly, in 2024 % nTSH >5 mIU/l was higher in non-endemic *vs.* endemic counties and higher in urban *vs.* rural population, a shift from previous studies, where the percentage was higher in endemic and rural areas.
Conclusion
The current salt iodization program for households and bakery industry ensures an adequate iodine intake in schoolchildren. Discordantly, nTSH levels indicate a persistent mild-moderate ID in neonates, suggesting ID in pregnant women. A potential explanation for this discrepancy may be a lower intake of iodized salt and bread, main sources of dietary iodine, during pregnancy and a trend towards a more plant-based (vegetarian and vegan) diet, which contains negligible quantities of iodine. As non-iodized salt and diet alternatives are more expensive, this might potentially be the reason for the decreased mUIC and increased % nTSH >5 mIU/l recently observed in the urban areas.

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PS3-09-03

A decade long of subacute thyroiditis: a descriptive analysis from a tertiary center in bucharest

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Background
Among thyrotoxicosis causes, a relatively rare encounter is subacute thyroiditis (SAT), a pathology with viral etiology, characterized by anterior neck pain and other inflammatory signs. The diagnosis can be difficult and treatment is not yet standardized.
Methods and objective
Retrospective analysis of SAT cases diagnosed in our clinic between January 2014-December 2024.
Results
41 patients were included, 37 (90.24%) of them were females. Mean age at diagnosis was 45.76 ± 8.71 years. 34.14% of patients could identify a recent viral infection. The major complaint was local pain, indicated by 85.36% of patients. 48.78% reported symptoms compatible with hyperthyroidism such as peripheral tremor, insomnia, excessive sweating or palpitations. 24.39% of them reported dysphagia. Median time form onset of symptoms until diagnosis was 3 weeks (IQR$=2$). Median ESR was 71 (IQR$=41.5$) mm/h and median C-reactive protein was 71.4 (IQR$=103.05$) mg/l. 81.57% patients had TSH levels below 0.1uUI/ml. Overall, median TSH was 0.022 (IQR$=0.05$) uUI/mL. FreeT4 levels were on average 1.56 ± 0.78 times the upper limit. ATPO and antithyroglobulin antibodies were positive in 2 (6.89%), respectively 6 (27.27%) cases. On thyroid ultrasound, hypoechogenic areas suggestive of SAT were described in 94.87% cases, 82.14% had decreased vascularity and 79.31% of them had cervical inflammatory lymphadenopathies. Twelve patients reported self-medication with non-steroidal anti-inflammatory drugs (NSAID) prior to their presentation in clinic. In 70% of cases, clinicians prescribed glucocorticoids (GC) and the preferred compounds were methylprednisolone, prednisone and rarely dexamethasone. Median dose of glucocorticoids at the beginning of treatment was 30 mg (IQR$=20$) equivalent of prednisone, with doses ranging from 10 to 45 mg. Fifteen patients (38.46%) received both GC and NSAID. Eleven patients (28.2%) received only NSAID. In 53.84% of cases, beta-blockers were recommended. Follow-up data at more than three months postdiagnosis were available in 23 patients. Of them, 30.43% remained hypothyroid. Statistical analyses showed no differences between these patients and those with normal thyroid function, in terms of time until diagnosis, hormonal levels at onset of disease and inflammatory markers. Initial dose of GC was significantly higher in those who remained euthyroid at 3 months after diagnosis (31.78 vs 18.75, $P = 0.039$).
Conclusions
SAT diagnosis requires integration of anamnestic, clinical and laboratory results, ultrasound imaging being of utmost importance. Although treatment is generally individualized on a case-by-case basis, more studies are necessary to evaluate the best therapeutic approach in order to practice evidence-based medicine.

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PS3-09-04

Determination of an age-specific tsh reference interval in individuals $>$ 65 years using the atellica IM 1600 analyzer in a croatian population

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Objectives
Serum thyroid-stimulating hormone (TSH) concentrations tend to increase with age, which complicates the interpretation of thyroid function tests in elderly individuals. The use of a universal upper reference limit may therefore lead to overdiagnosis of subclinical hypothyroidism in older populations. The aim of this study was to determine the distribution of TSH values and establish a reference interval in individuals older than 65 years in a Croatian population from central Croatia using the Atellica IM 1600 Analyzer.
Methods
The study included individuals older than 65 years from a Croatian population from central Croatia. Serum TSH, anti-thyroid peroxidase antibodies (anti-TPO), and anti-thyroglobulin antibodies (anti-Tg) were measured using chemiluminescent immunoassays on the Atellica IM 1600 analyzer (Siemens Healthineers, Erlangen, Germany). A total of 92 subjects aged >65 years were initially included. Individuals with a history of thyroid disease, thyroid therapy, or previous thyroid surgery were excluded. Thyroid autoimmunity was assessed by measuring anti-TPO and anti-Tg antibodies, and individuals with antibody concentrations >60 U/mL were excluded from the reference population. Overall, 10 subjects had elevated thyroid antibodies and were excluded. One extreme TSH value (11.437 mIU/l) was identified as an outlier and removed prior to calculation of the reference interval.
Results
The final reference population consisted of 79 individuals (55 women and 24 men). The mean TSH concentration was 2.35 mIU/l, while the median was 1.90 mIU/l. The interquartile range (IQR) was 1.37–2.58 mIU/l. The observed minimum and maximum TSH concentrations were 0.36 mIU/l and 6.97 mIU/l, respectively. The calculated TSH reference interval (2.5–97.5 percentile) for individuals older than 65 years was 0.58–6.65 mIU/l. When analyzed by sex, the reference interval was 0.60–6.78 mIU/l in women and 0.62–5.74 mIU/l in men.
Conclusion
In this Croatian population from central Croatia older than 65 years, the upper reference limit for TSH was 6.65 mIU/l, which is higher than the commonly used upper limit of 4.0 mIU/l. These findings support the use of age-specific reference intervals for TSH in elderly individuals, as application of conventional limits may lead to potential overdiagnosis of subclinical hypothyroidism.

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PS3-09-05

Thyroid hormone metabolism and cardiac adaptation in aortic stenosis

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Background
Aortic stenosis (AS) is characterized by chronic left ventricular pressure overload leading to concentric remodeling, metabolic stress, and progressive functional decline. Beyond structural adaptation, AS induces systemic neurohormonal and metabolic changes, including alterations in thyroid hormone conversion. While thyroid-stimulating hormone (TSH) reflects central regulation, free triiodothyronine (FT3) and the FT3/FT4 ratio more accurately represent peripheral thyroid hormone activity and myocardial metabolic efficiency. These parameters may therefore provide insight into the metabolic phenotype and functional reserve of patients with AS.
Methods
Our cross-sectional study included 71 patients with echocardiographically confirmed AS. Thyroid function parameters (TSH, FT3, and FT4) were analyzed in relation to clinical severity (NYHA functional class), metabolic reserve (hemoglobin), and hemodynamic severity (mean transvalvular gradient). Correlation and multivariable analyses were performed to explore the association between thyroid metabolism and disease burden.
Results
FT3 levels correlated inversely with NYHA class ($\rho = -0.355$, $P = 0.0047$), suggesting that patients with lower FT3 values experienced greater symptomatic limitation and reduced exercise tolerance. The FT3/FT4 ratio showed a similar negative correlation with NYHA class ($\rho = -0.320$, $P = 0.012$) and a positive correlation with mean transvalvular gradient ($\rho = 0.506$, $P = 0.016$), remaining an independent predictor after adjustment for age and sex. FT3 also correlated positively with hemoglobin ($\rho = 0.438$, $P = 0.00052$), indicating that low FT3 levels reflect systemic catabolic and inflammatory stress. TSH showed no significant association with any clinical or echocardiographic parameters.
Conclusions
In AS, reduced peripheral T4-to-T3 conversion reflects impaired metabolic adaptation to chronic cardiac stress rather than primary thyroid dysfunction. The FT3/FT4 ratio can be used as a sensitive biomarker, linking myocardial energetic demand, systemic metabolism and disease severity.
Keywords
thyroid hormones, FT3/FT4 ratio, aortic stenosis, low T3 syndrome, deiodinase activity, cardiac metabolism, NYHA functional class

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PS3-09-06

Intraoperative decline in parathyroid hormone determines postoperative parathyroid function

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Introduction and objective
In patients undergoing total thyroidectomy (TT), the risk of postoperative hypoparathyroidism (hypoPT) determines clinical management. We aimed to estimate 1) the incidence of hypoPT and 2) assess the importance of intraoperative parathyroid hormone (ioPTH) decline on hypoPT development.
Methods
Retrospective cohort study of adults ($\geq$18 years) undergoing TT with ioPTH measurements from May 2021 to December 2024. We sampled baseline PTH after induction of anaesthesia and final PTH approximately 10 minutes after thyroid excision. We analysed the ioPTH decline (%) and used a 75% prespecified cutoff to determine high or low risk patients. The postoperative medical supplementation was guided by ionized calcium and subjective symptoms. HypoPT was defined as the requirement for alfacalcidol treatment at discharge. Transient hypoPT was defined as discontinuation of alfacalcidol within 12 months after TT and permanent hypoPT as continued use of alfacalcidol. We calculated determining factors for hypoPT development including receiver operating characteristic curves and univariable logistic regression estimated odds ratios (ORs).
Results
We included 272 TT patients in the cohort (mean age 53 years; 72% women). Postoperative hypoPT occurred in 47 patients (17%), including 27 (10%) transient and 20 (7%) permanent. Median ioPTH decline was higher in patients with hypoPT than without (92% vs 51%; $P < .001$). Using the 75% cutoff, we determined any hypoPT with a sensitivity of 96% (45/47), specificity 84% (190/225), positive predictive value 56% (45/80), and negative predictive value 99% (190/192). Discrimination was strong for the $\geq$75% cutoff (AUC, 0.89; DeLong $P = .023$). Optimal cutoffs of ioPTH to determine hypoPT was 78% for any hypoPT (sensitivity 93%, specificity 86%) and 79% for permanent hypoPT (sensitivity 100%, specificity 80%). An ioPTH decline $\geq$75% was by far the strongest risk factor for development of hypoPT (OR: 57; 95% CI, 16–204; $P < .001$).
Conclusions
Use of ioPTH decline $\geq$75% strongly discriminated the risk of postoperative hypoPT after TT. With this new risk stratification, we can allocate TT patients to either high or low risk of postoperative hypoPT and ensure a sufficient medical and clinical support for patients at risk and reduce follow-up for low-risk patients.
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PS3-09-07

