# Endocrine Abstracts

**September 2024** Volume 101
ISSN 1479-6848 (online)

## 46th Annual Meeting of the European Thyroid Association ETA 2024

**7-10 September 2024, Athens, Greece**


ETA European THYROID Association

published by bioscientifica

Online version available at
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## 46th Annual Meeting of the European Thyroid Association ETA 2024

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# Oral Presentations

## Oral Session 1: Topic Highlights

### OP-01-01

**Birth defects in children born to mothers with thyroid disease: biochemical assessment in 20,399 pregnancies substantiates that thyroid function and thyroid autoimmunity are not the causal links**

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Objectives
An increased risk of birth defects with the use of antithyroid drugs (ATDs) in early pregnancy has been found in large epidemiological studies. It remains debatable whether this risk associates with the medical treatment, maternal thyroid function or thyroid autoimmunity. We aimed to evaluate the risk of birth defects in relation to maternal thyroid function and thyroid autoantibodies in early pregnancy.
Methods
Retrospective study including pregnant women and their live-born children from the Danish National Birth Cohort (DNBC), 1997-2003, and the North Denmark Region Pregnancy Cohort (NDRPC), 2011-2015. Pregnant women with known thyroid disease were not included to exclude any exposure to ATDs. Blood samples drawn in early pregnancy (median week 10) were used for retrospective assessment of maternal TSH and free T4 in both cohorts (Dimension Vista and ADVIA Centaur, Siemens Healthineers). Thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) were assessed in the full NDRPC as well as TSH-receptor antibodies (TRAb) in a sub-cohort of the NDRPC. The applied cut-offs were TPO-Ab $>$ 60 U/ml, Tg-Ab $>$ 33 U/ml, and TRAb $>$ 0.27 U/ml. Information on birth defects was obtained via linkage to Danish registers that also held information on potential confounders. Logistic regression was used to calculate adjusted odds ratio (aOR) with 95% confidence interval (95% CI) for birth defects in the pooled cohort investigating the continuous explanatory variables of TSH and free T4.
Results
Altogether 20,399 live-born pregnancies were studied including 7,433 pregnancies from the DNBC and 12,966 from the NDRPC. A total of 702 children (3.4%) had birth defects in the pooled cohort, and maternal median TSH (no birth defects; 1.13 mIU/l, birth defects; 1.19 mIU/l, $P = 0.1$) and free T4 (no birth defects; 15.5 pmol/l, birth defects; 15.7 pmol/l, $P = 0.3$) did not differ by outcome of birth defects, which was substantiated in adjusted analyses (TSH; aOR 1.02 (95% CI: 0.99-1.05), free T4; 1.01 (0.98-1.05)). In the NDRPC, the prevalence of birth defects was overall 4.1% and did not differ by maternal autoantibody status (TPO-Ab positive; 4.1%, $P = 0.9$; Tg-Ab positive; 4.4%, $P = 0.4$, TRAb positive; 3.9%, $P = 0.7$).
Conclusions
In a large cohort of Danish pregnant women, no evidence was found that maternal thyroid function or thyroid autoantibodies in early pregnancy associate with the risk of birth defects. Results inform the debate regarding the underlying mechanisms for birth defects in children born to mothers with thyroid disease.

DOI: 10.1530/endoabs.101.OP-01-01

### OP-01-02

**Reprogramming myeloid bone marrow progenitors in non-medullary thyroid cancer using trained immunity**

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Objective
The prognosis of patients with metastasized and radioactive iodine refractory non-medullary thyroid cancer (NMTC) is poor and treatment options are limited. In NMTC tumors, myeloid cells, such as tumor-associated macrophages, are abundant and have an immunosuppressive and pro-tumoral phenotype. Trained immunity describes a specific epigenetic and metabolic program in innate immune cells that leads to an increased proinflammatory phenotype. The aim of the present study is to assess whether this mechanism can be used to reprogram the myeloid cells, from different bodily compartments, from patients with NMTC and thus whether this could be explored as a new treatment strategy for NMTC patients.
Methods
Peripheral blood and bone marrow were obtained from 36 NMTC patients with different NMTC histological forms (29 differentiated and 6 anaplastic NMTC) and 9 healthy volunteers. White blood cell counts and subtypes were measured in whole blood and compared between healthy controls and patients. Peripheral monocytes and CD34-positive bone marrow progenitors from bone marrow were isolated and in these cells trained immunity was induced *ex vivo* using different stimuli. Subsequently those cells differentiated into macrophages which were restimulated by TLR-agonists to measure cytokine production. Additionally, macrophage phenotype was assessed using flowcytometry.
Results
White blood cell counts and percentages of different subtypes were comparable between healthy controls and patients with differentiated NMTC. However, compared to healthy controls and patients with differentiated NMTC, patients with anaplastic NMTC showed significantly higher white blood cell counts, with higher percentages of neutrophils and lower percentages of lymphocytes. In peripheral monocytes derived macrophages, trained immunity could be induced with the stimuli β-glucan and interleukin-4 (IL-4), characterized by an increased production of proinflammatory cytokines IL-6 and TNF after restimulation with either LPS or Pam3Cys. The fold change of increase of cytokine production was lower in NMTC patients than in healthy volunteers. Flowcytometry showed that β-glucan-, IL-1β- and IL-4-trained stem cells developed into macrophages with lower CD206 and CD163 and higher CD86 expression, markers associated with a less immunosuppressive and more anti-tumoral phenotype.
Conclusion
Using our *ex vivo* model, we show that reprogramming of myeloid progenitor cells from patients with NMTC in our trained immunity setting is possible. This results in macrophages with increased proinflammatory cytokine production and differentiation towards an anti-tumoral phenotype. This suggests that trained immunity might be explored as a potential novel treatment strategy for patients with aggressive forms of NMTC.

DOI: 10.1530/endoabs.101.OP-01-02

### OP-01-03

**Novel Tr-β selective agonist TG68 promotes anti-inflammatory, lipid-lowering and anxiolytic effects**

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Recent advances in drug discovery and development allowed the identification of THRβ-selective thyromimetic TG68 as a powerful lipid lowering and anti-amyloid agent. To expand our knowledge on the therapeutic potential of this novel thyromimetic, we investigated its anti-inflammatory effects in *in vitro* human models of neuroinflammation. Subsequently, we performed *in vivo* studies on high fat diet (HFD) obese/insulin resistant mice, a well-established model of obesity/neuroinflammation, to investigate the effects of TG68 on behavior, bodyweight (BW), energetic metabolism, and neuroinflammation. Pre-treatment of human microglia cells (HMC3) with TG68 (0.1, 1, and 10μM), followed by inflammatory stimulation with LPS (10μg/ml)/ TNF□- (50 ng/ml) for 24 h, resulted in a significant ($P < 0.05$) decrease of pro-inflammatory IL-6, and a significant increase of anti-inflammatory IL-10. It is well known that β-amyloid oligomers can activate microglia to secrete proinflammatory factors. In our experimental settings, exposure of HMC3 cells to 10 μM Aβ25-35 for 24h led to a significant ($P < 0.05$) increase of TNF-α and IL-6 release. In Aβ-treated cells, the pre-treatment with 10μM TG68 for 24h reduced TNF-α and IL-6 and increased IL-10 levels. Taken together, these findings suggest the potential of TG68 to prevent neuroinflammation and Aβ-induced neurotoxicity. Next, we demonstrated that in HFD-mice (CD-1 male mice; HFD C1090-60; 10 weeks), treatment with TG68 (10 mg/kg/day; 2 weeks; in drinking water) significantly ($P = 0.02$) reduced anxiety-like behavior in stretch-attend posture (SAP) tests, while producing a 12% BW loss and a significant ($P < 0.05$) decrease in blood glucose and lipids levels. Due to the observed significant differences in circulating metabolic

markers, we performed qPCR on serum, adipose tissue, and hypothalamus, to assess whether TG68 administration could counteract the changes in gene expression of metabolic and inflammatory markers induced by HFD. Our analysis revealed that TG68 limited HFD-induced decrease of SIRT6, PPARγ, and ADIPOQ expression in adipose tissue, while inducing a decrease of leptin and APOD expression. An increased expression of GLUT1 and GLUT5 was also observed at the hypothalamic level. Systemic inflammation, with elevated serum levels of TNFα- and IL6 was highlighted in obese mice, associated with decreased hypothalamic expression of BDNF. Notably, chronic administration of TG68 induced a significant reduction of TNFα- and IL6 serum levels, and a significant increase of BDNF expression, further supporting its neuroprotective role. Overall, these data indicate that TG68 may represent a promising multitarget agent for the treatment of interlinked diseases such as obesity and NDD.

DOI: 10.1530/endoabs.101.OP-01-03

## OP-01-04

### Unveiling severe adverse events of antithyroid drugs in patients with graves' disease; a real-world multicenter cohort study

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Objectives
Although antithyroid drugs (ATD) offer potent therapeutic benefits for treating Graves' disease (GD), they can occasionally lead to rare, potentially life-threatening adverse events (AEs), such as agranulocytosis or toxic hepatitis. As the incidence and characteristics of these life-threatening AEs in Korea have not been widely investigated, we aimed to identify the real-world features of ATD-related severe AEs.
Method
We analyzed 19,975 patients (14,444 women; mean age, 42.9 ± 14.2 years) diagnosed with GD at four tertiary referral hospitals between 2002 and 2020, with a median follow-up time of 19.9 months. GD was defined as cases with the ICD-10 code E05 and those who have received ATD at least once. Agranulocytosis was defined as absolute neutrophil count (ANC) $<500/\mu L$; toxic hepatitis was defined as aminotransferase $>5$ times the upper limit of normal (ULN), total bilirubin $>3$ times the ULN, or prothrombin time-international normalized ratio $>1.5$ times the ULN.
Results
Agranulocytosis occurred in 50 (0.25%) patients; moderate neutropenia ($500 \leq ANC < 1000/\mu l$), in 222 (1.11%); and mild neutropenia ($1000 \leq ANC < 1500/\mu l$), in 947 (4.74%). The incidence of ATD-induced toxic hepatitis was 1.80% (359/19,975). The median time to onset of agranulocytosis was 39.5 days (Interquartile range [IQR], 27-303 days), while for toxic hepatitis, it was 64 days (IQR 21-355 days). Among patients with agranulocytosis, methimazole (MMI) was used in 38 (76%) and propylthiouracil (PTU) in 13 (26%). Regarding toxic hepatitis, 270 patients (75.2%) received MMI and 33 (9.19%) received PTU. Six individuals (0.03%) required liver transplantation, and there were no cases of bone marrow transplantation. The daily mean dosage of ATD increased the risk of agranulocytosis (adjusted OR 1.01, 95% CI 1.01-1.02), and toxic hepatitis (crude OR 1.01, 95% CI 1.007-1.014). Other risk factors for toxic hepatitis included male gender, older age, PTU use, and underlying liver disease.
Conclusions
The incidence of ATD-induced agranulocytosis and toxic hepatitis is comparable to previously reported rates. However, actual life-threatening AEs seem to be rare in Korea.

DOI: 10.1530/endoabs.101.OP-01-04

## OP-01-05

### Dabrafenib and trametinib in BRAFV600E anaplastic thyroid cancers: an italian real-word series

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Background
Anaplastic thyroid cancer (ATC) is a lethal tumor with a median overall survival of 6 months. In about 30-40% of cases, a $BRAF^{V600E}$ mutation is present. In 2018 dabrafenib and trametinib (D/T) have been approved in USA for $BRAF^{V600E}$-mutated ATC, while no approval has been obtained so far in Europe. Up to December 2022, D/T were provided by the company for BRAF-altered cancers within a compassionate named program. Here we report the results from an Italian cohort of ATC patients.
Methods
We retrospectively collected data from 8 Italian centers. Primary endpoint was the overall response rate (ORR) per RECIST 1.1 according to investigator judgment; secondary aims were progression-free survival (PFS); overall survival (OS) and treatment safety. D (150 mg twice daily) and T (2 mg daily) were administered until disease progression, toxicity, or patient's withdrawal of consent. PFS and OS were calculated by Kaplan-Meier analysis.
Results
Between May 2018 and December 2022, 19 ATC patients received D/T. M/F were 10/9; median age at diagnosis was 69 years (range: 40-80 years). 16 cases (84%) were pure ATC, while 3 were characterized by a mixed histology (papillary thyroid cancer + ATC). $BRAF^{V600E}$ has been assessed either through RT-PCR (42%) or NGS (58%). Stage IVC was present in 63% of patients at diagnosis. When D/T was started, 14 patients (74%) were treatment naïve; 5 patients had only locoregional disease, whereas 14 had distant metastases in lungs, liver, bone, lymph nodes or other sites. ORR was 74% (14 PR), whereas disease stability (SD) was achieved in 3 patients and 2 experienced disease progression (PD) at the first evaluation. Treatment withdrawn occurred due to PD in 13 patients (65%), death (10%), toxicity (5%), or treatment-unrelated complications (5%). Treatment was well tolerated, with the most common grade $\geq$ 3 adverse events being fever (15%), diarrhea (5%), and pneumonia (5%). Median (m) OS was 21 months (9.9 months-NA); mPFS for naïve patients and pretreated was 8.3 (7.2 months-NA) and 3.6 (2.3 months-NA), respectively. At the time of cut-off analysis (April 2023), 5 patients were still alive, with 3 under D+T.
Conclusions
This is the largest Italian series of $BRAF^{V600E}$ ATC patients treated with D/T. The drug combination confirms its activity, especially in ATC naïve patients, suggesting the use of D/T in the early phase of disease. Since March 2023, D/T has been approved for $BRAF^{V600E}$ ATC patients in Italy (law 648/96).

DOI: 10.1530/endoabs.101.OP-01-05

## OP-01-06

### Cut&tag reveals distinct TRA2-specific DNA binding profiles in HIPSC-derived cardiomyocytes

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Objective
Thyroid hormone receptors (TRs) are important ligand-dependent regulators of thyroid hormone target gene expression. In contrast, the role of TRα2, a thyroid hormone receptor α splice variant that is unable to bind thyroid hormones, remains enigmatic for more than 30 years. However, its evolutionary conservation in eutherian mammals and high expression levels in some cell types as well as under 'pathological conditions' such as heart failure strongly indicate its physiological relevance. While *in vitro* data from ectopically

expressed TRα2 suggested a weak antagonistic activity to other TRs, no functional data on the endogenous TRα2 isoform was available due to the lack of reliable isoform-specific antibodies. Therefore, we aimed to gain insights into isoform-specific actions in different cell types by using induced pluripotent stem cell (iPSC) lines expressing endogenously tagged TRα isoforms.
Methods and Results
To enable specific detection of TRα isoforms, we introduced two different tags into the *THRA* locus of human iPSC lines by a CRISPR/Cas9-based approach. As a result, the derivative cell lines are either expressing TRα1 C-terminally tagged with a 2×HA tag or TRα2 C-terminally tagged with a 3×FLAG tag. We then differentiated the iPSCs to cardiomyocytes and confirmed the presence of cardiomyocyte differentiation markers MLC2a, MLC2v, cardiac Troponin-T and α-Actinin by immunofluorescence staining as well as flow cytometry analysis. Applying a CUT&Tag (Cleavage Under Targets and Tagmentation) approach, we obtained isoform-specific DNA binding profiles in both iPSCs and cardiomyocytes. While the majority of binding sites were shared between both isoforms in hiPSCs, we surprisingly found in addition a specific set of genes to be exclusively bound by TRα2 but not TRα1 in cardiomyocytes.
Conclusions and Outlook
Our recent data reveal the first isoform-specific genome-wide DNA binding profiles of TRα at endogenous receptor levels. While the binding profiles for both isoforms were highly similar in hiPSCs, TRα2-specific binding to promoters of a specific family of genes was exclusively seen in cardiomyocytes, indicating a TRα2-specific function in the heart. How isoform-specificity of DNA binding is regulated and whether TRα2 forms distinct protein complexes regulating gene expression is currently under investigation. Based on our findings, which reveal TRα2-specific activities in cardiomyocytes, it is tempting to speculate whether TRα2 also exerts distinct physiological activities in other cell types.

DOI: 10.1530/endoabs.101.OP-01-06

## Oral Session 2: Thyroid Hormone Action in the Brain

### OP-02-01

**Thyroid hormone transporters MCT8 and OATP1C1 exhibit cell-autonomous functions within the oligodendroglia cell lineage in the mouse CNS**

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Persistent hypomyelination is not only a key symptom of patients with an inactive MCT8 but also represents a prominent feature in mice with a combined inactivation of the thyroid hormone (TH) transporters Mct8 and Oatp1c1 (so-called DKO mice). This phenotype might be explained by an impaired TH passage across the brain barrier cells and consequently, a profound TH deficiency in the CNS of these animals. Alternatively, combined Mct8/Oatp1c1 deletion may result in an impeded TH transport into oligodendrocytes and/or their precursor cells thereby compromising oligodendrocyte maturation and myelination. To clarify the cell-specific function of Mct8/Oatp1c1 in myelin formation, we studied proliferation and differentiation pattern of oligodendroglia cells in mice lacking both TH transporters within the oligodendrocyte lineage only (so-called OL CKO mice) at different postnatal time points and included DKO animals for comparison. Immunofluorescence studies revealed normal expression of different mature myelin markers in adult OL CKO mice. However, at postnatal day 12, expression of these proteins was strongly reduced in OL CKO mice comparable to DKO animals suggesting a transient delay in myelination in these cell-specific TH transporter animals. We further enumerated Olig2/Pdgfra immunopositive oligodendrocyte precursor cells (OPC) as well as Olig2/CC1 expressing mature oligodendrocytes and could indeed detect a similarly reduced number of myelinating oligodendrocytes in OL CKO and DKO mice at P12. Yet, in contrast to DKO animals that clearly displayed an oligodendrocyte maturation impairment, the percentage of OPCs and myelinating oligodendrocytes was surprisingly normal in OL CKO mice pointing to an unaffected maturation. However, at all time points OL CKO mice showed a reduced number of Olig2 positive cells indicating an overall decreased oligodendroglia pool size. Altogether, our studies confirmed a cell-autonomous function of Mct8/Oatp1c1 within the oligodendroglia lineage putatively for early lineage development while the persistent hypomyelination seen in DKO mice is largely a consequence of the overall decreased TH content inside the brain. Ongoing studies are expected to disclose during which developmental time window Mct8 and Oatp1c1 are required to ensure proper oligodendroglia cell lineage commitment and survival thereby ultimately affecting the total number of oligodendrocytes in the murine CNS.

DOI: 10.1530/endoabs.101.OP-02-01

### OP-02-02

**Gestational hypothyroxinemia in dehal1ko mice: discordant T3-dependent gene expression in brain regions and autistic-like phenotype in the offspring**

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Gestational hypothyroxinemia (GH) is a common event in human pregnancy generally attributed to iodine deficiency (ID). GH has been associated with the risk of neurodevelopmental defects in the offspring, including autistic traits. However, autistic children are mostly euthyroid, for which the role of thyroid hormones in the phenotype remains under debate.
Aim
To generate a mouse model of maternal hypothyroxinemia using moderate ID (mID) in iodine-recycling defective *Dehal* 1KO dams, and determine the consequences on thyroid hormone economy, behavior and brain gene expression in the progeny.
Methods
Wild type or *Dehal1* KO dams were fed sufficient iodine (NID) or mID during gestation and lactation. From weaning, pups were switched to standard iodine diet (SD). Plasma T4 and T3 were measured by LC-MS-MS in dams at midgestation (G10), in F1-pups at postnatal-day 20 (PN20) and in F1-adults at PN150. Brain hippocampi and cerebella from PN20 and PN150 mice were collected for hormone quantification and gene expression changes of T3-signaling (*Thra, Thrb, Hr, Rora*) and neurodevelopmental genes *(Reln, Nrg, Pvalb, Mag, Klf9*) using qRT-PCR. Adult mice fulfilled behavioral tests for social interaction (three-chamber), obsessive-compulsive activity (marble burying), anxiety (elevated plus-maze) and mobility (open field).
Results
Only *Dehal1* KO-mID dams developed hypothyroxinemia (T4-G10: $22 \pm 4$ vs. $36.5 \pm 3$ ng/ml; $P < 0.05$). Their pups were hypothyroid at weaning (T4-PN20: $36 \pm 3.3$ vs. $50.4 \pm 3$ ng/ml; $P < 0.05$). Consistently, their hippocampi and cerebella were T4-hypothyroid (Hippocampi: $3.4 \pm 1$ vs. $7.5 \pm 1.8$ pmol/g, $P < 0.05$; Cerebella: $3.2 \pm 0.5$ vs. $4.8 \pm 0.8$ pmol/g, $P < 0.05$) while T3 was normal and elevated, respectively. T3-dependent gene expression was globally reduced by 32-90%. After 4-months SD, KO-mID adults became fully euthyroid. However, strikingly, hippocampi were discordantly T4-hyperthyroid, with 40-170% increased *Thrb* and *Hr* expression in males, while females showed 20-50% decreased transcription of *Thra, Thrb* and *Hr*. Cerebella normalized T4 and T3, however, T3-dependent gene expression remained low for *Thra, Thrb, Rora* in females. Behaviorally, such "euthyroid" adults showed 40-78% decrease in sociability index ($P < 0.05$; greater in females), increased compulsivity (2-7 folds, $P < 0.01$; major in males), anxiety index (15%; $P < 0.05$) and reduced locomotion only in males (44%, $P < 0.005$). Neurodevelopmental genes were abnormally expressed in hippocampi, showing significant 30-40% downregulation of *Reln* and *Nrg* and 1.5-26 folds upregulation of *Klf9, Pvalb and Mag.*
Conclusions
Moderate ID in *Dehal1* KO dams leads to GH. The progeny is hypothyroid at weaning, but euthyroid as adults under iodine sufficiency, despite showing abnormal behavior, discordant brain T4 and T3, and dysregulation of T3-dependent neurodevelopmental transcription, suggesting region- and sex-specific epigenetic modulation of low T3 during brain development.

DOI: 10.1530/endoabs.101.OP-02-02

## OP-02-03

**Thyroid hormone transporters MCT8 and OATP1C1 are required for proper angiogenesis in the mouse CNS**

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Disturbed brain development and function represents a hallmark of Mct8/Oatp1c1 double knockout (DKO) mice, a well-established mouse model for human MCT8 deficiency. This phenotype can be explained by an impaired TH transport across brain endothelial cells causing a profound brain TH deficiency. Yet, to which extent the brain capillary network formation is compromised in DKO mice has not been elucidated. Here, we examined brain capillary network formation in wildtype, single ko and DKO mice at postnatal day P6, P12, P21 and P120. To this end, we performed immunofluorescence studies using the endothelial cell marker CD31 and quantified vessel network parameters in brain vibratome sections. While measurement of CNS capillary parameters at P6 revealed a similar vessel network in all experimental groups, quantification of cortical vessel length and branching at P12 unraveled an almost 50% reduction only in DKO mice. Similar defects could also be detected at P21 and P120 in the DKO brain indicating permanent vessel formation impairments. Interestingly, small capillaries, in which under normal conditions Mct8 is preferentially expressed, were found to be the most affected. We also assessed transcript levels of capillary markers by qPCR and observed a significantly reduced CD31 as well as glucose transporter Glut1 expression in DKO mice. Transcript levels of angiogenic factors were also found to be significantly reduced in isolated brain blood vessels of DKO mice compared to controls. As we recently demonstrated a strong improvement of brain maturation in DKO mice upon TH analog Triac treatment, we wondered whether Triac application was also sufficient to restore brain angiogenesis. Indeed, measurement of brain capillary parameters in DKO mice treated with Triac (400 ng/g bw) between P1 and P11 revealed normal vessel parameters already at P12. Further studies are ongoing to define the exact critical time window during which Triac can restore brain angiogenesis in DKO animals. Collectively, our studies disclosed a permanently compromised brain capillary network formation in Mct8/Oatp1c1 deficient mice possibly leading to insufficient nutrient and/or oxygen supply. Moreover, postnatal Triac treatment was sufficient to normalize brain vessel parameters in DKO mice underscoring the relevance of proper TH action in CNS angiogenesis.

DOI: 10.1530/endoabs.101.OP-02-03

## OP-02-04

**Exploring the role of TRβ in the process of cortical neuron differentiation**

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Thyroid hormone (TH) action is required for the adequate brain development. While TRα1 is recognized as the predominant receptor mediating most of these effects in brain tissue, the expression of both TRα and TRβ during development prompts further examination on their respective role. The study aims to investigate the role of TRβ during cortical neuron differentiation, taking advantage of induced pluripotent stem cells (iPSCs) obtained from patients with resistance to thyroid hormone β (RTHβ) who exhibit variable neurocognitive/behavioral defects. To achieve this, peripheral blood mononuclear cells (PBMCs) from RTHβ patients with anxiety and/or severe short-term memory defects, or from healthy individuals, were expanded and reprogrammed into iPSCs that were then differentiated into cortical neurons using a validated protocol. Quantitative real-time PCR analysis was conducted on the resulting cortical progenitors and neurons. The findings revealed expression of *THRB* transcripts, with a ratio of 1:2 relative to *THRA*, supporting the potential involvement of TRβ in the neurological development. Then, we detected differences in the expression levels of various neural markers related to synaptic plasticity and the complex molecular mechanisms underlying learning and memory, such as Neuroplastin and Neurexin, in cortical neurons derived from RTHβ patients compared to those from controls. Additionally, a marked decrease was seen in the expression levels of vesicular glutamate transporters (VGLUT1 and VGLUT2) in the RTHβ samples. Intriguingly, studies in animal models linked VGLUT1 deficiency to deficits in visual attention, anxiety, and depression, while the expression of VGLUT1/2 correlated with learning and memory processes. Interestingly, electrophysiological experiments demonstrated that only the *THRB* mutant neurons failed to generate action potentials. This study reveals critical differences in several biomarkers of neuronal development and function in neurons differentiated from RTHβ iPSCs. The contribution of TRβ to TH action in the developing brain might be underestimated. *This study is partially founded by the project ADAM-THAD (PNRR-MR1-2022-12375726).*

DOI: 10.1530/endoabs.101.OP-02-04

## OP-02-05

**A Novel MCT8 point-mutant mouse model shows effectiveness of phenylbutyrate treatment**

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Objectives
Pathogenic variants in monocarboxylate transporter 8 (MCT8, SLC16A2) cause motor and intellectual disability and movement disorder (Allan-Herndon-Dudley Syndrome, AHDS). The mutation affects the transport of thyroid hormones across plasma membranes, including the blood-brain-barrier. While knockout mouse models for Mct8 have allowed important insights into the physiological function of Mct8, most patients are carrying pathogenic missense variants. Recently, an "avatar" mouse model was described, which is carrying the pathogenic P321L variant. These mice replicate several characteristics of AHDS patients without the need of additional mutation of Oatp1c1 or Dio2. Here, we describe the generation and characterization of a novel Mct8 L223R mouse model, which we aim to treat with phenylbutyrate.
Methods
We have generated a mouse model carrying the L223R mutation in the mouse Mct8 gene (L291R in human). Western blots and deiodinase activity assays were performed in liver, kidney, and brain. Thyroid hormone uptake assays were performed in primary astrocytes treated or not with phenylbutyrate.
Results
Western blots revealed elevated expression of Mct8 in kidney and liver. Elevated deiodinase activities in liver, kidney, and brain support the pathogenicity of the mutant protein in mice - similar as described for Mct8-KO mice. In the brain, the number of PV-expressing interneurons was reduced at 28 days in the primary somatosensory cortex. Primary astrocytes showed diminished T3 uptake compared to controls. Treatment with phenylbutyrate greatly increased TH uptake in Mct8 L233R astrocytes.
Conclusion
We present a novel Mct8-mutated mouse model which recapitulates key features of the disease. Most importantly, phenylbutyrate treatment restored TH uptake into primary astrocytes.

DOI: 10.1530/endoabs.101.OP-02-05

# Oral Session 03: Young Investigators Session / Clinical + Translational

## OP-03-01

**Impact of reclassification of oncocytic and follicular thyroid carcinoma by the 2022 who classification**

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Introduction
The 2022 WHO Classification categorizes oncocytic (OTC) and follicular thyroid carcinoma (FTC) based on the degree of capsular and vascular invasion into minimally invasive (MI), encapsulated angioinvasive (EA) and widely invasive tumors (WI). While associations with clinical outcomes have extensively been studied in FTC, for OTC robust clinical data is lacking. The aim of this study is to investigate the newly defined categorization by the 2022 WHO Classification on clinical outcomes in OTC compared to FTC.
Methods
All adult FTC and OTC patients treated at a tertiary referral hospital between 2000 and 2016 were retrospectively included ($n = 141$). All tumors were thoroughly revised independently by two pathologists applying the 2004 and 2022 WHO Classification. Kaplan-Meier curves were used to study the association of the 2004 and 2022 WHO Classification with overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS) and incidence of radioactive iodine (RAI-) refractory disease.
Results
52 OTC and 89 FTC patients were included. OTC patients were older at diagnosis (61.7 years vs 51.7 years), and more often male (50% vs 23.6%). After revision, 28.8% of OTC tumors were reclassified (7 from MI to EA and 8 from WI to EA), resulting in 5 MIOTC, 15 EAOTC and 32 WIOTC. In FTC, 38.2% tumors were reclassified (20 from MI to EA and 14 from WI to EA), resulting in 32 MIFTC, 34 EAFTC and 23 WIFTC. Compared to the 2004 WHO Classification, the 2022 WHO classification showed a better risk stratification for DSS, with an intermediate prognosis in EAOTC and EAFTC. Ten-year DSS with the 2022 WHO Classification were 100% for MIOTC, 92.3% for EAOTC and 56.5% for WIOTC, compared to 100% (MIOTC) and 64.2% (WIOTC) following the 2004 WHO Classification. Similar trends were observed for RAI-refractory disease, but not for OS and RFS.
Conclusion
To our knowledge, our study is the first to show that classification of OTC and FTC into three subcategories based on the extent of invasiveness (i.e. MI, EA and WI), as defined by the 2022 WHO Classification, substantially improves discrimination between low, intermediate and high risk patients, especially for DSS and RAI-refractory disease.

DOI: 10.1530/endoabs.101.OP-03-01

## OP-03-02

**Impact of physical activity and its maintenance in the efficacy and safety of tyrosine kinase inhibitors in advanced thyroid carcinoma patients**

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Background
Tyrosine kinase inhibitors (TKIs) have been shown to improve progression-free survival (PFS) in advanced thyroid cancer (TC), though their administration is burdened by multiple adverse events (AEs). Maintaining optimal drug dosage for optimal tumour response can be challenging and prehabilitation, aiming to improve patient well-being before cancer treatment, is becoming relevant in this context. While some information exists for other cancers, no data are available for advanced TC patients treated with TKIs.
Objectives
To evaluate the impact of physical activity and its maintenance on the safety and efficacy of TKIs in advanced TC.
Methods
This preliminary analysis involved 18 patients: 10 Differentiated TCs (DTCs), 3 Poorly Differentiated TCs (PDTCs), 5 Medullary TCs (MTCs), treated for an average time of 45 (6-180) months with Lenvatinib ($n = 12$), Vandetanib ($n = 4$), and Cabozantinib ($n = 2$). Three modified long-form International Physical Activity Questionnaires (IPAQ) were retrospectively administered for each patient at different time points (T0, before TKI treatment; T1, intermediate; T2, at last follow-up). Metabolic equivalents (METS) were calculated for each time point and the patients were consequently classified as low, moderately, or highly active. Quality of Life Questionnaire-Core30 (QLQ-C30) and QLQ-Thyroid Cancer Module (QLQ-THY34) were also administered. Basal Eastern Cooperative Oncology Group Performance Status (ECOG PS) was assessed, and AEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE v5.0). Tumour response was evaluated following Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Results
A reduction in METS during treatment was significantly associated with AEs of grade $\geq 3$ ($P = 0.04$, from T0 to T1 and $P = 0.02$ from T0 to T2). Among all AEs, fatigue (grade $< 3$) mostly limited patients' activity status during TKI treatment. High METS levels at T2 correlated statistically with higher QLQ-C30 functional state points ($P = 0.05$, $r = 0.49$). Moreover, being highly active at T2 was associated with fewer AEs compared to low active patients (*40 vs 82%*, $P = 0.09$). Patients with a highly active lifestyle at T0 experienced fewer TKI interruptions (*43 vs 82%*, $P = 0.09$) and TKI dose reductions (*20 vs 64%*, $P = 0.1$). Progressive disease (PD) occurred less frequently in patients who remained highly active through treatment (*12 vs 38%*, $P = 0.2$).
Conclusions
Our data show for the first time that the preservation of physical activity is associated with milder AEs, thus reducing the need for TKI reduction/interruptions, improving PFS. This preliminary study gives the opportunity for wider and prospective research on the impact of (pre)habilitation in patients undergoing systemic treatment for advanced TC.

DOI: 10.1530/endoabs.101.OP-03-02

## OP-03-03

**Effects of tocilizumab treatment in corticosteroid-resistant graves' orbitopathy**

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Introduction
Treatment of Graves' Orbitopathy (GO) remains a challenge. Approximately 20-30% of patients show resistance or incomplete response to high-dose glucocorticoid therapy. According to current guidelines the use of tocilizumab (TCZ), a monoclonal antibody against IL6 receptor, has been proposed as one of the second-line therapies.
Objectives
Our aim was to assess the efficacy and safety of TCZ treatment in patients with glucocorticoid-resistant GO.
Methods
We are currently conducting a prospective, observational, single-center study of glucocorticoid-resistant GO treated with TCZ. This report aims to present the effects of TCZ therapy of the first 19 enrolled patients from 2021-2024. TCZ was administrated at a dose of 8 mg/kg, given once every four weeks (4 cycles). The primary outcomes were disease improvement assessed by the modified EUGOGO composite ophthalmic score, and improvement of quality of life. Response to treatment was considered positive in case of improvement of at least 2 of the following features in 1 eye, without concomitant deterioration in the other eye: a. decrease in eyelid aperture by at least 2 mm, b. decrease in exophthalmos by at least 2 mm, c. increase in eye motility by at least 8°, d. decrease in 7-item clinical activity score (CAS) by at least 2 points. The secondary outcomes were: achievement of disease inactivation, improvement in soft tissue signs and symptoms, proptosis and adverse effects.
Results
Nineteen patients (38 eyes) with active glucocorticoid-resistant GO (13 females, median age 49 years, median duration of GO 12 months) were included. The follow-up period after first dose was 16 weeks. We observed improvement in composite ophthalmic score in 11 out of 19 patients. In 12/19 and 11/19 patients

we noted ≥6 points improvement in GO-QOL subscales for visual functioning and appearance, respectively. Diplopia improved (Gorman scale) in 2 out of 14 patients. The improvement in seven-item CAS by ≥2 points was reported in 15 out of 19 patients (disease inactivation CAS≤1 in 6/19 patients). Moreover, analyzing individual eyes we observed: the reduction of proptosis by at least 2 mm in 15/32 eyes, the reduction of palpebral aperture by at least 2 mm in 15/38 eyes; the reduction of lagophthalmos by at least 2 mm in 4/9 eyes. Adverse events during TCZ treatment were mild and minor. Progression of GO during treatment did not occur.