Apophenia or epiphany? the gordian knot of LT4/LT3 replacement therapy in current hypothyroidism guidelines

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Combined LT4/lT3 replacement therapy remains controversial. This controversy largely reflects the inconsistency of the available evidence, the relatively small sample sizes included in previous studies, and important limitations in study design. The strongest rationale for LT4/lT3 treatment applies to athyreotic or thyroidectomized patients, who cannot rely on thyroidal T3 secretion and are therefore more dependent on peripheral T4-to-T3 conversion mediated by type 2 deiodinase (DIO2). DIO2 activity is influenced by both genetic and acquired factors. In particular, the Thr92Ala polymorphism has been associated with lower postsurgical fT3 concentrations despite LT4 treatment, which has led to the proposal of genotype-guided individualized therapy. Evidence suggests that the effect of the DIO2 Thr92Ala polymorphism is genotype dependent, with little or no effect in Thr/Thr individuals, a greater reduction in fT3 in Thr/Ala carriers, and the greatest risk of reduction in Ala/Ala homozygotes. Across different ethnic cohorts, the reported frequency of heterozygotes ranges from approximately 0.39 to 0.60, whereas the frequency of Ala/Ala homozygotes ranges from approximately 0.12 to 0.34. Athyreotic non-thyroidectomized patients are mainly individuals with autoimmune thyroiditis. In these, in addition to commonly detected antibodies (anti-TPO, anti-TG, antiTSH-R), antibodies against DIO2 have also been identified. Although the clinical significance of anti-DIO2 autoantibodies remains uncertain, studies suggest that they may be associated with altered thyroid hormone handling and treatment response. As DIO2 is not confined to the thyroid gland, and also expressed in many peripheral tissues in which local T4-to-T3 conversion occurs, anti-DIO2 antibodies could have functional relevance beyond the thyroid itself. Anti-DIO2 antibodies have been detected in approximately 26.5% of patients with both Hashimoto's thyroiditis and Graves' disease. In addition, a 2005 study showed that some sera from patients with Hashimoto's thyroiditis increased precipitation of D2 activity, suggesting that these antibodies may interfere with D2 function in at least a subset of patients. Selenium status represents another important determinant of DIO2 activity. No published study has simultaneously evaluated all of the relevant factors that may influence all forementioned DIO2-dependent thyroid hormone homeostasis factors. Future studies should therefore adopt a rigorous stratified design. Only then will it be possible to commend or condemn the use of combined LT4/lT3 treatment. Because studies of this kind are methodologically and logistically demanding, Monte Carlo simulation may provide a useful complementary approach for modeling the above scenarios under conditions of uncertainty through repeated random sampling. The results of our calculations will be presented.
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Clinical Cases (non-cancer) 2

PS3-10-01

Switching between hypothyroidism and hyperthyroidism: an unusual case report of brittle grave's disease

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Introduction
Alternating states of hypothyroidism and hyperthyroidism are infrequent occurrences among clinical scenarios of autoimmune thyroid disorders. In extremely rare cases, fluctuations in thyroid hormones are the result of coexisting thyroid receptor stimulating (TSAb) and blocking (TBAb) antibodies. Common assays measure both as thyroid receptor antibodies (TRAb), regardless of their biological activity. Their complex pharmacodynamics, pharmacokinetics, and the interplay between them are yet to be understood as there are few cases described so far.
Case report
A 29-year-old female, with a history of neglected Grave's disease and recent episode of pneumonia, was brought to the emergency department on 25th January 2026, after suffering cardiac arrest. Upon admission she was intubated, with rapid atrial fibrillation rhythm and was hemodynamically stable. Shortly after admission her clinical status worsened with increased need for vasopressors and inotropes, alongside betablockers, amiodarone and dexamethasone. A thyroid panel was requested, showing a suppressed TSH (0.0013uUI/ml). Thyroid echography revealed an enlarged gland, suggestive of autoimmune thyroiditis and increased color flow Doppler signal. Thyrotoxic crisis was suspected and until complete panel was available, 60mg/day methimazole was initiated. The following day, results revealed moderately increased thyroid hormones (FT4 was 1.55 times upper limit of normal (ULN) and FT3, 1.28 times ULN). TRAb were positive (25.92, with ULN 1.75 UI/l). Methimazole dose was down titrated to 30mg/day. Clinical status improved and cardiac support was no longer necessary. On 31st January, repeated panel showed FT4 at lower limit with decreased FT3 and the antithyroid drug was further decreased to 20 mg/day. Thyroid hormones continued to decline, reaching levels below the lower normal limit, so methimazole was stopped on 3rd February. Hypothyroidism persisted and 3 day later substitution with levothyroxine commenced with 25 mg/day, progressively increasing up to 75 mg/day. On 26th February, on treatment, her FT4 and FT3 levels were within range, with suppressed TSH and decreased TRAb (5.07 UI/l). On 4th March, her FT3 levels rose above normal levels, with further suppression of TSH. Levothyroxine dose was decreased to 50 mg/day. TSAb were assessed showing increased levels, and levothyroxine stopped. Methimazole was reinstated and up titrated to 30mg/day.
Conclusions
Levothyroxine treatment and antithyroid drugs are reported to influence the expression and quantity of stimulating and blocking antibodies, resulting in contrasting clinical pictures of fluctuating hyperthyroidism and hypothyroidism, as highlighted in this unusual case of Grave's disease. Awareness of this scenario can help clinicians to recognize and offer appropriate management in such difficult cases.

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PS3-10-02

Carbimazole resistant graves' disease: a case report

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Background
Graves' disease is the most common autoimmune cause of hyperthyroidism and usually responds well to antithyroid drugs (ATDs). Resistance to ATDs is rare and poses significant therapeutic challenges due to the absence of standardized management guidelines. ATD resistance is generally defined as persistent biochemical and clinical hyperthyroidism despite adequate doses of thionamides for at least 4–6 months with confirmed adherence.
Case Presentation
We report a 24-year-old woman with a five-year history of Graves' disease who presented with persistent symptoms of thyrotoxicosis including palpitations, weight loss, tremors, and heat intolerance. Examination revealed tachycardia (120/min), diffuse goiter, and mild inactive exophthalmos. Laboratory evaluation showed suppressed TSH with elevated free T3 and free T4 levels. Anti-TPO antibodies were positive, while TSH receptor antibodies (TRAb) were negative. Thyroid ultrasound demonstrated diffuse enlargement with markedly increased vascularity ("thyroid inferno"). Despite supervised high-dose carbimazole therapy, the patient remained thyrotoxic. Adjunctive therapy including beta-blockers, dexamethasone, and cholestyramine provided minimal biochemical improvement. Screening for malabsorption, including celiac disease, was negative. The patient was subsequently switched to propylthiouracil (200 mg twice daily), with only partial biochemical response. Given persistent thyrotoxicosis and the risk of long-term drug toxicity, definitive surgical management with total thyroidectomy was undertaken, following which the patient achieved biochemical remission and was maintained on levothyroxine replacement.
Discussion
Antithyroid drug resistance is uncommon and the underlying mechanisms remain incompletely understood. Proposed mechanisms include impaired intrathyroidal accumulation of thionamides, accelerated hepatic metabolism of antithyroid drugs, reduced bioavailability due to malabsorption, and increased thyroid hormone turnover in highly vascular or enlarged thyroid glands.
Conclusion
This case highlights the importance of recognizing true ATD resistance after excluding non-adherence and malabsorption. Early consideration of definitive therapy, particularly thyroidectomy, can provide rapid and effective control of hyperthyroidism when medical therapy fails.

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PS3-10-03

Pazopanib-associated destructive thyroiditis mimicking thyroid malignancy on ultrasound

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Tyrosine kinase inhibitors (TKI), including pazopanib, are widely used in the treatment of metastatic renal cell carcinoma and are frequently associated with thyroid dysfunction. The most commonly described mechanism is destructive thyroiditis, typically presenting with transient thyrotoxicosis followed by hypothyroidism. Although thyroid dysfunction during TKI therapy is well recognised, most reported cases describe biochemical abnormalities or nonspecific ultrasound findings. Presentations mimicking thyroid malignancy are rarely described and may represent a significant diagnostic pitfall. We report the case of an 80-year-old man with metastatic papillary renal cell carcinoma receiving pazopanib therapy. Approximately three months after treatment initiation, routine laboratory evaluation revealed biochemical thyrotoxicosis with suppressed TSH and elevated free thyroid hormones. Thyroid autoantibodies, including TPOAb, TgAb and TRAb, were negative. The patient was initially asymptomatic, although he later reported mild weight loss and anorexia. An initial thyroid ultrasound performed outside our institution showed a markedly enlarged gland with multiple poorly defined hypoechoic nodules, associated with multiple small cervical lymph nodes with reactive characteristics. These findings were considered highly suspicious for thyroid malignancy, and cytological evaluation was suggested. Subsequent ultrasound examinations performed at our institution demonstrated multiple bilateral ill-defined hypoechoic inflammatory areas compatible with subacute destructive thyroiditis rather than malignancy. The lesions displayed a poorly defined bilateral pseudonodular pattern typical of inflammatory thyroid disease. During follow-up, the patient developed anterior cervical pain associated with increased inflammatory changes, suggesting a transient inflammatory flare. Given the clinical context of TKI therapy and the biochemical pattern suggestive of destructive thyroiditis, a conservative management strategy with close clinical, biochemical and imaging surveillance was adopted. Antithyroid treatment with methimazole was briefly initiated; however, thyroid function rapidly evolved towards hypothyroidism, leading to treatment withdrawal. Serial imaging over the following months showed progressive regression of these abnormalities, with marked reduction of the hypoechoic areas and eventual near-complete resolution of the previously described lesions. No suspicious cervical lymphadenopathy was identified on subsequent ultrasound examinations. Thyroid function stabilised under levothyroxine replacement therapy, which is currently maintained. Although thyroid dysfunction during TKI therapy is well recognised, reports of pazopanib-associated thyroiditis presenting with ultrasound features highly suggestive of thyroid malignancy remain scarce in the literature. This case highlights the importance of recognising drug-associated destructive thyroiditis as a potential mimic of thyroid cancer. Careful correlation between clinical context, biochemical findings and serial imaging may support a conservative management strategy and help avoid unnecessary invasive diagnostic procedures.