Conclusion

Our results further support TCZ as an effective and safe therapeutic option for patients with glucocorticoid-resistant GO.

Key words

Graves' disease; thyroid orbitopathy; second-line treatment; tocilizumab; glucocorticoid-resistant orbitopathy

DOI: 10.1530/endoabs.101.OP-03-03

## OP-03-04

### T3 analogue triiodothyroacetic acid (TRIAC) treatment and survival in MCT8 deficiency: an international real-world cohort study

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Objectives

MCT8 deficiency results from a rare X-linked genetic defect in the thyroid hormone monocarboxylate transporter (MCT) 8. MCT8 deficiency is characterized by severe neurocognitive disabilities and peripheral thyrotoxicosis. Mortality rates in MCT8 deficiency are high with 30% dying during childhood. The T3 analogue triiodothyroacetic acid (Triac) has been proven to safely alleviate peripheral thyrotoxicosis in patients with MCT8 deficiency. As thyrotoxicosis is linked to increased mortality, we investigated whether Triac treatment could improve survival in paediatric and adult male patients with MCT8 deficiency.

Methods

We investigated the effects of Triac on all-cause mortality in patients with MCT8 deficiency. Genetic, clinical, biochemical and treatment data were collected from 173 sites in 48 countries through an international consortium on MCT8 deficiency, including Triac Trial, a Triac off-label cohort, and published cases in literature. The impact of mutations on MCT8 transporter function was assessed in transfected cells and classified as mild, moderate or severe loss-of-function (LoF). Baseline characteristics, including age at symptom onset, age at diagnosis, country of residency, LoF, disease features, presence of a feeding tube, and prior treatment aiming to alleviate thyrotoxicosis were compared using Mann-Whitney U and Chi-Square test (5% level of significance). Missing data were imputed with multiple imputation prior to Kaplan-Meier, Log-rank, and Cox proportional-hazards models carried out to estimate the effect of Triac on survival.

Results

We screened 484 males with MCT8 deficiency of whom 228 were included. Patients were excluded because (i) they were born before the disease's discovery in 2004 ($n = 152$), (ii) limited data ($n = 68$) or (iii) unknown LoF ($n = 36$). Baseline characteristics between Triac-treated ($n = 111$) and untreated patients ($n = 117$) were similar, except for untreated patients residing less often in Western countries (57 vs 78%). Median follow-up after diagnosis was 4.8 years [IQ$R = 2.7–8.4$] and we observed 32 deaths (5 treated vs 27 untreated). Triac-treated patients had a 3-times lower risk of all-cause mortality (H$R = 0.28$, 95%CI=0.09–0.91, $P$-value $<0.05$). No other baseline characteristics did significantly affect survival or the effect of Triac treatment.

Conclusions

In this international real-world cohort study, we showed that Triac treatment in paediatric and adult patients with MCT8 deficiency was associated with a 3-times lower risk on mortality. This corroborates previous findings indicating that Triac sustainably alleviated key clinical features resulting from peripheral thyrotoxicosis. To verify the robustness of our results, ongoing analyses aim to minimize confounding and immortal time bias, which pose potential threats to validity in cohort studies.

DOI: 10.1530/endoabs.101.OP-03-04

## OP-03-05

### Predictors of disease progression in patients with suspicious lymph nodes after initial treatment for thyroid carcinoma

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Objective

The clinical course of metastatic lymph nodes in patients with differentiated thyroid cancer is unclear, due to the lack of universal criteria defining disease progression. The aim of the present study was to evaluate the characteristics of suspicious lymph nodes in patients with differentiated thyroid cancer, in order to distinguish lesions with an indolent behaviour and to identify potential predictors of disease progression.

Methods

We retrospectively studied 122 patients with ≥1 cervical lymph node suspicious for metastasis upon first-line treatment for thyroid cancer. We evaluated the growth of the target (i.e., the largest) lesion. We compared patients whose target lesion displayed an indolent behaviour (growth rate >3 mm/year) and patients with a faster increase in size of the target lymph node (growth rate >3 mm/year), aiming to assess potential outcome predictors.

Results

Patients with lymph nodes growing >3 mm/year (12.3%) were older ($P = 0.0003$), with significantly more advanced and aggressive primary tumours. Their target lesions were more frequently in the lateral neck ($P = 0.031$) and were larger ($P = 0.003$) at diagnosis. Around 45% of these patients developed distant metastases (*versus* 9.3%, $P = 0.0001$) and they more commonly required second-line treatments ($P = 0.0002$). Following a multivariate logistic regression analysis, the diameter of the target lesion at diagnosis resulted an independent positive predictor of a target LN growth rate >3 mm (Odds Ratio (OR) 1.71, 95% Confidence Interval (CI) 1.27-2.29). An initial diameter >8 mm was identified as the best threshold to differentiate suspicious lymph nodes growing >3 mm/year. We also compared subjects with and without distant metastases, to identify potential predictors of a more aggressive disease. A widespread disease was significantly associated with an older mean age at tumour diagnosis (56.7 *versus* 40.2 years, $P = 0.0005$), larger (median diameter: 30 *versus* 15 mm, $P = 0.0024$) primary tumours with a higher risk of recurrence (ATA high risk: 7/17 (41.2%) *versus* 17/105 (16.2%), $P = 0.021$), and more frequent presence of suspicious target lesions in the LC (9/17 (51.9%) *versus* 27/105 (25.7%), $P = 0.023$). At the multivariate analysis, the target LN diameter resulted an independent predictor of distant metastases (OR 7.18, 95% CI 2.19-23.5).

Conclusions

In thyroid cancer patients, about 88% of suspicious lymph nodes enlarge slowly over time, with active surveillance being a feasible strategy for their management. Suspicious lesions >8 mm are at higher risk of growing >3 mm/year, are more frequently associated with distant metastases, and more likely need further treatments.

DOI: 10.1530/endoabs.101.OP-03-05

## OP-03-06

### The association of maternal thyroid function with offspring iq and brain morphology: persistency into early adolescence and relevance of tpoab positivity

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Background
Maternal thyroid hormones regulate neurodevelopment of the fetus. Maternal thyroid dysfunction has been associated with lower offspring IQ and alterations in brain morphology in early childhood, but it remains unknown if these associations persist as development progresses.
Methods
We performed a prospective cohort study including participants from an ongoing birth cohort in Rotterdam, the Netherlands, with data on gestational thyroid function and offspring IQ (measured by the Wechsler Intelligence Scale for Children) and/or brain MRI data at the follow-up visit at age 13 years. For participants who did not participate at 13 years, MRI data from the follow-up visit at 10 years were included. We excluded those with a pre-existing thyroid disorder, twin pregnancy, IVF pregnancy, and suboptimal-quality MRI data or major incidental finding. Regression analyses were adjusted for gestational age at blood sampling, maternal age, ethnicity, education level, smoking, child sex and age at outcome assessment. We assessed effect modification by TPOAb positivity and age of outcome assessment.
Results
After exclusions, 2464 mother-child pairs were included. Thyroid function tests were measured during pregnancy at a median of 13.2 weeks of gestation (IQR 12.1-14.6) and offspring brain morphology at a median age of 13.3 years (9.9–13.8). There was an inverse U-shaped association of maternal FT4, but not TSH, with cortical grey matter volume (GMV; $P = 0.049$), with no association found with white matter volume (WMV). In TPOAb positive women, there was an inverted U-shaped association of TSH and FT4 with GMV and between FT4 and WMV, while any association in TPOAb negative women was absent. Overt hypothyroidism was associated with lower total GMV (-92 $cm^3$, CI -144 to -41), cortical GMV (-71 $cm^3$, CI -116 to -27), subcortical GMV (-7.8 $cm^3$, CI -11.8 to -3.7) and total WMV (-69 $cm^3$, -111 to -26). Overt hyperthyroidism was associated with lower total GMV (-24 $cm^3$, CI -45 to -3.3) and cortical GMV (-23 $cm^3$, CI -40 to -5). Sensitivity analyses revealed that the associations of maternal thyroid function with offspring brain morphology persisted between age 5 to 16 years, but that there was no longer an association of maternal thyroid function with offspring IQ at the median age of 15 years.
Conclusion
The association of maternal thyroid function with brain morphology persisted throughout follow-up, while the association with child IQ-scores was no longer present, in contrast to previous follow-up visits. This discrepancy could be attributed to differences in IQ tests used, or neuroplasticity influenced by societal factors impacting child IQ scores. The previously reported inverse U shaped associations seemed to be primarily driven by TPOAb positive women. These results underscore the importance of sufficient thyroid hormone availability during pregnancy.

DOI: 10.1530/endoabs.101.OP-03-06

## Oral Session 04: Young Investigators Session / Basic

### OP-04-01

**Identifying novel DIO1 inhibitors to modulate hepatic T3 availability in context of non-alcoholic fatty liver disease**

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Objectives
Deiodinase type 1 (DIO1), a selenocysteine-containing enzyme belonging to the deiodinase (DIO) family, plays an essential role in the systemic and local modulation of thyroid hormone (TH) availability. However, DIO1 plays a dual role by not only converting the prohormone thyroxine (T4) to the active triiodothyronine (T3) but also degrading T3 to the inactive 3,3'-diiodothyronine (3,3'-T2). DIO1, by acting on sulfated TH metabolites, further contributes to TH inactivation and elimination. In the liver, T3 concentrations affect glucose, lipid, and cholesterol metabolism. Alterations to the local TH concentrations play a role in the progression of hepatic diseases; e.g., subclinical hypothyroidism is associated with the development of non-alcoholic fatty liver, and a hepatic TH drop might aggravate this disease. DIO1, the prominent hepatic deiodinase, is a critical target to modulate hepatic T3 concentrations. Therefore, by pharmacologically inhibiting hepatic DIO1 and its role as a T3-degrading enzyme, we hope to steer the local T3 concentrations and aid in the prevention and clearance of hepatic steatosis.
Methods
We used a High Throughput Screening (HTS) assay, based on iodide-catalysed Sandell-Kolthoff reaction, to identify novel and potent DIO1-selective inhibitors by screening 69344 small molecular weight compounds and using an enzyme preparation of human recombinant DIO1 (hrDIO1). We determined the potency and isoenzyme specificity of the shortlisted hits by testing them using enzyme preparations from all three human DIO isoenzymes over a wide inhibitor concentration range (5 nM - 20 μM). We further assessed these shortlisted candidates for their cytotoxic and DIO1-inhibitory effects on intact hrDIO1 overexpressing HEK293 cells.
Results
The HTS assay flagged known DIO1 inhibitors like propylthiouracil (PTU) and genistein, corroborating its efficacy. Based on a revalidation screen of 352 compounds, we prioritised 26 compounds to characterise the DIO1-selective inhibition comprehensively. We identified 15 DIO1-selective compounds (IC50s $< 1$ μM), that are more potent than the bonafide DIO1-selective inhibitor PTU, which also blocks thyroperoxidase. The shortlisted candidates exhibit either no or mild cytotoxic effects when incubated at 10 μM for 24 hours, and most are capable of inhibiting DIO1 in intact cells.
Conclusions
We successfully identified novel and highly potent DIO1-selective inhibitors whose IC50 values are in the nanomolar range. We characterised these inhibitors for their cytotoxicity and DIO1-inhibition in intact cells. Unravelling the role of hepatic T3 in lipid and energy metabolism and modulating T3 concentrations via DIO1 inhibitors may provide novel avenues for therapeutic intervention and exerting antisteatotic effects.

DOI: 10.1530/endoabs.101.OP-04-01

### OP-04-02

**Thyroid hormone transporters MCT8/OATP1C1 deficient mice exhibit increased seizure susceptibility together with an imbalanced hippocampal neurotransmission**

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In humans, inactivating mutations in the thyroid hormone transporter MCT8 result in a severe psychomotor retardation characterized by neurological impairments and frequent epileptic seizures of unknown etiology that are thought to derive from a reduced transport of TH across brain barriers and into neural cells. Here, we aimed to investigate the mechanisms underlying the seizure susceptibility in MCT8 deficiency by using Mct8/Oatp1c1 double knockout

(dKO) mice, a well-established mouse model for this pathology. We first assessed seizure susceptibility in dKO mice by subjecting the animals to the convulsant agent pilocarpine and found a highly reduced seizure threshold and a stronger response to seizure induction in TH transporter deficient mice. Analysis of the brains 12h after seizure induction revealed a strong expression of the neuronal activation marker cFos together with increased somatostatin transcript and protein levels in hippocampi of dKO animals. To unravel possible alterations underlying the differential seizure response, we studied the expression pattern of inhibitory and excitatory neuronal components by immunofluorescence, *in situ* hybridization and qPCR during early postnatal development (P12) and in adulthood (P120). Our analysis revealed an abnormal development of the inhibitory GABAergic as well as the excitatory glutamatergic and cholinergic systems in the hippocampus of dKO animals. Increased expression levels of glutamate receptor subunits (such as NMDA receptor subunits Nr1 and GluN2b) and cholinergic metabotropic receptors were observed in adult dKO mice. Alterations in neurotransmitter systems could be further confirmed by LC-MS/MS analysis using hippocampal homogenates of adult control and dKO mice that revealed a decrease in proteins involved in ion homeostasis and neuronal activity (such as Kir4.1 and Atp2b2) in dKO hippocampi. Altogether, our results point to an aberrant development of different neurotransmitter systems in the absence of TH transporters Mct8/Oatp1c1 that leads to an imbalance excitatory *versus* inhibitory neuronal signaling that ultimately culminates in increased seizure susceptibility.

DOI: 10.1530/endoabs.101.OP-04-02

## OP-04-03

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

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Background
Disrupted thyroid hormone (TH) homeostasis has devastating effects on human neurodevelopment. THs are critical signaling molecules in neurodevelopment, acting on differentiation of neural cells, migration, synaptogenesis and myelination, 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 in brain are mainly derived from animal models. We utilized human induced pluripotent stem cell (hiPSC) technology to investigate the role of DIO3 in a human model for early brain development.
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. hiPSCs-derived neurons contained all the key players in TH cellular signaling. In parallel, we inactivated DIO3 in neural cells using iopanoic acid (IOP), a small molecule that blocks DIO3 activity. Cells were cultured with different T3 concentrations (0-3-10 nM). We used immunocytochemistry, gene expression and DIO3 and metabolism assays as readouts.
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* in DIO3 KO vs wild-type *NGN2* neurons. Both outcomes were validated in IOP-treated neural cultures. We also examined the differentiation potential of neural progenitor cells to neural networks in absence of DIO3 by IOP treatment. Our preliminary immunocytochemistry data showed an increase in cells containing neuronal nuclear protein (NeuN), a biomarker for neurons, when the activity of DIO3 is diminished.
Conclusion
Our results suggest that impaired DIO3 activity may lead to excessive TH action in neural cells and, thereby, compromising normal brain development. We hypothesize that a high DIO3 activity is required in early brain development to maintain stemness and prevent premature neural differentiation. Our model represents a versatile tool to investigate cellular TH regulation and action not only for neural development but in other stem cell models.

DOI: 10.1530/endoabs.101.OP-04-03

## OP-04-04

### Blood-brain barrier leakage and neurovascular unit ultrastructural alterations as new pathophysiological mechanisms for MCT8 deficiency

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Background
The monocarboxylate transporter 8 (MCT8) is a transmembrane thyroid hormone-specific transporter expressed at the brain barriers, as the blood-brain barrier (BBB) and in neural cells, with a key role in maintaining cerebral thyroid hormone homeostasis. Inactivating mutations in the MCT8 gene (*SLC16A2*) lead to the developmental rare X-linked disease known as MCT8 Deficiency or Allan-Herndon-Dudley Syndrome (AHDS). This disease is characterized by peripheral hyperthyroidism, delayed neurodevelopment, hypomyelination, and severe psychomotor disorders. The underlying pathophysiological mechanisms of AHDS remain unclear, with a lack of effective treatments available for the neurological condition of the disease, being the bypass of the MCT8-deficient BBB the main therapeutic challenge for the delivery of thyroid hormone-related drugs. Thus, the study aimed to evaluate the integrity and permeability of the BBB in conditions of MCT8 Deficiency.
Methods
Neurovascular unit ultrastructure was studied by transmission electron microscopy and pericytes were studied by immunofluorescence. BBB permeability and integrity were analyzed by immunohistochemistry, BBB non-permeable dye infiltration assays, and histological microhemorrhage-staining techniques. Brain blood vessel density was evaluated by blood vessel fluorolabeling and *in vivo* magnetic resonance angiography. Finally, angiogenic-related factors expression was studied by qRT-PCR. The studies were carried out both in an MCT8-deficient subject and in *Mct8/Dio2* KO mice, a murine model for AHDS, and their respective controls.
Results
Ultrastructural analysis of the BBB of *Mct8/Dio2* KO mice revealed significant alterations in neurovascular unit integrity, increased transcytotic flux, and edematous perivascular astrocytes. No qualitative changes were observed in the pericyte population. We also found functional alterations in BBB permeability, as shown by an increased IgG infiltration, as well as increased infiltration of the non-permeable dyes Sodium Fluorescein and Evans Blue, along with increased presence of brain microhemorrhages. We also observed alterations in angiogenesis, with reduced blood vessel density in adult mice and altered expression of angiogenesis-related factors during BBB development. Similarly, the human MCT8-deficient brain showed increased BBB permeability to IgG and decreased blood vessel density.
Conclusions
These findings represent a novel pathophysiological mechanism for MCT8 Deficiency, revealing a disruption in the BBB integrity and functionality and neurovascular unit ultrastructural alterations. These results open a new field for potential therapeutic targets for the neurological symptoms of the disease and unveil magnetic resonance angiography as a new non-invasive *in vivo* technique for disease progression evaluation.

DOI: 10.1530/endoabs.101.OP-04-04

## OP-04-05

### Investigating the role of DICER1 in thyroid tumorigenesis

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The abnormal expression of miRNAs has been linked to the development of multiple tumors, including thyroid tumors [1,2]. Dicer1 is an essential enzyme for the biogenesis of microRNAs that has been found to be dysregulated in various cancers, notably, its expression is decreased in papillary thyroid carcinoma (PTC) [3,4]. Multiple studies suggest Dicer1 as haploinsufficient tumor suppressor gene: while the loss of one allele promotes tumorigenesis, the complete loss of Dicer1 prevents tumor formation [5,6,7,8]. So far, the impact of partial or total loss of Dicer1 in thyroid cancer has never been addressed. To further understand the consequences of partial or complete inactivation of Dicer1 in thyroid tumorigenesis, we inactivated one (+/-) or two alleles (-/-) of Dicer1 in thyroid cells in a transgenic mice model developing a PTC, following RET/PTC3 oncogene expression exclusively in the thyroid. While homozygous inactivation led to a significant decrease in tumor growth, tumors with hemizygous loss of Dicer1 were larger. Additionally, homozygous inactivation led to a significant increase of vimentin positive cells. All tumors showed normal expression of thyroglobulin and T4. In parallel, the impact of Dicer1 partial or total loss was assessed *in vitro*. Stable Dicer (+/-) cell lines were generated by Crispr-cas9 from TPC1 cells, a human PTC derived cell line largely characterized. No (-/-) cell lines could be generated, supporting the idea that Dicer1 loss is lethal. Therefore, siRNA against Dicer1 was transfected into Dicer1 (+/-) cell lines to further decrease its expression. RNA sequencing and transcriptomic analysis revealed alterations in proliferation, cell cycle and cell locomotion. BrdU staining following siDicer1 transfection revealed a slow-down of the cell cycle, with lower percentages of cells in S-phase and higher percentages of cells in G0-G1-phase, as well as cyclin A, B and E downregulation. Furthermore, transwell invasion and migration assays showed a decrease of invasive and migrating cells following transfection of siRNA against Dicer1. These results were confirmed in another PTC derived cell line, BCPAP and one non tumoral thyroid cell line, HTori3. Globally, our results allow us to better understand the function of Dicer1 in thyroid cancer tumorigenesis and suggest Dicer1 as an attractive target for novel therapeutic strategies.

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DOI: 10.1530/endoabs.101.OP-04-05

## OP-04-06

### Single cell analysis of a thyroid cancer cell line resistant to lenvatinib

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Differentiated thyroid cancer (DTC) has a high survival rate and is usually treated with surgery followed by treatment with radioactive iodine (RAI). However, some patients are refractory to RAI (RAI-R DTC) and show decreased survival. This leads to progression of the disease, and the only approved treatment for those patients are multikinase inhibitors, lenvatinib being the most widely used. However, patients end up developing resistance to MKIs. Here we aim to study the mechanisms of resistance to lenvatinib to identify potential biomarkers of response, as well as potential therapeutic targets. We used the TPC-1 cell line, derived from a papillary thyroid carcinoma, and established a cell line resistant to lenvatinib (TPC-1 LR) by treating the cells with gradually increasing doses of lenvatinib for 6 months. To better understand the mechanisms by which drug resistance arises, we analysed the transcriptome using single-cell RNA-sequencing (scRNA-seq) for two controls (parental TPC-1 and TPC-1 treated with DMSO) and two time points along the process of generation of drug-resistant cells (TPC-1 LR5 and TPC-1 LR8.6 cultured at 5 µM —intermediate point— and 8.6 µM —final point—, respectively). ScRNA-seq data was obtained using 10x Genomics and CellRanger, and analysed using the R package Seurat. Results showed that sensitive (controls) and resistant cells clustered separately, indicating that lenvatinib significantly affects the transcriptome. We found no differences between controls (identified as the same cluster), while resistant cells were divided in different clusters. We identified 220 and 551 overexpressed genes ($logFC > 1$, adj $pval < 0.05$) in TPC-1 LR5 and TPC-1 LR8.6 cells when compared to control cells, respectively, with 74 common genes among those. We performed a gene ontology analysis and found overexpressed genes in TPC-1 LR5 associated with negative regulation of the hippo signalling pathway and cell adhesion and migration, while overexpressed genes in TPC-1 LR8.6 cells were associated with different metabolic pathways. These results were also validated in bulk RNA-seq data. Based on these data and publicly available datasets of thyroid cancer patients, we selected some differentially expressed genes to further study their role in lenvatinib resistance *in vitro*. In conclusion, we have identified potential candidate genes involved in lenvatinib resistance, which could lead to a novel combination drug therapy for RAI-R DTC patients.

DOI: 10.1530/endoabs.101.OP-04-06

# Oral Session 5: Thyroid Dysfunction-1

## OP-05-01

### A novel point of care device accurately and rapidly measures thyrotropin in capillary blood

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Objective

Point-of-care (POC) technologies, where the sample collection and biomarker measurement are undertaken immediately can reduce turnaround times for such measurements to a period of minutes and facilitate prompt diagnosis of e.g. thyroid dysfunction. This streamlined process is especially useful in the primary care setting, and in resource-poor environments such as developing countries, where recalling patients to receive their diagnosis can be challenging. To realize this potential, POC systems must perform to a level consistent with corresponding central lab-based systems. We have prospectively evaluated the analytical performance and clinical utility of a new, rapid POC thyrotropin (TSH) assay (Wondfo).

Methods

TSH concentration was measured in serum, whole blood and capillary blood using Wondfo or with two automated reference analyser platforms (serum only, Abbott TSH Alinity I and Roche Cobas e411). For Wondfo, 75 µl of the drawn blood sample are required, which are transferred on the test stripe for a 15-minute incubation, only. TSH levels are shown by the signal intensity of fluorescence-labelled detector antibodies.

Results

Seven hundred thirty consecutive, unselected outpatients (median age 46 years, 572 women) with various autoimmune and non-autoimmune thyroid diseases

were included. Three hundred eighty-two subjects, 218, and 130 were euthyroid, hypothyroid, and hyperthyroid, respectively. TSH measurements were user-independent. Linearity was very good and recovery rate was 97–127%. When measured simultaneously in two POC Wondfo devices, the slope of the regression line was 1.03 (serum) and 1.02 (blood), with Spearman's correlation of 0.99 for both. Total intra-and inter-assay variation [CV%] was 12.1% and 16.2%, respectively. Total CV% was 10.6-22.6% and 14.5-21.6% in serum and whole blood, respectively. TSH measurements between the POC assay and the reference analysers correlated strongly ($r = 0.93$–$0.96$). There was no relevant influence of the user-performance on the POC device. The CVs were 13% and 17% in serum and potassium-EDTA whole blood, respectively, and were within the range expected from the overall CVs of the POC device. Prolongation of incubation time increased TSH results of 12% (13%) and 33% (35%) after two and five additional minutes in serum (blood), respectively. Total haemolysis, but not elevated bilirubin or lipemia, disrupted TSH measurement.

Conclusions

For the first time, a POC system, which accurately measures TSH from three commonly used matrices is introduced. This rapid POC device was straightforward to use without need for specialist technicians and demonstrated user-independent analytic performance very suitable for clinical diagnosis and differential diagnosis of thyroid dysfunction.

DOI: 10.1530/endoabs.101.OP-05-01

## OP-05-02

### Exploring the relationship between TSH levels and cardiovascular health in euthyroid individuals: insights from elsa-brasil study

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Serum levels of TSH in euthyroid individuals are frequently associated with favorable outcomes. However, whether this association is merely an epiphenomenon of longevity or whether TSH may correlate with a metabolic protective profile is unclear. We investigated the putative association between TSH serum levels and cardiovascular outcomes in euthyroid participants. We hypothesized that participants with higher TSH might present a protective cardiovascular clinical profile. We critically analyzed the baseline data from the cohort study ELSA-Brasil. Thyroid function was evaluated in 11,179 participants aged between 35 and 74 years, who were classified as euthyroid and followed by $7,7 \pm 0.6$ years. Biochemical analytes, including serum glucose, triglycerides, total cholesterol, LDL, HDL, Lp(a), and ApoB, were evaluated. Clinical data were assessed, looking for relevant outcomes such as coronary disease, heart failure, and all-cause mortality. A statistical analysis compared TSH as predictive of biochemical and clinically relevant outcomes. TSH was linearly correlated with age (Spearman rank$= +0.024$; $P = 0.012$). Individuals with hypertriglyceridemia have higher levels of TSH ($1.97 \pm 0.835$ mIU/l) than individuals without hypertriglyceridemia ($1.86 \pm 0.814$ mIU/l, $P < 0.05$). Individuals without diabetes have higher serum TSH levels ($1.89 \pm 0.818$ mIU/l) than individuals with diabetes ($1.80 \pm 0.831$ mIU/l $P < 0.05$). Patients with established coronary disease and heart failure had lower TSH levels ($1.76 \pm 0.813$ mIU/l and $1.67 \pm 0.846$ mIU/l) than those individuals who did not have these conditions ($1.88 \pm 0.820$ mIU/l and $1.88 \pm 0.820$ mIU/l, $P < 0.05$ respectively). We failed to demonstrate a correlation between TSH and cholesterol, LDL, HDL, Lp(a), and ApoB. We categorized individuals into higher and lower TSH groups based on the median. Individuals with TSH higher than the median presented a longer survival time than those with TSH lower than the median, suggesting that TSH might be correlated with a better survival rate. Our data reinforce that euthyroid individuals with higher TSH levels have a biochemical profile associated with cardiovascular risk, such as hypertriglyceridemia. However, the increase in An increased risk of cardiovascular events does not accompany TSH. In contrast, individuals with higher TSH presented with the absence of diabetes, coronary disease, heart failure, and better survival. More studies are warranted to investigate the mechanisms behind the association of TSH with cardiovascular protection and longevity.

DOI: 10.1530/endoabs.101.OP-05-02

## OP-05-03

### Cardiovascular risk and mortality in a large italian cohort of patients with resistance to thyroid hormone β (RTHβ)

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Objective

decreased survival and higher cardiovascular risk have been reported in a UK cohort of RTHβ patients, but there is no evidence from other countries.

Methods

retrospective study of an Italian cohort of RTHβ patients, carrying heterozygous pathogenic variants in the *THRB* gene and diagnosed in the period between 1984 and 2023. We collected records at diagnosis of 284 cases, whereas longitudinal data were available in 249 RTHβ patients. We studied the impact of thyroid function tests and recognized risk factors for cardiovascular disease (hypertension, dyslipidemia, overweight and diabetes) on overall mortality and major cardiovascular events (MACEs). Publicly available datasets were used to compare these data with those of the general Italian population.

Results

The variants identified in this cohort are included in the three hot spot clusters of the THRB gene. Hyperkinetic arrythmias were the most common manifestation, with a prevalence of sinus/supraventricular tachycardia and atrial fibrillation of 40% and 18%, respectively. A total of 71 MACEs occurred in 47 RTHβ patients (27%) including 15 fatal events, resulting in a premature morbidity and mortality. MACEs and all-cause deaths occurred in RTHβ 6.5 and 11 years earlier than in the reference population. Free-T4 levels 1.6 folds over the upper limit of normal is the threshold significantly associated with premature (<55 years) cardiovascular manifestations. At univariate analysis dyslipidemia, high fasting glucose/diabetes were associated with MACEs, but only hypertension and male gender remained significantly associated with MACEs and atrial fibrillation with mortality at multivariate analysis. Previous thyroidectomy or radioiodine therapy had no significant effect in the prevention of MACE or all-cause mortality.

Conclusions

Italian RTHβ patients have an increased cardiovascular risk, which is higher in men and in those with fT4 levels above 30 pmol/l. As in the general population, lifestyle interventions and/or pharmacological treatments for hypertension, metabolic disorders, and overweight are recommended to lower this risk. Pharmacological trials should be prompted to evaluate the role of betablockers and thyroid hormone analogues for primary prevention.

DOI: 10.1530/endoabs.101.OP-05-03

## OP-05-04

**The quality of life impact of weight gain in treated hyperthyroidism**

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Objectives
Quality of life (QoL) is reduced in treated hyperthyroidism compared to age- and sex-matched controls. We previously reported excessive weight regain with the treatment of hyperthyroidism. Whether the treatment-related weight gain is affecting QoL of this patient group is unknown.
Methods
With a cross-sectional study design and data utilization from a prospectively completed database, we enrolled patients with treated hyperthyroidism. We included adult patients with overt hyperthyroidism six months to eight years' post-diagnosis. We excluded patients with thyroiditis and any medications, major comorbidity or surgery, which could significantly affect the weight. The primary outcome was to examine whether percentage weight change ($PWC = Weightlast - Weighto/Weighto \times 100\%$) after the treatment of hyperthyroidism was predictive of QoL. We utilized thyroid-specific (ThyPRO), generic and custom-made questionnaire tools and patient notes alongside self-completed questionnaires. We measured anthropometrics, body composition analysis and obtained a thyroid and cardiometabolic blood profile. QoL was pre-specified in three arms: 'cosmetic complaints' (M1) and a composite of 'tiredness and overall QoL' (M2) and 'depressivity and anxiety' (M3) domains (ThyPRO). We employed multiple linear regression for data analysis. We included age, sex, TSH categories (at assessment) and disease duration as covariates. We performed corrections for multiple testing (Banjamini-Hochberg method). Ethics approval was obtained.
Results
We included 108 patients; 68 (63%) females with mean (SD) age at 50 (14.5) yrs. Approximately, 80% had Graves' disease and 74% were solely treated with antithyroid drugs. Weight gain of 7.2 (6.2) kg was observed over a disease duration of 41 (22.5) months. Analysis showed a good model fit for M1 ($F(6,101) = 8.50$, $P < 0.001$, $R^2 = 33.6\%$) and M2 ($F(6,101) = 4.22$, $P = 0.001$, $R^2 = 20\%$), but not for M3 ($F(6,101) = 1.8$, $P = 0.107$, $R^2 = 9.7\%$). PWC had a predictive value on 'cosmetic complaints' ($b = 1.06$, $t = 4.70$, $P < 0.001$) but not on 'tiredness and overall QoL' ($b = 0.483$, $t = 1.80$, $P = 0.075$) domains. In secondary analysis, the PWC was not significant in predicting relevant domains of the SF-36 nor the EQ-5D surveys, likely indicating the reduced sensitivity of these tools in hyperthyroidism. When we asked patients to rate disease-related concerns, the three main perturbations included weight gain, fatigue and fear of recurrence (3/5, 2.7/5 and 2.7/5, respectively with 5/5 indicating severe concern/symptom). PWC was a significant predictor of self-reported weight gain ($b = 0.061$, $t = 3.57$, $P < 0.001$).
Conclusions
Weight gain has an adverse impact on some aspects of QoL, particularly cosmetic complaints, and is the most highly scored concern/symptom of patients with hyperthyroidism. This cumbersome aspect of treatment of hyperthyroidism needs more emphasis.

DOI: 10.1530/endoabs.101.OP-05-04

## OP-05-05

**Effect of the T3 analogue triac on patient-centered outcome measures in patients with MCT8 deficiency: post-hoc analysis of the international triac trial I**

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Background
Monocarboxyate transporter 8 (MCT8) deficiency is a rare neurodevelopmental and metabolic disorder caused by mutations in the thyroid hormone transporter MCT8. The Triac Trial I and subsequent real-world data showed that T3 analogue Triac safely normalizes serum T3 concentrations and ameliorates symptoms of peripheral thyrotoxicosis in paediatric and adult patients.
Objective
To study the effect of Triac on patient-centered outcome measures in the Triac Trial I.
Methods
We performed post-hoc analyses on caregiver-reported patient-centered outcome measures from the multicentre, phase 2, single-arm, open-label Triac Trial I. In this trial, 40 patients with MCT8 deficiency completed 1 year of Triac treatment. At baseline, during clinical visits and at the end of the study, semi-structured interviews were held with caregivers on complex needs and daily care challenges, including motor skills, sleep problems, seizure frequency and most prominent changes. Moreover, parents were asked to report perceived changes in (thyrotoxic) symptoms such as increased perspiration and hyposialia.
Findings
The most prominent changes upon Triac treatment reported by caregivers were improved interaction (22/39), greater alertness (19/39), improved motor skills (12/39), improved head control (7/39), and improved sleep (8/39). For one patient, also negative changes were reported, specifically increased constipation and higher unsettledness. Compared to the baseline visit, excessive perspiration was much less reported (48,6% vs. 8,1%) and less hyposialia (30,6% vs 22,2%) was observed by the caregivers at the end study visit. Seizures and continence were reportedly unchanged. All parents (40/40) preferred to continue Triac treatment.
Interpretation
Treatment with Triac exerts beneficial effects on several patient-centered outcome measures in MCT8 deficiency, corroborating earlier studies that showed positive effects of Triac on clinical and biochemical outcomes in patients with MCT8 deficiency.

Acknowledgements
On behalf of the Triac Trial I study group (names will appear in presentation or poster).

DOI: 10.1530/endoabs.101.OP-05-05

## OP-05-06

**Systematic review of mortality and long-term major cardiovascular events (MACE) following different treatment approaches for hyperthyroidism**

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Objectives
Hyperthyroidism affects up to 3% of the population and is associated with arrhythmias, which predispose to myocardial infarction, stroke and pulmonary embolism. Multiple studies indicate that all-cause and cardiovascular mortality are higher in patients with hyperthyroidism compared to the general population. However, associations between treatment modalities for hyperthyroidism and long-term health outcomes remain unclear. This study aims to analyse the literature and establish whether any of these treatments revert the long-term effects of hyperthyroidism.
Methods
Medline and Embase were searched for studies on the effects of different treatments for hyperthyroidism (antithyroid drugs (ATD), radioactive iodine (I-131) and thyroid surgery) on mortality and major adverse cardiovascular events (MACE) in adult patients. References and citations of selected full-text studies were screened. Two reviewers independently assessed eligibility and extracted the data. Bias was assessed with the Ottawa-Newcastle Scale. Outcome data were pooled to compare pairwise hazard rates (HR) using random effects (REML). The study forms part of the network meta-analysis registered in Prospero at the Centre of Reviews and Dissemination (CRD42024524000).
Results
The included studies consisted of large routinely collected cohorts at the national or regional level (Wales, Taiwan, Sweden, Hong Kong, Finland and England), together comprising data on 294,738 patients with average follow-up ranging from 1.5-10.5 years. There was only one study comparing the effects of treatment to the matched background population, showing an increased mortality risk after

ATD and I-131 not resolving hyperthyroidism, but not when I-131 induced hypothyroidism within 1 year. When treatment approaches were compared pairwise (5 studies), surgery significantly improved survival when compared with ATD (H$r$ = 0.43 [95%CI: 0.30-0.62]). The survival after surgery (0.66 [0.41-1.06]) or ATD (0.85 [0.66-1.09]) compared with I-131 therapy was not statistically different. Risk of MACE (4 studies) was increased in all treatment groups when compared to matched controls without hyperthyroidism (ATD: 1.72 [1.23-2.41], I-131: 1.85 [1.17-2.98], surgery: 1.11 [1.03-1.19]). Pairwise comparisons of treatments (3 studies) indicated the highest reduction of MACE risk when surgery was compared to ATD (0.52 [0.25-1.07]), but the effect did not reach statistical significance ($P$ = 0.08). I-131 did not significantly affect MACE risk compared with ATD or surgery (ATD: 0.89 [0.61-1.29], surgery: 0.65 [0.25-1.68]).

Conclusion

Surgery was associated with improved outcomes in mortality and MACE when compared with medical treatment. Current data comparing long-term health consequences following different treatment approaches for hyperthyroidism are sparse. Further studies are needed to support informed decision-making when choosing the optimal therapeutic approach for hyperthyroidism.

DOI: 10.1530/endoabs.101.OP-05-06

## OP-05-07

### Long-term outcomes of LT4/LT3 combination treatment for persistent hypothyroid symptoms

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Objective

LT4/LT3 combination treatment for persistent hypothyroid symptoms is increasingly used and requested by patients, but the efficacy and side effects of long-term therapy remain largely unexplored. This study aimed to describe the patient group experiencing a long-lasting effect of LT4/LT3 and to evaluate the impact on Quality of life (QoL) and hypothyroid symptoms.

Method

In this cross-sectional study, we invited 147 patients. We included 66 patients (64 female) who initiated LT4/LT3 combination treatment between 2010 and 2018. ThyPRO39 was used to evaluate QoL, and a validated symptom score was used to assess symptoms. The patients were classified as responders (patients with long-lasting effects of LT4/LT3 therapy) *versus* non-responders (patients without any improvement related to combination therapy). QoL data and symptom scores were compared to historical data from the general population and data from patients with persistent symptoms (QoL) before initiating combination therapy and untreated hypothyroid patients (symptom scores).

Results

The participants (54 responders and 12 non-responders) were a median of 56 years and had had LT3 for 4.2 years. Comorbidity was seen in 74% of patients; 17% had experienced depression, and 46% had had a period of stress. QoL in the responder group was similar to historical data from the general population. However, surprisingly, symptom scores were high and at the same levels as symptom scores seen in untreated hypothyroid females ( $<$60 years). T3 dose was increased during the follow-up period in 24% of responders, and 38% had s-TSH below the reference range ( $<$0.4mU/l). When comparing QoL in the responders TSH $<$ 0.4mU/l *versus* TSH $>$ 4.0, a tendency of better scores were seen in the "Anxiety" score (10 vs 18, $P$ = 0.01), "Emotional susceptibility" score ( 13 vs 21, $P$ = 0.02) and ThyPRO composite score (17 vs 23, $P$ = 0.04,) in the patients having TSH $<$ 0.4, however not significant when adjusting for multiple testing. When comparing Symptom scores, low TSH was associated with lower scores regarding "Mood lability"(14% vs 55% having normal TSH, $P$ = 0.003). Two patients had known osteoporosis, and one was diagnosed with atrial fibrillation (all in the responder group). Complaints of other side effects were absent.

Conclusion.

Evaluated on QoL, the patients in the responder group experience QoL comparable to the background population after 4 years of treatment, with few side effects. Surprisingly, despite good QoL they still report as many hypothyroid symptoms as younger women with untreated overt hypothyroidism.

DOI: 10.1530/endoabs.101.OP-05-07

# Oral Session 6: Translational Thyroid Cancer Research

## OP-06-01

### The role of TPO antibodies in immune escape of aggressive tumors of thyroid follicular cells

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Introduction

Our previous observations suggested that high titers TPO antibodies titers limit the extent of differentiated thyroid cancer.[1] Other studies found an opposite effect, especially when it comes to indolent tumors. We designed the present study to assess whether TPO antibodies have differential effects on the expansion/progression of aggressive (AGG) as opposed to non-aggressive (NAG) tumors of follicular cells origin (TCFO).

Methods

For the present work we gathered data from thyroid surgeries performed at four centers, in two countries [USA: 1 (2007-2013) and Greece: 3 (2021-2023)] on gender, age, surgical pathology and preoperative TPO antibody titers. AGG thyroid cancers were deemed those tumors producing distant metastases, spreading to multiple lymph nodes (LNs) ($\geq$ 10 or $\geq$ 6 with a positive malignant to benign ratio $\geq$ 75%), those requiring $\geq$ 2 courses of I-131 therapy or large structural local recurrences. The remainder were considered NAG. Subjects with benign histology (BEN) served as controls. TPO antibody titers were grouped in five categories: very low (VL) ($<$ 1 IU/ml), low (L)(1 - 10 IU/ml), intermediate (IN) (10 - 30 IU/ml), high (HI) (30-300 IU/ml) and very high (VH) ($\geq$300 IU/ml). AGG thyroid cancer incidence was compared among different subgroups.

Results

We reviewed a total of 11,212 surgeries and 1,943 subjects had available preoperative TPO antibody titers: $n$ = 995 (51.2%) with TCFO. The population's mean age was 46.7$\pm$14.9 years, significantly higher in BEN (47.7$\pm$15.1) compared to TCFO (45.7$\pm$14.6), and higher in non-AGG (46.2$\pm$14.5), compared to the AGG (40.2$\pm$15.3) subgroup, $P$ $<$ 0.01 for all comparisons. Overall $n$ = 1477 (76.0%) were females; 736/1487 (49.5%) with TCFO, which was significantly lower compared to the 55.6% (259/466) found in males, ($P$ = 0.02). Based on the above criteria, AGG were significantly more common in VL ($P$ = 0.018) and less common in H ($P$ = 0.016) patients' subgroups (see table).

| TPO Ab Titer | BEN | DTC | NON-AGG | AGG | Total |
|---|---|---|---|---|---|
| VL ($\leq$ 1) | 308 (32.2%) | 285 (28.6%) | 347 (37.6%) | 38 (52.1%) | 693 |
| L (1-10) | 106 (11.1%) | 99 (9.9%) | 95 (10.3%) | 4 (5.5%) | 205 |
| INT (10-30) | 208 (21.7%) | 210 (21.1%) | 195 (21.1%) | 15 (20.9%) | 418 |
| HI (30-300) | 190 (19.8%) | 199 (20.0%) | 192 (20.8%) | 7 (9.6%) | 389 |
| VH ($>$300) | 146 (15.2%) | 102 (10.3%) | 93 (10.1%) | 9 (12.3%) | 248 |
| Total | 958 | 995 | 922 | 73 | 1943 |

Conclusions

Aggressive forms of thyroid cancers are more commonly found in patients with very low and more rarely in those with high TPO antibody titers. Our findings imply that the lack of TPO antibodies in aggressive thyroid cancers is a means of immunity escape. An intact humoral, albeit autoimmune, response seems protective in that regard.

Reference

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DOI: 10.1530/endoabs.101.OP-06-01

## OP-06-02

**Clinical utility of circulating tumoral dna analysis by multi-gene ngs panels in therapy monitoring of advanced sporadic medullary thyroid carcinoma patients**

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Objectives
In the personalized medicine era, application of multi-gene Next Generation Sequencing (NGS) panels may be used to analyze plasma circulating tumoral DNA (ctDNA) obtained by liquid biopsies of tumor patients improving management of patients undergoing targeted therapy. This analysis may identify genetic alterations responsible for response and/or resistance during target therapy and may be useful in identifying other biomarkers. Aim of this study was to evaluate the clinical relevance of NGS analysis of ctDNA in patients affected by sporadic Medullary Thyroid Carcinoma (sMTC) during systemic therapy with kinase inhibitors.
Methods
We studied 8 multi-metastatic sMTC patients harboring either RET ($n = 7$) or HRAS ($n = 1$) mutations in tumoral tissue. All patients were treated with iRET selpercatinib ($n = 6$) or multi-kinase inhibitors (MKI) ($n = 2$), and 4 patients were treated with selpercatinib after progression during previous treatment with (MKI). All patients showed stable disease during therapy. Plasma samples were collected in 4 time-points before therapy start and during follow-up; ctDNA was obtained from 4ml of plasma and analyzed using the Oncomine Pancancer Cell-free DNA NGS panel (Thermo Fisher) that covers mutations and gene fusion in 52 cancer genes. Mutation allele frequency (AF) of mutations were correlated to the status of disease.
Results
Good quality data were obtained from all ctDNA samples reaching limit of detection (LoD) values up to 0.1%. The driver mutation was detected in 5/8 RET-positive patients and AF values dropped during therapy showing a good correlation with disease status and serving as additional biomarker for disease monitoring. In the plasma of patient harboring a HRAS K117N non-hotspot mutation in tissue, we found a mutation in exon 5 of the Estrogen Receptor type 1 (ESR1) with AF=35%; the same mutation was confirmed as somatic in the tumoral tissue. Moreover, the same ESR1 mutation was detected at low AF in the ctDNA of other 2 patients suggesting that it was acquired during tumoral progression. Additional pathogenic mutations in TP53 and GNAS, not previously detected in tumoral tissue, were detected at low AF in plasma of other 3 patients suggesting the presence of other subclones that may emerge during treatment.
Conclusions
These data show that multi-gene combined DNA/RNA panels can be useful to monitor treatment response with kinase inhibitors also in advanced sMTC. While the driver mutation AF correlated with disease status, emergence of additional genetic biomarkers may contribute to disease progression and could provide additional actionable alterations for targeted therapies.

DOI: 10.1530/endoabs.101.OP-06-02

## OP-06-03

**Digoxin treatment does not reinduce uptake of radioiodine in metastatic radioiodine refractory non-medullary thyroid carcinoma**

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Objective
Patients with non-medullary thyroid carcinoma (NMTC) that are refractory to radioactive iodine (RAI) have a bad prognosis. For these patients, treatment options are limited. RAI refractoriness is the result of reduced RAI uptake by NMTC cells, caused by loss of function of the Na/I symporter. Strategies for restoring the ability of NMTC cells to take up RAI, so called "redifferentiation", are promising treatment modalities. Preclinical studies have shown that the cardiac glycoside digoxin restored RAI uptake, both in human cell lines as in a murine model. Also, a retrospective study showed that RAI uptake was better preserved in NMTC patients treated with digoxin for cardiologic indications than in matched patients who were not treated with digoxin. In this prospective single-center open-label study we investigated whether treatment with digoxin could re-induce clinically relevant RAI uptake in patients with metastasized RAI refractory NMTC.
Methods
Eight NMTC patients with metastasized RAI refractory NMTC with at least one measurable target lesion of $\geq 1$ cm, without a direct indication for systemic treatment and without contraindications for digoxin treatment were included between November 2022 and June 2023. Before treatment a baseline [123I]NaI-scintigraphy was performed. Thereafter, patients were treated for 3 weeks with digoxin with starting doses dependent on age and weight. For safety reasons, the usual therapeutic range for digoxin was aimed for; 0.5-2.0 ng/mL. After 1 week, the blood concentration of digoxin was measured and the digoxin dose was adjusted if necessary. After 3 weeks, a new [123I]NaI-scintigraphy was performed. If this second scintigraphy showed clinically relevant RAI uptake, a [131I]NaI-treatment would be performed within 1 week. Digoxin treatment was stopped after the second [123I]NaI-scintigraphy or after [131I]NaI-treatment in case of successful reinduction of RAI-uptake.
Results
Seven patients (5 papillary carcinoma and 2 oncocytic carcinoma) completed the digoxin treatment and were evaluable. An eighth patient discontinued the study because of an digoxin-unrelated emergency indication for a CT with iodinated contrast agent. None of these 7 patients showed clinically relevant RAI-uptake after digoxin treatment. Digoxin treatment was generally tolerated well. No digoxin-related serious adverse events occurred during the study. Increased fatigue was the only adverse event occurring in more than one patients, presenting in 4 out of 7 evaluable patients.
Conclusion
Contrary to results from preclinical trials, in this study digoxin treatment does not reinduce RAI uptake in patients with metastasized and RAI refractory NMTC. Future studies are needed to identify effective redifferentiation strategies for patients not eligible for kinase inhibitors.

DOI: 10.1530/endoabs.101.OP-06-03

## OP-06-04

**Clinically relevant germline genetic variants and somatic fusions underlying paediatric thyroid cancer risk and aggressiveness**

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Introduction
Paediatric thyroid cancer (TC) is characterised by higher aggressiveness and recurrence rates compared to adult TC. The risk stratification system for paediatric TC is simplified relative to that of adults. Paediatric tumours mostly harbour gene fusions, while adult TC frequently present oncogenic point mutations. Yet, 40-50% of genomic alterations driving tumourigenesis and

conferring aggressiveness to radiation-unrelated paediatric papillary TC (PTC) remain unknown.
Objective
To clinically and molecularly characterise a series of radiation-unrelated paediatric PTC cases.
Methods
Twenty-one paediatric PTC cases followed in our institution were stratified into 3 risk groups, according to American Thyroid Association (ATA) guidelines for paediatric TC. Tumours from 15 high-, 2 intermediate- and 4 low-risk cases, as well as 6 normal thyroid tissues were studied through whole-exome and transcriptome sequencing, and DNA methylation arrays. Bioinformatics analyses were performed to identify candidate genetic variants, rearrangements, and methylation/expression patterns.
Results
Seven male and 14 female patients, aged 5-18 years, were studied. All patients remain alive as of the latest update, with high-risk cases often requiring $\geq 2$ $I^{131}$ treatments. In the transcriptome analysis, the high-risk group showed lower expression of thyroid differentiation-related genes and upregulation of MAPK signalling genes, compared to the other groups. Exome analysis unveiled genetic alterations in 17/21 (81%) patients, with 11 patients (52%) carrying germline variants classified *in silico* as likely pathogenic in known tumour predisposition genes [ *CHEK2* ($n = 1$), *DICER1* ($n = 1$)], thyroid function-related, and other genes [ *HHEX* ($n = 1$), *FOXE1* ($n = 2$), *DUOX1* ($n = 1$), *DUOX2* ($n = 1$), *AXIN1* ($n = 1$), *FGFR4* ($n = 1$), *NTHL1* ($n = 1$), *ROS1* ($n = 1$)]. Additional variants are being evaluated. *DICER1* variants (germline and somatic) were found exclusively in low-risk patients (4/4), all presenting two hits. Noteworthy, $BRAF^{V600E}$ and *RAS* hotspot mutations were absent in all cases. Gene fusions were identified in 43% of PTC [ *RET* (67%), *NTRK* (33%)], coexisting or not with the aforementioned germline variants. Global methylation analysis clearly grouped tumours into risk-related clusters.
Conclusions
The high prevalence of germline variants identified in this study suggests that hereditary predisposition frequently underlies TC aetiology in radiation-unrelated paediatric cases. Particularly, these results reinforce the role of *DICER1* as driver of less aggressive paediatric PTC. The detection of somatic gene fusions, mainly in the high-risk cases, supports patients' eligibility for available targeted therapies. Methylation profiling highlighted its potential utility for risk stratification and prognostic assessment. The ongoing study of an additional validation cohort of 18 paediatric cases may provide molecular support for current ATA guidelines.

DOI: 10.1530/endoabs.101.OP-06-04

## OP-06-05

**Molecular profiling of low-risk papillary thyroid carcinomas (MPTC) on active surveillance**

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Introduction
active surveillance (AS) is feasible and safe for low-risk papillary thyroid carcinoma with diameter $\leq$ 1.3 cm (mPTC), as this type of cancer shows a low percentage of progression. At the present time, there are no prognostic factors which could help to identify mPTCs at higher risk of progression. The aim of this prospective study is to find a specific molecular signature of cases that showed disease progression during AS and which would allow their early identification.
Methods
NGS sequencing of fine needle aspiration cytology (FNAC) specimens from 95 patients enrolled in the AS program was performed to analyze key somatic driver alterations or gene fusions implicated in PTC tumorigenesis. TERT promoter analysis was performed using Sanger sequencing or droplet digital PCR (ddPCR). Disease progression was defined as the growth of the mPTC (at least 3 mm in all the three diameters) or the appearance of a metastatic lymph node.
Results
BRAF p.V600E mutation was found in 66.3% (63/95) of mPTC cases and it was the most common somatic alteration, followed by RAS oncogene mutations, detected in 3.2% of cases (3/95: 2 NRAS and 1 KRAS), and gene fusions, detected in 3.2% of cases (3/95: 1 RET-PTC1, 1 TGF-NTRK1, 1 ALK imbalance). No TERT promoter mutations (C228T and C250T) were found in the analyzed mPTC cases (84/95). After a median follow-up of 24 months, 8/95 patients (8.4%) showed a disease progression: 2/8 (25%) showed an increase in nodule dimensions, while 6/8 (75%) showed the appearance of small lymph node metastasis. All these 8 patients were submitted to surgery, and they all had a PTC at the final histological diagnosis. Five (5/8) patients had a BRAF p.V600E mutation, 1/8 patient had a RAS mutation, while 2/8 showed no mutations. It was observed that all the BRAF p.V600E positive cases showed lymph node metastases, while the only case with a RAS mutation had progression due to nodule enlargement. The comparison between the molecular profile and the clinical outcome of the mPTC cases (stable *versus* progressing disease) showed no correlation ($P$-value = 0.06) and could not identify a molecular signature for mPTC cases indicating a higher risk of disease progression.
Conclusions
the identification of the most common driver mutations, such as BRAF, RAS, or gene fusions, is not helpful for the early identification of mPTC cases that will show disease progression during follow-up in the AS program.

DOI: 10.1530/endoabs.101.OP-06-05

## OP-06-06

**Clinical implications of the gut microbiome in anaplastic thyroid cancer**

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Background
Despite the use of aggressive, multimodal therapy (surgery + radiation therapy + systemic therapy), management of advanced thyroid cancers such as anaplastic thyroid cancer (ATC) remains a major challenge. Identifying predictive biomarkers of treatment response are primordial to improving overall survival for patients with ATC. Gut microbiota have been linked to both treatment response and levels of adverse effects to treatment in cancers such as melanoma or colorectal cancer, but there is yet to be an evaluation of the gut microbiome and its relation to thyroid cancer. Our goal is to interrogate the gut microbiome of patients diagnosed with ATC and evaluate potential predictive markers for treatment outcomes.
Methods
Between April 2019 and October 2023 and following informed written consent, stool samples were collected using a cold-chain temperature controlled at-home collection kit from patients diagnosed with histopathologically proven ATC. Patient demographic characteristics, molecular testing data, and treatment modalities were collected. Overall survival (OS) was measured from date of pathologic confirmation of disease to date of death, with patients censored at date of last follow-up. For the microbiome analyses,16Sv4 rRNA gene sequencing data was generated and processed with DADA2 and the SILVA database. Microbiome diversity and taxonomic analysis were carried out in R using the phyloseq, vegan, ape, and ancombc packages. The Kaplan-Meier method was used to estimate OS, while the log-rank test was used to assess between-group differences and the Cox proportional hazard was used to assess relative risk ratios.
Results
A total of 21 patients with ATC were included in this study (13 females and 8 males). Targeted therapy (71%), immunotherapy (IO) (86%), and external beam radiation therapy (62%) were the most frequent treatment modalities. Microbial alpha and beta-diversity indices were not associated with OS. However, the abundance of *Turicibacter* spp . was associated with increased OS in patients receiving different types of therapy including IO. In patients receiving IO, the presence of Proteobacteria was associated with poor OS.
Conclusions
To our knowledge, this is one of the first studies to evaluate the gut microbiome in a large cohort of anaplastic thyroid cancer patients. There was no association between alpha and beta-diversity and survival. The presence of Proteobacteria was associated with a poorer prognosis, while a higher abundance of *Turicibacter* spp. was associated with increased survival. These early signals warrant for further work in this field in an effort to improve patient outcomes with this deadly disease.

DOI: 10.1530/endoabs.101.OP-06-06

## OP-06-07

**Performance of the mir-thype new version algorithm in classification of thyroid indeterminate nodules: latin american multicenter validation study**

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Background
Thyroid nodules are present in nearly 60% of the population, representing the most frequent endocrine disease. Fine-needle aspiration (FNA) cytopathology classifies 20%–30% of nodules as indeterminate (Bethesda 3 and 4), a scenario in which molecular tests are recommended aiming to avoid unnecessary diagnostic surgeries.
Objective
The aim was to evaluate the diagnostic performance of the new v2 algorithm of mir-THYpe full molecular classifier test for preoperative diagnosis of cytologically indeterminate thyroid nodules, optimized by the use of new machine learning techniques, larger sample cohort size, multicentricity and association of DNA-mutation analysis.
Methods
A multicenter validation study was conducted on a set of 2.372 thyroid nodules with Bethesda 3 and 4 cytology from 15 academic, community and private centers in Brazil, Argentina and Peru. Eligibility criteria were met in 510 nodules. The FNA smear slides were used to obtain and analyze microRNA expression and DNA mutations (BRAF V600E and pTERT C228/250T) by qPCR. Molecular data from 306 (150 benign/156 cancer + NIFTP) nodules were used to retrain and optimize the mir-THYpe v2 algorithm, using random forest, SVM and neural networks machine learning techniques. For final validation, molecular data from 204 (151 benign/53 cancer + NIFTP) thyroid nodules were used to measure diagnostic performance. Anatomopathological data were used as gold-standard for blinded comparison.
Results
In the validation set, 61.8% of the samples were assigned as Bethesda 3 (126) and 38.2% as Bethesda 4 (78). The v2 algorithm had a specificity of 94% (95% Cl, 84-99), a sensitivity of 89% (95% Cl, 83-94) and an accuracy of 91% (95% Cl,86-94). At 26% cancer prevalence, the negative predictive value was 98% (95% Cl, 94-99) and the positive predictive value was 76% (95% Cl, 66-83) with a benign call rate of 68% (138/204). The v2 algorithm was able not only to classify but also to identify as medullary thyroid carcinoma (MTC) in all the MTC samples (5/5).
Conclusion
The optimized classifier demonstrated a high diagnostic performance for identifying benign nodules, which may potentially obviate diagnostic surgery in 68% of patients with indeterminate nodules, and up to 89% of all benign nodules cytologically indeterminate. The BRAF and pTERT status analysis, added to the ability to rule-in cancer samples may help to guide prognostic decisions, including surgery extension and individualized treatments.

DOI: 10.1530/endoabs.101.OP-06-07

# Oral Session 7: Thyroid Hormone Mechanisms in Diseases

## OP-07-01

**The protective role of androgen on experimental graves'hyperthyroidism in balb/c mice**

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Objective
Graves' disease (GD) exhibits a higher prevalence in females compared to males. Sex hormones might influence susceptibility of this disease. Studies have shown that 5α-dihydrotestosterone (DHT) treatment can provide protection against GD. In order to further confirm the protective effect of different forms of androgen against GD and its preventive mechanism, the current investigation was designed to explore gender difference and response to testosterone or DHT treatment in the mice model of GD.
Methods
Female and male BALB/c mice were injected three times at three weekly intervals with adenovirus expressing the human thyrotropin receptor A-subunit to induce GD model. Castration and androgen treatment in mice were conducted a week before the first immunization. Four weeks after the third immunization, the incidence and the severity of GD were observed by the determination of serum TBI, TT4, FT4 of castrated males as well as androgen treated females, and the immune response of Th1/Th2/Th17/Treg were analyzed by measuring the expression and secretion levels of T lymphocyte cytokine from spleen using flowcytometry and ELISA.
Results
Lowered TT4, slightly lowered levels of FT4 and the low proportion of hyperthyroidism were displayed in males compared to females. Both T and DHT significantly reduced the levels of TT4, FT4 and the degree of thyroid hyperplasia. The analysis of T cell flowcytometry showed that the expression of CD4 + INF-γ + among CD4 + T cell in males was lower when compared to females, and androgen depletion mildly increased the percentage of CD4 + CD25 + and CD4 + CD25 + Foxp3 + in CD4 + T cell. Androgen treatment not only significantly inhibited the expression of CD4 + INF-γ +, but also promoted the expansion of CD4 + CD25 + and CD4 + CD25 + Foxp3 population within CD4 + T cells. In this study, the ELISA analysis results of cytokine secretion products of T cells also displayed that exogenous androgen treatment inhibited the secretion of INF-γ and IL-10.
Conclusions
Supplemental exogenous androgen treatment provided protection against Graves' hyperthyroidism in BALB/c genetic background mice. Suppressed Th1 and/or Th2 immune response and extended Tregs population may be one mechanism that is responsible for the protective role of androgen.

DOI: 10.1530/endoabs.101.OP-07-01

## OP-07-02

**Abrogation of hepatic trβ action attenuates acetaminophen-induced acute liver injury in mice**

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Objectives
Drug-induced acute liver failure (ALF) is a rare but life-threatening clinical scenario which occurs in individuals without pre-existing liver disease. Intoxication of the pain-reliever acetaminophen (APAP) is a well-known trigger for ALF. The cytochrome P450 enzyme CYP2E1 converts APAP to the toxic metabolite *N* -acetyl- *p* -benzoquinone imine (NAPQI) which is inactivated by endogenous glutathione. If glutathione is depleted, NAPQI triggers hepatocellular necrosis leading to ALF. It is well known that triiodothyronine (T3) positively favors e.g. hepatocyte proliferation via thyroid hormone receptor β (TRβ) signaling. However, in how far hepatic TRβ action impacts disease progression of APAP-induced acute liver injury is not known so far. Using the APAP mouse model, we asked whether and if yes how abrogation of hepatic TRβ action influences the progression of acute liver injury.

Methods
Acute liver injury was induced via i.p. injection of 300 mg/kg body weight of APAP (or solvent control) in male C57BL/6J control (WT) mice and male mice with hepatocyte specific TRβ knockout (hepTRβKO). One hour to 24 hours post APAP intoxication, liver histology, liver function test, hepatic T3-responsive markers and APAP metabolism were evaluated.
Results
In WT mice, APAP resulted in pericentral hepatocellular necrosis and increased serum transaminase activities with a maximum peak 24 hours post intoxication. Abrogation of hepatic TH action in hepTRβKO mice attenuated APAP-induced acute liver injury. More in detail, 24 hours after APAP injection pericentral hepatocellular necrosis and elevated serum transaminases were absent, whereas 12 hours after APAP injection injured hepatocytes surrounding central veins were observed. T3-responsive markers revealed successful abrogation of hepatic TRβ signaling. APAP metabolism was evaluated by hepatic expression of Cyp2e1 and glutathione, both located in hepatocytes surrounding central veins.
Conclusions and outlook
Our data indicate that abrogation of hepatic TRβ action attenuates disease progression of APAP-induced acute liver injury in male C57BL/6J mice. The results provide novel insights how local hepatic thyroid hormone action impacts ALF and harbors great translational potential for new treatment strategies, e.g. to antagonize or agonize local thyroid hormone action depending on the disease status.

DOI: 10.1530/endoabs.101.OP-07-02

## OP-07-03

**Characteristics of hyaluronan metabolism during myofibroblast differentiation in orbital fibroblasts**

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Objectives
Differentiation of orbital fibroblasts (OFs) into myofibroblastic phenotype contributes to tissue remodelling in thyroid eye disease (TED). Our study aimed to investigate the impact of TGF-β1 induced myofibroblast differentiation on hyaluronan turnover, with a particular focus on the expression of its key enzymes.
Methods
OF cultures were established from tissue samples acquired from decompression surgeries of patients with TED (TED-OFs; $n = 4$) and during other ophthalmic surgeries (enucleation) for non-orbital eye diseases as controls (non-TED-OFs; $n=5$). To induce myofibroblast differentiation, the medium was supplemented with TGF-β1 (5ng/ml). Measurements were performed after 24 and 72 hours. Proliferation rate was determined by the detection of BrdU incorporation. Hyaluronan content of the supernatant and the amount of pericellular hyaluronan were measured using an ELISA-like technique. The mRNA expression of myofibroblast markers and enzymes playing a pivotal role in hyaluronan metabolism were determined by real-time PCR.
Results
Upregulation in the mRNA expression of alpha-1 type-1 collagen, α-smooth muscle actin and fibronectin indicated that OFs underwent myofibroblast transdifferentiation after stimulation by TGF-β1. After 72 hours, proliferation rate of both untreated and treated cultures declined; the decrease in the proliferative capacity was less marked in TGF-β1 treated (i.e. myofibroblast) cells ($p < 0.0005$). In parallel the amount of hyaluronan in the pericellular coat, but not in the supernatant of myofibroblasts, increased compared to untreated cells by 72 hours (non-TED-OFs $p < 0.0001$, TED-OFs $p < 0.0001$). TGF-β1 was a potent stimulator of hyaluronan synthase-1 (HAS-1) expression (non-TED-OFs $p < 0.0001$, TED-OFs $p < 0.0001$ at both time points), while no significant increase was found in the expression of HAS2 and HAS3. The expression of both type 1 hyaluronidase (HYAL-1) and cell migration inducing protein (CEMIP, a recently discovered hyaluronidase) diminished following myofibroblast differentiation at 72h (non-TED-OFs $p < 0.0001$, TED-OFs $p < 0.0001$ and non-TED-OFs $p < 0.001$, TED-OFs $p < 0.001$, respectively). The expression of transmembrane protein 2 (TMEM2), the regulator of hyaluronan catabolism through CEMIP was elevated after 72 hours of TGF-β1 treatment (non-TED-OFs $p < 0.01$, TED-OFs $P < 0.05$).
Conclusions
Orbital fibroblasts undergoing myofibroblast transdifferentiation are characterized by decreased hyaluronan turnover due to the downregulated expression of two hyaluronidases. The accumulation of hyaluronan in the pericellular coat leads to an increase in oedema due to its large water binding capacity, which can negatively affect the course of TED. Our results suggest that hyaluronidases could be potential targets in the treatment of TED.

DOI: 10.1530/endoabs.101.OP-07-03

## OP-07-04

**Absence of cholesterol gallstone formation in male C57BL/6 mice by abrogation of hepatic thyroid hormone action**

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Objectives
Cholesterol gallstone disease has a prevalence of 10-15% being one of the most common gastrointestinal pathologies. It is well known that thyroid hormone (TH) impacts the hepatobiliary system. Epidemiological studies suggest a link between thyroid dysfunction and cholestatic liver disease. In our previous studies we could confirm that a severe systemic TH deficiency promotes cholesterol gallstone formation in C57BL/6 mice. Using the lithogenic mouse model, in the present study we investigate whether more subtle changes in the systemic TH status or abrogation of hepatic TH action impact cholestatic liver disease.
Methods
To study the impact of systemic TH status on cholesterol gallstone formation, male C57BL/6 wildtype (WT) mice received a six weeks lithogenic diet either under iodine sufficient or iodine deficient condition. Male hepatocyte specific TRβ knockout (hepTRβKO) mice received a six weeks lithogenic diet to investigate the role of abrogated hepatic TH action on cholestatic liver disease. Biliary cholesterol gallstone and crystal prevalence, liver histology, liver and thyroid functions test, TH- and cholestasis-responsive markers were evaluated.
Results
Cholesterol gallstones were observed in lithogenic diet supplemented WT mice under iodine sufficient condition (57%). In the iodine deficient group, a higher prevalence of cholesterol gallstone formation (80%) was observed, and the low iodine regiment reduced both systemic TH concentration and hepatic *deiodinase 1* (*Dio1*) mRNA expression. In hepTRβKO mice successful abrogation of hepatic TH action was determined, whereas systemic TH status was not altered. A six-week lithogenic diet treatment could not induce macroscopic visible cholesterol gallstones in hepTRβKO mice which cannot be explained by cholestasis-responsive markers. In hepTRβKO mice a reduced lipid content and elevated gene expression of the cytochrome P450 enzyme *Cyp2c39* was observed.
Conclusions and outlook
Systemic TH deficiency increases the pro-lithogenic response of male C57BL/6 mice leading to a higher cholesterol gallstone prevalence. Abrogation of hepatic TH action in male hepTRβKO mice shows an anti-lithogenic effect by preventing mice against cholesterol gallstone formation. This is associated with an elevated expression of hepatic *Cyp2c39* encoding for an n-3 fatty acid producing enzyme. The results provide new insights into the regulatory principle of local TH action in the hepatobiliary system.