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PS3-10-04

Skin rash following initiation of methimazole therapy: a diagnostic and management challenge in graves' disease

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Introduction
Graves' disease is an autoimmune disorder and the most common cause of hyperthyroidism. Treatment options include antithyroid drugs (methimazole and propylthiouracil), radioactive iodine ablation and thyroidectomy. Although antithyroid drugs are generally safe, adverse reactions may occur and lead to treatment discontinuation, potentially complicating the management of hyperthyroidism.
Case Report
A 33-year-old female, original from Brazil, with no significant prior medical history and no chronic medication, presented to the emergency department in June 2024 for palpitations. She was then diagnosed with hyperthyroidism due to Graves' disease (TRAb 20 U/l) and new-onset diabetes mellitus (glycated hemoglobin: 11.9%) that was confirmed to be of autoimmune etiology. Treatment with methimazole, propranolol and insulin were initiated, and the patient was subsequently followed in the endocrinology clinic with progressive adjustment of insulin and methimazole dosages. In March 2025, she developed an almost daily pruritic maculopapular rash, which she related with methimazole intake. Skin lesions were sometimes accompanied by lip edema and resolved spontaneously within a few hours, with rapid improvement after antihistamine therapy. Suspecting a hypersensitivity reaction to methimazole, treatment was switched to propylthiouracil until October 2025. During this period, she reported persistent pruritus without maculopapular lesions, leading to the switch back to methimazole with concomitant therapy with bilastine. In January 2026, approximately one hour after methimazole intake, she developed edema of the lips and tongue which led to prompting immediate discontinuation of methimazole. Given the presumed hypersensitivity to synthetic antithyroid drugs and suboptimal control of hyperthyroidism, total thyroidectomy was proposed. Preoperative preparation included Lugol's solution and prednisolone. Meanwhile, the patient continued to experience pruritic rash and edema despite discontinuation of antithyroid medication. An allergology consultation was requested, and chronic spontaneous urticaria was diagnosed. Hypersensitivity to antithyroid drugs was excluded, including by a negative drug provocation test with methimazole. Following thyroidectomy, the patient remains under follow-up on fourfold-dose second-generation H1-antihistamines, with persistent urticaria and partial improvement of disease activity.
Conclusion
Chronic spontaneous urticaria is commonly linked to underlying autoimmune conditions, particularly autoimmune thyroid disease, and may resemble antithyroid drug hypersensitivity, complicating the management of Graves' disease. Therefore, the onset of urticaria after starting antithyroid drug therapy should not be automatically interpreted as drug hypersensitivity, and alternative diagnoses should be considered. This case emphasizes the importance of a multidisciplinary approach to ensure accurate diagnosis and avoid unnecessary treatment modifications.

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PS3-10-05

Refractory amiodarone-induced thyrotoxicosis treated with total thyroidectomy: a case report

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Introduction
Amiodarone is a class III antiarrhythmic agent widely used for refractory supraventricular and ventricular arrhythmias. Amiodarone-induced thyrotoxicosis (AIT) is classified into two types: type 1 (iodine-induced hyperthyroidism in diseased glands) and type 2 (destructive thyroiditis without underlying thyroid disease), although mixed forms are frequent. While oral glucocorticoids represent first-line treatment for type 2 AIT, the 2018 European Thyroid Association guidelines recommend total thyroidectomy promptly in patients whose thyrotoxicosis is unresponsive to medical therapies. We report a case of type 2 AIT refractory to prolonged high-dose medical treatment, successfully managed with total thyroidectomy.
Case Report
A 77-year-old woman with hypertension, depression, and paroxysmal atrial fibrillation was treated with amiodarone from January 2023 to August 2025. Thyroid function remained normal during treatment. Two months after amiodarone withdrawal, she presented to the emergency department with palpitations and hand tremor. Laboratory evaluation revealed severe thyrotoxicosis: TSH 0.005 μUI/mL, free T4 4.48 ng/dL (3× upper limit of normal), free T3 8.99 pg/mL (2× upper limit of normal). Thyroid autoantibodies were negative. Thyroid ultrasound demonstrated a normal-sized gland with decreased vascularization, consistent with type 2 AIT. Initial treatment included methimazole 20 mg/day, prednisolone 20 mg/day, and propranolol. Despite escalation to methimazole 40 mg/day and prednisolone 60 mg/day, thyrotoxicosis worsened (free T4 >7.77 ng/dL, free T3 11.10 pg/mL). The patient experienced recurrent atrial fibrillation with rapid ventricular response requiring hospitalization. After discharge, persistent thyrotoxicosis continued despite four months of high-dose therapy, with marked fatigue impacting daily activities. Given refractory disease and high cardiovascular risk, total thyroidectomy was recommended. Following multidisciplinary evaluation and preoperative optimization achieving near-euthyroidism with high-dose treatment, the patient underwent total thyroidectomy in February 2026. Postoperative recovery was uneventful with successful treatment confirmed by normalized thyroid function.
Conclusions
This case illustrates the clinical challenge of refractory type 2 AIT. Although glucocorticoids usually restore euthyroidism, some cases have a prolonged course, particularly those with severe thyrotoxicosis at presentation. Restoration of sinus rhythm is unlikely until euthyroidism is achieved, and prolonged exposure to thyroid hormone excess increases cardiovascular morbidity. The 2018 European Thyroid Association guidelines recommend total thyroidectomy for patients unresponsive to medical therapies, emphasizing that this decision should involve a multidisciplinary team. In this patient, four months of aggressive combined therapy failed to achieve sustained control, justifying surgical intervention. Total thyroidectomy provided definitive resolution and should be considered when medical treatment fails, particularly when thyrotoxicosis significantly impacts quality of life and cardiovascular stability.

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PS3-10-06

Patient with resistance to thyroid hormone syndrome treated initially with anti-thyroid medication

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Introduction
Differentiating **Resistance to Thyroid Hormone syndrome (RTH)** from **thyroid-stimulating hormone–secreting pituitary adenoma (TSHoma)** is essential because management differs significantly: RTH is usually managed conservatively or medically, whereas TSHoma may require pituitary surgery. We describe a patient with RTH who was initially treated as hyperthyroidism before appropriate evaluation established the correct diagnosis.
Case Report
An 18-year-old male with familial hyperlipidaemia underwent thyroid function testing demonstrating elevated free thyroxine (fT4) 28.5 pmol/l (reference range 10–23) with inappropriately non-suppressed thyroid-stimulating hormone (TSH) 1.73 mIU/l (0.45–4.50). He was started on carbimazole, with progressive dose escalation as fT4 failed to normalise. On referral, fT4 remained elevated at 29.3 pmol/l with TSH 17.75 mIU/l. The patient had no thyrotoxic symptoms, no family history of thyroid disease, and was clinically euthyroid. There was no goitre and visual fields were grossly normal. Repeat testing using an alternative assay showed: Free T4 22 pmol/l (8–21), Free T3 6.8 pmol/l (3.5–6), TSH 0.83 mIU/l (0.34–5.60). Free T4 by equilibrium dialysis was 2.4 ng/dL (0.8–2.0), making binding protein interference unlikely. To distinguish TSHoma from RTH: Anterior pituitary hormones normal, Alpha-subunit: not elevated and peripheral markers of thyrotoxicosis (ferritin, sex hormone-binding globulin): normal TRH stimulation test demonstrated an 11-fold rise in TSH, supporting RTH. Genetic testing confirmed a mutation in the thyroid hormone receptor-β gene. As the patient was asymptomatic, no treatment was initiated.
Conclusion
Dynamic testing of the hypothalamic-pituitary-thyroid axis has high specificity in differentiating TSHoma from RTH, while genetic sequencing confirms RTH. However, mutations are undetectable in approximately 15% of patients, and up to

one-quarter may have incidental pituitary lesions, potentially confounding diagnosis. Management of RTH is symptom-directed. β-blockers may be used for symptomatic relief, 3,3,5-triiodothyroacetic acid (TRIAC) is an alternative therapy, and TSH suppression may be considered in patients with significant goitre to prevent thyroid enlargement.

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PS3-10-07

Resistance to thyroid hormone B in a patient with pituitary microadenoma after total thyroidectomy

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Context
Thyroid hormone resistance β (RTHβ) is a rare autosomal dominant disorder due to *THRB* germline mutations, resulting in elevated TSH with high or high-normal free T4 (fT4) and/or T3. Diagnosis is challenging post-thyroidectomy or with pituitary lesions, requiring exclusion of TSH-secreting adenoma (TSH-oma) and assay artifacts.
Case Description
A 40-year-old woman with a history of total thyroidectomy for benign nodular disease had persistently elevated TSH levels (14-24 mIU/l) with normal-high fT4 (1,4-1,7ng/dl; 18–22 pmol/l) and normal TT3 while receiving LT4 125-150 μg daily (2-2,5μg/kg). She reported fatigue and frequent palpitations. Laboratory assessment excluded analytical interference in thyroid function tests. Mildly elevated prolactin was the only abnormality in anterior pituitary hormones testing, while subsequent pituitary magnetic resonance imaging demonstrated a microadenoma. Glycoprotein α-subunit was also normal. A T3 suppression test with liothyronine 100 μg/day for 10 days reduced TSH to 0.20 mIU/l and resulted in fT3 10.13 pg/mL (15.6 pmol/l; reference 1.58–3.92 pg/mL [2.4–6.0 pmol/l]), fT4 0.79 ng/dL (10.2 pmol/l; reference 0.70–1.48 ng/dL [9.0–19.1 pmol/l]), while sex hormone–binding globulin (SHBG) remained normal (85.9 nmol/l (19.8–155.2)), consistent with liver resistance (in contrast to expected elevated SHBG levels in thyrotoxicosis/TSH-oma). The significant TSH suppression excluded TSH-oma (autonomous secretion). Family evaluation showed normal thyroid function tests in her mother and half-sister, while her father was unavailable for testing (deceased). Subsequent Sanger sequencing identified a heterozygous *THRB* variation (c.949G>T) coding a dominant negative missense variant of the cluster II (p.Ala317Ser) within the ligand-binding domain of TRβ, confirming the diagnosis of RTHβ.
Conclusion
RTHβ should be considered in athyreotic patients under LT4 treatment with discordant thyroid function tests (elevated TSH with high-normal fT4) to avoid misclassification as TSH-oma even in the presence of a pituitary lesion. Dynamic testing with high-dose T3 suppression and additional biochemical evaluation can aid the differential diagnosis, while *THRB* sequencing establishes a definitive diagnosis and guides appropriate long-term management.

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PS3-10-08

Emergent total thyroidectomy under VV-ECMO support for refractory thyroid storm complicated by pulmonary thromboembolism after COVID-19: a case report

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Introduction
Thyroid storm (TS) is a life-threatening complication of severe thyrotoxicosis requiring rapid multidisciplinary management. We report a rare case of COVID-19–associated TS complicated by pulmonary thromboembolism (PTE) and cardiogenic shock successfully treated with veno-venous extracorporeal membrane oxygenation (VV-ECMO)–supported emergency thyroidectomy.
Case report
A 44-year-old male presented with progressive chest discomfort and palpitations four weeks after SARS-CoV-2 infection. He had no prior history of thyroid disease. Thyroid function tests demonstrated severe thyrotoxicosis (free thyroxine 7.90 ng/dL, triiodothyronine 3.98 ng/mL, TBII 16.8 ng/mL). Shortly after arrival he developed ventricular tachycardia and cardiogenic shock requiring cardiopulmonary resuscitation. Veno-arterial ECMO was initiated and successfully weaned after four days. Despite two weeks of intensive medical therapy including antithyroid drugs, beta-blockers, steroids and potassium iodide, thyrotoxicosis and respiratory failure worsened. Chest computed tomography revealed extensive PTE involving the main and segmental pulmonary arteries causing refractory hypoxia requiring VV-ECMO support. As the patient's condition deteriorated further, emergency total thyroidectomy was performed three hours after VV-ECMO initiation. The operation lasted approximately one hour and a 90-g thyroid gland was removed without complications. Postoperatively VV-ECMO was successfully discontinued the same day. Thyroid hormone levels rapidly normalized (T3 3.94→0.54 ng/mL; fT4 8.57→1.59 ng/dL). The patient recovered well and was discharged on postoperative day 18.
Conclusion
This case demonstrates that early surgical intervention should be considered in refractory TS when medical therapy fails. VV-ECMO can provide effective respiratory support enabling safe thyroidectomy in critically ill patients with severe thyrotoxicosis and cardiopulmonary instability.

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Hyperthyroidism 3

PS3-11-01

Painless subacute thyroiditis during treatment of graves deasese mimicking antithyroid therapy

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Introduction
Graves disease is the most common cause of hyperthyroidism and is typically treated with antithyroid medications. The coexistence of subacute thyroiditis in patients with Graves disease is rare and can lead to diagnostic confusion, especially when thyrotoxicosis worsens despite therapy. Recognizing atypical presentations is essential for timely diagnosis and management.
Case Report
A 41-year-old woman with Graves' disease started Methimazole therapy, showing initial clinical and biochemical improvement. Shortly after, she developed a viral illness with persistent fever and profound fatigue, without anterior neck pain or thyroid tenderness. Thyroid ultrasound was unremarkable. Laboratory tests revealed worsening thyrotoxicosis with markedly elevated inflammatory markers (CRP 136 mg/l, ESR 80 mm/h). Painless subacute thyroiditis was suspected. Prednisolone 30 mg daily was initiated, leading to rapid improvement and resolution of systemic symptoms. After eight weeks, glucocorticoids were discontinued. The patient later experienced recurrence of hyperthyroid symptoms, and antithyroid therapy was resumed.
Conclusions
Subacute thyroiditis can occur during treatment of Graves' disease and may mimic treatment failure due to worsening thyrotoxicosis. Atypical presentations without neck pain can complicate diagnosis. Awareness of this overlap is critical for timely recognition, avoiding misdiagnosis, and ensuring appropriate management.

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PS3-11-02

Subacute thyroiditis in a thyroid remnant: a rare presentation of subacute thyroiditis after subtotal thyroidectomy

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Introduction
Subacute thyroiditis is a self-limiting inflammatory disorder of the thyroid gland, primarily associated with viral or post-viral etiologies, particularly Epstein-Barr

virus (EBV). It is characterized by neck pain and transient thyroid dysfunction, with diagnosis often complicated by atypical presentations that may overlap with other comorbid conditions. Management typically includes nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids to reduce inflammation, with careful consideration of potential drug interactions. The diagnosis of geriatric patients is often complicated by comorbidities and polypharmacy, which can obscure symptoms and hinder clinical evaluation.
Case Report
A 79-year-old female was initially diagnosed with a multinodular goiter and underwent subtotal thyroidectomy 10 years ago. She was prescribed levothyroxine and is currently maintained on an alternating dosing regimen, achieving an euthyroid state. Five years ago, the patient was diagnosed with diabetes mellitus and dyslipidemia. She remains on pharmacologic therapy, exhibiting suboptimal glycemic regulation while maintaining optimal LDL and triglyceride levels. The patient's medical history includes arterial hypertension, arrhythmias, erosive gastritis, and diverticulitis. Laboratory evaluations revealed chronic hypercalcemia, ultimately diagnosed as primary hyperparathyroidism caused by a left parathyroid adenoma. A DEXA scan showed osteoporosis in the left forearm and osteopenia in the hip and lumbar areas. The patient declined surgery and chose to manage her condition medically, for which bisphosphonates were prescribed. Recently, an abdominal MRI for acute diverticulitis suggested a possible adrenal adenoma on the right gland, but hormonal evaluation was normal, classifying it as an incidentaloma. The patient presented for an early evaluation following several days of severe throat pain, fatigue, and palpitations. The examination revealed pain upon palpation of the left thyroid gland. An ultrasound of the neck revealed residual thyroid tissue on the left, exhibiting increased vascularity and a hypoechoic fluid collection along the posterior wall, accompanied by edema in the surrounding soft tissues. Laboratory assessments revealed elevated CRP and EBV IgG levels, low EBV IgM levels, and TSH at the lower limit of normal, alongside increased FT4 levels. The overall findings were suggestive of subacute thyroiditis. Consequently, levothyroxine was temporarily tapered to optimize laboratory and clinical findings, along with NSAID and corticosteroid therapy.
Conclusion
Diagnosing subacute thyroiditis in elderly patients after subtotal thyroidectomy remains challenging due to complex comorbidities and overlapping symptoms. Accurate diagnosis requires careful monitoring of thyroid hormone levels and consideration of potential drug interactions, as disease progression may exacerbate pre-existing arrhythmias, necessitating a comprehensive and multidisciplinary clinical approach to management.

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PS3-11-03

The burden of thyroid dysfunction over time: effects on quality of life in graves' disease

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Introduction
Graves' disease (GD) is the leading cause of hyperthyroidism and is associated with significant physical, psychological, and social impairment. However, the long-term impact of periods of thyroid dysfunction on quality of life remains poorly understood.
Objective
This study aimed to evaluate the impact of the duration of thyroid dysfunction on quality of life in patients with Graves' disease who were in a sustained euthyroid state.
Materials and Methods
This study included patients with GD who were evaluated during euthyroidism. Quality of life was assessed using the ThyPRO-39 questionnaire. Data regarding treatment modalities, epidemiological characteristics, thyroid function biomarkers, and overall thyroid function control during follow-up were collected.
Results
A total of 185 patients were included, with a mean age of 54 $\pm$ 14 years and a mean follow-up of 943 $\pm$ 855 days. Most patients were female (88.1%), and 15.2% had a history of tobacco use (current or former). Regarding treatment, 54% were receiving antithyroid drugs (ATD), 26.5% had been treated with radioiodine followed by levothyroxine replacement (RAI), and 19.5% were in remission. Mean TSH was 2.43 $\pm$ 2.58 mIU/l and mean FT4 was 1.25 $\pm$ 0.32 ng/dL. Regarding thyroid function status during follow-up, the mean duration of hyperthyroidism was 32 $\pm$ 30 days, subclinical hyperthyroidism 361 $\pm$ 291 days, euthyroidism 688 $\pm$ 620 days, subclinical hypothyroidism 376 $\pm$ 312 days, and overt hypothyroidism 262 $\pm$ 212 days. Patients treated with RAI spent significantly fewer days in euthyroidism compared with those receiving continuous ATD therapy and those in remission ($P < 0.005$). In the ThyPRO-39 questionnaire analysis, a longer duration of hyperthyroidism was associated with greater impairment in the appearance domain. In contrast, a longer duration of subclinical hypothyroidism was associated with significantly worse overall quality of life ($P < 0.005$). No significant differences were observed in the remaining domains.
Conclusion
These findings suggest that thyroid dysfunction may have long-lasting effects on quality of life, even in patients who subsequently achieve sustained euthyroidism. Hyperthyroid and hypothyroid phases appear to affect patients differently, with certain domains being more negatively impacted by hyperthyroidism, whereas others may be more adversely affected during subclinical hypothyroidism.

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PS3-11-04

Quality of life in graves' disease patients: what are the key factors

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Introduction
Graves' disease (GD) is the leading cause of hyperthyroidism worldwide. For these patients, restoring euthyroidism is a crucial step in regaining their quality of life (QoL). However, data on the individual factors affecting QoL remain limited.
Objectives
The aim of this study was to evaluate the QoL and determine the independent contribution of demographic factors, particularly age, gender, and thyroid function biomarkers, to QoL impairment.
Materials and methods
The study included GD patients treated with antithyroid drugs (ATD) or radioactive iodine (RAI), followed by levothyroxine replacement, and disease remission in a sustained euthyroid state, which were evaluated and compared using the ThyPRO-39 questionnaire to assess QoL outcomes. Patients were analyzed regarding epidemiological features and thyroid function biomarkers.
Results
The study included 185 patients with a mean age of 54 $\pm$ 14 years; 88.1% of patients were female; 15.2% presented history of tobacco use (prior or current); 54% of patients were in ATD use, 26.5% used RAI and levothyroxine replacement and 19.5% were in remission; 82% of had no signs of TED, 17% of patients had mild TED, 1% of patients presented moderate to severe TED. Regarding thyroid biomarkers, mean TSH was 2.43 $\pm$ 2.58 mUI/l, mean FT4 was 1.25 $\pm$ 0.32 ng/dL, mean TT4 was 10.37 $\pm$ 6.27 ug/dL, mean FT3 was 3.25 $\pm$ 0.76 ng/dL, and TT3 was 1.17 $\pm$ 0.49ng/dL. TT3/TT4 ratio 0.12 $\pm$ 0.05 and FT3/FT4 ratio was 2.70 $\pm$ 0.84 Evaluating the impact of the TT3/TT4 ratio on the Qol, a higher ratio correlated to worse overall quality of life as well as more symptoms of depression and impact on daily life ($P < 0.005$). Age also plays a significant role in QoL impact, with older age correlating with greater impact on appearance, social life, emotional susceptibility, and worse overall QoL ($P < 0.005$). Female patients had worse scores for hypothyroidism symptoms, goiter symptoms, hyperthyroidism symptoms, eye symptoms, tiredness, cognitive complaints, emotional susceptibility, social life impact, appearance, and overall quality of life compared with male patients ($P < 0.005$). No other factors significantly affected QoL.
Conclusion
Our results imply that QoL is affected differently by biological and epidemiological factors, with age, gender, and TT3/TT4 balance as crucial determinants of QoL impairment.