DOI: 10.1530/endoabs.101.OP-07-04

## OP-07-05

**Altered skull and bone morphology in hyperthyroid knock-in mice with TSHR M453T and D633H mutations**

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Background
Constitutively active thyrotropin receptor (TSHR) mutations are the primary cause of non-autoimmune hyperthyroidism (NAH). The TSHR is a key regulator of thyroid function, which, through thyroid hormones, plays a crucial role in bone formation and resorption. Beyond influencing skeletal bone growth, thyroid hormones also regulate craniofacial development. Furthermore, in addition to thyroid hormones an independent role of TSH on bone development has been proposed. Here we evaluated the impact of constitutively activating mutations (CAM) in TSHR on craniofacial and bone development.
Methods
To understand the role of TSHR CAM in bone development we investigated our previously generated TSHR knock-in (KI) mouse models with patient-derived TSHR D633H and M453T mutations. TSHR D633H homozygous mice present mild transient hyperthyroidism at 2 months of age. TSHR M453T homozygous mice, on the other hand, exhibited a dietary iodine dependent, stronger, hyperthyroid state. Cranium morphometry, micro-computed tomography (μCT) and 3-point bending tests were performed.
Results
Homozygous TSHR D633H and M453T mice showed altered craniofacial morphology, with notable changes in skull dimensions and snout length compared to WTs. Malocclusion incidence was higher in HOM and HET mice compared to WT, independent of sex. TSHR D633H mice showed no significant differences in bone structural or mechanical properties. In contrast TSHR M453T mice showed alterations in BMD and structural characteristics of trabecular bone that were dependent on dietary iodine concentration, with no notable effects observed in cortical bone. No obvious differences in body or tail lengths were observed in TSHR D633H mice. TSHR M453T homozygous mice showed decreased tail length at weaning depending on dietary iodine concentration but the difference disappeared shortly after. No differences in body length were observed.
Conclusion
This is the first *in vivo* study to reveal NAH effects on bone morphology. Our findings suggest that TSHR CAMs, particularly D633H and M453T mutations, may influence craniofacial morphology and malocclusion incidence in mice. BMD and bone structural characteristics appeared to depend on dietary iodine content in homozygous mice. Further investigations are needed to evaluate more precise mechanisms of TSHR role in skeletal development.

DOI: 10.1530/endoabs.101.OP-07-05

## Oral Session 8: Pregnancy

### OP-08-01

**Clinically relevant differences between routinely used immunoassays for thyroid function testing: a danish study of non-pregnant and pregnant adults**

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Objective
Thyroid function tests are common biochemical analyses and agreement between the routinely used immunoassays is important for diagnosis and monitoring of thyroid disease. Efforts are continuously made to align the biochemical assays, and we aimed to evaluate agreement between immunoassays used in a clinical laboratory setting among non-pregnant and pregnant adults.
Methods
We performed a cross-sectional study including serum samples from 192 Danish blood donors (non-pregnant adults) and from 86 pregnant women in the North Denmark Region. The samples were used for measurement of thyroid-stimulating hormone (TSH), total thyroxine (TT4), and total triiodothyronine (TT3) with three routinely used automatic immunoassays (Alinity, Abbott Laboratories, Cobas, Roche Diagnostics, and Atellica, Siemens Healthineers). Assay agreement was evaluated by comparison of the medians using Kruskal-Wallis test or Mann-Whitney U test as appropriate. Furthermore, reference intervals for TSH, TT4 and TT3 were established in non-pregnant adults ($n = 162$) as the 2.5 and 97.5 percentiles among thyroid autoantibody-negative (thyroid-peroxidase antibodies $< 60$ U/mL and thyroglobulin antibodies $< 33$ U/mL.
Results
In non-pregnant adults, levels of all thyroid function tests were higher with Cobas and Atellica than with Alinity as reflected by the median TSH (Alinity: 1.39 mIU/l; Cobas: 1.57 mIU/l; Atellica: 1.74 mIU/l, $P < 0.001$), TT4 (Alinity: 88.8 nmol/l; Cobas: 98.1 nmol/l; Atellica: 97.2 nmol/l, $P < 0.001$), and TT3 (Alinity: 1.52 nmol/l; Cobas: 1.81 nmol/l; Atellica: 1.69 nmol/l, $P < 0.001$). Similarly, levels were higher with Cobas than with Alinity among pregnant women as seen for median TT4 (Alinity: 106 nmol/l; Cobas: 127 nmol/l, $P < 0.001$) and TT3 (Alinity: 1.77 nmol/l; Cobas: 2.47 nmol/l, $P < 0.001$), and a parallel non-significant trend was seen for TSH (Alinity: 1.90 mIU/l; Cobas: 2.33 mIU/l, $P = 0.2$), Established reference intervals in non-pregnant adults with each of the assays showed higher upper reference limits with Cobas and Atellica than with Alinity, and the reference intervals were for TSH (Alinity: 0.46-3.44 mIU/l, Cobas: 0.57-3.96 mIU/l, Atellica: 0.57-4.23 mIU/l), TT4 (Alinity: 63-121 nmol/l, Cobas: 68-138 nmol/l, Atellica: 64-135 nmol/l), and TT3 (Alinity: 1.17-2.02 nmol/l, Cobas: 1.35-2.58 nmol/l, Atellica: 1.25-2.27 nmol/l,).
Conclusions
Results of thyroid function tests obtained with different immunoassays were not interchangeable when evaluated among pregnant and non-pregnant adults. The distinct differences are relevant for clinical decision making and emphasize the necessity of clinical laboratory information when different assays are used for diagnosis and monitoring of patients with thyroid disease.

DOI: 10.1530/endoabs.101.OP-08-01

### OP-08-02

**Stimulating TSH-receptor antibodies in early pregnancy using the turbo TSI bioassay: a study of 3,028 pregnant women in the north denmark region**

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Objective
TSH-receptor antibodies (TRAb) are key markers to distinguish Graves' disease from gestational hyperthyroidism in pregnancy in clinical practice. We aimed to measure stimulating TRAb (TSI) using the Turbo TSI bioassay for establishment of early pregnancy cut-off and comparison with immunoassay measurements of TRAb.
Methods
We performed a retrospective cohort study within the North Denmark Region Pregnancy Cohort (2011-2015) and identified a random cohort ($n = 2,686$) as well as a 'low TSH cohort' of women with TSH $< 0.1$ mIU/l in early pregnancy ($n = 438$). Stored biobank samples were used for TSI measurement with the Turbo TSI bioassay (Quidel/Ortho-Clinical Diagnostics) and compared to previous TRAb measurements with an immunoassay (BRAHMS TRAK Human, Kryptor Compact, Thermofisher Diagnostics Aps). A method- and pregnancy-specific cut-off (95-percentile) for the Turbo TSI bioassay was established among healthy reference individuals in the random cohort ($n = 2,299$) using Regression on Order Statistics. TRAb- and TSI-status was compared in the 'low TSH cohort', and TSH, β-hCG, thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (Tg-Ab) status were evaluated. Quidel/Ortho-Clinical Diagnostics supported the Turbo TSI bioassay measurements.
Results
The established cut-off for TSI was 0.0418 IU/l for the Turbo TSI bioassay and previously found to be 1.0 IU/l for the TRAb immunoassay. In the 'low TSH cohort', 43 women were positive for TSI (9.8%), and 22 women were positive for both TSI and TRAb (group 1). On the other hand, 28 women had discrepant TSI and TRAb results being either positive or negative (group 2), and 388 were negative for both TSI and TRAb (group 3). Median TSH differed by antibody status and was lower in the TSI and TRAb positive group (group 1; 0.004 mIU/l, group 2; 0.020 mIU/l, group 3; 0.038 mIU/l, $P = <0.001$) as was median β-hCG (group 1; 56 IU/l, group 2; 87 IU/l, group 3; 102 IU/l, $P = <0.001$), and this group was also more often positive for TPO- and/or Tg-Ab (group 1; 81.8%, group 2; 39.3%, group 3; 7.7%, $P = <0.001$).

Conclusions
This is the first study to measure TSI in a large cohort of early pregnant women, and a method- and pregnancy-specific cut-off for TSI was established. A high agreement between TSI and TRAb was seen among women with low TSH in early pregnancy, and women positive for TSI and TRAb had more severe hyperthyroidism and biochemical markers compatible with autoimmune thyroid disease rather than gestational hyperthyroidism.

DOI: 10.1530/endoabs.101.OP-08-02

## OP-08-03

**Detailed morphological phenotyping of maternal thyroid function and offspring brain development: a vertex-wise approach including assessment of gyrification**

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Background
Thyroid hormone is an important regulator of fetal brain development. Low and high maternal free thyroxine concentrations during pregnancy have been associated with less grey matter and cortex volume. However, it remains unknown whether certain areas of the brain are differently affected. We used state-of-the-art brain MRI analyses in the largest mother-offspring imaging cohort worldwide to further elucidate how maternal thyroid function during early pregnancy affects offspring brain morphology.
Aim
To study the association of maternal thyroid function with local offspring cortical development including gyrification indices using vertex-wise analysis without predefined anatomic boundaries.
Methods
We selected participants from a population-based prospective birth cohort with available measurements of maternal TSH or FT4 during the first half of pregnancy and offspring brain MRI scans at age 10 years ($n$ = 1,980). Multivariable linear regression was used to study the associations of gestational TSH and FT4 concentrations and (sub)clinical thyroid disease entities with surface-based cortical measures including cortical thickness, surface area, volume, gyrification and white/gray matter ratio using a vertex-wise approach.
Results
Lower TSH concentrations across the continuum were associated with smaller surface area in the inferior parietal region (β [se]: -0.015 [0.004] mm2 per 1 mU/l TSH). We found an inverted U-shaped association of FT4 with gyrification in the fusiform gyrus. Subclinical ($n$ = 28) and overt hyperthyroidism ($n$ = 20) were associated with smaller surface area in the rostral middle frontal and lateral occipital regions, respectively. Children born to hyperthyroid mothers also had less gyrification in the insular cortex, the pars opercularis of the inferior frontal gyrus and precentral region. Maternal thyroid function was not associated with cortical thickness or volume, or white/gray matter ratio.
Conclusions
Maternal thyroid function is associated with cortical gray matter morphology in specific brain regions. Our finding of less gyrification after gestational hyperthyroidism is in line with studies in hyperthyroid animals and D3 knockout mice. These findings enhance further understanding of previously identified global brain morphology associations. Further research is needed to replicate our findings and assess potential functional consequences related to developmental differences in specific anatomical areas.

DOI: 10.1530/endoabs.101.OP-08-03

## OP-08-04

**Fluid intelligence evaluation through raven's progressive matrices in adult patients with congenital hypothyroidism detected by neonatal screening**

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Background
Congenital hypothyroidism (CH) is the most frequent cause of preventable cognitive deficit. With newborn screening program, natural history of this disease has changed thanks to the precocious treatment with levothyroxine (LT4). In a previous study we evaluated psychosocial outcome and quality of life of 62 adults with primary CH diagnosed in the screening era, finding only small differences from controls in concentration ability and mood, while social and work adaptation, autonomy and educational attainment resulted comparable to their healthy peers. Regarding neuropsychological outcome, various studies have shown a possible persistence of subtle cognitive deficit in patients with CH during childhood, but only few data are available about long-term outcome in adult subjects with CH.
Objective
To evaluate neurocognitive performances of adult subjects with CH precociously treated with LT4 through a common non-verbal intelligence test.
Patients and methods
We performed a neurocognitive evaluation in a group of 30 young adults with primary CH by different etiologies (thyroid agenesis, ectopy, *in situ* thyroid gland) individuated through newborn screening, treated with LT4 within the first few weeks of life and regularly subjected to clinical checks and therapeutic adjustments at the same Centre. Results have been compared with a control group of 28 healthy subjects (with homogeneous distribution of age, sex and family socio-cultural background). The tool used for the evaluation was the Raven's Standard Progressive Matrices test (SPM-38), which is a well-validated *culture-fair* indicator of abstract reasoning and fluid intelligence.
Results
Data don't show significative differences in the test's scores between patients and controls; dividing patients by timing of LT4 initiation, performances at test still don't result different. Considering severity of CH at birth, patients with FT4 value at diagnosis less than 5 pmol/l obtained slightly lower scores than patients with FT4 higher at birth, but differences are not significative.
Conclusions
Neonatal screening results effective to obtain an adequate neuropsychological development in adult patients with CH early diagnosed and regularly monitored. Deficit in CH correctly treated with LT4 could be subtle and function-specific, which is why the evaluation will be extended to a larger group of subjects using specific neurophysiology tools for certain brain functions.

DOI: 10.1530/endoabs.101.OP-08-04

## OP-08-05

**Maternal thyroid function and biochemical markers of placental function in early pregnancy**

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Objective
A link between levels of maternal thyroid hormones in pregnancy and the biochemical markers of placental dysfunction, soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), has been brought forward. Sparse evidence is available on the dynamics of sFlt-1 and PlGF in early pregnancy and the association with maternal thyroid function in early pregnant women specifically.
Methods
A retrospective cohort study within the North Denmark Region Pregnancy Cohort, 2011-2015, that contained maternal blood samples ($n$ = 17,647) drawn in early pregnancy as part of prenatal screening for chromosomal anomalies. The samples were later used for assessment of thyroid-stimulating hormone (TSH) (ADVIA Centaur XPT, Siemens Healthineers). For the present study, a random sub-group of pregnant women ($n$ = 858) were selected for measurement of sFlt-1 and PlGF as well as β-human chorionic gonadotropin (β-hCG) (Kryptor Compact,

ThermoFisher Scientific). Regression analysis was used to evaluate the association between maternal TSH and β-hCG and pregnancy week-specific percentile levels of sFlt-1 and PlGF. Results were reported as geometric mean and adjusted beta coefficient (aβ) including potential confounders.
Results
Blood samples were drawn in median pregnancy week 10 (range 4-16). When evaluating the association between maternal TSH and categories of the placental biomarkers, higher percentile levels of sFlt-1 and PlGF associated with lower TSH in crude and adjusted analyses (Table). An opposite association between the placental biomarkers and β-hCG was found, with higher levels of β-hCG for increasing levels of sFlt-1 and PlGF (Table). Finally, high levels of β-hCG (> 75 percentile) associated with lower TSH (aβ 0.60 (95% CI: 0.48-0.75)).
Conclusions
In a large cohort of Danish pregnant women, higher levels of sFlt-1 and PlGF associated with lower levels of TSH. In contrast, higher levels of the placental biomarkers associated with higher levels of β-hCG. Considering the physiological link between TSH and β-hCG in early pregnancy, an intermediate role of β-hCG in the association between maternal thyroid function and biochemical markers of placental function may be proposed in this early window of pregnancy.

| | n | Mean TSH (mIU/L) | aβ | 95% CI | Mean | aβ β-hCG (IU/L) | 95% CI |
|---|---|---|---|---|---|---|---|
| sFlt-1 | | | | | | | |
| < 25 percentile | 235 | 1.18 | Ref. | | 35.8 | Ref. | |
| 25-75 percentile | 415 | 0.86 | 0.76 | 0.65-0.88 | 55.1 | 1.56 | 1.38-1.76 |
| > 75 percentile | 208 | 0.75 | 0.66 | 0.55-0.81 | 82.6 | 2.34 | 2.05-2.67 |
| PlGF | | | | | | | |
| < 25 percentile | 210 | 1.03 | Ref. | | 46.4 | Ref. | |
| 25-75 percentile | 407 | 0.95 | 0.97 | 0.83-1.12 | 54.9 | 1.19 | 1.05-1.35 |
| > 75 percentile | 241 | 0.75 | 0.78 | 0.64-0.96 | 59.9 | 1.27 | 1.10-1.47 |

DOI: 10.1530/endoabs.101.OP-08-05

## Oral Session 9: Basic Thyroid Cancer Research

### OP-09-01

**Epigenetic deregulation and dedifferentiation in thyroid cancer**

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Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. Despite most patients having an initial good prognosis, some patients progress and become resistant to standard radioiodine treatment. Importantly, effective markers or therapies are not yet available. Many of these patients present tumours with high levels of dedifferentiation, having lost some or most of their thyrocyte-specific features. As DTC patients present low levels of mutations, epigenetics has been considered as a field to be explored in this disease. Our group has previously reported an increased global DNA hypomethylation in distant metastatic and dedifferentiated thyroid cancer. However, the role of epigenetics in thyroid cancer dedifferentiation is poorly understood. Our aim is to study the epigenetic mechanisms underlying DTC dedifferentiation to identify new prognostic biomarkers as well as potential therapeutic targets. Here, we correlated DTC tumour differentiation to a previously reported set of epigenetics-associated genes, named Epifactors. Tumour differentiation was defined using the Thyroid Differentiation Score (TDS), established by TCGA. We correlated the expression of these Epifactors to TDS values of patient samples using different publicly available datasets. DNA methylation levels were also taken into account. Based on these analyses, we selected a group of 14 genes, named EpiGenes. Their expression has a clear link with TDS values, suggesting their potential role in DTC dedifferentiation. Moreover, these EpiGenes are also associated with other clinical prognostic markers, such as risk factor. Our findings are currently being validated *in vitro* in different cell lines. We observed that a change in expression of some of these EpiGenes resulted in a change in TDS gene expression. Further steps include validation in multiple cell lines and 3D cell line systems. In conclusion, we have identified candidate epigenetic factors that will help to better understand DTC dedifferentiation and may be future therapeutic targets for advanced thyroid carcinomas.

DOI: 10.1530/endoabs.101.OP-09-01

### OP-09-02

**TP53 mutations associate with poor response to lenvatinib treatment for advanced thyroid cancer**

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Background
Poorly differentiated (PDTCs), anaplastic (ATCs) thyroid cancers and few well differentiated thyroid cancers (WDTC) are particularly aggressive and refractory to all treatments, including tyrosine kinase inhibitors (TKIs). Since in other tumors, *TP53* mutations are related to a poorer response to TKIs treatment, we aimed to investigate the impact of *TP53* mutations on thyroid cancer response to Lenvatinib (LEN) treatment.
Methods
We investigated the molecular profile (including *TP53* mutations) of 30 tumor tissues (23 WDTCs and 7 PDTCs/ATCs) obtained at surgery from patients subsequently treated with LEN (initial median dose of $20 \pm 6.8$ mg/day) for a mean time of 31 months (range 6-84). Moreover, we evaluated by statistical analyses the association between *TP53* mutations, clinico-pathological features, and tumor response rate to LEN defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), according to revised Response Evaluation Criteria in Solid Tumors (RECIST) criteria guidelines version 1.1.
Results
Among the 30 tumor tissues, 8 (4 WDTCs and 4 PDTCs/ATCs) harbored *TP53* mutations within exons 5-8 encoding the DNA binding domain of the protein. Univariate analysis, according to LEN response, revealed *TP53* mutations as a significant predictor of poor response to this TKI. Indeed, all the 8 patients with *TP53* mutations developed PD during LEN ($P = 0.005$). Considering the best morphological response (BMR), 6 patients achieved a temporary SD, while the other 2 showed a PD. Kaplan–Meier curve demonstrated that patients harbouring *TP53* mutations has a shorter Overall Survival (OS) rate than wild type tumors ($P = 0.0007$). This difference remained significant also considering only patients affected with DTC ($P = 0.0453$) or with PDTC/ATC ($P = 0.049$). In addition, patients harboring *TP53* mutations showed a shorter progression-free survival (PFS) rate than those *TP53* wild type ($P = 0.0005$). This difference remained significant also considering only patients affected with DTC ($P = 0.026$) or with PDTC/ATC ($P = 0.049$). Similarly, considering PFS rate associated to BMR, patients harbouring *TP53* mutations showed a shorter PFS rate than the wild type ones ($P = 0.016$).
Conclusions
We demonstrated for the first time in advanced thyroid cancer that the presence of inactivating mutations in *TP53* is associated to worse OS and PFS rates during Lenvatinib treatment. Thus, the evaluation of the tumor molecular profile and particularly of *TP53* mutations is crucial for the selection of the best therapeutic option for patients with progressive thyroid cancer.

DOI: 10.1530/endoabs.101.OP-09-02

### OP-09-03

**Role of the oncogene UHRF1 in thyroid cancer differentiation, progression and response to lenvatinib**

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Objectives
The oncogene *UHRF1* (Ubiquitin-like with PHD and RING Finger domains 1) codifies for a nuclear protein which primarily acts as epigenetic regulator during the replication phase, but also as cycle cell regulator upon DNA damage. The overexpression of this oncogene has been documented in several human cancers, including thyroid cancers (TCs), and correlates with both tumour aggressiveness and response to treatment. Regarding TC, scanty data are available on limited series showing that *UHRF1* is overexpressed in tumours with respect to normal tissues and seems to associate with the degree of differentiation, while no data are available for benign thyroid tumours and non-invasive follicular thyroid neoplasms with papillary- like nuclear features (NIFTPs). Interestingly, in hepatocarcinoma cell lines *UHRF1* was found to be downregulated after Lenvatinib (LENV) treatment, a multi tyrosine kinase inhibitor also used in patients harbouring advanced radioiodine refractory TCs. Moreover, it is known that the expression of *UHRF1* is downregulated by functional p53. Since we demonstrated that *TP53* mutations are associated to the resistance of LENV in patients with advanced TC, we aimed to evaluate *UHRF1* expression levels in a larger series of malignant and benign tumours as well as in TC cell lines. Moreover, we explored the possible association of *UHRF1* mRNA levels with *TP53* mutational status and the response to LENV in both patients and in *vitro* models.
Methods
The expression analysis of *UHRF1* gene was done by qRT-PCR in 45 malignant and 12 benign TCs, 17 metastases, 26 normal thyroid tissues, as well as in 4 TC cell lines. Increasing doses of LENV were used to treat two TC cell lines, known to be TP53 mutated and resistant to LENV (B-CPAP and SW1736), and two TC cell lines *TP53* wild type and sensitive to LENV treatment (TPC-1 and IHH-4). The expression of *UHRF1* mRNA was evaluated after 72 hours treatment.
Results
A significant increase in *UHRF1* mRNA levels was observed with increasing tumour aggressiveness and progression in both TC tissues and cell lines. Moreover, *UHRF1* resulted to be over-expressed in TC tissues of patients harbouring *TP53* mutations or developing LENV resistance. *in vitro* models showed that the treatment with increasing dose of LENV induced a significant reduction of *UHRF1* levels only in TPC-1 cell line with functional p53.
Conclusions
Our study showed a significant association between *UHRF1* expression levels and TC aggressiveness and progression. *UHRF1* expression resulted to be also associated with the presence of *TP53* mutations and to LENV resistance. Overall, these data indicating UHRF1 as a possible new diagnostic and prognostic biomarker for TC. Future studies will investigate targets of UHRF1, that might be involved in the mechanism of resistance to LENV

DOI: 10.1530/endoabs.101.OP-09-03

## OP-09-04

**Tumour heterogeneity and evolution in advanced thyroid cancer through multiregion and longitudinal sampling**

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Background
Tumour heterogeneity and evolution present significant challenges in advanced thyroid cancers, contributing to treatment resistance and disease progression. NOMINATE (NCT05837260) is a multicentre, prospective biological sampling study which aims to investigate the genomic diversity of thyroid cancers and assess the utility of circulating tumour DNA (ctDNA) for delineating evolutionary forces driving treatment failure and resistance. We present our latest progress in trial recruitment and preliminary data of a pilot study of a patient with medullary thyroid cancer to illustrate our methodology of DNA analyses using state-of-the-art sequencing and computational methods.
Methods
NOMINATE (NCT05837260) is multicentre, prospective study aiming to collect clinical samples from 120 patients with advanced thyroid cancers (iodine-refractory, medullary and anaplastic) and is open for recruitment. Blood samples for ctDNA extraction are collected at regular intervals over a 2-year period, in addition to fresh or formalin-fixed tumour samples. For the pilot study, comprehensive whole-exome sequencing (WES) was performed on Illumina sequencing platforms following standardised protocols. ichorCNA was used to estimate tumour fraction in plasma cell-free DNA (cfDNA). State-of-the-art computational methods including Mutect2, VarScan2, CNVkit and TitanCNA were utilised for DNA variant analyses. Subclonal reconstruction was performed using Pyclone and ClonEvol to map the evolutionary histories and trajectories of these cancers.
Results
As of March 2024, we have recruited 46 patients on the NOMINATE clinical trial. We present a pilot study of a patient with sporadic, *RET* -mutated metastatic MTC and showed that low-coverage whole-genome sequencing (WGS) (~1x) as a screening method for tumour purity estimation in plasma cfDNA was possible. WES revealed shared and distinct mutations between primary tumour, lymph node metastasis and plasma ctDNA. Subclonal populations identified using Pyclone and ClonEvol showed unique clustering of mutations for phylogeny and clonal ordering.
Conclusions
Our findings demonstrate a robust and feasible approach in unravelling the molecular landscape of advanced thyroid cancers and interrogates the role of tumour heterogeneity in disease progression and treatment resistance. We aim to develop the value of using ctDNA as a non-invasive biomarker in capturing tumour dynamics and heterogeneity in informing personalised therapy.

Keywords
Advanced thyroid cancer, tumour heterogeneity, multiregion sampling, circulating tumour DNA, subclonal reconstruction, cancer evolution.
DOI: 10.1530/endoabs.101.OP-09-04

## OP-09-05

**Tracing the molecular route to progression in defective mirna biogenesis benign vs malignant thyroid lesions**

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Alterations in *DICER1* and *DGCR8* have been observed in benign thyroid manifestations, well-differentiated and recently reported in poorly-differentiated thyroid cancers (PDTC). The involvement of 2 miRNA biogenesis genes in benign and malignant thyroid tumors highlights the key role of miRNAs in the thyroid gland.
Objectives
To determine the deregulated miRNAs involved in benign and malignant thyroid tumors associated with miRNA biogenesis defects and pinpoint key effectors in tumor progression.

Methods
We genotyped hotspot mutations in 4 miRNA-processing genes in 66 pediatric and 385 adult thyroid lesions. Combining newly identified cases with previous in-house cases, whole exome sequencing (WES) ($n = 18$), miRNA profiling ($n = 38$) and/or methylome was performed in benign and malignant DICER1-/DGCR8-mutated cases. Shared miRNA profiles of DICER1- and DGCR8-mutated cases were interrogated and profiles unique to benign or malignant samples were determined. The spatial transcriptome of 1 DICER1 and 1 DGCR8 case with different histological components was profiled.
Results
We found *DICER1* mutations in 9 samples (1 adult, 8 pediatric). No alteration in other miRNA biogenesis genes was detected. WES of DICER1-/DGCR8-mutated samples denoted the classical mutually exclusive pattern with alterations in canonical thyroid cancer (TC) driver genes while demonstrating a putative mutational route to progression. Interrogation of miRNA expression profiles across DICER1-/DGCR8-mutated and control cases encompassing 5 histological subtypes revealed 36 differentially expressed (DE) miRNAs shared by DICER1-/DGCR8-mutated TCs and 2 DE miRNAs shared by benign thyroid lesions highlighting 34 miRNAs unique to the malignant status. Pathway analyses of the predicted miRNA targets of DICER1-/DGCR8-mutated TCs showed an association with known cancer signaling (MAPK, TGFβ) and cell cycle pathways, which were not observed in DICER1-/DGCR8-mutated benign lesions. Spatial transcriptomics analysis showed larger differences in the stroma of the mutated cases than in the thyroid follicular cells. Pathways associated with angiogenesis, dedifferentiation and Notch and Hedgehog signaling were upregulated in DICER1-PDTC stroma. DGCR8-FND and DGCR8-microPTC showed less remarkable differences between their stromal and epithelial components.
Conclusion
*DICER1* alterations were more prevalent in children and seen in a wide variety of histological subtypes, highlighting the importance of uncovering DICER1 syndrome patients. *DGCR8* mutations are rare in both pediatric and adult cohorts. Moreover, a novel mutational landscape of progression was observed in DGCR8 cases. DICER1-/DGCR8-mutated TCs showed an effect on known TC signaling (despite the lack of MAPK alterations in DICER1-mutated cases) and cell cycle pathways, DICER1-/DGCR8-mutated benign lesions did not. Spatial transcriptomics analysis showed larger differences in the stroma of the mutated cases than in the thyroid follicular cells.
DOI: 10.1530/endoabs.101.OP-09-05

## Oral Session 10: Thyroid Dysfunction-2

### OP-10-01

**Effect of smoking status on TSH receptor antibody (TRAB) levels following treatment for graves' disease**

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Background
Graves' disease is an autoimmune condition leading to hyperthyroidism and characteristically elevated TSH receptor antibody (TRAb). TRAb levels typically fall post-treatment with anti-thyroid drugs (ATDs) and are used in identifying risk of relapse. Tobacco smoking is a risk factor for reduced treatment efficacy of ATDs. We intended to evaluate the effect of smoking on changes in TRAb levels in patients treated for Graves' disease.
Methods
We analysed a database that prospectively collected information regarding patients treated for Graves' disease at Queen Elizabeth Hospital, Gateshead. Inclusion criteria was any patients treated for 9 months or longer with ATD. TRAb level data was taken at treatment initiation and 12 months (+/- 3 months). Patients without data at these two time-points were excluded ($n = 60$). Smoking status was recorded as current smoker (CS), ex-smoker (XS), or life-long non-smoker (NS). TRAb reduction from baseline was measured as a percentage change for each group, using multivariable linear regression analyses. Other independent variables included were age, sex, race and duration of treatment with ATDs.
Results
In 374 patients, mean baseline TRAb levels for the NS, XS and CS groups were 8.9, 8.0 and 9.5 U/l, respectively. Smoking status was an independent predictor of the percentage drop in TRAb levels at 12 months ($P = 0.03$). Current smokers had higher 12-month TRAb levels with lesser relative reduction. The number of cigarettes smoked daily demonstrated negative independent correlation with change in 12-month TRAb ($P = 0.03$).
Conclusions
There is a significant correlation between smoking status and TRAb at 12-months, both as a relative and absolute value, which probably explains the higher relapse risk seen in CS. The extent of tobacco consumption also appears relevant, highlighting that reducing the number of cigarettes smoked may be beneficial in lowering TRAb levels and potentially the risk of relapse after ATD cessation.
Keywords
TSH receptor antibody (TRAb), smoking, Graves' disease
DOI: 10.1530/endoabs.101.OP-10-01

### OP-10-02

**Towards personalized TSH reference ranges: a genetic and population-based approach in three independent cohorts**

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Background
Serum thyroid-stimulating hormone (TSH) measurement is the diagnostic cornerstone for primary thyroid dysfunction. There is high inter-individual, but limited intra-individual variation in TSH concentrations, largely due to genetic factors. The currently used wide population-based reference intervals may lead to inappropriate management decisions.
Methods
A polygenic score (PGS) including 59 genetic variants was used to calculate genetically-determined TSH reference ranges in a thyroid disease-free cohort ($n = 6,834$). Its effect on reclassification of diagnoses was investigated when compared to using population-based reference ranges. Next, results were validated in a second independent population-based thyroid disease-free cohort ($n = 3,800$). Potential clinical implications were assessed in a third independent population-based cohort including individuals without thyroid disease ($n = 26,321$) as well as individuals on levothyroxine (LT4) treatment ($n = 1,132$).
Results
PGS was a much stronger predictor of individual TSH concentrations than FT4 (total variance in TSH concentrations explained 9.2-11.1% vs. 2.4-2.7%, respectively) or any other non-genetic factor (total variance in TSH concentrations explained 0.2-1.8%). Genetically-determined TSH reference ranges differed significantly between PGS quartiles in all cohorts, while the differences in FT4 concentrations were absent or only minor. Up to 24.7-30.1% of individuals, previously classified as having subclinical hypo- and hyperthyroidism when using population-based TSH reference ranges, were reclassified as euthyroid when genetically-determined TSH reference ranges were applied. Individuals in the higher PGS quartiles had a higher probability of being prescribed LT4 treatment compared to individuals from the lower PGS quartiles (3.3% in Q1 vs. 5.2% in Q4, $P_{for\ trend} = 1.7 \times 10^{-8}$).
Conclusions
Individual genetic profiles have potential to personalize TSH reference ranges, with large effects on reclassification of diagnosis and LT4 prescriptions.
DOI: 10.1530/endoabs.101.OP-10-02

## OP-10-03

**Compensatory rise in TSH when blocking sympathetic activity in cold exposed hunters in east greenland**

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Background
Thyroid hormones interact with sympathetic stimulation for activating Brown Adipose Tissue (BAT) during cold exposure. Triiodothyronine (T3) upregulates the expression of Uncoupling Protein-1 (UCP1), a protein in BAT essential for heat production. Studies of human cold exposure have demonstrated both increased production and clearance of T3. Greenlandic hunters are characterized by mandatory chronic cold exposure, and cold adaptation is inevitable. Hence, they provide an exquisite model for evaluating metabolic effects of cold exposure.
Aim
We aimed to explore the dynamics of thyroid hormones when blocking sympathetic activity in Greenlandic hunters during winter to explore mechanisms of brown adipose tissue activation.
Methods
We conducted a 10-day study of Greenlandic hunters ($n = 7$) in East Greenland during February. The sympathetic system was blocked using a non-selective beta blocker for 7 consecutive days. A group of non-hunter Greenlanders ($n = 8$) from the same settlement were included for comparison. All participants were healthy men. Blood samples were drawn daily for measurement of TSH and thyroid hormone levels and thyroglobulin in serum (s-Tg).
Results
At baseline, TSH was higher (median 1.99 mIU/l vs. 1.76 mIU/l), T3 lower (median 3.27 pg/mL vs 3.45 pg/mL), and s-Tg higher (median 18.44 µg/l vs 12 µg/l) among hunters compared to controls. After blocking the sympathetic system, s-Tg decreased initially and recovered to pre-blocking level following a marked rise in TSH (median 3.09 mIU/l) among the cold exposed hunters.
Conclusion
The dynamics of thyroid hormones show different patterns in the hunter group than the control prior to intervention as well as after intervention. When blocking the sympathetic nervous system, TSH increases followed by recovery of s-Tg to the pre-blocking level. A possible explanation is that when blocking the activation of BAT via the sympathetic system, TSH increases to uphold the production of T3, needed for maintaining BAT activity and the obligatory heat production among cold exposed hunters in East Greenland during winter.