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PS3-11-05

Dual etiology of hyperthyroidism: a case of marine–lenhart syndrome

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Introduction
Graves' Disease (GD), the most common cause of hyperthyroidism, is driven by stimulatory TSH receptor antibodies (TRAbs). TRAbs activate the TSH receptor on thyroid follicular cells, resulting in increased production of T3 and T4. Functioning thyroid nodules (toxic adenoma and toxic multinodular goiter) are a common finding in clinical practice. Coexistence of thyroid functioning nodules and Graves' disease is called Marine-Lenhart syndrome. This is a rare condition, and the reported prevalence is approximately 0.26% to 4.1%. Because this entity combines two distinct etiologies of hyperthyroidism, it may present with diagnostic and therapeutic challenges, making recognition important for appropriate management.
Case Report
Previously healthy, 38-year-old female visited the clinic with a 2-week history of palpitation, fatigue, heat intolerance, weight loss, excessive sweating, hair loss, and anxiety. The patient was tachycardic with systolic hypertension. Physical examination revealed tremors of the upper extremities, hyperreflexia, and moist skin. Lid lag and Graphe's sign were absent. Laboratory studies showed suppressed levels of TSH, elevated FT4, ANTI-TPO, ANTI-TG, and TRAB. Thyroid Ultrasound revealed a highly vascularized, mildly enlarged gland (18.8 sm3). In the right lobe, there was a heterogeneous solid nodule measuring 20X17mm with ill-defined borders. Scintigraphy showed increased uptake in both lobes, with a more focal hot nodule in the right lobe. The patient was started on methimazole and beta-blocker therapy. After normalization of TFT, FNA was performed with the results of BSRTC IV. While gradually tapering the methimazole dosage, disease recurrence developed, and total thyroidectomy was performed. Patient started Hormone replacement therapy with additional supplementation of Calcium and Vitamin D3. Patient's condition improved, with normalization of laboratory parameters accompanied by resolution of clinical symptoms.
Conclusion
This case demonstrates Graves' disease with a concomitant toxic adenoma, a rare form of hyperthyroidism known as Marine–Lenhart syndrome. Recognition of MLS can be challenging because of its overlapping clinical and biochemical features with other causes of hyperthyroidism. However, accurate diagnosis is crucial, as patients often exhibit a suboptimal response to antithyroid drug therapy and frequently require definitive treatment options such as surgery or RAI, underscoring the importance of comprehensive diagnostic evaluation to guide appropriate management and optimize patient outcomes.

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PS3-11-06

Propylthiouracil-induced MPO-ANCA positivity: a diagnostic challenge in thyroid disease

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Introduction
Propylthiouracil (PTU) is a recognized cause of antineutrophil cytoplasmic antibody (ANCA) positivity, particularly myeloperoxidase (MPO)-ANCA, and may rarely trigger drug-induced ANCA-associated vasculitis (estimated to occur in up to 3% of patients) after months to years of therapy. Clinical manifestations range from mild symptoms to severe organ involvement, including glomerulonephritis and pulmonary involvement, such as alveolar hemorrhage or pneumonitis. Distinguishing isolated serological positivity from true vasculitic disease is essential, especially in patients with overlapping respiratory manifestations that may complicate the clinical picture.
Case report
A 72-year-old woman was referred to a specialized thyroid consultation for evaluation of suspected MPO-ANCA vasculitis in the setting of hyperthyroidism treated with PTU for the past two years. Her medical history was notable for severe asthma, chronic sinonasal disease, and treatment with mepolizumab. The only reported symptoms were episodes of nasal bleeding and asthma exacerbations. During PTU therapy, borderline/positive MPO-ANCA was detected, raising concern for vasculitis. However, multidisciplinary assessment, including Rheumatology and Pulmonology, found no clear clinical features of systemic vasculitis. Sinonasal computed tomography showed inflammatory mucosal thickening of the paranasal sinuses, while initial chest computed tomography revealed bronchiectatic changes and small pulmonary nodules, later showing marked improvement on follow-up imaging. Additionally, bronchoalveolar lavage was performed, revealing lymphocytic alveolitis with no evidence of *Aspergillus*, *Pneumocystis*, or acid-fast bacilli. After PTU withdrawal, MPO-ANCA became negative, supporting a drug-related etiology rather than primary vasculitic disease. Simultaneous thyroid evaluation documented multinodular disease with suspicious bilateral nodules, and the patient was referred for further thyroid-directed management, including cytological and surgical assessment.
Conclusion
This case highlights the diagnostic challenge of interpreting MPO-ANCA positivity in patients receiving PTU, particularly in the presence of respiratory comorbidities that may mimic vasculitic involvement. The absence of unequivocal systemic manifestations, together with serological negativization after PTU discontinuation, strongly supports PTU-induced MPO-ANCA positivity. Early recognition of this association and multidisciplinary evaluation are crucial to avoid misdiagnosis, unnecessary immunosuppression, and delays in appropriate thyroid treatment.

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PS3-11-07

Methimazole-induced agranulocytosis: a case report

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Introduction
Agranulocytosis is one of the most severe and fearsed adverse effect associated with the use of thionamides, occurring in less than 1% of patients. Fever, odynophagia, oral ulcers, or general malaise are warning signs/symptoms that should prompt the immediate performance of a complete blood count with leukocyte differential.
Case Report
56-year-old autonomous woman with Graves' disease diagnosed four months earlier and treated with Metibasol (15 mg/day). She presented to the emergency department with a four-day history of fever, nocturnal hyperhidrosis, odynophagia, vomiting, and mental confusion. On physical examination, she had a temperature of 38°C, blood pressure of 114/70 mmHg, heart rate of 120 bpm, polypnea, dehydration, cervical edema and pain, and anxiety. Burch–Wartofsky score: 55 points. Laboratory analysis revealed leukopenia (290/μL), neutropenia (10/μL), CRP 30.43 mg/dL, procalcitonin 9.27 ng/dL, TSH <0.01 (0.27-4.20 uUI/mL), free T4 4.03 ng/dL(0.93-1.70 ng/dL), free T3 10.20 pg/mL (2.57-4.43 pg/mL), and TSH receptor antibodies 30.6 IU/l (<1.8 IU/l). Cervical CT showed circumferential edema and a globular thyroid gland, without focal lesions. The patient was admitted to an isolation room due to febrile neutropenia with acute tonsillitis. Treatment was initiated with piperacillin/tazobactam, filgrastim, and propylthiouracil (PTU) 200 mg every 8h, and methimazole was discontinued. Within the first 24h, clinical deterioration occurred, with worsening cervical edema, dysphagia, dysphonia, persistent fever, and pancytopenia. PTU was discontinued, and propranolol 10 mg every 8h, hydrocortisone 100 mg every 8h, and cholestyramine 4 g every 8h were initiated. She was admitted to the intensive care unit for 48h, with favorable clinical evolution and no need for ventilatory support. During hospitalization, the patient showed progressive improvement with reduction of edema, apyrexia, and resolution of compressive symptoms. TSH remained <0.01, with a decrease in free T4 (2.12 ng/dL) and free T3 (2.90 pg/mL). Hydrocortisone was reduced to 50 mg every 12h, lithium 800 mg/day was started, PTU was reintroduced at 50 mg twice daily, and the remaining therapy was maintained. She was discharged eleven days after admission with resolution of tonsillitis, improvement of thyroid function, and prescribed prednisolone 20 mg/day, lithium 800 mg/day, PTU 100 mg/day, and cholestyramine 4 g every 8h.
Conclusion
Routine monitoring of leukocyte counts is not recommended, as agranulocytosis occurs abruptly. Given its potential severity, it is essential to inform patients about warning signs and symptoms at the initiation of treatment with thionamides.

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PS3-11-08

Painful thyrotoxicosis mimicking subacute thyroiditis: an atypical presentation of graves' disease

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Introduction
Painful thyroid disease is most commonly caused by Subacute thyroiditis, whereas Graves' disease typically presents with painless thyrotoxicosis. Atypical presentations may lead to diagnostic uncertainty and inappropriate initial management. We present a case of painful thyrotoxicosis without goiter or nodules, ultimately diagnosed as Graves' disease with a concomitant infection.
Case Report
A 56-year-old man presented with a 10-day history of anterior neck pain radiating to the jaw and subfebrile temperature. He had been treated with antibiotics and non-steroidal anti-inflammatory drugs without improvement. Physical examination revealed a tender thyroid gland. Ultrasonography suggested thyroiditis without enlargement or nodules. Laboratory tests showed ESR 36 mm/h, suppressed TSH (0.05 μIU/mL), leukocytes 9.2×10?/l, and mildly elevated FT4 (1.87 ng/dL). Initial suspicion was subacute thyroiditis; The patient denied any preceding viral infection. Further testing revealed ferritin 124 ng/mL, elevated anti-TPO and anti-TG antibodies, and anti-TSH receptor antibodies 4.94 IU/l. Thyroid scintigraphy showed 1.4% radiopharmaceutical uptake, confirming Graves' disease. Antithyroid therapy was initiated, and the patient was referred to an infectious disease specialist. On the same day, due to hectic fever, he was hospitalized, and testing revealed Syphilis. Following comprehensive treatment, his condition improved. At one-month follow-up, FT4 normalized, and antithyroid therapy was adjusted.
Conclusions
Painful thyrotoxicosis, even without goiter or nodules, does not exclude Graves' disease. Comprehensive evaluation, including antibody testing and thyroid scintigraphy, is essential to avoid misdiagnosis with Subacute thyroiditis. Clinicians should recognize that atypical forms of Graves' disease may mimic inflammatory thyroid disorders, emphasizing the importance of thorough diagnostic assessment.

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Goitre & nodules 2

PS3-12-01

Infected thyroid CYST with já subclinical thyrotoxicosis secondary to nosocomial escherichia coli urinary tract infection: a case report

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Introduction
Infected thyroid cysts are a rare clinical entity, as the thyroid gland is relatively resistant to bacterial invasion, due to its capsular encasement, rich vascular supply, lymphatic drainage and high iodine content. Hematogenous spread from a distant site of infection is considered one possible mechanism.
Case report
We report the case of an 81-year-old woman, with no prior known history of thyroid disease, hospitalized for right lower limb cellulitis, which has been successfully treated with cefazolin, who subsequently developed a nosocomial urinary tract infection (UTI) caused by ESBL-producing *Escherichia coli*, requiring the restart of antibiotic therapy. On the day 27 of hospitalisation, she presented with fever, neck pain and a tender, erythematous and warm anterior cervical swelling measuring approximately 4 cm. Computed tomography revealed a large cystic lesion measuring 64 x 51 x 61 mm in the right thyroid lobe, causing contralateral tracheal deviation and surrounding tissue inflammation. Thyroid function tests demonstrated subclinical thyrotoxicosis (thyroid-stimulating hormone (TSH) 0.07(0.35-4.94) μUI/mL, free thyroxine (fT4) 1.41 (0.70-1.48) ng/dL) and thyroid ultrasonography confirmed a cystic lesion occupying most of the right lobe, with the left lobe normal in size and morphology. Percutaneous aspiration revealed purulent fluid and microbiological culture identified *Escherichia coli*, consistent with the prior UTI. Despite intravenous ertapenem therapy and two repeated aspirations, the patient remained febrile, with persistently inflammatory marker elevation and enlargement of the cystic lesion. Surgical intervention was subsequently performed to achieve definitive source control, as interventional radiology with expertise in neck procedures was not available. The patient showed resolution of the infectious process, with disappearance of fever and normalization of inflammatory markers. Thyroid function recovered, with TSH 0.96 μUI/mL, fT4 0.91 ng/dL and free triiodothyronine 2.15 ng/dL.
Conclusion
This case illustrates a rare presentation of an infected thyroid cyst secondary to hematogenous spread from a nosocomial ITU, highlighting that infection can occur in tissues that are relatively resistant to bacterial invasion, such as the thyroid, even in patients under antibiotic therapy. Transient thyrotoxicosis may accompany acute thyroid infection, normalizing after resolution. The case also underscores the importance of timely, multidisciplinary management, which contributed to a favourable clinical outcome.

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PS3-12-02

Autonomously functioning thyroid nodule presenting in a euthyroid patient: diagnostic role of SPECT-CT

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Introduction
Autonomously functioning thyroid nodules (toxic adenomas) are a common cause of hyperthyroidism. In iodine-deficient regions, they account for approximately 30–50% of hyperthyroidism cases due to the high prevalence of nodular thyroid disease. Countries in Eastern Europe, including Georgia, have historically been considered iodine-deficient regions where nodular thyroid pathology remains frequent. At the molecular level, toxic adenomas are most commonly associated with somatic activating mutations of the TSH receptor (TSHR) gene or the GNAS gene, resulting in constitutive activation of the cAMP signaling pathway and autonomous thyroid hormone production. Typically, autonomously functioning thyroid nodules result in overt or subclinical thyrotoxicosis. However, detection of a hyperfunctioning thyroid nodule in a biochemically euthyroid patient is relatively uncommon and may complicate diagnosis and management. Functional imaging can play a critical role in identifying such lesions.
Case Presentation
We report a female patient who had been under endocrinological follow-up for approximately 10 years due to nodular thyroid disease with preserved thyroid function. Serial ultrasonography demonstrated multinodular enlargement of the thyroid gland. Fine-needle aspiration biopsy was repeatedly recommended but declined by the patient. The patient later presented with compressive cervical symptoms, including a sensation of neck fullness, intermittent dysphagia, and nonspecific symptoms: fatigue, hair loss, brittle nails, cold intolerance, emotional lability, and decreased concentration. Physical examination revealed dry skin and a diffusely enlarged thyroid gland with multiple palpable nodules. Laboratory evaluation revealed markedly reduced ferritin levels (<7.8 ng/mL), vitamin D deficiency (20.3 ng/mL), borderline vitamin B12 levels, and dyslipidemia characterized by elevated total cholesterol and LDL levels. Thyroid function tests showed a euthyroid hormonal profile, with mildly suppressed TSH. Thyroid ultrasonography confirmed hyperplastic multinodular goiter. SPECT-CT imaging revealed a hyperfunctioning ("hot") nodule in the lower third of the left thyroid lobe, with markedly reduced radiotracer uptake in the surrounding thyroid tissue, consistent with a toxic adenoma.
Conclusion
This case demonstrates a toxic thyroid adenoma presenting in a clinically and biochemically euthyroid patient, an uncommon presentation for autonomously functioning thyroid nodules. Functional imaging with SPECT-CT was crucial for identifying thyroid autonomy, highlighting that autonomous nodular activity may precede overt biochemical thyrotoxicosis. The core objective of early detection is to prevent potential multisystem complications associated with toxic adenomas, including cardiovascular disorders, metabolic disturbances, osteoporosis, and neuropsychiatric manifestations.

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PS3-12-03

Infectious complications after thyroid needle procedures: a case report of infected thyroid cyst following percutaneous ethanol injection and a narrative review

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Introduction
Percutaneous ethanolinjection (PEI) is a safe and effective treatment for symptomatic thyroid cysts. While minor adverse events are common, infectious complications are exceedingly rare, with only isolatedconfirmedreports available in literature. We report a rare case of an infected thyroid cyst after PEI and provide a review of infectious complications associated with thyroid needle procedures.
Case Report
A 44-year-old woman with a large recurrent right thyroid cyst (32 mL) underwent ultrasound-guided PEI. Under sterile conditions, 27 mL of fluid were aspirated and 9 mL of 95% ethanol instilled. Three weeks later, the patient presented with progressive neck pain and low-grade fever (37.8°C). Ultrasounddemonstrate-denlargement of the treated cyst with heterogeneous internal debris and surrounding inflammatory changes. Serial ultrasonographic monitoring was pivotal in documenting the rapid response to therapy andthe subsequentresolution of the inflammatory process. Laboratory tests showed marked systemic inflammation (WBC 13.97 $\times$ 10^3/μL, 81.6% neutrophils; CRP 11.94 mg/dL; ESR 85 mm/h). Following a diagnosis of suspected infectious transformation, the patient received systemic broad-spectrum antibiotics (ceftriaxone) and corticos-teroids (prednisone), resulting in rapid clinical improvement and normalization of inflammatory markers.
Review of the Literature
Our review identified 20 cases of infectious or suspected infectious complications after thyroid needle procedures, including fine-needle aspiration (FNA), PEI, andthermalablation (TA). While FNA is the mostfrequentlyassociated procedure, complications after PEI remain extremely uncommon (4 casesidentifiedincluding ours).*Staphylococcus aureus*was themostfrequentlyisolated pathogen. Notably, there is currently no consensus on management: strategies reported in literature vary widely and inconsistently, ranging from conservative antibiotic therapy to ultrasound-guided drainage, emergency incision, or even total thyroidectomy.
Conclusions
Infectious complications after PEI are rare but clinically significant. The lack of standardized management underscores the need for clinical vigilance. Early recognition through ultrasound and inflammatory markers is essential; prompt initiation of broad-spectrum antibiotic therapy can be successful as a primary conservative approach, potentially preventing abscess formation and the need for more invasive surgical interventions.

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PS3-12-04

Calcitonin screening in thyroid nodules: regional experience from adjara, georgia

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Background
Routine measurement of serum calcitonin in patients with thyroid nodules remains controversial. Although calcitonin is an established biomarker for medullary thyroid carcinoma (MTC), its diagnostic yield varies between populations. Data from the South Caucasus region are limited, and no regional studies from Adjara, western Georgia, have evaluated calcitonin levels in relation to ultrasound risk features.
Objective
To evaluate serum calcitonin levels in patients with thyroid nodules and explore their association with ultrasound risk stratification in a regional cohort from Adjara, Georgia.
Methods
This cross-sectional observational study included 97 patients with thyroid nodules referred for endocrinology evaluation at a clinic in Batumi, Adjara. Demographic data, thyroid function tests (TSH, FT4), and serum calcitonin levels were collected. Thyroid nodules were assessed by ultrasound and classified according to the EU-TIRADS system. Ultrasound characteristics including echogenicity, calcifications, nodule number, and nodule orientation (taller-than-wide vs wider-than-tall) were recorded. According to our laboratory reference values, the upper limit of normal serum calcitonin is $\leq$6.4 pg/ml in women and $\leq$9.54 pg/ml in men. Associations between calcitonin levels and clinical or ultrasound parameters were evaluated using Spearman correlation, Mann–Whitney tests, and ANOVA.
Results
A total of 97 patients were included (mean age 45 $\pm$ 15 years, predominantly female). Most nodules were classified as EU-TIRADS 3–4, with multinodular thyroid disease frequently observed. Mean serum calcitonin was 1.3 $\pm$ 0.9 pg/ml (range $<$0.5–4 pg/ml), remaining within the laboratory reference range in nearly all patients. ANOVA revealed a modest association between calcitonin levels and EU-TIRADS categories ($P = 0.048$). Calcitonin levels were also associated with the presence of calcifications (Mann–Whitney $P = 0.041$), while no association was observed with nodule orientation, echogenicity, age, TSH levels, or number of nodules ($P > 0.05$). No cases suggestive of medullary thyroid carcinoma were identified.
Conclusion
In this regional cohort from Adjara, Georgia, serum calcitonin levels remained within the normal range in the vast majority of patients with thyroid nodules. Modest associations were observed with EU-TIRADS categories and the presence of calcifications, while no cases suggestive of medullary thyroid carcinoma were identified. These findings suggest a low diagnostic yield of routine calcitonin screening in this population.