DOI: 10.1530/endoabs.101.OP-10-03

## OP-10-04

**The relation between circulating free thyroxine (FT4) and thyroid stimulating hormone (TSH) levels is very different in people taking levothyroxine vs those who are on no thyroid hormone replacement**

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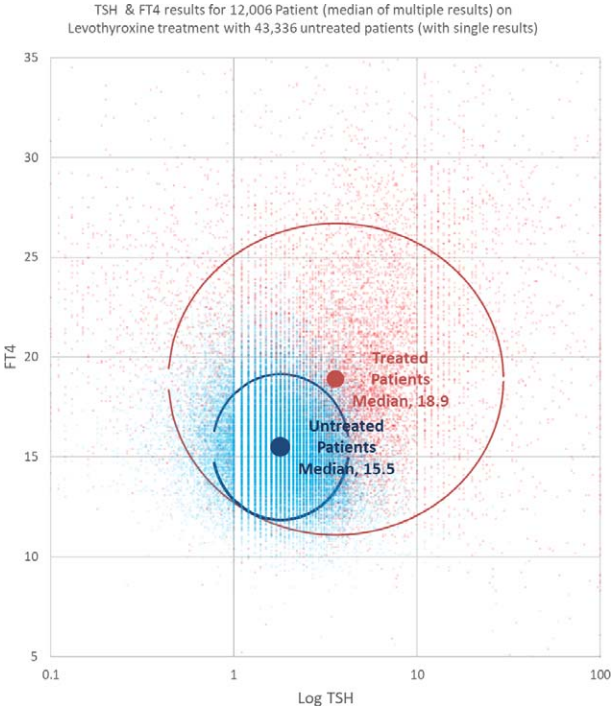
Introduction
There continues to be much discussion around optimization of thyroid hormone status in hypothyroid individuals. The ideal therapeutic goal in hypothyroidism would be to restore clinical and biochemical euthyroidism via physiologic thyroid hormone replacement. This concept may seem straightforward, but there are subtleties that have only recently been recognized. We here looked the way that FT4 and TSH related to each other in a large laboratory sample of people who underwent a check of thyroid function (TFT) split between those on levothyroxine replacement (monitoring test) and those who underwent a TFT check as a screening test for thyroid hormone imbalance (not on levothyroxine).
Methods
TFT test (FT4 and TSH) results were taken from the Salford Hospital (UK) laboratory system for 2009-2012. The request includes a tick box for 'on levothyroxine' (yes or no). Age and sex of patients was also available. To minimise comorbidity effects only samples taken in GP Practices were used and for untreated patients only those who had single tests results were used. For treated patients, the median value across all their results were used. Cluster analysis compared the log(TSH) and FT4 values between treated and untreated population to highlight the % of treated patients achieving levels similar to the untreated population. Analysis examined the impact of age and sex on this difference cluster boundaries calculated using 95% & 5% percentile value for both log TSH and linear FT4. This analysis was repeated for split by age (<60 & >=60) and sex male/female.
Results
Total data included 290,000 tests for 130,000 patients. However, the FT4/TSH results were used from 12,006 (F 9,231 / M 2,775 & (age <60 5,850 & age >= 60 6,567)) treated patients with 43,846 actual test results. These were compared to the single results for 43,394 untreated patients (F 24,386 / M19,008 & Age<60 32,537 / Age>=60 10,857). Cluster analysis showed overall for untreated patients' median values for TSH=1.8 mUnits/l and FT4=15.5 pmol/l, with 24% patients falling outside the 5%/95% limit, while for treated patients median TSH=3.6mUnits/l (+100% vs untreated) and FT4=18.9 pmol/l (+22%), with 22 % of treated patients falling outside the treated 5%/95% percentile boundary. When considered against the untreated boundary 75% of treated results fell outside; by sex females 78%, males 68%; by age <60 73%, >=60 74%.
Conclusion
The current treatment regimens being applied of either low or high dose levothyroxine are not delivering the expected laboratory TFT profiles, with significant numbers of treated patients being well outside the expected values - both TSH and FT4 being significantly higher. This effect seems to be more prevalent in women than men, which is more concerning given the higher number of women requiring treatment.




DOI: 10.1530/endoabs.101.OP-10-04

## OP-10-05

**Whole-brain computational anatomy in graves' disease: morphometric imprint of pathology and recovery**

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Objectives
In CogThy, a longitudinal study on Graves' disease, we previously showed that medial temporal lobe volumes (hippocampus and amygdala) are smaller in hyperthyroid patients than in matched thyroid-healthy participants. Longitudinally, we saw a volume increase in the patients in the sense of a recovery of the brain under treatment. In the present work, we conducted a corresponding analysis on the whole brain.
Methods
Automatic segmentations of T1-weighted images (baseline and 15 months after diagnosis) were carried out with MAPER software and the Hammers Atlas Database, augmented to 120 subcortical and cortical regions. We considered regional context class components (background, cerebrospinal fluid, grey matter (GM), white matter (WM), GM and WM summation (GMWM), total volume). Using a split-sample approach, we separated the exploration (hypothesis generation) from the validation. During the exploration, we identified clusters of regions using prior knowledge ("natural clusters") and a data-driven approach (affine propagation (AP)). For entities showing notable differences at baseline, we formulated hypotheses and tested them on the validation set, claiming significance for differences with $P < 0.05$ after accounting for multiple comparisons (Benjamini-Hochberg).
Results
At baseline at diagnosis in severe hyperthyroidism (FT4 > 50 pmol/l), several entities were significantly different between patients and controls: five individual regions, seven natural clusters, and one AP cluster (cf. Table). None of these entities differed between patients and controls at follow-up, suggesting a recovery effect.
Table 1 Adj: Benjamini-Hochberg adjusted. indiv: Individual region. NC: natural cluster. AP: data-driven cluster. Diff %: patient/control volume difference (positive if entity is larger in patients).

| Entity | Adj *P*-value | Type | Diff % |
|---|---|---|---|
| Gyrus parahippocampalis et ambiens left GMWM | 0.006 | indiv | -9.9 |
| Middle frontal gyrus left total | 0.016 | indiv | 5.5. |
| Inferior frontal gyrus right GM | 0.069 | indiv | 12.4. |
| Medial orbital gyrus left total | 0.021 | indiv | 10.3. |
| Subgenual frontal cortex right WM | 0.030 | indiv | 10.1. |
| Frontal lobe bilateral | 0.043 | NC | 3.7 |
| Frontal lobe left | 0.021 | NC | 6.5 |
| Top 3 frontal lobe WM left | 0.030 | NC | 5.6 |
| Temporal lobe left GMWM | 0.006 | NC | -11.3 |
| Medial temporal lobe bilateral GMWM | 0.006 | NC | -5.7 |
| All regions larger in patients on exploration | 0.006 | NC | 1.9 |
| All regions smaller in patients on exploration | 0.006 | NC | -6.3 |
| Medial orbital gyrus right (*) | 0.021 | AP | 9.0 |

Conclusion
Graves' disease produces a morphometric imprint in the patient's brain beyond the medial temporal lobe, namely in the frontal lobe. This suggests that imaging biomarkers derived via quantitative image analysis should be further explored fo

DOI: 10.1530/endoabs.101.OP-10-05

## Oral Session 11: Molecular Thyroidology

### OP-11-01

**Thyroid Hormone Receptor A1 is a novel regulator of P53 functions**

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Thyroid hormone receptor a1 (TRa1) mediates the genomic action of thyroid hormone (T3). The biology of TRa1 in growth, differentiation, and development is well studied, but how TRa1 could crosstalk with key regulators involved in cancer development is largely unknown. In the present study, we used an epithelial cell line (NCM460D, referred to as 460D hereafter), established from normal human colon mucosal epithelium as a model to explore the interaction of TRa1 with the tumor suppressor p53. It is known that mutations in p53 promote progression of colorectal cancer. Using viral transduction, we prepared 460D cells stably expressing wild-type p53 (460D-WTp53) or mutant p53R248G (460D-MTp53). We further exogenously and stably expressed TRa1 into 460D-WTp53 (460D-WTp53-TRa1) and 460D-MTp53 cells (460D-MTp53-TRa1). Analysis showed that 460D-MTp53 cells grew faster than 460D-WTp53 cells *in vitro*. However, TRa1 inhibited cell proliferation in both 460D-MTp53 and 460D-WTp53 cells. Consistent with the *in vitro* findings, 460D-MTp53 cells induced larger xenograft tumors than 460D-WTp53 cells. Remarkably, TRa1 suppressed xenograft tumor growth induced by 460D-MTp53 or 460D-WTp53 cells. Immunohistochemical analysis (IHC) showed that Ki-67 positively stained tumor cells were in the order of 460D-WTp53 > 460D-WTp53-TRa1; 460D-MTp53 > 460D-MTp53-TRa1, indicating that TRa1 suppressed p53-induced tumor cell growth. IHC analysis indicated that cleaved capase-3 positively stained tumor cells were in the order of 460D-WTp53-TRa1 > 460D-WTp53; 460D-MTp53-TRa1 > 460D-MTp53, indicating that TRa1 induced apoptosis. To understand how TRa1 suppressed 460D-WTp53 and 460D-MTp53 functions, we first ascertained whether TRa1 could physically interact with WTp53 or MTp53. Using co-immunoprecipitation assay, we found that TRa1 physically associated with WTp53 or MTp53. The cyclin-dependent kinase inhibitor 1(the $p21^{Cip1/Waf1}$ gene) is known to be a WTp53 direct target gene, with p53 binding cis-regulatory elements on the promoter of the *p21* gene. We found that the extent of the expression of the *p21* mRNA was 460D-WTp53 > 460D-WTp53-TRa1. However, in 460D-MTp53 cells, there were no apparent changes in the expression of the *p21* mRNA by TRa1. Consistent with mRNA expression, chromatin immunoprecipitation analysis of 460D-WTp53-TRa1 cells showed that binding of WTp53 to the *p21* promoter was reduced ~50% when p53 was associated with TRa1. Taken together, our findings indicate that TRa1 is a novel negative regulator of p53 functions via suppression of p53 transcription. Considering reports that somatic *TP53* mutations occur in 38-50% of human cancers, our studies raise the possibility that TRa1 could be a potential molecular target in human cancers.

DOI: 10.1530/endoabs.101.OP-11-01

### OP-11-02

**KLHL14 and its anti-sense lncrna are involved in thyroid cells differentiation**

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Kelch-like protein 14 (KLHL14) is a member of the Kelch protein family acting as a subunit of E3-ubiquitin ligase. KLHL14 and its antisense lncRNA, KLHL14-AS, are among the most enriched transcripts in the developing mouse thyroid. Recently, we showed that KLHL14-AS is a tumor suppressor in thyroid carcinomas (TC) involved in the maintenance of differentiation and proliferation rate of thyroid follicular cells. KLHL14 is a tumor suppressor in Diffuse Large B Cell Lymphoma, its role in TC is unknown. Herein we investigate the implication of KLHL14 in thyroid cells differentiation also exploiting mice thyroid organoids. qPCR analysis highlighted a positive correlation between the two genes in many human TC cell lines of different histological subtypes, with their gradual downregulation being correlated to cancer progression, thus to cells differentiation. Moreover, the rescue of KLHL14 by transfection in anaplastic TC cells, in which it is normally absent, enhances the transcription of many specific markers, such as Thyroglobulin, NKX2-1 and FOXE1. Finally, RNA expression analyses on mice-derived thyroid organoids revealed that KLHL14 levels increase in several conditions which promote cells differentiation, i.e. media-induced differentiation or photon irradiation. Our findings reveal that KLHL14, as previously demonstrated for its antisense, seems to be involved in thyroid cells differentiation. Incoming studies with mice-derived thyroid organoids model will clarify the importance of KLHL14 in this process and also in TC differential diagnosis or drug-response prediction.

DOI: 10.1530/endoabs.101.OP-11-02

### OP-11-03

**Molecular mechanisms of triac in the treatment of resistance to thyroid hormone beta (RTHβ)**

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Background
Resistance to thyroid hormone (TH) beta (RTHβ), caused by mutations in the *THRB* gene, is characterized by elevated serum (F)T4 accompanied by non-suppressed TSH concentrations. Disease features arise from variable resistance to TH action in tissues expressing Thyroid Hormone Receptor (TR) β and from thyrotoxic effects in tissues expressing TRα1, most notably the heart. A recent clinical study showed a 3-times higher risk of cardiovascular morbidity and mortality for RTHβ patients, indicating the necessity of effective treatment options. For some symptomatic patients, the T3-analogue TRIAC has been employed successfully to suppress TSH, thereby lower circulating TH concentrations. However, the exact mechanism by which TRIAC works in RTHβ, is as yet unclear. Here, we linked biochemical data from patients with molecular studies to investigate whether TRIAC exerts its effects through activation of mutant TRβ or by stimulating residual wild-type TRβ.
Methods
We collected biochemical data from 18 RTHβ patients treated with TRIAC in 3 centres. Receptor function for TRβ mutants, including 16 missense mutations and two indel mutations, was studied in the TRβ2 pituitary isoform background. Transcriptional activity was measured using two TRE-luciferase reporters for respectively a positively and negatively T3-regulated gene DR+4-TRE, TSHα-TRE).
Results
TRIAC substantially reduced TSH and concomitantly FT4 concentrations in all patients. In contrast, our *in vitro* studies showed that the indel mutants ΔG432- and R438fsx445-TRβ2 mediated no transcriptional responses on either TRE. All missense TRβ2 mutants displayed impaired T3-dependent receptor activity with similar EC50 and IC50 values for T3 and TRIAC, except for R316H-TRβ2 which showed a 5-fold lower EC50/IC50 value for TRIAC compared to T3.
Conclusion
TRIAC has beneficial effects *in vivo*, even though most TRβ2 mutants are insensitive to TRIAC or equally sensitive compared to T3 *in vitro*. These results suggest that the main mechanism of TRIAC in lowering TSH in RTHβ patients is increased activation of the remaining wild-type receptor rather than engagement of the mutant receptor. However, some mutants, as exemplified by R316H-TRβ2 in our panel, may have preference for TRIAC and hence patients carrying these mutations may respond particularly well to TRIAC therapy. Our studies may provide insights into mechanisms of action of TRIAC in RTHβ and may shape future studies developing therapies for RTH syndromes.

DOI: 10.1530/endoabs.101.OP-11-03

## OP-11-04

**Systematic screening of natural compounds: impacts on thyroid transcriptional activity and NRF1/NRF2 activation**

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Background and objectives
Recent studies have identified pleiotropic roles for the Nrf2 antioxidant response in the physiology of the thyroid gland and in the pathophysiology of various thyroid diseases. Various natural compounds have antioxidant properties and/or thyroidal effects, but it is not well known whether and how the two are related. The aim of the present study was to characterize in a systematic manner the thyroidal and antioxidant effects of natural compounds.
Methods
We performed a low-throughput manual chemical screen of >400 natural compounds in thyroid follicular cell lines stably transfected with reporter constructs. We used the rat PCCL3 cell line in its wild-type form as well as a PCCL3 Nrf2-knockout clone generated via CRISPR/Cas9 mutagenesis. The following read-outs were assessed: Nrf2 transcriptional activity (ARE-luciferase); Nrf1 protein stabilization (Nrf1-delta-luciferase); cell viability (CellTiter-Glo); reporter gene expression of the thyroid hormone precursor thyroglobulin (TG-luciferase); reporter gene expression of the sodium-iodide symporter (NIS-luciferase); and iodine uptake by the cells. For compounds showing activity in the respective assays, the mRNA and protein levels of NIS, TG, and the antioxidant gene Nqo1 were assayed by qRT-PCR and Western blot, respectively.
Results
Among other findings, we observed that certain compounds paradoxically induced higher transcriptional activation of the ARE in Nrf2-knockout cells than in wild-type cells. Further studies showed that these compounds were potent activators of Nrf1, which is highly expressed in the thyroid *in vivo*. As a further example, the flavonoid compound bavachin was found to increase iodine uptake by the cells in an Nrf2-independent manner. Importantly, bavachin was also able to reverse the decrease in iodine uptake that is induced by exposure to lithium, a drug used in the treatment of bipolar disorder.
Conclusions
In conclusion, screening of natural compounds in thyroid cell lines can yield relevant hits with potential therapeutic relevance in thyroid diseases.

DOI: 10.1530/endoabs.101.OP-11-04

## OP-11-05

**Perinatal exposure to tbbpa interferes with the establishment of the thyroid axis at young age and the ability to cope with metabolic challenges in adulthood**

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Obesity incidence is continuously increasing worldwide. It does not solely result from excess calorie intake and sedentary lifestyle. Environmental endocrine disrupting chemicals (EDCs), could also be involved, deregulating fat storage and energy balance. Thyroid hormones (THs) play major role for maintaining energy balance. They are well known to control all aspects of metabolism, acting both centrally and in peripheral metabolic organs to control lipid and carbohydrate metabolism, as well as metabolic-cellular mechanisms such as mitochondrial activity and thermogenesis. The hypothalamus-pituitary-thyroid gland (HPT) axis, which controls both metabolism and TH homeostasis, is set up during development. Thus, any perinatal perturbation of this axis could have major metabolic consequences at the adult age. EDCs, such as TBBPA (a flame-retardant known to affect TH signalling) are detected in human amniotic fluid and milk, it hence poses a threat to early development of the hormonal systems. In a previous study, we have shown that exposure to TBBPA during gestation causes changes in HPT axis regulation shortly after birth, but the consequences of these perinatal changes on adult homeostasis were not investigated. Here, we studied if perinatal exposure to TBBPA interferes with the ability of two mouse strains with different thyroid and metabolic capacities, the C57BL/6J and the WSB/EiJ mice, to cope with high fat-high sucrose diet (HFHS, mimics Western diet) at the adult age. We compared the metabolic responses of these two strains to the chemical exposure and diet. Pregnant dams received 10 mg/kg/d TBBPA or vehicle for 4 weeks (last week of gestation through lactation). The progeny followed a HFHS diet from 2 to 6 months of age. We compared four groups for each strain: vehicle+control diet, vehicle+HFHS diet, TBBPA+control diet and TBBPA+HFHS diet. We have shown that TBBPA exposure transiently lowers the circulating thyroxine levels at young age but these levels were recovered at adult age. In C57BL/6J strain, perinatal TBBPA exposure combined with HFHS at adult age leads to more pronounced weight gain, perturbed glucose homeostasis and changes in adipose tissues (histological aspect and mitochondrial respiration assessed by Seahorse mitostress test), while WSB/EiJ mice do not experience these obesogenic effects of TBBPA. Our results reveal the obesogenic effect of a perinatal TBBPA exposure in a genetic background dependent manner, providing a proof of principle that perinatal period is very sensitive to environmentally relevant EDC exposure, and that interfering with the setup of thyroid axis during perinatal period could have dramatic consequences on health in adulthood.

DOI: 10.1530/endoabs.101.OP-11-05

## OP-11-06

**Unraveling the genetic landscape of hypothyroidism: insights from a multi-ancestry GWAS meta-analysis**

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Autoimmune hypothyroidism, also known as Hashimoto's thyroiditis (HT), is a common autoimmune thyroid disorder with a prevalence of 3-5% in the United States and Europe. Despite its high prevalence and high heritability (~70%), very little is known about the genetic basis of autoimmune hypothyroidism. To improve our understanding of the genetic signatures associated with HT development, we conducted a genome-wide association studies (GWAS) and follow-up analyses using ten cohorts encompassing multiple ethnicities. The GWAS and subsequent meta-analysis included 43,113 cases and 1,196,957 controls. Cases were defined as individuals with an ICD9/10 code for autoimmune thyroiditis or unspecified hypothyroidism. Individuals free of thyroid disease were included as controls. The association analyses were adjusted for age, sex, population structure, and relatedness. Secondary analyses included colocalization with mRNA levels in tissues of the hypothalamus-pituitary-thyroid axis using the GTEx and DICE datasets, pathway and functional enrichment analyses including single-cell data, pheWAS, genetic correlations, and two-sample Mendelian randomization to assess causal effects of HT. In the ancestry-combined HT GWAS, we identified 155 significant ($P < 5e-8$) independent genetic associations, of which 58 variants in 28 loci represent novel associations. Six loci were specific for European ancestry individuals. We identified 149 colocalizations (posterior probability $> 0.85$) in protein coding genes from whole blood, thyroid, pituitary, and hypothalamus tissue, and 161 colocalizations in the immune cells, predominantly in different types of T-cells. These colocalizations encompassed several genes integral to the thyroid hormone production and regulation like *TG* and *PDE8B*, and immune regulatory genes including *VAV3* and *IRF5*. Pathway analyses revealed an enrichment of HT associated genes involved in the immune system, encompassing besides immune cells also the spleen, and highlighting the importance of T-cells and natural killer cells in the HT process. Using single-cell sequencing data, we found a significant contribution of natural killer T-cells within the thyroid. PheWAS and genetic correlation results revealed pleiotropy with other autoimmune diseases, like rheumatoid arthritis, Sjogren syndrome, celiac disease, and thyroid related traits including thyroid hormone levels and Graves' disease. Prevalent HT indicated causal effects on increased risk of myocardial infarction, reduced waist circumference, increased levels of TSH and reduced T3. Using a well-defined case definition, our analyses identified novel loci associated with HT and highlight potential shared mechanisms underlying HT with other autoimmune diseases and the variability in thyroid hormone measurements. These results improve our understanding of HT and provide insights into the genetic basis of the disease across ancestries.

DOI: 10.1530/endoabs.101.OP-11-06

## OP-11-07

### Hepatocyte-specific DIO3 knockout influences energy metabolism in female mice

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Objective
Energy homeostasis is maintained through a complex interplay of processes, like energy substrate shuttling, breakdown, storage, and distribution. Thyroid hormones (THs) are key modulators of energy metabolism in the liver. In adult mouse liver, local hepatic TH availability is mediated via deiodinases, Dio1 and Dio3. During development, Dio3 is particularly important to provide protection from high concentration of maternal T3 and diminished in adulthood. However, local re-expression of Dio3 is evident upon cancer development, tissue damage and fasting.
Method
To assess the impact of modulating local TH availability on liver energy homeostasis, we used a mouse model with hepatocyte-specific genetic deletion of Dio3 (Alb-Cre; Dio3fl/fl). Evaluation of energy metabolism was carried out via metabolic phenotyping and indirect calorimetry, as well as via analysis of hepatic energy storage, such as hepatic triglyceride and glycogen content.
Result
In the first characterization, three-month-old male and female Alb-Cre; Dio3fl/fl mice fed with normal chow showed regular growth and organ size, circulating TH concentrations (T4, T3, rT3) and hepatic expression of T3-regulated genes. However, normal chow fed female Alb-Cre; Dio3fl/fl mice displayed elevated hepatic triglyceride and glycogen content. On the one hand, fed with a western diet for 12 weeks, female Alb-Cre; Dio3fl/fl mice tended to use more lipid as energy source based on metabolic characterization (e.g., body composition, RER, fatty acid oxidation), accompanied by a lower food and water intake. However, these mice showed similar weight gain as their controls, indicating an altered energy metabolism. On the other hand, during 24 hours fasting, female Alb-Cre; Dio3fl/fl exhibited impaired energy expenditure reduction and therefore a higher loss of lean mass, suggesting dysregulated energy metabolism. However, there was no difference in any of these parameters between male Alb -Cre; Dio3fl/fl mice and their controls.
Conclusion
Based on our data of 12 w dietary intervention and 24 h fasting with TH-related metabolic analysis, hepatic Dio3 plays a role in adaptation of the energy metabolism in a sex-dependent manner.

DOI: 10.1530/endoabs.101.OP-11-07

# Oral Session 12: Clinical Thyroid Cancer Research

## OP-12-01

### Predictive factors of persistent disease in a large cohort of pediatric patients with differentiated thyroid carcinoma

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Objectives
Differentiated thyroid carcinoma (DTC) in pediatric patients has peculiar clinical, pathological, and molecular characteristics, making its management different from the adult patients. Our study aimed to evaluate the outcome and predictive factors for persistent disease in a large cohort of pediatric patients.

Methods
We performed a multicentric Italian study, enrolling patients aged ≤18 years old, diagnosed with a DTC, since January 2000, and with available outcome information. Persistent disease included both biochemical and structural persistence. Biochemical incomplete response (BIR) was considered if serum thyroglobulin was detectable and/or thyroglobulin antibodies were increasing, with negative imaging, and structural incomplete response (SIR) was considered in case of identified locoregional or distant metastasis.
Results
We enrolled 538 patients; 75% were female, with a median age (interquartile range, IQR) of 15 (13-17) years. Papillary thyroid cancer was diagnosed in 93.5% of patients and more than 50% had lymph node metastases at diagnosis. Vascular invasion and gross extrathyroidal extension were reported in 40% and 17% of patients, respectively. T4 tumors were the 5% of the entire cohort. Radioactive iodine treatment (RAIT) was administered in the large majority of patients (92.5%), with a median activity of 50 mCi (IQR 30-100 mCi). Around one quarter of patients received more than one RAIT cycle, with a total median activity of 88 mCi (30-151.5 mCi). At the whole-body scan (WBS) obtained after the first RAIT, 25% of patients had a lymph nodal uptake and 10% an uptake in at least one distant metastasis. After a median follow-up of 85 months (42-126 months), 414 patients (77%) had an excellent response, 124 patients (23%) had a persistent disease: 68 patients (12.6%) a BIR and 56 patients (10.4%) a SIR. Persistent disease was associated to a higher need of lateral neck compartment lymphadenectomy, papillary histotype (compared to follicular), multifocality, gross extrathyroidal extension, vascular invasion, T4 and N1 according to the 8th edition, the need of RAIT, the finding of lymph node and distant metastases at WBS after RAIT. After multivariate analysis, the variables significantly associated to persistent disease were: gross extrathyroidal extension (OR 2.81, 95% CI 1.49-5.32, $P = 0.0015$) and the finding of a lymph node uptake at WBS after RAIT (OR 3.31, 95% CI 1.77, 6.19, $P = 0.0002$).
Conclusions
We report data on the largest Italian series of pediatric DTCs. Tumor outcome is generally favorable, despite the high frequency of advanced stage at diagnosis. Persistent disease is more frequent in case of gross extrathyroidal extension and positive lymph node uptake after the first RAIT.

DOI: 10.1530/endoabs.101.OP-12-01

## OP-12-02

**Insights from active surveillance: patterns of papillary thyroid carcinoma growth and conversion surgery outcomes**

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Objectives
Studies on active surveillance (AS) for low-risk papillary thyroid carcinoma (PTC) have shown that tumors typically enlarge to some degree during youth but stabilize thereafter. However, concerns still exist regarding cases exhibiting rapid progression during observation. The present study reviewed AS outcomes since the 1990s and investigated tumor growth patterns alongside delayed conversion surgery results.
Methods
Patients with low-risk PTC (all T1a, occasional T1b, N0M0) autonomously selected their preferred management option (AS or immediate surgery). Tumor enlargement was defined as a ≥3 mm increase in maximal diameter from the initiation. Changes in tumor size were categorized into five groups: A (stable), B (early increase, ≤5 years of follow-up), C (late increase, >5 years of follow-up), D (rapid increase after stability, ≥5 mm increase per year), and E (decrease). Conversion surgery was generally performed when the tumor diameter reached 13 mm, concerns about extrathyroidal extension (ETE) arose, lymph node metastasis (LNM) appeared, or patient preference changed.
Results
AS involved 705 patients with a mean age at presentation of 53.4 ± 12.8 years and a median follow-up duration of 8 years (range, 1-29). Group distribution was as follows: 561 patients in group A (79.6%), 71 in group B (10.0%), 32 in group C (4.5%), 4 in group D (0.6%) and 37 in group E (5.2%). Conversion surgery rates were 4.8% ($n = 27$), 36.6% ($n = 26$), 15.6% ($n = 5$), 100% ($n = 4$), and 2.7% ($n = 1$) for each group, respectively. Notably, one case in group B was poorly differentiated thyroid carcinoma, and one in group D exhibited PTC with nodular fasciitis-like stroma. The remainder were conventional ($n = 59$) or follicular-variant ($n = 2$) PTC. Although six cases had minimal ETE and 12 had LNM, no recurrence has been observed in those who underwent conversion surgery thus far. Thirty-three patients (46.5%) in group B and 14 (43.8%) in group C who continued AS subsequently showed halted growth. Cases with cystic components displayed significantly greater variability in tumor size compared to those without ($P = 0.039$).
Conclusions
Long-term AS data indicate that most tumor enlargement occurs within 5 years, with over 40% experiencing growth cessation during observation. Rapid enlargements are rare. Moreover, identifying high-risk cases is exceedingly uncommon. Tumors with cystic changes exhibit significant variability in tumor diameter. AS can be considered a safe management approach for low-risk PTC.

DOI: 10.1530/endoabs.101.OP-12-02

## OP-12-03

**Patients with medullary thyroid carcinoma and long term treatment with vandetanib: a study from the endocan –tuthyref network**

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Introduction
Vandetanib was the first tyrosine kinase inhibitor approved for the first line systemic treatment of progressive metastatic or locally advanced medullary thyroid carcinomas (MTC). Previous studies reported median duration of treatment (DOT) around 20 months with a subset of patients presenting long-term responses. Little is known on the impact of RET mutation status on the response duration.
Objectives
To evaluate the proportion and compare characteristics of vandetanib long term treated (LgTT) patients, vs short term treated patient (ShTT) in the MTC cohort of the French ENDOCAN-TUTHYREF network.
Method
Multicenter retrospective study on MTC patients with first line vandetanib treatment identified in the ENDOCAN-TUTHYREF database. Patients with less than 3 months treatment were considered non-evaluable and excluded from the analysis ($n = 28$). LgTT were defined as patients receiving Vandetanib more than 24 months Their characteristics were compared to that of patients treated less than 24 months (ShTT) using non parametric tests. Factors associated with overall survival (OS) were evaluated using log-rank test.
Results
From126 patients identified in the database, diagnosed between 1971 and 2022, who received vandetanib as first line systemic treatment (median follow-up 38 months (IQR 18-81)), 60% (71/118 evaluable) had RET mutation, 67%(85/126) were progressive at treatment initiation and 42% (53/126) were LgTT. Their median DOT was 49 months compared to 11 months in the ShTT group. Adverse events (AE) led to treatment discontinuation in 18/126 patients while 125 AE in 61 patients led to a dose decrease. Reasons for discontinuation were not different between the two groups. An objective response was observed in 38% of LgTT and 14% of ShTT ($P$-value = 0.013). Lower ECOG ($P$-value = 0.04), longer delay between diagnosis and treatment ($P$-value = 0.02) were associated with LgTT; metachronous distant metastasis ($P$-value = 0.05) and younger age at treatment ($P$-value = 0.06) tended to be associated with LgTT, while RET mutation status ($P$-value = 0.4, NA = 8), sex, progressive disease at initiation, vandetanib dose

and localization of metastasis were not associated with LgTT. OS since treatment initiation was longer in LgTT than in ShTT (90.7 (71.5-176.4) vs 26 (18.7-42.7) months in ShTT, $P$-value $= 4.10^{-7}$) while OS from treatment discontinuation was comparable between the 2 groups (17.7 (10.4-38.6) vs 12.9 months (8.85 -27), $P$-value $= 0.7$).

Conclusion

Among MTC patients treated with first line vandetanib, long-term disease control was observed in 42% regardless RET mutation status, and associated with metachronous metastatic disease and longer delay between diagnosis and treatment.

DOI: 10.1530/endoabs.101.OP-12-03

## OP-12-04

**Pronosthyc: prognostic factors in radioiodine refractory differentiated thyroid cancer with distant metastases, a multicentric study from a french network of referral centers**

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Background

Radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients with distant metastases show poor survival rates. However, patients' outcome can be very heterogeneous, with cases spanning from microscopic slowly growing metastases to symptomatic, rapidly progressive disease. The aim of this study was to assess the overall survival (OS) of RAI-R DTC patients with distant metastases and to identify the prognostic factors associated with OS.

Patients and methods

A retrospective analysis of consecutive cases of distant metastatic RAI-R DTC, diagnosed between 1990 and 2022 in 10 referral centers in France, was performed. Survival was estimated using the Kaplan-Meier method and the associated prognostic factors were assessed by Cox's model.

Results

The study cohort included 899 patients: 52.1% females, with a median age of 65 years (range:20-90) at RAI-R DTC diagnosis. The median follow-up was 4.8 years (range:0.1-40.1) and almost all patients (95.9%) underwent primary tumour resection. Thyroid tumors were papillary in 55.6%, follicular in 12.2%, oncocytic in 10.6% and poorly differentiated in 21.6% of the patients. Metastases were synchronous to primary diagnosis in 325 (39.4%), macroscopic ($>1$ cm) in 425 (48.2%) and multiple organs were involved in 83.4% of the cases. The most represented distant metastatic sites were the lung (84.3%), mediastinal lymph nodes (48.1%) and bone (46.8%). In a subgroup of 332 patients (37%) driver mutation status was assessed: 63% BRAFV600E mutation, 29.5% RAS mutation (NRAS 21%, HRAS 5%, KRAS 3.5%) and 6% gene fusions (involving RET (3%), NTRK (2%) and ALK (1%). More than half of the patients (58%) were treated with systemic therapies at some point during the follow-up. After the diagnosis of RAI-R DTC, median OS was 9.5 years the 5- and 10-year OS rates were 74.8% and 48.1%, respectively. In multivariate analysis, some factors were associated with a poorest survival: age $\geq 55$ years (Hazard-ratio (HR) $= 2.54$ 95%CI 1.84-3.57), multiple metastatic sites (H$r$ $= 2.80$ 95%CI 1.80-4.64), macroscopic metastatic volume (H$r$ $= 1.98$ 95%CI 1.54-2.55), presence of $^{18}$FDG-PET uptake (H$r$ $= 2.08$ 95%CI 1.30-3.52), whereas primary tumor resection (H$r$ $= 0.50$ 95%CI 0.31-0.86), differentiated tumor type (H$r$ $= 0.53$ 95%CI 0.41-0.68) and metachronous metastatic presentation (H$r$ $= 0.64$ 95%CI 0.50-0.82) were associated with a longer OS.

Conclusions

The independent clinical, histological and radiological prognostic factors identified can stratify the OS of RAI-R DTC patients and support clinical decisions in this challenging context.

DOI: 10.1530/endoabs.101.OP-12-04

## OP-12-05

**Real world outcomes of patients with radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) treated in 1l with lenvatinib 24 mg: an international multicenter real-world study in europe and canada**

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Objectives

Lenvatinib was approved for the treatment of patients with radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) in Europe in 2015 and Canada in 2016. This study investigated real-world clinical outcomes in patients with RAI-R DTC initiated with 24 mg lenvatinib once daily as first-line monotherapy in Europe and Canada.