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PS3-12-05

Subclinical hyperthyroidism due to graves' disease and a large mixed hyperfunctioning nodule: an atypical case of marine-lenhart syndrome

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Introduction
Marine-Lenhart Syndrome (MLS) is defined as the coexistence of Graves' disease (GD) and autonomously functioning thyroid nodules. It represents a rare cause of thyrotoxicosis, accounting for less than 5% of GD cases, and is typically associated with overt hyperthyroidism. We report an atypical presentation of MLS characterized by a large mixed solid–cystic thyroid nodule causing compressive symptoms in the setting of subclinical hyperthyroidism.
Case presentation
A 33-year-old woman was referred to the Endocrinology Department for evaluation of multinodular goiter and suppressed TSH: 0.08μIU/mL. She reported left-sided cervical compression and a visibly enlarged neck. Her medical history included juvenile idiopathic arthritis, acquired partial lipodystrophy (in the context of autoimmune disease), polycystic ovary syndrome, combined hyperlipidemia, and depression. She was under metformin, fenofibrate, magnesium, cholecalciferol, and escitalopram. Thyroid ultrasound (US) revealed a 16mm cyst in the superior right lobe (RL), a 14mm mixed nodule in the inferior RL and a heterogeneous 40mm mixed solid–cystic nodule in the inferior left lobe (LL). Laboratory evaluation: TSH 0.13μUI/mL; fT4 7.9pmol/l (7.9 - 14.4); fT3

[Abstract PS3-12-03]

Procedure	Cases (n)	Onset Range	Typical Pathogen(s)	Management	Outcome
FNA	14	3 days – 3months	*Staphylococci, P.acnes, E. coli*	Antibiotics, Drainage, Surgery	Recovery/Thyroidectomy
PEI	4	1 day – 3 weeks	*S.aureus*, Negative/Not spec.	Antibiotics, Drainage, Surgery	Full Recovery
TA	2	1 – 4 weeks	Notidentified	Antibiotics, Surgery	Resolution/Pending

5.9pmol/l (3.8 - 6.0); TSH receptor antibodies (TRAb) 1.8UI/l (<1.5). Methimazole 2.5mg once daily was initiated. Fine-needle aspiration (FNA) of the 4cm nodule was performed in order to relieve compressive symptoms, which was successfully achieved. Cytological evaluation was non-diagnostic. Follow-up US after 7 months: a 44mm mixed nodule in the inferior LL, a 19mm isoechoic nodule in the superior LL, a 15mm hyperechoic nodule in the midle RL and four pericentimetric nodules in the RL. Under methimazole therapy, laboratory tests showed: TSH 2.45µUI/mL; fT4 7.8pmol/l; fT3 5.3pmol/l. The patient performed a Technetium-99m scintigraphy, to decide which nodules should be submitted to FNA; it demonstrated diffusely increased thyroid uptake, suggestive of GD, as well as a dominant hyperfunctioning nodule in the inferior LL, corresponding to the 4.4cm nodule identified on US. Additionally, it raised suspicion for hypofunctioning nodules in the inferior RL and superior LL. This case was discussed in a multidisciplinary team meeting and, taking into account the patient's preferences—namely her desire for pregnancy in the medium term—surgical treatment was proposed. The patient is currently awaiting total thyroidectomy.

Conclusions

MLS should be considered in patients with nodular goiter and biochemical hyperthyroidism, even when hormone excess is mild. Careful integration of ultrasound findings, immunological markers, and scintigraphy is essential for accurate diagnosis and optimal management.

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PS3-12-06

Intrathyroidal ectopic thymus in children: clinical and ultrasound characteristics

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Objective

To evaluate the significance of clinical and ultrasonographic features for diagnosing intrathyroidal ectopic thymus (IET) in children.

Methods

A single-center prospective study was conducted on patients aged 0–18 years with thyroid nodules confirmed by ultrasound (US). All patients underwent an evaluation of their hormonal status and anthropometric parameters as well as thyroid US examination. A retrospective analysis of the US characteristics of any focal thyroid lesions was performed.

Results

The prospective study included 65 patients (28 girls [43.1%] and 37 boys [56.9%]) aged 1 to 15 years (median 8.48 ± 2.98 years). All patients were in a euthyroid state without therapy (median TSH 1.85 mIU/l). Height SDS was 0.72 ± 1.03 [0.47 – 0.98], BMI SDS was -0.30 ± 0.95 [-0.53 – 0.06]. Thyroid nodules sized were <1 cm and from 1 to 2 cm were most common (55.4% and 27.7% of cases, respectively). Nodular lesions of <5 mm occurred in 13.8% of cases. The nodules were hypoechoic in 92.3% of patients, isoechoic in 4.6% of patients, and anechoic in 3.1% of patients. All nodules had a clear and even contour. Hyperechoic inclusions were observed in most cases (93.8% of patients). The nodules were of triangular shape in transverse view is 7.7% of the subject. Homogeneous echotexture of the background thyroid tissue was observed in 100% of cases.

Discussion

IET is characterized by a distinct US phenotype differing it from malignant pathology. Its hallmark feature is the combination of hypoechogenicity with smooth contours and specific hyperechoic inclusions (likely representing thymic fat or connective tissue). While hypoechoic nodules on US-examination typically raise malignancy concerns, these specific features indicate a benign process. A key diagnostic strategy involves identifying the native thymic tissue and comparing its US characteristics with the intrathyroidal lesion. Matching echogenicity and internal structure between the two sites serve as a specific marker for thymic ectopia, helping to distinguish it from papillary thyroid carcinoma. Normal hormonal and anthropometric profiles confirm IET does not affect growth or thyroid function. Clinically, recognizing this pattern enables non-invasive diagnosis of IET, potentially eliminating unnecessary fine-needle aspirations (FNA) and frequent monitoring, which may - reduce psycho-emotional stress for the patients' families.

Conclusions

Pediatric IET typically manifests as small (<2 cm), solitary nodules with reduced echogenicity, smooth contours, and hyperechoic inclusions. This signature ultrasound pattern serves as a reliable marker for differential diagnosis, preventing unjustified invasive interventions.

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PS3-12-07

Recent results of minimally invasive treatment of gray zone (TBSRTC III-IV) thyroid nodules

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Objectives

To evaluate the recent results of laser interstitial thermotherapy (LITT) in patients with nodular goiter with cytological TBSRTC III-IV category.

Method

In 2020-2025, LITT performed under ultrasound control in 63 patients with nodular goiter. Group I: TBSRTC - III ($n = 24$); Group II: TBSRTC - IV ($n = 39$). The laser type: GaAlAs diode laser (VELAS II-30F). Selection criteria - low risk of metastasis. The criteria for a positive result: volume reduction rate (VRR) ≥70% and TBSRTC class reduction. Partial positive result – absence of one of the signs. Negative result – an absence of both signs.

Results

Group I: 84,2% ($n = 20$) - positive result. In 15,8% ($n = 4$) - negative or partial positive result. Group II: 80,7% ($n = 34$) - positive result. In 19,3% ($n = 5$) - negative or partial positive result. The median VRR after the LITT session for group I - 75.38 (67.6; 84.9), and for group II - 85.0 (59.7; 94.4). The control FNAB for group I ($n = 3$) - TBSRTC II. The control FNAB for group II: TBSRTC II – 7 (17,9%), TBSRTC III – 4 (10,3%), TBSRTC V – 1 (2,6%) patient respectively. The specific energy value in patients with a positive result was: 2162.7 (1297.5; 4,517.3) in comparison with 471.0 (324.7; 818.0) J/cm^3 in patients with a negative result, ($P < 0.001$). In 6,3% of patients ($n = 4$) complications in the form of hematoma were noted.

Conclusion

The use of LITT of treating gray zone nodes has a positive result provided that the specific energy in the first session is 2162 J/cm^3

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Hypothyroidism 3

PS3-13-01

Hashimoto's encephalopathy: a rare but curable condition

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Introduction

Hashimoto's encephalopathy is a rare neurological complication of autoimmune thyroiditis. This diagnosis should be considered when neuropsychiatric symptoms are associated with positive antithyroid antibodies (ATAs). It is an autoimmune condition with a favorable prognosis, characterized by a high response to corticosteroid therapy. Diagnosis may be delayed, particularly in older patients, where symptoms may easily be attributed to aging.

Case Report

An 82-year-old woman treated for hypothyroidism with levothyroxine for two years was referred to the neurology department because of progressive memory impairment and headaches over several weeks. The patient, a retired educator, raised concerns among her family because of speech, mood, and behavioral disturbances, associated with slowed thinking. Family interviews also revealed sleep and concentration difficulties. No paresthesias, arthralgias, or myalgias were reported. Physical examination showed psychomotor retardation and an anterograde amnesia syndrome with a hippocampal profile. The remainder of the examination, including ophthalmological assessment, was unremarkable. Cognitive evaluation using the Mini Mental State Examination (MMSE) scored 16/30. Laboratory investigations revealed no inflammatory syndrome. Liver and renal function tests, blood glucose, calcium, and electrolytes were normal. Thyroid function tests showed an elevated TSH level of 7.338 µIU/mL (reference range 0.48–4.64) with normal FT4. Alzheimer's disease was initially suspected. Lumbar puncture with cerebrospinal fluid (CSF) analysis of Alzheimer's biomarkers showed normal phosphorylated tau protein (pTau). Electroencephalography (EEG) was unremarkable. Brain CT scan and MRI revealed cortical–subcortical atrophy with bilateral hippocampal atrophy. Anti-neuronal antibodies

were negative. Antithyroid antibodies were strongly positive: anti-thyroglobulin (ATG) at 228 IU (15 times the normal level) and anti-thyroperoxidase (ATPO) at 20 IU (twice the normal level). Hyperhomocysteinemia was also noted at three times the normal value (59.95 µmol/l). Antinuclear antibodies (ANA) and anti-DNA antibodies were negative, and antithyroid antibodies in CSF were negative. The diagnosis of Hashimoto's encephalopathy was established based on acute encephalopathy symptoms and strongly positive antithyroid antibodies, in the absence of metabolic, infectious, vascular, or neoplastic causes. The patient improved within weeks after intravenous corticosteroid bolus followed by oral therapy, with stable radiological findings.

Conclusion

Hashimoto's encephalopathy is a rare condition that should be considered in cases of unexplained neuropsychiatric symptoms, particularly in older adults where they may be misattributed to aging or dementia.

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PS3-13-02

Levothyroxine malabsorption revealing undiagnosed celiac disease in a patient with primary hypothyroidism: a case report

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Introduction

Celiac disease (CD) and autoimmune thyroid diseases frequently coexist due to shared autoimmune mechanisms and genetic susceptibility, particularly involving human leukocyte antigen (HLA) class II haplotypes such as DQ2 and DQ8. Patients with CD have an increased prevalence of thyroid disorders, including hypothyroidism. In untreated CD, intestinal mucosal damage may impair the absorption of levothyroxine, resulting in unstable thyroid function despite apparently adequate replacement therapy. Recognition of this association is essential for optimal management.