Methods

A retrospective patient chart review was conducted. The study cohort comprised RAI-R DTC patients initiated with lenvatinib monotherapy as first line treatment between May 28, 2015, and January 31, 2022 (France, Germany, Italy, Spain, United Kingdom), or August 9, 2016, and January 31, 2022 (Canada). Data were extracted by prescribing physicians from individual patients' electronic health records and captured via an electronic case report form. All patient data were de-identified prior to analyses. Clinical outcomes assessed included provider-reported best overall response, progression-free survival (PFS), and overall survival (OS). Time to event endpoints were assessed using Kaplan-Meier methods.

Results

203 patients with RAI-R DTC were included; 54.2% of patients were male and 95.5% of patients were white. At lenvatinib initiation, median [IQR] patient age was 59 [50 – 66] years; 54.7% of patients had stage III or IV disease, with the proportion of patients with lung / lymph node / bone metastases in 54.2%, 47.8% and 42.4%, respectively. Over the available follow-up period (median [Range] 18.0 [0.1 – 48.1] months), 55 (27.1%) patients discontinued first line lenvatinib treatment, the majority ($n = 34$, 61.8%) due to disease progression, and 25 (12.3%) patients reduced their dosage, predominantly due to physician reported undesirable tolerability ($n = 19$, 76.0%) or impact on quality of life ($n = 6$, 24.0%). Second line treatment was initiated in 24 (11.8%) patients, the majority ($n = 18$, 75.0%) of whom received cabozantinib. Provider-reported best overall response with lenvatinib was reported to be complete ($n = 47$, 23.2%) or partial ($n = 115$, 56.7%) response in 79.8% of patients. Median [IQR] time to best response was 7.6 months [4.8 – 13.3]. Median PFS on first line lenvatinib was 41.7 months (95% CI: 26.5-NR). Median OS in patients treated with lenvatinib was not reached. Estimated OS rates were 96.1% (95% CI: 92.3-98.0) at 12 months and 85.6% (95% CI: 79.3-90.1) at 24 months. Median [IQR] duration of lenvatinib was 17.9 months [12.7 - 21.8].

Conclusions

The robust sample size of our study underscores the clinical effectiveness of first line lenvatinib among patients with RAI-R DTC, affirming its relevance in real world clinical settings across Europe and Canada, whilst also supporting the findings of the SELECT study.

DOI: 10.1530/endoabs.101.OP-12-05

## OP-12-06

**Insight of prospective nora (no radioiodine ablation) study in patients with differentiated thyroid carcinoma (DTC)**

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Objectives
Radioiodine therapy with ablative purposes is less and less used in low (LR) and intermediate (IR) risk DTC patients. The aim of this prospective ongoing study is to evaluate the clinical trend over time of patients with DTC who do not receive treatment with radioiodine.
Methods
Patients with high or intermediate-high risk in whom radioiodine treatment was performed after surgery were excluded. Data of 425 consecutive patients with DTC who joined our department for the first post-operative assessment (September 2016-December 2019), were evaluated.
Results
Most patients (70.6%) were females; the median age at diagnosis was 50 years. Total thyroidectomy was performed in 84.1% while lobectomy in 15.9%. Median tumor dimension was 1.4 cm. Histology revealed a prevalence of CV-PTC ($n$ = 200,47.1%) and FV-PTC ($n$ = 135,31.8%); aggressive variants of PTC were 11.8% ($n$ = 50), while only 5.4% ($n$ = 23) were FTC, 3.8% ($n$ = 16) NIFT-P and 0.2% ($n$ = 1) oncocytic tumor. In 41.9% of cases tumor was multifocal and in 12.7% mETE was detected. Lymph nodes metastases were present in 7.5% of cases. According to ATA 2015 guidelines, 316 (74.4%) patients were LR and 109 (25.6%) IR. After excluding patients treated with lobectomy and those with NIFT-P, 345/425 (81.2%) were evaluated at the first post-operative evaluation [median 4 months]. Of these, 253/345 (73.3%) showed not interfering TgAb (TgAb-neg), and median Tg value was 0.18 mg/l; conversely, 90 (26.1%) patients had interfering TgAb (TgAb-pos) with a median value of 23.5 IU/ml. Median TSH value was 0.54 mUI/l. Neck US was negative for persistent disease in all cases. Following this evaluation, 32 (9.3%) patients performed radioiodine treatment for histologic features of greater aggressiveness. After a median of 49 months, 313 patients were on follow-up without any additional treatment. Of these, 273 (87.2%) were TgAb-neg with a median Tg value of 0.15 mg/l and 40 (12.8%) were still TgAb-pos with a median TgAb value of 20 IU/ml. Median TSH value was 0.98 mUI/l. In all cases neck US persisted negative.
Conclusions
In LR and IR DTC patients, post-operative evaluation is able to discriminate patients requiring radioiodine treatment ($<10\%$). In our series, all patients who were not immediately treated after the first post-operative evaluation did not experience disease recurrence after a median of 4 years of follow-up. Therefore, when properly selected, not only LR but also some IR DTC can successfully and safely avoid the $^{131}$I treatment.

DOI: 10.1530/endoabs.101.OP-12-06

## OP-12-07

**Randomized clinical trial of prophylactic central neck dissection in 2100 papillary thyroid carcinoma patients with clinically negative central neck metastasis: an interim analysis of a single institution**

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Background
Prophylactic central neck dissection (pCND) in patients with no clinical nodal disease (cN0) is one of the major concern and ongoing controversy in thyroid surgery. However, there are no clear evidence because prospective randomized clinical tirals are still not enough to make definite recommendations. The purpose of our study was to investigate prognostic pros & cons of pCND to provide reliable evidence on this topic.
Method
A total of 2,100 PTC patients were randomly assigned to two groups according to pCND status between March 2013 and November 2022 at Samsung Medical Center (SMC). After dropping 299 patients who met exclusion criteria such as gross invasion or central lymph node metastasis or refuse study enrollment...etc, a total of 1,801 PTC patients were included for the final analysis. We compared recurrence and surgery-related outcomes between the two groups- with pCND group (C group) and without pCND group (N group) according to surgery extent.
Results
Mean follow-up duration was 51.2 months (range, 6.8-106.7months). Overall recurrence was detected in 19 (1.0%) patients: 17 (0.9%) in the N group and 2 (0.1%) in the C group regardless of surgery extent. In 1259 lobectomy patients, recurrence occurred in 15 (1.2%) patients: 13 (1.0%) in the N group and 2 (0.2%) in the C group. Recurrence in pre-existing nodule of contralateral lobe was the most frequent. In 542 total thyroidectomy patients, there were 4 (0.7%) patients with recurrence: 4 (0.7%) in the N group and 0 (0.0%) in the C group. Of 4 recurred patients in N group, 3 patients had lateral neck recurrence and only one patients present central neck recurrence. Unfavorable surgery-related outcomes such as transient hypocalcemia, transient VCP, and the incidence of inadvertent parathyroidectomy were significantly higher in the C group.
Conclusion
Despite of rare recurrence(1.1%), pCND decreased overall recurrence, however, we hardly found a relevant relationship between pCND and central neck recurrence in cN0 patients because recurrence in this study seemed to be related to surveillance of the nodules in the contralateral lobe, not pCND per se. Regarding surgical complication, pCND increased the risk of unintentional removal of parathyroid gland, transient hypoparathyroidism, and transient RLN injury. Considering balance between the risk and benefit of pCND, pCND should be considered in advanced cases and performed by experienced surgeon if needed. Personalized decision making is recommended in PTC patients without evident node metastasis. Further follow-up is required to elucidate a practical role of pCND.

DOI: 10.1530/endoabs.101.OP-12-07

# Oral Session 13: Thyroid Eye Disease

## OP-13-01

**VRDN-003, a full antagonist antibody to IGF-1R for thyroid eye disease (TED): phase 1 results show potential for subcutaneous administration**

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Objectives
Prior phase 2 proof-of-concept results showed the clinical activity of 2 intravenous (IV) infusions of VRDN-001 in active and chronic thyroid eye disease (TED). VRDN-003 is a next-generation antibody that has the same binding epitope as VRDN-001 but includes a half-life extension modification. We present preliminary results from an ongoing phase 1 study showing the effect of VRDN-003's half-life extension on its pharmacokinetics (PK), pharmacodynamics (PD), and safety profile when administered as IV infusion vs subcutaneous (SC) injection.
Methods
Healthy volunteers (HVs) were randomized to receive a single dose of VRDN-003 or placebo in the following dose cohorts: IV 5.0 mg/kg, IV 15.0 mg/kg, SC 300 mg, or SC 600 mg. Preliminary treatment-emergent adverse events (AEs) were assessed through December 12, 2023, and will continue to be assessed through study exit (120 days). Preliminary PK parameters including bioavailability were assessed by noncompartmental analysis, and a 2-compartment Population PK model was employed to simulate exposures following repeat SC dosing at different intervals (Q2W, Q4W, Q8W).
Results
Twenty-eight HVs received either VRDN-003 IV ($n$ = 8), VRDN-003 SC ($n$ = 12), placebo IV ($n$ = 4), or placebo SC ($n$ = 4). AEs were reported by 25% (2/8) of participants who received VRDN-003 IV, 25% (3/12) who received VRDN-003 SC, and 13% (1/8) who received placebo. Of the AEs, 3 were deemed treatment-related by the investigator, all occurring in VRDN-003 SC–treated participants and all grade 1/mild as follows: injection site reaction, insomnia, and hepatic enzyme increased (both AST and ALT approximately 2 times the upper limit of normal, resolved during follow-up). No serious AEs were reported. VRDN-003 half-life was estimated to be 40–50 days, 4–5 times longer than that

of VRDN-001. Bioavailability was estimated to be approximately 60% after SC administration. Based on simulated dosing regimens, VRDN-003 could be administered SC less frequently than the current Q3W regimen for VRDN-001 (e.g., SC Q4W or Q8W) while reaching similar exposure levels observed with VRDN-001 IV Q3W in its prior phase 2 study.
Conclusion
These results show the potential for VRDN-003 SC dosing regimens. A single dose of VRDN-003 was well tolerated with an extended half-life 4–5 times longer than that of its parent molecule, VRDN-001. Safety and efficacy of VRDN-003 SC are planned to be further assessed in clinical studies enrolling patients with TED.

DOI: 10.1530/endoabs.101.OP-13-01

## OP-13-02

**Response to teprotumumab is independent of race, ethnicity, and age**

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Objective
Thyroid eye disease (TED) patients may experience pain, proptosis and diplopia. Teprotumumab significantly improved proptosis in three trials in patients with high clinical activity score (CAS), recent-onset TED, and one trial in low CAS, longer-duration TED patients. We report pooled proptosis response in patient subgroups, and across high and low CAS trials.
Methods
Patients $\geq$18 years from three clinical trials in the US and EU (NCT01868997, NCT03298867) and Japan (OPTIC-J; jRCT2031210453), with Graves' disease and recent-onset ($\leq$9-month duration) active TED (CAS$\geq$4, $\geq$3 for OPTIC-J), were included. Patients received eight infusions of teprotumumab or placebo (q3 week dosing) with the final visit at Week-24. Observed proptosis response ($\geq$2 mm improvement) at Week24 is reported by tobacco use (yes/no), race (White/Asian), and age ($<$65/$\geq$65). Cochran-Mantel-Haenszel (CMH) tests compared teprotumumab vs placebo. Pooled proptosis response rate was calculated across the 3 high CAS trials (above), and one trial in low CAS patients with TED duration $\geq$2-$<$10 years (NCT05002998) using CMH adjusted for study and tobacco use status, and non-responder imputation for missing.
Results
In the high CAS, recent-onset TED trials, of 111 teprotumumab and 114 placebo patients, 68.5% (76) and 76.3% (87) were female, respectively; mean (SD) age 50.3 (12.4) and 51.1 (13.1) years; mean (SD) TED duration 5.49 (2.32) and 5.98 (2.40) months; and 78.4% (87) and 73.7% (84) were never/former smokers. At Week-24, in the 3 high CAS trials, 80.2% (89/111) teprotumumab and 14.0% (16/114) placebo patients were proptosis responders ($P$ $<$.0001). In smokers, 70.8% (17/24) teprotumumab and 23.3% (7/30) placebo patients were proptosis responders; in non-smokers, 82.8% (72/87) teprotumumab and 10.7% (9/84) placebo patients were proptosis responders ($P$ $<$.0001 for both). In White patients, 78.9% (56/71) teprotumumab and 15.8% (12/76) placebo patients were proptosis responders; in Asian patients, 90.0% (27/30) teprotumumab and 10.0% (3/30) placebo patients were responders ($P$ $<$.0001 for both). In patients $<$65 years, 79.2% (76/96) teprotumumab and 13.4% (13/97) placebo patients were responders; in patients $\geq$65 years, 86.7% (13/15) teprotumumab and 17.6% (3/17) placebo were responders ($P$ $<$.0001 for both). Across the 4 trials in patients with high and low CAS, 153 and 134 patients received teprotumumab and placebo, respectively. At Week 24, 75.2% (115/153) teprotumumab and 15.7% (21/134) placebo patients were proptosis responders ($P$ $<$0.0001).
Conclusions
Teprotumumab treatment led to significantly higher proptosis response *versus* placebo in all subgroups by tobacco use, race and age, and across the trials including patients with high and low CAS.

DOI: 10.1530/endoabs.101.OP-13-02

## OP-13-03

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.OP-13-03

## OP-13-04

**Target-tissue immunophenotyping of patients with thyroid eye disease before and after therapy with steroids, tocilizumab and rituximab**

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Objectives
The treatment of active moderate-to-severe Thyroid Eye Disease (TED) consists of intravenous methylprednisolone (ivMP) as first-line, and several other immunosuppressants as second-line, including tocilizumab (TCZ) and rituximab (RTX), two humanized antibodies targeting IL6-receptor and CD20, respectively. The characterization of target-tissue-resident lymphocyte subpopulations before and after treatment might help to personalise TED treatment, by elucidating the different mechanisms of action.
Methods
Lymphocytes were derived from blood and paired ultrasound-guided fine-needle aspiration (US-FNA) of thyroid and neck lymph nodes (LNs) in 8 patients with moderate-to-severe active TED at two time-points: before and a mean of 5 months after TED treatment: ivMP ($n$ = 3), TCZ ($n$ = 3) and RTX ($n$ = 2). The obtained lymphocytes were analysed with two techniques: 1) characterization of T and B lymphocyte subpopulations by flow cytometry immunophenotyping with a 21 surface/intracellular staining panel; 2) detection of intracellular cytokines and T-cell early-activation markers CD69 and CD40L (CD154), induced on T cells during lymphoid activation. The interaction between CD40, expressed on the surface of B lymphocytes, and CD40L is involved in B-cell activation and differentiation in memory cells.
Results
TCZ and ivMP did not induce significant changes of T and B lymphocyte subpopulations in blood, thyroid or LNs. In contrast, RTX induced depletion of CD19+ B cells in all three target depots, associated with a reduction of follicular helper T cells (Tfh) in LNs in one patient, while immunophenotyping of the second patient treated with RTX is ongoing. CD69 and CD40L blood-expression were decreased after TCZ and RTX therapy, but not after IvMP. CD69 and CD40L expression analysis within LNs was available in one patient treated with RTX, and was also decreased post-treatment.
Conclusions
Our preliminary results show that both TCZ and RTX, both not ivMP, induced a reduction of CD69 and CD40L T-cell activation markers, suggesting a specific effect on T-cell antigen presentation and B-cell co-stimulation. As expected RTX, and not TCZ or ivMP, also acts as B-cell depleting agent. LNs and thyroid US-FNA is a well tolerated and repeatable technique, allowing the analysis of tissue-resident lymphocytes pre- and post-immunotherapy. We are currently increasing the number of patients analysed pre- and post- immunotherapy for TED, to elucidate the mechanisms of action and potentially guide in the choice of TED treatment.

DOI: 10.1530/endoabs.101.OP-13-04

## OP-13-05

**Efficacy of teprotumumab on medical and surgical resistant don**

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Dysthyroid Optic Neuropathy (DON) is a rare but sight threatening complication of Graves orbitopathy (GO), secondary to optic nerve compression or optic nerve stretching. A previous study from our group showed that medical and surgical treatment of DON according to EUGOGO guidelines resulted in a significant recovery in 70% of DON. However 30% had only partial or no recovery. Teprotumumab is an Insulin Growth Factor -1Receptor inhibitor (IGF-1R) showing impressive results in the remission of inflammation and orbit remodeling, but little is known about its effect on DON.
Objective
To investigate Teprotumumab efficacy on severe and steroid and surgical resistant DON.
Patients and methods
6 patients (1 M and 5 F), for a total of 8 eyes, with steroid and surgical resistant GO and DON, were treated between July 2021 and February 2023 with intravenous teprotumumab infusion (10 mg/kg for first infusion, and 20 mg/kg for the subsequent) every three weeks at our referral center for GO. Clinical and ophtalmological parameters were collected retrospectively. Recovery was defined as significant, partial or none, based on evolution of BCVA and VF mean deviation (MD). Treatment was authorized by French health authorities according to the severity and sight threatening conditions.
Results
Median age was 54.5 years, median follow-up duration from the first teprotumumab infusion was 53 weeks (36-69). All patients had previously received intravenous glucocorticoids infusion and surgical orbital decompression, with only partial or absent recovery of DON. At inclusion median CAS was 4 [4-6.23] and median protrusion was 24 mm [20.7-25.5]. Median BCVA was 0.41 LogMAR [0.17-0.62] and median MD visual field defect 3.3dB [2.8-3.9]. 4/6 patients received the complete 8 infusions regimen, while the remaining two were respectively treated with 6 full-dose, and 4 half-dose infusions because of side effects. At the end of teprotumumab treatment (post-tepro) median CAS was 0 [0-0.25], median proptosis was 17 mm [16.2-19.2] with a median gain of 6.5 mm [4.2-7.2]. At last Follow-up (FU) median CAS was 1 [0-2.25], and proptosis 20.5 mm [16.5-21]. At the end of treatment significant visual improvement was found in 5/8 eyes, while it was absent in 1/8 and partial in 2/8. At the end of follow-up,7/8 (87.5%) eyes had significant recovery, median BCVA was 0.02 logMAR [-0.00-0.11] and median visual field defect MD 1.2 [0.2-2.4], with a median visual field MD improvement of 74% [35-92]. Main side effects were: alopecia (50%), hearing impairment (33,3%) with hearing loss registered in one patient at the end of treatment, and diarrhea (33.3%) which led to a discontinuation of treatment after 4 half-dose infusions
Conclusion
This preliminary study on a small patient group shows very promising data about teprotumumab efficacy on resistant DON, with significant improvement of this sight threatening condition.

DOI: 10.1530/endoabs.101.OP-13-05

## OP-13-06

**Prognostic factors and outcomes of intravenous glucocorticoid pulse therapy in moderate-to-severe thyroid eye disease**

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Objectives
The objective of our retrospective cohort study was to identify prognostic factors associated with treatment success in patients with active moderate-to-severe Thyroid Eye Disease (TED) undergoing intravenous glucocorticoid (ivGC) therapy, defined as the absence of the necessity for additional rehabilitative surgery after treatment completion. Additional objectives encompassed evaluating changes in ophthalmological parameters and thyroid-specific markers correlated with TED development and severity by the conclusion of the treatment period. We aimed to optimize disease management strategies by predicting treatment outcomes and identifying potentially responsive individuals.
Methods
At the Department of Endocrinology and Metabolism at Charité – University Hospital of Berlin between 2014 and 2021, 146 patients received standard ivGC pulse therapy as per ATA/EUGOGO guidelines over a 12-week period. Ophthalmological assessments, including visual field examinations, assessments of visual acuity, diplopia, Clinical Activity Score (CAS) and proptosis, were conducted before and after treatment alongside regular blood examinations evaluating thyroid hormone and antibody levels. Appropriate tests were implemented to assess differences in ophthalmological and thyroid parameters before and after treatment, as well as regression models to determine predictive factors associated with treatment outcomes.
Results
Current smoking (Odds Ratio, $Or = 3.243$, $P = 0.010$), rather than smoking history, emerged as a significant predictor of the need for additional surgery following ivGC treatment. Similarly, baseline diplopia ($Or = 2.971$, $P = 0.049$) was also identified as a significant predictor. Antithyroid drug (ATD) treatment showed marginal significance ($Or = 0.388$, $P = 0.077$), indicating a potential predictive role in the requirement for rehabilitative surgery. Following treatment completion, only the CAS and diplopia exhibited statistically significant reductions ($P < 0.001$ for both), while other ophthalmic parameters did not demonstrate significant changes. Although there was a notable trend towards reduction in Thyrotropin Receptor Antibodies (TRAbs), this change did not reach statistical significance.
Conclusions
Our study underscores the significant opthalmological improvements achieved with ivGC treatment, reflected in the CAS and the reduction of diplopia, a prominent feature impacting the quality of life in Thyroid Eye Disease, which could partially be mediated through reductions, albeit non-significant, in TRAbs. Identifying predictors of treatment efficacy with immunosuppressive therapy, including smoking and baseline diplopia, emphasizes the need for personalized intervention strategies. Moreover, the marginal significance of ATD underscores the importance of maintaining euthyroidism, both to prevent exacerbation and to optimize outcomes during ivGC treatment.

DOI: 10.1530/endoabs.101.OP-13-06

## OP-13-07

**Long-term outcome of graves' orbitopathy following treatment with sirolimus (RAPAMYCIN)**

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Objectives
Sirolimus is an immunosuppressive drug with anti-fibrotic and anti- proliferative activities. Recently, sirolimus (given off-label as a second-line treatment) was found to be associated with a better outcome of Graves' orbitopathy (GO) at 24 weeks compared to methylprednisolone. Here we conducted a retrospective study to investigate the efficacy and safety of sirolimus compared with methylprednisolone over a longer period of time.
Methods
Data from 40 consecutive patients with moderate-to-severe and active GO [10 men and 30 women, age: 56.6 (13.4) yr.], 20 of whom treated with sirolimus

(2 mg orally on first day, followed by 0.5 mg/day for 12 weeks) and 20 with methylprednisolone [500 mg iv/weekly (6 weeks), 250 mg/weekly (6 weeks)], were collected. Primary outcome: overall outcome (composite evaluation) of GO at 48 weeks. Secondary outcomes: overall GO outcome at 24 weeks; at 24 and 48 weeks: 1) outcome of single eye features; 2) outcome of quality of life (GO-QoL); 3) mean change in proptosis; 4) TSH-receptor antibodies (TRAbs); and 5) GO relapse at 48 weeks; 6) adverse events.

Results

The overall GO outcome at 48 weeks did not differ between the two groups, in spite of a trend to a greater proportion of responders in sirolimus group (70% vs 55%). At 24 weeks, the prevalence of responders was greater in sirolimus group (70% vs 35%; $P = 0.03$). A reduction $\geq 2$ points in clinical activity score (CAS) was more frequent in sirolimus patients both at 24 (80% vs 40%; $P = 0.01$) and 48 weeks (75% vs 60%; $P = 0.03$). The proportion of GO-QoL responders (appearance subscale) at 24 weeks was greater in sirolimus group (62.5% vs 26.3%; $P = 0.03$). No difference was observed for the remaining outcome measures. We registered 6 mild adverse events (AE) (4 patients) at 24 weeks and 8 (7 patients) at 48 weeks in the sirolimus group vs 20 mild AE (15 patients) at 24 weeks and 8 (6 patients) at 48 weeks in methylprednisolone group, none requiring discontinuation of the treatment.

Conclusions

Treatment with sirolimus is followed by a greater overall response of GO and CAS compared with methylprednisolone at 24 weeks, with a similar trend at 48 weeks. A more prolonged period of treatment with sirolimus may be required for a better outcome to be observed over a longer period of time. Our data, together with the safety of sirolimus, confirm sirolimus as a possible alternative treatment for moderate-to-severe and active GO.

DOI: 10.1530/endoabs.101.OP-13-07

# Poster Presentations

# Poster Session 1
# Autoimmunity

## PS1-01-01

### Modelling of mechanical stimuli through piezo1 receptor activation and its effect on adipogenic differentiation of orbital fibroblasts

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Introduction
In the pathogenesis of thyroid eye disease (TED) activated fibroblasts in the orbital connective tissue show increased proliferation, hyaluronan (HA) production, and adipogenic differentiation potential. As a result of these, the orbital tissue volume expands and the intraorbital pressure increases. Mechanical stimuli, including high intraorbital pressure, may lead to the activation of mechanosensitive receptors, such as Piezo1, whose presence in orbital fibroblasts (OF) and role in the adipogenesis of OF has not been studied yet. Piezo1 can be activated *in vitro* by its synthetic ligand, Yoda1.
Methods
TED orbital ($n = 5$) and NON-TED orbital ($n = 5$) fibroblast lines were studied. We analysed the expression of Piezo1 by Western blot and fluorescent imaging and its functionality by intracellular Ca measurement. On days 0, 4, 8 and 12 of *in vitro* induction of adipogenic differentiation, the effect of Piezo1 activation on lipid accumulation was measured by Oil Red O staining (ORO). RT-PCR was performed to analyse the expression of CEBPβ, CEBPδ, CEBPα, PPARγ and FABP4.
Results
Functional Piezo1 expression was confirmed in OF. During adipogenesis, lipid accumulation increased at all examined time points ($P < 0.0001$); the proportion of cells entering adipocyte differentiation was intrinsically higher in TED OF, compared to NON-TED cultures. Piezo1 activation by Yoda1 treatment reduced lipid accumulation measured by ORO staining in TED OFs by an average of 14,2% on day 8 ($P = 0.015$) and 28.5 % on day 12 ($P < 0.0001$). After adipogenic induction CEBPβ and CEBPδ expression increased ($P = 0.027$ and $P = 0.029$, respectively), which was inhibited by Piezo1 activation (CEBPβ $P = 0.038$; CEBPδ $P = 0.003$). PPARγ and CEBPα mRNA expressions also increased under adipogenic conditions ($P < 0.0001$and $P < 0.0001$, respectively), which was strongly inhibited by Yoda1 treatment on day 8 (TED $P < 0.0001$) and day 12 ($P < 0.0001$). FABP4 expression was enhanced throughout adipogenesis ($P < 0.0001$); Yoda1 decreased it by day 8 and day 12 ($P = 0.046$ and $P = 0.019$, respectively).
Conclusions
Differentiation into adipocytes is characteristic of OF derived from the orbital connective tissue of TED patients. We found that OF express functional Piezo1 receptor. Intraorbital pressure modifies the mechanical properties of the tissue and presumably activates Piezo1, which, based on our *in vitro* results, inhibits the adipogenesis of fibroblasts by reducing the expression of the major transcription factors of the adipogenic cascade. The mechanosensitive ion channel Piezo1 may have a role in regulation of adipogenesis in the presence of increased intraorbital pressure. The investigation of the role of the Piezo1 receptor may help to identify new treatment options.

DOI: 10.1530/endoabs.101.PS1-01-01

## PS1-01-02

### Thyrotropin receptors stimulating antibodies in pediatric patients with graves' disease using ultra-rapid turbo bioassay

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Background
Thyrotropin receptor (TSH-R) stimulating autoantibodies (TSAb) are present in 95-99% of patients with Graves' disease (GD). TSAb are functional, impact thyroid function, and are clinically relevant. This study we performed in pediatric patients with dynamic of Graves' disease before and during methimazole therapy and in a patient with Hashimoto's thyroiditis (HT) using a novel and ultra-rapid TSAb bioassay.
Methods
All samples from patients with autoimmune thyroid disease (AITD) and healthy controls were tested at the accredited and certified academic thyroid lab of the JGU Medical Center (Mainz, Germany) with a new "TurboTM" TSAb bioassay (Thyretain®, Quidel) with a readout that is based on a cyclic AMP-activated luciferase. The negative values for anti-thyroid receptor antibodies were: < 0,024 IU/l Results: Median age was 12 years (patients $n = 80$ / healthy controls $n = 35$; 12/10.5 years) and female: male ratio was 1,65. Of 80 samples, 43 (52.5%), 30 (36,5%) and 7 (11%) were hyperthyroid, hypothyroid and euthyroid respectively. The TSH-R-Ab assays were negative in 35 healthy controls devoid of autoimmune thyroid and endocrine disorders. Of 80, selected pediatric AITD patients (GD and HT), 41 were positive for TSAb. In the TurboTM cAMP TSAb assay was detected TSAb in 36 untreated GD patients (100%) and 5 treated by methimazole samples. The TurboTM TSAb bioassay highly correlated with thyroid function ($P = 0.028$). Three of 80 (3.75%) samples showed dual TSH-R-Ab positivity.
Conclusions
This is the largest reported collective of TSAb-positive samples in pediatric Graves' disease, measured by a rapid and reliable "TurboTM" TSAb bioassay. TSAb markedly affects thyroid function. Furthermore, the novel TurboTM stimulating bioassay is clinically useful in the monitoring of pediatric Graves' patients.

Key words
Graves' disease, autoimmunity, TSAb, children

DOI: 10.1530/endoabs.101.PS1-01-02

## PS1-01-03

### Specific patterns of orbital-resident B and T lymphocytes are related to different clinical presentations of thyroid eye disease

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Objectives
Thyroid Eye Disease (TED) is an autoimmune process affecting orbital tissues, characterized by an active florid inflammation phase, followed by an inactive fibrotic phase. Treatments include immunosuppressants, usually glucocorticoids (GC), administered in the active phase, and rehabilitative orbital surgery in the inactive phase. The most severe TED cases are characterized by dysthyroid optic

neuropathy (DON), requiring emergency GC and surgical treatments. We aimed to study if specific phenotypes of orbital-infiltrating lymphocytes are related to different clinical TED manifestations.
Methods
Lymphocytes were isolated from peripheral blood and orbital tissues of 19 patients undergoing orbital decompression for inactive TED (TED-I), and 11 patients for DON. Among the 19 TED-I patients, 11 had never been treated with GC (TED-I-Naïve), whereas 8 TED-I patients received GC to inactivate TED a median time of 3 years before surgery (TED-I-postGC). All DON patients also had signs of active orbital inflammation and were treated with GC before orbital decompression (mean 3 months). Isolated lymphocytes were immunophenotyped by flow cytometry with a 21 surface/intracellular staining panel.
Results
DON and TED-I-post-GC patients showed marked orbital T and B cell infiltration, calculated as the number of cells per gram of tissue, compared to TED-I-Naïve patients. DON patients showed an increased frequency of orbital CD19+ B, follicular T helper (Tfh), and germinal center B and T cells, compared to TED-I-Naïve patients. The degree of orbital infiltrating B and Tfh cells negatively correlated with the duration of TED disease in a simple linear regression model ($P = 0.02$ and $P = 0.03$, respectively).
Conclusions
Our findings suggest that the degree of orbital B and T lymphocyte infiltration correlates with TED activity and duration, and the presence of B and T lymphocytes involved in germinal responses seem predominant in the most severe and active cases of TED complicated with DON. Interestingly, the orbital infiltration of TED-I patients who were previously treated with GC (TED-I-postGC) was similar to that of DON, and markedly higher compared with TED-I patients who never received GC (TED-I-Naïve). While lymphocytic infiltrates in more active and severe TED cases may persist in the orbit independently of GC treatment, they appear to be less evident in milder and spontaneously self-limiting forms of TED. The observed negative correlation between the degree of orbital B and T cell infiltration and TED duration may explain why immunosuppressive treatments have the highest efficacy if administered in the early phases of disease.

DOI: 10.1530/endoabs.101.PS1-01-03

## PS1-01-04

**Production of chemerin by orbital fibroblasts during myofibroblast and adipocyte differentiation**

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Introduction
During the course of thyroid eye disease (TED) immune cells infiltrate the orbital connective tissue leading to overstimulation of orbital fibroblasts (OFs). In the persistent inflammatory environment, OFs differentiate into myofibroblasts or adipocytes, simultaneously creating two phenotypes with different morphology and function. Activated OFs secrete pro-inflammatory cytokines and growth factors and contribute to the prolonged inflammation, among other things by producing chemotactic proteins. Chemerin is a potent chemoattractant that triggers chemotaxis of macrophages and natural killer cells, promotes proliferation and it stimulates adipogenesis; its expression by OFs has not been studied yet. Our aim was to study the production of chemerin by OFs and during their differentiation into adipocytes and pro-fibrotic myofibroblasts.
Methods
We used primary cultures of OFs established from orbital connective tissue samples of patients with TED ($n = 5$). Myofibroblast differentiation was induced using 5 ng/ml TGF-β1 for 72 hours and verified by measuring α-smooth muscle actin (α-SMA) expression using RT-PCR. Adipogenic differentiation was induced and maintained for 12 days by adipogenic medium and lipid accumulation was measured by Oil Red O (ORO) staining. Supernatants were collected, then processed with Human Chemerin ELISA (R&D Systems, DY2324) commercial kit to detect chemerin production.
Results
We found that OFs originated from TED patients produced chemerin. Chemerin production was increased during TGF-β1-induced myofibroblast differentiation after 72 hours (mean fold increase ± SD: 3.4 ± 1.5, $P = 0.019$). On the other hand, the concentration of chemerin decreased in the cell culture supernatant during adipogenesis (concentration ± SD: 1.7 ± 0.8, 1.3 ± 0.6, 0.7 ± 0.6, 0.8 ± 0.5 ng/ml at days 0, 4, 8 and 12, respectively; $P < 0.0001$). Myofibroblast and adipocyte differentiations were confirmed by increased α-SMA expression and lipid accumulation, respectively.
Conclusions
In this study we have shown that orbital fibroblasts secrete chemerin and chemerin production increases after myofibroblast differentiation. These findings suggest that myofibroblasts may promote macrophage infiltration into the orbit which, according to the phenotype of macrophages, can perpetuate the inflammation or induce additional myofibroblast differentiation by secreting TGF-β. Although chemerin is known as an adipokine, adipogenesis in OFs has led to decreased chemerin expression. Further studies are needed to clarify the role of chemerin in the pathogenesis of TED.

DOI: 10.1530/endoabs.101.PS1-01-04

## PS1-01-05

**Interplay between thyroid hormones, liver gene expression, and thyroid eye disease in a murine model of graves' disease**

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Introduction
Graves' disease (GD), an autoimmune disorder characterized by hyperthyroidism and thyroid eye disease (TED), presents a multifaceted challenge in understanding its pathogenesis and developing effective treatments. The decision to conduct this analysis stems from a notable observation in our mouse model of GD/TED. Despite observing substantial alterations in the thyroid gland and orbit, we consistently encounter challenges in demonstrating significantly increased levels of thyroxine (T4), a hallmark of hyperthyroidism. This study aimed to elucidate the relationship between thyroid hormones and liver gene expression, focusing on thyroxine (T4), triiodothyronine (T3), and key liver genes involved in thyroid hormone metabolism, including deiodinase 1 (Dio1) and Thyroxine-binding Globulin (Serpina7).
Methods
Mice were divided into two groups: one immunized with the TSHR A-subunit to induce Graves' disease and the other with a control plasmid, ß-Gal, for comparison. Serum levels of total T4 (TT4), free T3 (FT3), and free T4 (FT4) were measured to evaluate thyroid function. Additionally, expression levels of Dio1 and Serpina7 in liver tissues were assessed to investigate their involvement in thyroid hormone metabolism. Histological examination was conducted on thyroid glands to assess hyperthyroidism and on orbits to evaluate TED pathology.
Results
Analysis revealed significant alterations in thyroids, orbits, and thyroid hormone levels in TSHR-immunized mice compared to controls, with elevated but not statistically significant TT4 and FT4 levels and altered FT3 levels. Dysregulated expression of Dio1 and Serpina7 in the livers of TSHR mice indicated disruptions in thyroid hormone metabolism. These findings suggest a potential association between thyroid hormone dysregulation and liver gene expression in TED pathogenesis.
Conclusion
Understanding the intricate interplay between thyroid hormones and liver gene expression in our GD/TED mouse model may offer insights into disease mechanisms and therapeutic targets. Targeting liver genes involved in thyroid hormone metabolism could represent a novel approach for managing Graves' disease and associated complications, including thyroid eye disease. However, the main result of this study is that we were able to show that our mouse model works and that the mice show pronounced hyperthyroidism and TED symptoms despite different T4 levels.

DOI: 10.1530/endoabs.101.PS1-01-05

## PS1-01-06

### Phenotypical and functional flow cytometry study of natural killer cells in graves' disease

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Objectives
Graves' disease (GD) arises from the stimulatory action of TSH receptor antibodies (TSH-RAb). The involvement of innate immune cells has been explored with contradictory results. Through natural cytotoxicity and production of cytokines, Natural Killer (NK) cells respond to various challenges and regulate other immune cells (dendritic cells, monocytes/macrophages, lymphocytes) either promoting or inhibiting their proliferation. NK cells are classified, based on CD56 and CD16 surface antigen expression, into high cytotoxic $CD56^{dim}CD16^{+}$ and cytokine-secreting $CD56^{bright}CD16^{-}$ NK subsets.
Methods
In this cross-sectional case-control study, we aimed to investigate peripheral NK cell frequency, subset distribution, phenotype and cytolytic function in GD patients enrolled at different stages of disease, compared with healthy controls (HCs). Flow cytometry assessed NK cell expression of activating (CD69, NKG2D, NKp30) and inhibitory (CD161, NKG2A) receptors, cytotoxic capacity (CD107a), and interferon (IFN)-γ release.
Results
A total of 128 patients were included (mean age 54 ± 17 years, 77% females), comprising 60 GD patients at diagnosis (GD_ND), 37 GD patients at 6 months of thyrostatic treatment (GD_6m), 9 at 15-18 months of treatment with negative TSH-RAb title (GD_18m), and 22 in remission (GD_r), and 82 HCs. Free thyroxine (FT4) levels were significantly and directly correlated with $NK\text{-}CD69^{+}$ frequency and inversely with $NK\text{-}CD107a^{+}$ ($P < 0.001$). In GD_ND, total NK and $CD56^{bright}CD16^{-}$ cells were significantly higher than in HCs and other GD groups as were $CD69^{+}$ cells. Compared to HCs, $NK\text{-}CD16^{+}$ and $NKp30^{+}$ NK cells were significantly more frequent in GD, while $NK\text{-}CD161^{+}$ NK cells were lower ($P < 0.05$). In HCs, total and $CD56^{bright}CD16^{-}$ cells expressing $NKG2D^{+}$ were significantly higher compared to GD_ND and GD_6m, while the frequency of $NKG2A^{+}$ cells was significantly lower compared to GD_ND. Percentages of $NK\text{-}CD107a^{+}$ and $NK\text{-}IFN\text{-}\gamma^{+}$ cells were lower ($P < 0.05$) in GD_ND compared to HCs.
Conclusion
At GD onset, the frequency of NK cells, especially those expressing activating receptors, was significantly higher than in HCs, GD patients under thyrostatic drugs, and in remission GD. This suggests NK cells may contribute to GD onset and progression. However, lower levels of NK cells expressing the cytotoxic marker CD107a and IFN-γ support an alternative hypothesis: increased activated NK cells may compensate for impaired cytotoxic activity, potentially limiting inflammation. Normalization of thyroid function correlated with reduced circulating NK cells, particularly activated subsets. These preliminary results suggest NK cell dysfunction involvement in GD pathogenesis may identify potential therapeutic targets for inflammation regulation.

DOI: 10.1530/endoabs.101.PS1-01-06

## PS1-01-07

### The prevelence of autoimmune thyroidit and the role of regulatory cells in its pathogenesis

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Introduction
Hashimoto's thyroiditis (HT) is multifactorial disease. Interaction between cellular and humoral immunity is base of HT's pathogenesis. HT's assessment is difficult because the prevalence of patient with an increased titer of thyroid's autoantibody and normal thyroid's function is high. Our research focuses on the estimating of the prevalence of HT in certain regions of the Russian Federation (Tula Region and Chechen Republic), and estimating functional activity and the quantity of T regulatory and B regulatory lymphocytes in blood from patients, who have features of HT. A more accurate understanding of role of regulatory cells in the immunotolerance disorders could be a base for the development of new prognostic markers and therapeutic strategies in the treatment of patients with HT.
Main part
The study was conducted in 3 districts of the Tula region (TR) ($n = 286$), 4 districts of the Chechen Republic (CR) ($n = 302$). The volume of the study was 588 adult people (over 18 years old). 19.9% participants in the TR, 27.15% in the CR have an elevated titer of AT-TPO in the blood serum. And 19.9% participants in the TR, 21.2% in the CR have ultrasound signs of autoimmune thyroid changes. Prevalence of hypothyroidism due to AIT is 16.4% in the structure of the general thyroid pathology in the TR; there are 13.36% in the CR. We analyzed amount and functional activity subsets of regulatory T and B cells (CD3hiIL-10hi and CD19hiCD38hiCD24hi) in subjects's blood: patient with isolated hypothyroidism in the outcome of HT ($n = 23$), carriers of antibodies to thyroid tissues ($n = 18$), patients with HT as a part of autoimmune polyglandular syndrome (APS) ($n = 20$), healthy donors (HD) ($n = 13$). We found significant differences in the amount of regulatory cells (CD19hiCD38hiD24hi B reg) during *in vitro* incubation without additional activation in groups carriers of antibodies (1.75% vs 3.0%; $P = 0.0003$) and in groups patients with HT as part of APS (1.5% vs 3.0% $P = 0.0002$) as compared with HD. A decrease in the induction of regulatory B cells was found only in the group of patients with HT as part of APS (2.3%, $P = 0.04$)
Conclusion
Our research has shown that carriers of autoantibodies and patients with HT as part of APS have reduced spontaneous activation of regulatory B cells *in vitro* and the latter has activation-induced induction of regulatory B cells in the comparison with HD. The quantity and induction of IL-10-producing T cells in the compared groups weren't significantly differ. The study is supported by the Russian Science Foundation, Grant No.22-15-00135

DOI: 10.1530/endoabs.101.PS1-01-07

## PS1-01-08

### *In vivo* effect of maraviroc, a CCR5 receptor antagonist, on the progression of thyroid eye disease

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Objective
Graves' disease (GD), also known as toxic diffuse goiter, is an autoimmune thyroid disorder caused by thyroid-stimulating autoantibodies (TSAb) against the thyrotropin receptor (TSHR), resulting in overstimulation of the thyroid gland and hyperthyroidism. Thyroid eye disease (TED) is a chronic inflammatory condition of the orbit and the most common extra thyroidal manifestation of Graves' disease (GD) affecting approximately 40% of GD patients. A complex immune-mediated cycle involving lymphocytes, adipocytes, and orbital fibroblasts underlies TED. The aim of this study was to evaluate the therapeutic effect of maraviroc, a CCR5 receptor antagonist, in Graves' disease and thyroid eye disease.
Methods
Mice were immunized with either a TSHR A-subunit plasmid for induction of Graves' disease or a with ß-Gal plasmid as a control. Maraviroc was administered orally to one of the TSHR immunized groups for eight weeks. The typical clinical features of thyroid eye disease and inflammation were assessed by serological and immunohistochemical analysis.
Results
Maraviroc treatment mitigated autoimmune hyperthyroidism without affecting body weight. In the orbit, it normalized brown adipose tissue levels and showed a trend towards reduced T-cell infiltration, albeit not statistically significant. Maraviroc also reduced macrophage infiltration, particularly F4/80+ macrophages, in the TSHR-immunized group.
Conclusion and outlook
In this study, a mouse model of GD and TED was used to compare the therapeutic effect of Maraviroc between TSHR immunized and ß-Gal control mice. Our results show that maraviroc blocks the development of the local pathologies of GD and TED in the severe phase of the autoimmune disorder and slightly prevents development of the autoimmune response. Our findings suggest a beneficial effect

of the drug on the outcome of experimental GO, but further studies are needed to better understand the molecular mechanisms of action of maraviroc and to develop therapies, especially for thyroid eye disease.

DOI: 10.1530/endoabs.101.PS1-01-08

## Anaplastic thyroid cancer

### PS1-02-01

**Estrogen-related receptor gamma (ERRγ) as a therapeutic target for anaplastic thyroid cancer and the synergistic killing effect of DN200434 (ERRγ inverse-agonist) and MK2206 (AKT inhibitor) in thyroid cancers**

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Objective
The first orphan nuclear receptors discovered were Estrogen Related Receptors (ERRs), which were recognized due to their sequence closeness to the classical estrogen receptors. Countless impartial studies have linked ERRγ to the onset and progression of several malignancies, including thyroid cancer. Moreover, it is recognized that ERRγ has a unique function in controlling metabolic effectors, cell cycle progression, and apoptosis in cancers of different kinds. We assessed the potential of Estrogen Related Receptor Gamma (ERRγ) as a therapeutic target by analyzing its expression levels in different cell lines of thyroid cancer. Furthermore, the anti-tumor activity of DN200434 (an inverse agonist of ERRγ) in combination with MK2206 (an Akt inhibitor), was investigated.
Methods
ATC cells (HTh7, 8505c) and PTC cells (KTC-1, TPC-1) were cultivated in their corresponding medium. CCK-assay was used to measure the IC50 value of DN200434 and MK2206 in ATC/PTC cells after 24 hours. Cells were treated with drugs alone or in combination for 24h to assess their inhibitory effect on the viability, apoptosis and cell cycle using flow cytometry. Additionally, western blot was used to enumerate the proteins level implicated in the cell cycle and apoptotic pathways. Following combination treatment, the colony formation assay was carried out in six-well plates with 500 cells per well. Crystal violet staining was followed by a count of large colonies with up to 50 cells.
Results
We observed that the IC50 of DN200434 and MK2206 was 30-45 μM and 10-20 μM in ATC/PTC cells at 24h, respectively. The combination of DN200434 and MK2206 in ATC/PTC cells synergistically enhanced cell cytotoxicity up to 70-75% as compared to DN200434 (5-15%) and MK2206 (10-20%) alone. Flow cytometry results showed significant apoptosis and cell cycle arrest at G0/G1 phase in the combination drugs treated cells respectively. Western blot data confirmed significant apoptosis in combination treated cells with increased level of cleaved caspase-3 and cleaved-PARP. A significant reduction (70-80%) in the colony forming ability was observed in combination treated cells.
Conclusion
Our findings show that DN200434 and MK2206 together can be employed as a treatment combination to treat advanced papillary thyroid cancer and anaplastic thyroid cancer. Before this powerful combination is put through clinical trials, more assessment of combination therapy in animal models or 3D spheroid models is needed.

DOI: 10.1530/endoabs.101.PS1-02-01

### PS1-02-02

**Thyroid fibrosarcoma as a rare differential diagnosis of anaplastic thyroid cancer: a case report**

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Introduction
Thyroid gland fibrosarcomas are very rare tumors, with only very few cases have been reported in the literature. Their similarity to anaplastic thyroid cancer poses a diagnostic challenge, often leading to misdiagnosis.
Case Report
We report the case of an 87-year-old female with a history of left thyroid nodule who underwent a left lobectomy and subsequently received levothyroxine therapy. She presented with a rapidly growing mass on the right thyroid gland. Her thyroid function was normal. Ultrasound revealed an ill-defined hypoechoic mass measuring 4 cm on the right thyroid. Fine-needle aspiration biopsy was performed, and cytology indicated Bethesda VI for anaplastic thyroid carcinoma. After the total thyroidectomy, the surgical pathological examination revealed a high-grade fibrosarcoma with extension into the strap muscle. Lymphovascular and perineural invasion was noted. Immunohistochemical staining showed positivity for smooth muscle actin, and negative for PAX8, TTF1, and thyroglobulin. Following surgery, adjuvant therapy with radiation and chemotherapy using ifosfamide was administered. However, the disease progressed with lung metastasis. The treatment was changed to administration of pazopanib, resulting in dramatic improvement of lung metastasis. However, the disease continued to progress, and patient passed away within 2 years after treatment initiation.
Conclusions
Although fibrosarcoma of the thyroid gland is exceedingly rare, it should be considered in the differential diagnosis of anaplastic thyroid carcinoma. Immunohistochemistry plays a crucial role in supporting the diagnosis. A multidisciplinary approach is essential for its management. In addition to surgery, emerging adjuvant therapies with kinase inhibitors have shown promise in improving patient survival.

DOI: 10.1530/endoabs.101.PS1-02-02

### PS1-02-03

**Low dose radiation can improve the therapeutic efficacy of immune checkpoint inhibitor in a mouse anaplastic thyroid cancer model**

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Background
Recently, immune checkpoint inhibitors (ICI) have been applied for the anaplastic thyroid cancer, and the need is increasing to optimize this treatment. The aim of this study is to investigate whether low dose radiotherapy can enhance the therapeutic efficacy of immune checkpoint inhibitor in a mouse anaplastic thyroid cancer model.
Methods
Mouse anaplastic thyroid cancer cell line TBP-3743 was implanted subcutaneously in C57BL/6 mouse. Mice were randomized into 5 groups after tumor reaching to 200 $mm^3$ : control group (Con), anti-PD-L1 treated group (PDL1), conventional dose radiotherapy group (CRT), combination of anti-PD-L1 with conventional dose radiotherapy group (PDL1 + CRT), combine anti-PD-L1 with low dose radiotherapy group (PDL1 + LRT). Mice were treated with two times of anti-PD-L1 antibody at day 1, day 4 and with one fraction of radiation at day 1 (Conventional dose: 8 Gy, Low dose: 0.8 Gy). After that, tumor size and survival were evaluated. Tumors were analyzed for CD8, Granzyme B at day 7. Tumors were analyzed for CD8, granzyme B using immunohistochemistry and for CD45+ cells using flow cytometry, and for the mRNA expression level of IL-12 using RT-qPCR at day 7.
Result
Combination therapy increased mouse survival and reduced tumor volume compare to monotherapy (Median survival Con, PDL1, CRT, PDL1 + CRT, PDL1 + LRT; 15d, 26d, 26d, 38d, 37d respectively, $P < 0.0001$). Leukocytes increased in PDL1, PDL1 + CRT, PDL1 + LRT groups in terms of CD45 expression after flow cytometry analysis. Cytotoxic CD8 T and NK cell significantly increased in combination therapy group (PDL1 + CRT, PDL1 + LRT) than PDL1 or CRT group ($P = 0.016$). IL-12 mRNA level in tumor from PD-L1 and combined therapy group were significantly increased compared to the CRT group.
Conclusion
Low dose radiotherapy appears to therapeutic efficacy of anti PD-L1 antibody comparable to the conventional dose radiotherapy in a mouse anaplastic thyroid cancer model.

DOI: 10.1530/endoabs.101.PS1-02-03

## PS1-02-04

**Progression of papillary thyroid carcinoma to anaplastic carcinoma in metastatic lymph nodes**

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Introduction
Aggressive forms of papillary thyroid carcinoma are more commonly observed; anaplastic and poorly differentiated types are rarer, but have a higher death rate. The transformation from papillary to anaplastic is a rare occurrence; it is even more uncommon for a small region of well-differentiated thyroid cancer to occur alongside the anaplastic form in metastatic lymph nodes.
Aim
We present a case of an aggressive form of papillary thyroid carcinoma – a tall cell variant, with demonstrated dedifferentiation to anaplastic carcinoma.
Case report
The 63-year-old female patient presented in our clinic for respiratory difficulties and dysphonia, associating a large goiter. The imaging tests demonstrated a large nodular goiter with compressive effects and the biological profile was within normal limits. The patient underwent a total thyroidectomy with bilateral lymphadenectomy. Eight metastatic lymph nodes and a tall oxyphilic variant of papillary carcinoma with soft tissue invasion were described by the histological examination. The patient was responsive to high doses of radioiodine therapy; whole-body scintigraphy showed an iodine-sensitive rest of the thyroid tissue, with high level of stimulated thyroglobulin and anti-thyroglobulin antibodies. One year after the diagnosis, the scintigraphy and the CT scan were negative, and the biological profile revealed a decreasing level of thyroglobulin and anti-thyroglobulin antibodies. After few months the patient relapsed, with large metastatic lymph nodes in the cervical and mediastinal compartment and pulmonary nodules suggesting distant dissemination on CT scan, decreasing level thyroglobulin and normal anti-thyroglobulin antibodies. The thyroid origin was confirmed after biopsy. The whole-body scintigram was negative, suggesting a resistant form to radioiodine treatment. We start treatment with tyrosine-kinase inhibitor without positive response. She underwent the second surgery for the large compressive lymph nodes in cervical compartment. The histopathologic exam with immunochemistry revealed small areas of papillary thyroid carcinoma – tall cells variety and predominant anaplastic carcinoma, with positive staining for MCK, TTF1, PAX8, Thyroglobulin being positive in isolated cells, and a 35% positive Ki67 in the tumor cells with solid pattern. The patient needed tracheostomy for bilateral cords paralysis. Her option was for palliative care.
Conclusion
Involved lymph nodes in papillary thyroid cancer increase the risk of recurrence, but usually do not change the prognosis. In the exceptionally cases the progression to anaplastic carcinoma is the most feared complication, with fatal outcome. The simultaneous occurrence of papillary and anaplastic thyroid carcinoma in the metastatic lymph node, along with radio-iodine resistance and a decreasing level of thyroglobulin, the rapid and poorly evolved metastasis affecting vital structures and the ineffectiveness of treatment are proofs of the dedifferentiation.

DOI: 10.1530/endoabs.101.PS1-02-04

## PS1-02-05

**Clinical and therapeutic particularities of anaplastic thyroid carcinoma**

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Aim
To study the clinical, evolutive and therapeutic features of anaplastic thyroid carcinoma.
Methods
Retrospective descriptive study of twenty patients managed for anaplastic thyroid carcinoma over a twenty-one-year period from January 2003 to December 2023.
Results
The mean age of our patients was 60 years. The average consultation time was 41.5 months, with extremes ranging from two months to 20 years. Eighteen patients consulted due to the appearance of a rapidly growing thyroid gland mass. One patient was referred for recent dyspnea. The appearance of polyadenopathy was the reason for consultation in another case. Three patients had dysphonia. The swelling was rigid in 85% of cases. Physical examination revealed cervical lymph nodes enlargement in ten patients. Vocal cord paralysis was noted in five cases, and decreased vocal cord mobility in three. Ultrasound-guided thyroid cytopuncture was performed in eight cases, revealing undifferentiated carcinoma in six. Surgery was performed after an average of one week. Biopsy was performed in seven patients with unresectable tumors. Thyroidectomy was performed in thirteen cases. All our patients were referred for radiotherapy. The evolution was fatal in all cases. The mean survival time in our series was 4 months, with extremes ranging from one to six months.
Conclusion
Anaplastic thyroid carcinoma is a rare but aggressive tumour. Despite multiple therapeutic modalities, its prognosis remains poor, with a survival rate of only a few months.

Key words
Thyroid carcinoma, Anaplastic, Surgery, Radiotherapy, CT
DOI: 10.1530/endoabs.101.PS1-02-05

## PS1-02-06

**NF1 mutations in anaplastic thyroid cancer: from genetic insights to therapeutic potential**

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Objective
NF1 alterations may be present in about 3% of Anaplastic thyroid cancers (ATC) in alternative to classic driver mutations; moreover, NF1 is included in several trials as target for therapy with MEK inhibitors. The objective of this study is to better characterize the role of NF1 in ATC.
Methods
For this purpose, DNA and RNA were extracted from 32 cases of ATC/PDTC. We firstly analyzed classic driver mutations with 2 Next-Generation Sequencing (NGS) custom panels able to detect mutations/indels and gene fusions. Cases negative from this analysis were analyzed with another panel spanning the entire NF1 tumor suppressor gene. Finally, TERT promoter mutations (C228T, C250T) were investigated as well using droplet digital PCR (ddPCR).
Results
Of the 32 patients analyzed, 7 cases (21.9%) showed driver mutations in BRAF (V600E and K601E), and 5 for RAS (1 HRAS Q61R, 1 HRAS G12R, 2 NRAS Q61K, 1 NRAS G13R + TP53). Other 15 cases were negative for driver mutations but showed different TP53 pathogenic variants (15/32, 46.9%) while the remaining 10 cases (10/32, 31.2%) were negative. TERT C228T mutation was detected in 15/32 (46.9%) cases. Subsequently, 15/25 negative cases were analysed for NF1 gene mutations and in 2 cases (2/15, 13.3%) we found pathogenic variants. In details, in a patient affected by simultaneous ATC and a micro-papillary thyroid carcinoma (mPTC) we found a NF1 pathogenic mutation affecting the donor splicing site upstream exon 39 in the ATC component; the same patient harbored a BRAF V600E mutation in the mPTC component. Interestingly, the 2 mutations were not shared within the 2 lesions. Analysis of the

NF1 transcript of the ATC component demonstrated the actual skipping of exon 39. In the second patient, we detected a deletion of two nucleotides in NF1 exon 49 resulting in a frameshift of the coding region and the introduction of a stop codon. Interestingly, in both ATC cases, we found co-occurrent TP53 pathogenic mutations. Since both genes, *NF1* and *TP53*, are located on the chromosome 17 we can hypothesize a synergic role of inactivation of these two tumor suppressor genes in the same lesion.

Conclusions

These data show that NF1 can occur in negative ATC and can act in occurrence with TP53. Since NF1 is used for targeted therapy in other types of cancer, its presence may offer an additional therapeutic option to these patients.

DOI: 10.1530/endoabs.101.PS1-02-06

## PS1-02-07

### Evaluation of the antineoplastic effect of cabozantinib in primary human cell cultures from anaplastic thyroid carcinoma

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Anaplastic thyroid cancer (ATC) is highly aggressive, and the clinical treatment and management is still challenging. In-depth knowledge of the pathways involved in the phases of tumour initiation and progression of ATC has shifted attention on the use of targeted and personalized therapies, that are based on the tumour's genetic profile. In this context, *in vitro* studies allow a good preclinical evaluation of the antineoplastic effect of the drugs. We aimed to test the antineoplastic effect of cabozantinib, a multikinase inhibitor that inhibits tyrosine kinase receptors that are involved in growth, angiogenesis and metastatic progression of tumour; moreover it was recently approved for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma, not eligible or refractory to radioactive iodine who have progressed during or after prior systemic therapy. We tested the drug in both continuous ATC cell lines, and in primary human ATC cells, that were obtained directly from ATC patients. The human primary cells were obtained from surgical thyroidal samples of three females and two males with ATC (55–81 years) with a tumour size range of 6–14 cm, at the moment of first surgical operation. As continuos cell lines we used the 8305C and CAL-62 lines. Our results showed firstly a good antineoplastic effect *in vitro* of cabozantinib in both continuous and primary ATC cells in inhibiting the proliferation of the tumoral cells as well as in increasing their apoptosis. These *in vitro* studies pave the way to a personalized therapeutic approach to be used in future clinical evaluation in patients with anaplastic thyroid cancer.

DOI: 10.1530/endoabs.101.PS1-02-07

## PS1-02-08

### Limited efficacy in adding lenvatinib for braf V600E-mutated anaplastic thyroid carcinoma (brafm-atc) progressing on braf-directed therapy

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Background

BRAF/MEK inhibitors (BRAF/MEKi) dabrafenib + trametinib have revolutionized the treatment of BRAFm-ATC, but response is often short-lived. We previously reported that addition of an anti-PD-1 immune checkpoint inhibitor (ICI) to BRAF/MEKi prolongs overall survival (OS). Yet, some patients still develop resistance and progress. In *BRAF* $^{V600E}$-mutated melanoma, OS is longer when BRAFi is continued beyond disease progression. Lenvatinib + pembrolizumab have shown promising efficacy in *BRAF* wild-type ATC. We aimed to study the efficacy of lenvatinib + continued BRAFi ± ICI after progression on BRAF/MEKi + ICI in metastatic BRAFm-ATC.

Methods

Retrospective study of BRAFm-ATC treated with lenvatinib + BRAFi ± ICI at progression on BRAF/MEKi + ICI. Primary outcome was median OS (mOS). Secondary outcomes were median progression free survival (mPFS) and disease control rate (DCR), defined as complete + partial response (PR) + stable disease (SD) as the best overall response (BoR). Survival was assessed by Kaplan-Meier method; BoR using RECISTv1.1.

Results

Thirteen patients with metastatic BRAFm-ATC, treated with lenvatinib + BRAFi ± ICI at progression on BRAF/MEKi + ICI between 3/1/14 and 10/15/23, were included. Data cut-off was 1/15/24. The table below highlights notable baseline characteristics. 10/12 (83%) evaluable specimens had a PD-L1 $\geq$ 1%. Mutational data at progression on BRAF/MEKi + ICI revealed acquired *RAS* mutations in 5/13 (38%) and *PIK3CA* mutation in 1/13 (8%). Median initial dose of lenvatinib was 10 mg (range, 10–20) and median duration of lenvatinib was 3 months (range, 0.7–13). Drugs combined with lenvatinib were: encorafenib ($n$ = 1), dabrafenib ($n$ = 1), encorafenib + pembrolizumab ($n$ = 1), dabrafenib + atezolizumab ($n$ = 1), and dabrafenib + pembrolizumab ($n$ = 9). Median initial dose of dabrafenib with lenvatinib was 100 mg twice daily (range, 75 – 150). All patients were exposed to an ICI during their treatment course but in 2 patients, the ICI was stopped prior to initiating lenvatinib due to immune-related toxicity. mOS from start of lenvatinib was 3 months (95% CI, 2.1–3.9). On lenvatinib + BRAFi ± ICI, DCR was 46% (SD in 4/13, PR in 2/13). BoR was progressive disease in 4/13 (31%) and non-evaluable in 3/13 (23%). mPFS was 2 months (95% CI, 1.4–2.6). At data cut-off, 2/13 patients continued therapy.

Conclusions

In patients with metastatic BRAFm-ATC progressing on BRAF/MEKi + ICI, lenvatinib + BRAFi ± ICI offer limited additional survival benefits. Limitations of our study include retrospective review with selection bias and variability in previous therapies among patients. Continued research efforts to identify effective second line therapies for BRAFm-ATC are warranted.

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|---|---|
| Median age at diagnosis – years (range) | 68.0 (51 – 75) |
| Prior therapy for ATC – no. (%) | |
| Radiation to the neck | 7 (54) |
| Primary neck surgery | 9 (69) |
| Surgery after neoadjuvant BRAF/MEKi | 4 (31) |
| **Median previous systemic therapies – no. (range)** | 1.0 (1 –3) |
| **Median duration of BRAFi before start of lenvatinib – months (range)** | 12.0 (4 – 53) |

DOI: 10.1530/endoabs.101.PS1-02-08

## PS1-02-09

### Clinical applicability of liquid biopsy for the management of anaplastic thyroid carcinoma (ATC), a monocentric experience

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Introduction

ATC is the most aggressive thyroid cancer with a median overall survival of 6-12 months. The early detection of targetable molecular alterations (MAs) and matched targeted therapies might improve the prognosis.

Objectives

To evaluate the clinical applicability of liquid biopsy (LB) for the molecular profiling of ATCs.

Methods

This monocentric study retrospectively analysed consecutive ATC patients seen from January 2021 to July 2023. Circulating free DNA (cfDNA) was assessed with FoundationOne®CDx assay within the STING trial (NCT04932525). Tissue molecular profile (TMP) was analysed by various routine NGS targeted panel. All patients underwent BRAF$^{V600E}$ status assessment by immunohistochemistry (IHC)

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Results
Thirty-three patients (19 females), median age 74, with *de novo* ATC in 17%, mixed in 24% and transformed in 24%, at stages IVA (6%), IVB (18%), IVC (76%) were included. The median turnaround time for LB was 12 days (range 7-19). ATC-related MAs were identified in 82% of TMPs and in 81% of LBs. The most frequent cfDNA MAs found were: TP53 (55%), TERT promoter (36%), RAS (30%), BRAF (24%), NF1 (15%), RB1 (12%), TSC1 (12%), FGFR2 (9%), BRCA2 (9%), TSC2 (9%), PTEN (9%) and PI3KCA (9%). MTOR pathway alterations were mutually exclusive and present in 13 (39%) cases. ATC-related MAs were identified in TMP only (and not in LB) in 4 cases including 2 $BRAF^{V600E}$, 1 *AFAPL12-BRAF* fusion and 1 $NRAS^{Q61R}$, whilst MAs were identified exclusively in 5 cases in LB only including 1 *RB1*, 2 *TERT* promoter, 2 *TP53*, 1 $BRAF^{V600E}$ + $HRAS^{G12S}$, 1 $BRAF^{L485\_P4\ L485\_P490>FN}$ and 1 *FGFR2* mutations. Almost all LB (5/6) that did not identify any ATC-related driver were sampled during or post-treatment. $BRAF^{V600E}$ mutation assessment was positive by TMP, IHC and cfDNA in 9 (27%), 8 (24%), and 7 cases (21%), respectively. There were 5 discordant cases: 3 patients had a $BRAF^{V600E}$ mutation in the TMP ($n = 3$) +/- IHC ($n = 1$) and not in cfDNA and responded to Dabrafenib + Trametinib (DT), with a progression-free survival of 5, 6 and 15 months, respectively. One patient had a $BRAF^{L485\_P4\ L485\_P490>FN}$ and one patient had $BRAF^{V600E}$ + $HRAS^{G12S}$ mutations in cfDNA (and not at IHC and in TMP) and they did not respond to DT.
Conclusions
Liquid biopsy is an effective tool with a rapid turnaround time for the molecular profiling of ATC, especially when performed at the baseline, before any treatment.

DOI: 10.1530/endoabs.101.PS1-02-09

## PS1-02-10

### Liquid biopsy in the follow-up of a patient with braf positive anaplastic thyroid cancer and breast cancer

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Introduction
Current imaging modalities for anaplastic thyroid cancer (ATC) have limited efficacy in evaluating remission and predicting recurrence due to residual disease. Circulating tumour DNA (ctDNA), isolated from liquid biopsies, could complement these methods and enhance diagnostic follow-up and disease monitoring. However, clinical follow-up studies using ctDNA in ATC remain scarce.
Case report
An eighty-one-year-old woman with a history of $HER2^+$ breast cancer (BC), in remission since 2021, presented in July 2022 with a 9 cm exophytic stage IVb ATC. Due to the patient's frail status, a 24-hour cytology-based *BRAF* p.V600E diagnosis was performed, and she was immediately put on Dabrafenib plus Trametinib (DT) therapy. A remarkable DT response was observed with tumour shrinkage to 6 cm (first month) and further to 3.4 cm (fourth month), with disappearance of the exophytic component. In the fifth month the patient underwent total thyroidectomy (TT), which was uneventful. Still under DT, a PET-CT scan performed 12 months later showed a new liver metastatic lesion, subsequently biopsied and diagnosed as a *BRAF*- negative BC metastasis. Six months later, the metastatic disease progressed with pronounced BC markers expression, without evidence of ATC recurrence. To investigate the utility of ctDNA concentration and ctDNA $BRAF^+$ (ct $BRAF^+$) analysis by droplet digital PCR (ddPCR), blood samples were collected between the diagnosis (baseline/pre-DT) and the end of follow-up and matched with PET-CT. Baseline ctDNA concentration decreased throughout follow-up (179 to 97 ng/mL), paralleling the tumour volume's reduction. Following TT, ctDNA stabilized at approximately 58.2 ng/mL, but increased one month prior to the emergence of BC liver metastasis (129 ng/mL). By the end of the follow-up period (at 18 months), the patient's ctDNA increased to 788 ng/ml. In this case, ctDNA levels varied along with ATC/BC disease burden. Baseline *ctBRA* $F^+$ was detected with a VAF of 4.3%. By the 3rd month and until the end of follow-up, $ctBRAF^+$ was no longer detected (0% VAF), despite the BC liver metastasis. The ddPCR- $ctBRAF^+$ assay sensitivity and specificity were 76.9% [95% CI 49-97%] and 91.6% [95% CI 64-99%], respectively. Notably, $ctBRAF^+$ aligned with pre-treatment *BRAF* diagnosis and ATC DT clinical response.
Conclusions
This case report suggests that ctDNA/ $ctBRAF^+$ may be useful as monitoring biomarkers for ATC, offering a promising method for assessing therapeutic response through minimally invasive and readily available methods. However, further studies are needed to validate the clinical utility of liquid biopsy in additional ATC cases, with longer follow-up periods.

DOI: 10.1530/endoabs.101.PS1-02-10

# Thyroid cancer case reports-1

## PS1-03-01

### Refractory thyroid carcinoma treated by sorafenib

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Introduction
The incidence of thyroid carcinoma is increasing worldwide, so much so that it is ranked 3rd cancer in women in Algeria; Fortunately, the incidence of refractory cancers remains stable. The latter represent a real therapeutic challenger. We report the experience of our service.
Material and method
Between 2018 and 2024, 545 differentiated thyroid carcinomas and 10 anaplastic carcinomas were consulted, 28 of which were classified as refractory carcinomas (5%). The refractory carcinomas appear progressive according to the RECIST criteria were treated with anti-tyrosine kinase type sorafenib, i.e. 9 patients treated (32%), including an anaplastic carcinoma. Divided between 3 women and 6 men with an average age of 59 years. All patients were initially classified at high risk of recurrence according to ATA2015 and all presented distant metastases (mainly bone and lung). The average treatment dose was 600 mg and the main side effect observed was high blood pressure. Two serious side effects were observed: tracheal hemorrhage and ischemic stroke. Tumor regression was observed in 2 patients but unfortunately the treatment was stopped in one of them due to the appearance of a serious side effect; lesion stability in 3 patients; progression of the disease leading to the cessation of treatment in 4 patients and a rebound phenomenon in one patient who decided to stop his treatment in view of the side effects.
Discussion and conclusion
Refractory thyroid cancers are rare but responsible for the majority of deaths linked to this cancer. The use of kinase inhibitors has made it possible to improve the outcome of these patients. On the other hand, in addition to the cost being high, they have a notable influence, responsible for side effects that often alter the quality of life, for a response that is not always present. Due to the complexity of these treatments, these patients are best managed by multidisciplinary groups.