Case Presentation

We report a 16-year-old female with a 10-year history of primary hypothyroidism and a positive maternal family history of thyroid disease. She presented with persistent fatigue, generalized weakness, weight instability, difficulty losing weight, and growth retardation. Her medical history was notable for recurrent iron, folic acid, and vitamin B12 deficiencies requiring repeated supplementation. Despite regular levothyroxine therapy, stable thyroid-stimulating hormone (TSH) levels were not achieved, and frequent dose adjustments were required. Her height was 157 cm and weight 67 kg. Laboratory evaluation revealed TSH 7.05 mIU/l (reference range 0.51–4.3) and free thyroxine (fT4) 15.7 pmol/l. Iron and folic acid levels were below the reference ranges. Thyroid ultrasound demonstrated a gland volume of 8 cm^3 with heterogeneous echotexture and small avascular anechoic areas measuring 2–3 mm. Radiographic examination of the right hip revealed synostosis of the growth plates. Due to persistent micronutrient deficiencies and suspected malabsorption, the levothyroxine dose was increased and gastroenterological evaluation was recommended. Three months later, the patient was diagnosed with celiac disease following gastroenterological assessment. A strict gluten-free diet was initiated. At follow-up, laboratory findings showed suppressed TSH (<0.005 mIU/l) and elevated fT4 (23.2 pmol/l), while iron and folic acid levels normalized. The patient also reported significant clinical improvement. Consequently, the levothyroxine dose was reduced to 88 µg/day.

Conclusion

This case highlights celiac disease as a potential cause of levothyroxine malabsorption and unstable thyroid function in patients with hypothyroidism. In individuals with persistent micronutrient deficiencies and fluctuating TSH levels despite appropriate therapy, evaluation for celiac disease should be considered. Early diagnosis and initiation of a gluten-free diet may improve both clinical status and thyroid hormone absorption.

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PS3-13-03

Skin hyperpigmentation as a clinical manifestation of isolated hypothyroxinemia: a case report

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Introduction

Isolated hypothyroxinemia is defined as a reduction in free thyroxine levels with normal thyroid-stimulating hormone (TSH) and has long been considered a condition without clear clinical manifestations. However, accumulating evidence suggests that even with normal TSH, thyroid hormone deficiency at the tissue level may have clinical significance, including effects on skin status and pigment metabolism. Of particular interest is the role of iodine deficiency as a leading factor in the development of isolated hypothyroxinemia in women, as well as its possible association with hyperpigmentation of exposed skin areas. Clinical observations showing regression of pigmentation following correction of iodine status highlight the importance of a broader view of the clinical manifestations of this condition.

Aim of the study

To present a clinical case illustrating a possible association between isolated hypothyroxinemia and skin hyperpigmentation and to evaluate the effect of iodine supplementation.

Materials and methods

A 35-year-old woman presented with progressive forehead hyperpigmentation lasting six months. Laboratory evaluation included prolactin, TSH, free thyroxine (fT4), vitamin D, and ferritin levels.

Results

TSH and prolactin levels were within the reference range, while fT4 was at the lower limit of normal. VitaminD, ferritin, and thyroid ultrasound findings were normal. Thyroid ultrasound was performed. Prophylactic potassium iodide was administered at a dose of 150 µg/day for six months. After six months of iodine supplementation, complete regression of forehead hyperpigmentation was observed, and euthyroid status was confirmed.

Conclusion

This case demonstrates that isolated hypothyroxinemia related to iodine deficiency may present with subtle cutaneous manifestations, such as forehead hyperpigmentation, which can be reversed with appropriate iodine supplementation. The findings emphasize the need to consider tissue-level thyroid hormone deficiency in women, even when TSH is normal, and highlight the clinical relevance of preventive iodine correction. Further experience with additional patients is needed to better understand the prevalence and spectrum of cutaneous manifestations in this condition.

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PS3-13-04

Hypothyoidism, an underappreciated metabolic derangement causing dyslipidemia

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Background

Dyslipidemia is an established major risk factor of atherosclerotic cardiovascular disease. Dyslipidemia can be caused by inherited genetic disorders such as familial hypercholesterolemia or can result from metabolic derangements, including hypothyroidism. Hypothyroidism is a commonly encountered clinical condition that affects between 4-10% of the population Generally, plasma level of LDL-C is remarkably elevated by about 30% in patients with overt hypothyroidism.

Case

we present a 32-year-old man presented to the emergency department with chest pain associated with dyspnea. Coronary angiogram done and acute coronary syndrome was diagnosed. Complete blood count, liver function tests, blood urea nitrogen, creatinine, were within normal limits. Plasma lipid levels were (total cholesterol 355mg/dL, low-density lipoprotein-cholesterol 230mg/dL) familial hypercholesterolemia was suspected. Rosuvastatin 20 mg daily was prescribed but two weeks later the patient developed severe myalgia and myositis the cardiologist stopped Rosuvastatin and alirocumab 75 mg/ml every two weeks. Three months later alirocumab was discontinued due to poor response and financial constraints and referred to endocrinology clinic to evaluate the possibility of secondary etiologies contributing to his dyslipidemia. Our patient Physical examination showed negative findings. No family history of dyslipidemia and ASCVD. We suggested rechecking lipid profiles and to evaluate thyroid status. Biochemical examination confirmed severe hypothyroidism TSH was 145 µIU/mL, FT4 was

0.1ng/dL. Plasma lipid levels were (total cholesterol 307mg/dL, low-density lipoprotein-cholesterol 220 mg/dL and Triglyceride111 mg/dL). However, the patient denied symptoms of constipation, cold intolerance or weight gain. Levothyroxine was prescribed and increased gradually. Three months later, thyroid function returned to normal, and lipid profiles returned to normal range without the need for lipid-lowering therapy.
Conclusions
Thyroid hormones play an important role in regulating the heart and lipid physiology. This case report underscores the importance of evaluation of secondary causes of dyslipidemia. Timely diagnosis and management of hypothyroidism can help avoid misdiagnosis and unnecessary treatment.

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PS3-13-05

Transition from hashimoto's thyroiditis to graves' disease: a case report

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Background
Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the most common autoimmune thyroid disorders and represent the leading causes of hypothyroidism and hyperthyroidism, respectively. Although up to 15–20% of patients with GD may later develop HT, the transition from HT to GD is considered rare. This phenomenon is thought to result from a shift in TSH receptor antibodies (TRAb) from blocking (TBAb) to stimulating antibodies (TSAb).
Case Presentation
We report the case of a 16-year-old female with Down syndrome diagnosed with Hashimoto's thyroiditis five years earlier. Initial evaluation showed TSH 8.4 mIU/l with normal FT4 and FT3, and positive anti-TPO and anti-thyroglobulin antibodies. Thyroid ultrasound revealed a hypoechoic gland with a 1.5 cm solid nodule in the right lobe; fine-needle aspiration cytology was benign (Bethesda II). The patient was started on levothyroxine 50 µg/day, achieving normalization of TSH (1.8 mIU/l) after three months. During follow-up, levothyroxine was gradually tapered and discontinued after two years, with thyroid function remaining normal for the following years. Three months prior to presentation, the patient developed tachycardia and unintentional weight loss of 6 kg. Laboratory tests revealed suppressed TSH ($<$0.005 mIU/l), elevated FT4 and FT3, and positive TSH receptor antibodies (TRAb 8.6 IU/l). Ultrasound showed markedly increased thyroid vascularity. Treatment with methimazole (20 mg/day) was initiated, leading to clinical improvement and normalization of FT4 and FT3 after eight weeks.
Conclusion
Conversion from Hashimoto's thyroiditis to Graves' disease is an uncommon but clinically important phenomenon. This case highlights the need to consider this transition in patients with autoimmune hypothyroidism who require progressive reduction or discontinuation of levothyroxine therapy. Measurement of TRAb may help establish the diagnosis and guide appropriate management.

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PS3-13-06

Vitamin d status and its relation to hashimoto's thyroiditis: a cross-sectional study among egyptian women

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Background
Vitamin D has a significant immunomodulatory effect. Vitamin D receptors are expressed on immune cells, suggesting a potential role in autoimmune diseases including Hashimoto's thyroiditis (HT).
Objective
To evaluate vitamin D status in patients with HT and correlate its level with thyroid function and ultrasound parameters.
Subjects and Methods
This cross-sectional study included 80 female subjects divided into two groups: Group 1 comprised 50 patients with hypothyroidism secondary to HT. Group 2 included 30 age-matched controls. All participants underwent history taking, clinical examination, and laboratory investigations including serum TSH, FT4, anti-TPO antibodies, total calcium, and 25-OH vitamin D levels measured by ELISA. Thyroid ultrasound was performed.
Results
Mean weight was significantly higher in cases (87.28 $\pm$ 10.52 kg) than controls (74.17 $\pm$ 10.13 kg) ($P < 0.001$). HT patients had significantly lower FT4 (0.74 $\pm$ 0.36 vs 1.15 $\pm$ 0.17 ng/dl), higher TSH (38.87 $\pm$ 54.69 vs 1.46 $\pm$ 0.52 mIU/l), and higher anti-TPO antibodies (340.6 $\pm$ 272.5 vs 3.87 $\pm$ 11.25 IU/ml) compared to controls ($P < 0.001$ for all). Serum 25-OH vitamin D was significantly lower in HT patients (13.96 $\pm$ 7.27 ng/ml) than controls (33.70 $\pm$ 9.75 ng/ml) ($P < 0.001$). Among HT patients, 48% had vitamin D deficiency ($<$ 12 ng/ml), 48% had insufficiency (12-$<$30 ng/ml), and only 4% had sufficient levels. Total serum calcium was also significantly lower in cases (8.09 $\pm$ 0.34 mg/dl) than controls (9.08 $\pm$ 0.36 mg/dl) ($P < 0.001$). Thyroid ultrasound revealed heterogeneous echogenicity and pseudonodular appearance in all HT patients, with significantly increased thyroid volume compared to controls (42.41 $\pm$ 17.39 vs 12.06 $\pm$ 2.05 ml, $P < 0.001$). A significant positive correlation was found between 25-OH vitamin D and total serum calcium levels ($r = 0.649$, $P < 0.001$).
Conclusion
Vitamin D deficiency and insufficiency are highly prevalent among Egyptian women with Hashimoto's thyroiditis. Serum vitamin D and calcium levels are significantly lower in HT patients compared to healthy controls. Further large-scale studies are recommended to investigate the causal relationship between vitamin D deficiency and thyroid autoimmunity.

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