DOI: 10.1530/endoabs.101.PS1-03-01

## PS1-03-02

### Two rare cases of benign struma ovarii with malignant recurrence

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Objective
Struma ovarii is an ovarian teratoma defined by the presence of thyroid tissue, that comprises more than 50% of the overall mass. It constitutes 2-5% of ovarian teratomas and 1% of all ovarian tumors. The majority of struma ovarii cases are benign. Malignant transformation of struma ovarii is very rare (less than 5% of all cases) and metastatic disease occurs even more rarely. Most malignant struma ovarii (MSO) cases account for papillary (70%) or follicular carcinomas. Highly differentiated follicular carcinoma arising from the ovary (HDFCO) is a rare version of struma ovarii that is accompanied by extra ovarian dissemination in the peritoneal cavity (also referred to as peritoneal strumosis), and sometimes by systemic dissemination. We report two cases initially diagnosed with benign struma ovarii that presented malignant transformation, specifically highly differentiated follicular carcinoma of the ovary (HDFCO) some years after the first diagnosis.
Methods
Case 1 concerns a 37-year-old female featuring HDFCO of the right ovary with multiple metastatic focuses who was diagnosed with benign struma ovarii 14 years ago. Case 2 concerns a 26-year-old female diagnosed with HDFCO of the left ovary. This patient was initially diagnosed with benign struma ovarii 6 years ago that recurred 4 years after the diagnosis.
Results
Both patients were treated with surgery, adjunctive total thyroidectomy, and radioactive Iodine (I-131) therapy. After ablation, suppression therapy with levothyroxine was initiated and they stayed closely monitored with abdominal imaging and thyroglobulin levels. Both patients showed biochemical disease persistence and one of our patients showed additional structural persistence. Thus, a second radioiodine treatment was recommended.
Conclusions
Early diagnosis of the rare HDFCO is significant and post-thyroidectomy radioiodine therapy is mandatory in the majority of cases. TSH suppression and thyroglobulin levels measurements are necessary for the patient's follow-up in adjunction with abdominal imaging. We emphasize the necessary cooperation of medical specialties in terms of multidisciplinary tumor boards of specialized referral centers for these cases.

DOI: 10.1530/endoabs.101.PS1-03-02

## PS1-03-03

### Rare thyroid gland tumors

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Objectives
We aim to describe the clinical features and the particular presentation of rare thyroid gland tumors and to discuss their management modalities
Materials and methods
In this study, we report 4 cases of the following rare thyroid gland tumors: Squamous cell carcinoma, Hamartoma and lymphoma of the thyroid gland.
Results
First case
A 85-year-old female presented with a 1-month history of dysphonia and dysphoni. Clinical examination revealed a swelling at the thyroid gland region measuring 2 cm. Ultrasound and computed tomography (CT) scan showed a heterogeneous goiter. The mass biopsy showed an infiltration of the thyroid gland by a Burkitt Lymphoma. The patient was placed under steroids and immunosuppressants. However, after a follow-up period of 1 month, symptoms did not regress.
Second case
A 44-year-old female presented with an inferior neck swelling with dysphagia. At clinical examination, we noted an inferior neck mass measuring 12 cm associated to an immobile right vocal fold. Ultrasound and CT scan showed a hypertrophy of the right thyroid gland lobe that repressed the trachea. We performed a partial right thyroidectomy and recorded a B lymphoma. The patient received chemotherapy. However, we lost the patient after 4 months due to a disease progression.
Third case
A 54-year-old female presented with a 4-cm mass at the thyroid gland region that was adherent to the trachea. It was associated to dysphonia and dyspnea CT scan revealed a right thyroid gland mass with a tracheal invasion. We performed a total thyroidectomy with a bilateral neck dissection. Histopathology demonstrated a papillary thyroid carcinoma associated to a squamous cell carcinoma. The patient received radioactive iodine treatment. Follow-up after 2 years did not show any disease recurrence.
Fourth case
A 4-year-old child presented with a lateral neck swelling evolving for 5 months. It measured 3 cm and was located at the right paramedian neck region. Ultrasound showed a regular, heterogeneous and hypo-vascularized peri-thyroid gland mass. At CT scan, the mass had a fat-like density without contrast enhancement. We performed a surgical resection of the mass. Peri-opertavely, the mass originated from the thyroid gland and had a lipoma-like aspect. Histopathological examination revealed a thyroid gland hamartoma. We did not record any recurrence after 6 months.
Conclusion
Non-epithelial forms of thyroid gland tumors are exceptional. They need to be suspected in atypical presentation of a thyroid gland mass.

DOI: 10.1530/endoabs.101.PS1-03-03

## PS1-03-04

### Retropharyngeal node metastasis from papillary thyroid carcinoma

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Background
Papillary thyroid carcinoma (PTC) commonly metastasis to paratracheal and jugular lymph nodes. Retropharyngeal lymph node metastasis (RPNM) from PTC are rare. The aim of this study is to discuss the feasibility of the treatment for PTC with RPNM in our institution.
Methods
Eight patients underwent surgical treatment for metastasis of thyroid papillary carcinoma to RPN that presented as a parapharyngeal or retropharyngeal mass at Severance hospital from 2010 to 2022. All patients had a history of total thyroidectomy as their initial treatment and 2 patients of all patients had synchronous lung metastases at primary diagnosis of PTC. Among them, 5 and 2 patients underwent had undergone ipsilateral and bilateral modified radical neck dissection, respectively as their initial treatment or the treatment for PTC recurrence. The remaining 1 patient undergone central compartment neck dissection only as the initial treatment. Of the 8 patients, 5 patients were identified to have RPL metastasis at primary diagnosis, the other 3 patients were at diagnosis of PTC recurrence.
Results
Metastatic RPN were successfully resected via transoral approach in all patients. The study group comprised of 6 females and 2 males with mean age of 38.13 $\pm$ 14.79 years. Mean follow-up was 67.98 $\pm$ 69.61 months. Five patients initially diagnosed PTC with RPNM underwent surgery and high-dose high-dose radioactive iodine (RAI). Three patients who diagnosed as PTC recurrence underwent RPN resection transorally and followed by high-dose RAI. All of the eight patients including two patients with lung metastasis repeatedly underwent high-dose RAI after the surgical treatment, and six patients who did not have lung metastasis were followed up with the normal range of on-Tg (mean 1.18 $\pm$ 2.19) and TgAb (mean 31.78 $\pm$ 44.70) and shows no local or distant recurrence.
Conclusions
Although the cases were rare, metastasis to the RPN should be considered at primary diagnosis and follow-up. Neck CT scan or MRI is recommended for the

diagnosis of RPNM, because these metastases will be missed by routine neck US. Complete thyroidectomy combined with transoral RPN resection is feasible and safe method for PTC with RPNM.

DOI: 10.1530/endoabs.101.PS1-03-04

## PS1-03-05

**Embryo/Fetus dose from [131I]nai therapy during an unsuspected pregnancy**

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Purpose
Based on ICRP recommendations, accidental exposure of embryo/fetus to radiation at any gestational age during [$^{131}$I]NaI therapy may result in wide range of genetic damage, cancer, and early death of the embryo/fetus. More than the limitation in clinical study due to ethical aspects, the previous studies performed radiation dosimetry in embryo/fetus using [$^{131}$I]NaI biodistribution in animal and Medical Internal Radiation Dose (MIRD) method with their uncertainties. Here we estimate the embryo/fetus radiation absorbed dose from maternal organs and thyroid gland of fetus in primary gestation age by [$^{131}$I]NaI using a more accurate Monte Carlo method.
Methods
An ICRP 110 digital female phantom with an embryo/fetus in the first 13 weeks' gestation was used, considering $^{131}$I energy spectrum for auger, β, γ and x-ray. The maternal uterus, thyroid, and ovary and embryo/fetus thyroid >9 weeks gastation were considered as sources and total embryo/fetus volume was considered as target. The factor [mGy/(MBq.h)], which represents the absorbed doses delivered to target per unit disintegration of radionuclide in source regions was calculated using a Monte Carlo method in 6-13 weeks gestation. This method provides a more realistic model for interaction of decayed particles and photons with tissue. All simulations were performed with GATE V7.2 (international OpenGATE collaboration). The GATE software is based on Geant4 toolkit.
Results
The absorbed dose results for 6-13 weeks gestation to embryo/fetus from maternal uterus, thyroid, and ovary were 0.146-0.272, 0.087-0.097, and 0.020-0.043 mGy/(MBq.h), respectively. The absorbed dose for the embryo/fetus from the ovary also increased with the age of the fetus, while it decreased with the age of the embryo/fetus from the uterus. Furthermore, there was no significant change with increasing embryo/fetus age in absorbed doses by embryo/fetus from maternal thyroid gland. Moreover, self-absorbed dose range to fetus from its thyroid was 0.233-0.408 mGy/(MBq.h), which is higher than absorbed dose from maternal organs. The most interesting result was fetus's absorbed dose from its thyroid gland after the 9$^{th}$ week, which reached the maximum in 9$^{th}$ weeks and decreased with increasing fetal age until the 13$^{th}$ week.
Conclusion
The results showed that the absorbed dose by the fetus in the fetal thyroid gland, as well as the absorbed dose by the maternal organs, contributed significantly to the total dose of [$^{131}$I]NaI absorbed by the fetus. Malformation and damages to central nervous system are the main risks of radiation to embryo/fetus after $^{131}$I-therapy that must be considered for continuing the pregnancy. Based on calculated factors, physicians or physicists can estimate the absorbed dose to embryo/fetus in pregnant cases by $^{131}$I-therapy with greater accuracy than before for a possible decision on termination of pregnancy.

DOI: 10.1530/endoabs.101.PS1-03-05

## PS1-03-06

**Subacute thyroiditis as the cause of a suspected thyroid nodule**

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Our study aim is to find out the frequency of misdiagnosing destructive focal lesions caused by subacute thyroiditis as thyroid cancer.

Methods and Results
The study was conducted at the Armenian American Wellness Center in 2023-2024. Thirty-four patients aged between 30-40 years participated in the study. All patients presented with TI-RADS4 nodules detected on ultrasound and were referred for fine needle aspiration (FNA) by the radiologist. An endocrinologist was consulted before the FNA was performed. After a detailed physical examination and collection of medical history, it was discovered that 16 of the patients (47%) had neck pain and a history of viral infection. In the 16 patients mentioned above (47%), anti-inflammatory treatment with steroid anti-inflammatory drugs was prescribed, and FNA was delayed. After two months, the ultrasound was repeated, and the findings were recorded. As a result, in 11 of 16 patients (68.75%), the inflammatory destructive foci were absorbed, leading to qualitative changes observed on ultrasound as TI-RADS 2-3. A total of 34 patients with TI-RADS 4 nodules were included in the study. Among them,18 underwent FNA, while for 16 patients, close observation was chosen. After two months, ultrasound assessments revealed that 5 out of the 16 patients showed TI-RADS 4, prompting FNA, while 11 out of the 16 patients presented with TIRADS 2-3, leading to the decision to defer FNA.
Conclusions
Therefore, if the thyroid ultrasound shows a TI-RADS 4 pattern and there is pain in the neck, elevated C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), it is recommended to start anti-inflammatory treatment and subsequently reassess the condition of the thyroid nodule.

DOI: 10.1530/endoabs.101.PS1-03-06

## PS1-03-07

**Pregnancy and persistent distant metastases in differentiated thyroid cancer (DTC); a case report**

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Introduction
Pregnancy is not considered as a risk factor for recurrence in a previously treated DTC with excellent response to therapy. However, in cases of structural or/and biochemical incomplete response, diligent monitoring is of value including, neck ultrasound (U/S), thyroglobulin (Tg) and Tg-antibodies assessment, especially in cases of distant metastatic disease where scarce data exist.
Case report
A 27-year-old female patient was diagnosed in 12/2017 with a left lobe papillary thyroid carcinoma (max diameter (d): 5 cm, infiltrative follicular pattern without extrathyroidal extension). Whole body scan (WBS) after radioiodine (RAI) (03/2018, 100 mCi) revealed uptake in the thyroid bed and lower lung fields (LLFs) (Tg: 227 ng/ml, TSH: 59.4 mUI/mL). 4 nodules (d < 5 mm) in the LLFs were documented in a chest computed tomography (CT) scan while a hypoechoic left cervical lymph node (LN) (d: 0.50 x 0.36 cm) was revealed in the U/S. 7 months (mos) after RAI (10/2018 - Tg: 1.94 ng/ml, TSH < 0.01 mUI/mL), diagnostic WBS under recombinant human TSH was negative for abnormal uptake (Tg: 7.64 ng/mL, TSH: 82.7 mUI/mL). During re-evaluation (07/2020 - Tg: 4.3 ng/mL, TSH < 0.01 mUI/mL) chest CT revealed suspicious nodule (d < 0.5 mm) of the left LLF (lingula) and a left axillary LN (d:11 x 4 mm), while neck U/S remained unchanged. In **02/2021** first pregnancy was documented (TSH throughout pregnancy: 0.01 - 0.03 mUI/mL); a gradual increase in Tg was observed to a maximum level of 32.6 ng/mL, noted one month after a healthy female offspring was delivered. Tg progressively decreased 3 mos later (19.1 ng/mL) without any therapeutical intervention. Nevertheless, due to persistently elevated levels (18 - 20 ng/mL) with unchanged neck U/S, second RAI (03/2022 - 150 mCi) was performed revealing uptake in the LLFs (Tg: 120 ng/mL, TSH: 43 mUI/mL). $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) - CT 5 mos later (08/2022 - Tg: 10.2 ng/mL, TSH: 0.01 mUI/mL), revealed nodules in, the left LLF (lingula) and the right middle lung lobe with, moderate/low and high FDG uptake, respectively; no remarkable change of the axillary and cervical LNs. In **11/2022** second pregnancy was documented (TSH throughout pregnancy: 0.01 - 0.05 mUI/mL); a gradual increase in Tg was afresh observed to a maximum of 115.36 ng/mL, noted one month after a healthy female offspring was delivered; Tg decreased 2 mos later to 54.52 ng/mL without any therapeutical intervention. $^{18}$FDG PET-CT revealed multiple nodules in the LLFs (d: 5 - 10 mm).
Conclusions
Two consecutive uncomplicated pregnancies led to the delivery of healthy offsprings in a female DTC patient with distant metastatic disease. Tg elevation during pregnancy was followed by structural disease progression, however, decrease to more than half, prior to any therapeutic intervention, possibly suggests that pregnancy related factors may wield a direct effect on Tg levels. Larger

studies with similarly selected DTC patients are needed towards evidence-based counseling of this patient subgroup.

DOI: 10.1530/endoabs.101.PS1-03-07

## PS1-03-08

**Unusual locations of a pappilary thyroid microcarcinoma**

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Distant metastasis in papillary thyroid microcarcinoma (PTMC) is rare but fatal; We report two cases of PTMC with skull and sellar region metastasis

Case 1

16-year-old M.A presents with a swelling in the parietal region of the skull. She consults for cephalgias, sensation of intracranial hypertention and right parietal hump appeared six months rather. The spinal IRM concludes a solidokystic osteolytic process of the right parietal worm with endocranial development and a local pachy meningeal reaction.. The patient underwent total exeresis of the tumor with cranioplasty. Histological examination revealed the diagnosis of a bone metastasis of vesicular carcinoma of the thyroid. With positive staining for thyroid transcription factor -1 (TTF-1) and thyroglobulin (TG). The thyroid echography found two suspicious nodules TIRADS5. The patient was operated on and underwent a total thyroidectomy with recural lymph node dissection and bilateral jugulocarotidien. The histological study of the piece is in favor of a bilateral papillary microcarcinoma of 4 mm at left and of 3 mm on the right classified PT1m N0 M1. Totalized isotopically by 100mCi I131 and suppressive treatment with thyroxine.

Case 2

A 62-year-old woman presented with non-secretory pituitary macroadenoma. MRI of the brain revealed a tumor of4.x5,3.x1,3 cm, extension into the cavernous sinuse. Underwent a simple biopsy in view of the haemorrhagic nature of the tumor. Histopathology revealed a tumor with diffuse papillary architecture. On immunohistochemistry: positive for TTF1, PAX8, thyroglobulin, TPO;Ki67 (10–15%) and negative for GH, LH, FSH, ACTH, TSH. A diagnosis of metastatic papillary carcinoma was made. Thyroid ultrasound revealed two micro nodules. After thyroidectomy the histopathology was papillary micro- carcinoma thyroid-follicular variant of 05 mm. She received radioiodine therapy.

Discussion

Lymph node metastasis or extraglandular extension has been reported in the few published cases of metastatic PTMC, the majority occurring within 5 years of the initial diagnosis. There have been case reports of PTMC with metastasis at unusual sites like the breast and cavernous sinus. All these cases were associated with a missed diagnosis of thyroid carcinoma, like our cases

Conclusion

There is no consensus for the treatment of PTMC with cavernous sinus metastasis or skull metastasis The treatment of children and adolescents with differentiated thyroid carcinoma is more controversial than the treatment of adults. Primarily because of the rarity of skull metastasis with thyroid carcinoma, the role of standard postoperative therapy for this situation has not been definitively established.

Key word

MPTC, skull metastasis, pituitary metastasis

DOI: 10.1530/endoabs.101.PS1-03-08

## PS1-03-09

**Intrathyroidal parathyroid carcinoma: a case report**

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Introduction

Parathyroid carcinoma (PTC) is a very rare neuroendocrine malignancy. It accounts for approximately 1% of primary hyperparathyroidism. Intrathyroidal localization is extremely rare.

Aim

On the basis of a case report and literature data, we describe the particularities of this rare pathological entity.

Observation

53-year-old female patient with history of recent venous thrombosis referred for management of a left thyroid nodule discovered by chance during a CT scan ordered to investigate severe anemia associated with secondary osteolytic bone lesions. Clinical examination revealed a 1 cm right paramedian basi-cervical swelling and an anodular left lobe. Cervical ultrasound showed a left thyroid nodule. Preoperative workup revealed normal calcium and phosphorus levels and a normal renal workup. The patient underwent left loboisthmectomy with extemporaneous examination showing atypical cells with vesicular neoplasms. The parathyroid glands were not visualized on the left side, and totalization was performed due to the patient's anaesthetic difficulties. The definitive anatomo-pathological examination with immunohistochemical study concluded to a parathyroid carcinoma of intrathyroidal localization. Postoperatively, the patient developed hypocalcemia requiring parenteral calcium supplementation with normal PTH value.

Conclusion

PTC is a very rare malignancy. Intrathyroidal localization is exceptional and presents a diagnostic challenge in the absence of clinical and morphological specificities.

DOI: 10.1530/endoabs.101.PS1-03-09

# Medullary thyroid cancer-1

## PS1-04-01

**Comprehensive appearance of men 2a due to CYS634ARG mutation**

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Introduction

MEN 2A is a rare hereditary cancer syndrome, which is inherited, as variety of autosomal dominant germline variants in the RET proto-oncogene.

Case report

We report a 29-year-old female with a past medical history of aggressive medullary thyroid carcinoma, with a high level of calcitonin, which occurred in the 2nd decade of her life. Total thyroidectomy was conducted in 2016, followed by the surgical extraction of a retroperitoneal paraganglioma approximately one year later in 2017. These manifestations were suspicious in terms of MEN 2 syndrome. Genetic testing for the most common RET proto-oncogene mutation (exon 16, codon 956) was conducted to rule out hereditary origins of the symptoms, yielding a negative result. After surgical interventions and therapy, stability was achieved, with a relative remission maintained for about five years. In 2023, during the visit ultrasound was performed and bilateral adrenal gland formations were revealed. Daily urine analysis indicated very high level of metanephrines. Also, hypercalcemia and hyperparathyroidism were indicated. Additionally, cutaneous lichen amyloidosis was noted during the objective clinical examination. Considering the clinical signs, investigation results, and the patient's history of aggressive MTC, paraganglioma, hyperparathyroidism, prematurely developed bilateral pheochromocytoma, and presence of cutaneous lichen amyloidosis, MEN2A appeared to be the most likely diagnosis. Importantly, there is no family history of MEN syndrome in the patient's family. At this stage, genetic testing using Next-Generation Sequencing was performed to detect RET germline variants, revealing a Cys634Arg mutation.

Conclusion

Numerous studies have demonstrated a strong association between the presence of Cys634Arg and susceptibility to hyperparathyroidism and bilateral pheochromocytoma. The objective of this case report is to underscore and draw attention to the propensity of the Cys634Arg mutation to manifest not only aggressive MTC but also premature pheochromocytoma and appear as comprehensive syndrome in the early stages of life. We highlight the fact that the premature onset of a highly aggressive form of medullary thyroid carcinoma, distinguished by extremely elevated calcitonin levels, is linked to an increased probability of earlier manifestation of accompanying symptoms. This case report emphasizes that more accurate attention to the general appearance of the patients and a precise physical examination could reveal the settings in which chronic manifestations take place, and the clinician might be able to prevent the irreversible aftermaths of the disease and save the patient from disastrous complications.

DOI: 10.1530/endoabs.101.PS1-04-01

## PS1-04-02

### Trends in the incidence, organization of care, and treatment of medullary thyroid cancer in the netherlands over the last three decades: a population-based study

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Introduction
The worldwide incidence of thyroid cancer has shown a steady incline over the past 35 years. While differentiated thyroid cancers are mostly responsible for this increase, population-based studies also show elevated medullary thyroid cancer (MTC) incidence rates. MTC is a rare, C-cell derived thyroid cancer, with a variable disease course that challenges treatment and follow-up. To enable adequate care of this rare cancer, international guidelines and centralization are of vital importance.
Objectives
Describe trends in the incidence, organization of care, surgical treatment and subsequent outcomes of MTC over 30 years in The Netherlands.
Methods
All patients with a histological MTC diagnosis between 1989 and 2018 were identified from the Netherlands Cancer Registry (NCR), and linked to the Dutch Pathology register (PALGA). Incidence rates, relative to the Dutch population, were determined and evaluated over time. Clinicopathological parameters and extent of lymph node surgery were extracted from PALGA pathology reports. Period A (1989 – 1998), period B (1999 – 2008) and period C (2009 – 2018) were compared.
Results
Throughout the 30 years, the population-adjusted incidence of MTC remained stable with $0.17 \pm 0.04$ diagnoses per 100,000 people, per year ($P = 0.247$). Of all 795 patients, 426 (54%) were female and 504 (63%) were treated in an academic hospital, at a median age of 48 years (IQR 34 – 61). Age at diagnosis increased over time from 42 years (IQR 25 – 61) in period A to 52 years (IQR 42 – 63) in period C ($P < 0.001$). The proportion of treatments occurring in an academic hospital increased from 41% of patients in period A, to 58% and 86% in period B and C, respectively (both $P < 0.001$). At primary treatment, a lymph node dissection was performed in 582 (73%) patients. Of these patients, 88%, 36% and 20% underwent a central neck dissection (CND), unilateral neck dissection and bilateral neck dissection, respectively. A CND was performed more frequently in period B and C than in period A ($P = 0.027$, $P = 0.009$, respectively). Overall survival improved from period B to C and A to C ($P = 0.022$, $P = 0.007$, respectively). The rate of locoregional recurrences remained stable over time.
Conclusions
This study shows a stable incidence of MTC in the Dutch population, over the last three decades. In addition, these data indicate a transition of treatment to academic hospitals, possibly resulting in better adherence to international consensus guidelines that advise prophylactic dissection of the central neck.

DOI: 10.1530/endoabs.101.PS1-04-02

## PS1-04-03

### The intratumoral infiltration of macrophages is associated with concomitant lymphocytic thyroiditis and possibly worse prognosis in patients with medullary thyroid carcinoma

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Introduction
Medullary thyroid carcinoma (MTC) accounts for up to 10% of thyroid cancers. Many of these patients present a syndromic phenotype, with multiple endocrine neoplasias, termed multiple endocrine neoplasia type 2 (MEN2), a genetic condition characterized by mutations in the RET gene. Despite many advances in the molecular biology of this disease, little is known about the immunopathology of the MTC tumor microenvironment.
Objective
The overall objective of this study was to investigate the immunophenotypic characteristics of infiltrating leukocytes in tumors of patients with MEN2 and MTC, correlating them with clinical-laboratory and anatomopathological data.
Methods
Twenty-six patients with histopathologically confirmed MTC were investigated. Patient tissues were reviewed to select the most representative areas for the construction of a tissue microarray (TMA). Immune cell markers, including tumor-associated macrophages (CD68) and subsets of tumor-infiltrating lymphocytes (CD3, CD4, CD8, CD20), as well as markers of immune activation (Granzyme-B, PD-L1), were analyzed. The presence of concomitant chronic lymphocytic thyroiditis was assessed by pathological scrutiny in normal parenchyma adjacent to the tumor. Statistical analysis was performed to investigate associations between immune markers and patient clinical characteristics.
Results
Three patients with MTC presented concomitant chronic lymphocytic thyroiditis. These patients showed a tendency toward a more aggressive clinical presentation with larger tumors ($P = 0.07$) and lymph node metastases in lateral compartments ($P = 0.03$). Our results demonstrated more frequent immune cell infiltration in malignant tissues compared to adjacent thyroid tissue. There was a significant association between PD-L1 and CD68 expression in various regions, suggesting a possible role of tumor-associated macrophages in the MTC immune microenvironment. The absence of CD68 cells was associated with the absence of thyroiditis in various tissue regions, indicating a possible immune escape mechanism of MTC. However, no significant associations were found between the presence of immune markers and the clinical status of patients during follow-up.
Conclusions
This study provides insights into the immunological processes in the MTC tumor microenvironment, highlighting the possible influence of tumor-associated macrophages and their relation to thyroiditis presence. However, further research is needed to fully understand the role of the immune system in MTC and its clinical relevance for patient prognosis and treatment.

DOI: 10.1530/endoabs.101.PS1-04-03

## PS1-04-04

### Evidence for the founder effect of V804L and V804M pathogenic variants affected kindred of brazilian families spreading multiple endocrine neoplasia 2A (MEN2A)

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Introduction
Medullary thyroid carcinoma may be associated with Multiple Endocrine Neoplasia type 2 (MEN2), resulting from germline mutations in the RET proto-oncogene.
Objective
We aimed to describe the molecular epidemiology of the pathogenic variants V804M and V804L of the RET gene through genetic population structure analysis.
Materials and Methods
We investigated molecular data from patients with MEN2A caused by RET mutation at codon 804 enrolled at BRASMEN (Brazilian Consortium of MEN). Peripheral blood was collected, and DNA was extracted. Analysis of haplotypes related to the RET gene was performed using capillary electrophoresis for the identification of 4 microsatellite loci, by the variable number of short tandem

repeats, that flank the RET gene. The definition of the haplotypes that carry the pathogenic variant in the RET gene was carried out using the Phase software for reconstruction, while GenePop was used to test if the studied loci are in Hardy-Weinberg equilibrium.
Results
We assessed data from 155 patients with a clinical diagnosis of MEN2A, who were divided into three groups according to the pathogenic variant that caused the MEN2A: 2 subpopulations for p.Val804Leu; c.2410G>C ($n = 44$, 12 families), and c.2410G>T ($n = 10$, 4 families) and one subpopulation for p.Val804Met: c.2410G>A ($n = 101$, 24 families). Individuals carrying the mutations c.2410G>C and c.2410G>T predominantly resided in the Ceará, a state in Northeast Brazil marked by European colonization. Individuals carrying the mutation c.2410G>A predominantly resided in the state of São Paulo, characterized by its multiethnic demographic structure. Our data showed that G>A ($P < 0,05$) and G>C ($P < 0,05$) subpopulations are not in Hardy-Weinberg equilibrium, while G>T ($P > 0,05$) is. The analysis of population genetic structure showed that the subpopulations had a high rate of endogamy (Fis=0,165), reinforcing that the preferential reproduction of individuals within these subpopulations may have amplified a founder effect that occurred in the historical past of the Brazilian population. However, the genetic distances between these subpopulations were moderate/low (Fst=0,051), suggesting that, despite the founder effect, genetic flows still occur between these subpopulations.
Conclusions
Our study suggests that three different founders may have originated the genetic diversity of patients with MEN2A and mutations at codon 804 of RET. Endogamy emerged as a phenomenon that may help to explain the differences between subpopulations of patients. More studies are warranted to unveil the molecular ancestry of mutations at the codon 804 of RET.

DOI: 10.1530/endoabs.101.PS1-04-04

## PS1-04-05

### Changing the paradigm: lobectomy for sporadic medullary thyroid cancer

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Objectives
Multicentric and bilateral tumour foci, usually associated to C cells hyperplasia, are typical of familial medullary thyroid cancer (MTC). On the other hand, sporadic forms are often monocentric. Thus, the question arises if total thyroidectomy is the best option for sporadic MTC, as currently suggested by International guidelines. In this context, a growing body of evidence, mostly coming from Asia, seems to support the possibility of a more conservative surgery. The main obstacle to this conservative approach could be the difficulty in preoperatively diagnose an MTC nodule, especially in Countries with a high prevalence of multinodular goitres. Aim of the present study was to evaluate: a) the performance of calcitonin (Ct) levels, ultrasound scans (US), and fine needle aspiration cytology (FNAC) in the preoperative identification of MTC and b) the number of total thyroidectomies that could have been avoided being the location of the MTC diagnosed preoperatively.
Materials and methods
We retrospectively analysed patients diagnosed with MTC in the last 30 years, treated with total thyroidectomy±lymphadenectomy, and followed in our Tertiary Care Hospital. Only patients with negative RET testing, histological report and at least one among pre-operative US, cytology (by FNAC), pre-operative Ct levels, and adequate follow up, were included ($n = 79$).
Results
Among the 79 patients with full clinical history, females were the 73.4% and the median age at diagnosis was 62 years. Median pre-operative basal Ct was 134 pg/ml, and median MTC size at histological evaluation was 11 mm. A strongly significant correlation was found between basal Ct levels and MTC size ($P$-value 0.000003). Only 3/79 (3.8%) patients had a bilateral MTC at histology. US was available in 51 patients, 26 of them (51%) had no nodules reported in the contralateral lobe, and histology confirmed in all cases (100%) the presence of a monolateral MTC, as preoperatively identified. In patients with bilateral nodules ($n = 25$), US correctly identified the lobe including the MTC in 12 cases (48%). Cytological result was positive or suspicious for MTC or malignancy in 32/50 (64%) FNAC performed on the nodule subsequently diagnosed as MTC at histology.
Conclusions
This is the first European study evaluating the feasibility of lobectomy± lymphadenectomy for MTC. We showed that US is a reliable tool to identify MTC pre-operatively even in a population with a high prevalence of multinodular goitre, and cytology diagnosed MTC in 64% of cases. In our cohort at least 51% of patients could have been initially treated with a more conservative surgery. Since pre-operative Ct levels strongly correlate with tumour volume, they can be used to identify the nodule to be submitted to FNAC.

DOI: 10.1530/endoabs.101.PS1-04-05

## PS1-04-06

### C-Cells hyperplasia, what is their role in the development of sporadic medullary cancer?

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Objectives
The aim of the present work was to verify if C-Cell hyperplasia (CCH) could be considered as a preneoplastic lesion of sporadic MTC and if CCH shares the same mutation profile of the main tumor
Methods
Forty-seven out of our whole series of 326 sMTC cases (14.4%) whose mutation profile was previously characterized by NGS were found to have CCH at histology. CCH formalin-fixed paraffin-embedded (FFPE) tissues were available in 20/47 selected cases. CCH area, identified by two independent pathologists, was micro dissected for DNA extraction: 15 cases were suitable for DNA analysis and 5 cases did not likely due to the very small area. CCH samples whose primary tumor was positive for a driver mutation were analyzed to track the same mutation by Sanger Sequencing and/or digital droplet PCR (ddPCR). In CCH samples whose primary tumor was negative, only *RET* Met918Thr was tracked.
Results
Eleven out of our selected 15 sMTC were found to be positive for the presence of a somatic mutation in the primary tumor: *RET* Cys634Arg $n = 1$; *RET* Met918Thr $n = 3$; *RET* Ser891Ala $n = 2$; *HRAS* Gln61Arg $n = 1$; *HRAS* Gly12Arg $n = 1$; *KRAS* Gly12Arg $n = 2$; *KRAS* Ala146Thr $n = 1$; four cases did not present any mutation. All but one CCH samples were negative for the mutations tracked. A *HRAS* Gln61Arg was found in a CCH samples (allelic frequency 0.4%) whose primary tumor was positive for the same mutation (allelic frequency 21.98%).This CCH positive case was ipsilateral of the main tumor and had a 30% of hyperplastic c-cells. The corresponding normal tissue was not affected by the *HRAS* mutation.
Conclusion
The present study showed that in most cases (10/11, 91%) CCH samples do not share the somatic mutation of the primary tumor thus hypothesizing that CCH is not related to sMTC development, and it could not likely be considered as a neoplastic precursor. The finding of a CCH case harboring the same mutation of the primary tumor suggests that in few cases CCH could be better considered as an emerging secondary tumor focus.

DOI: 10.1530/endoabs.101.PS1-04-06

## PS1-04-07

### Can haemithyroidectomy be an adequate treatment for nonhereditary medullary thyroid cancer (MTC)?

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Background
Total thyroidectomy and cervical lymph node resection is the standard treatment for MTC, as the cancer often occurs in both thyroid lobes and the incidence of lymph node metastasis reaches 80%, especially in patients with palpable tumor. However, previous analyses have included both hereditary and sporadic MTCs. In the ultrasound era, patients are referred for surgery earlier, often with not palpable MTCs, and the result of the germline RET oncogene mutation analysis is achievable before surgery. To date, bilateral tumors have been described in only 10% of sporadic MTCs, so we have undertaken an evaluation of the feasibility of hemithyroidectomy in this group, based on patients treated at our center.
Purpose
Evaluation of the clinical picture of sporadic MTC for the possibility of less radical surgical treatment.
Material and methods
Retrospective analysis of 658 patients with sporadic MTC treated in 2012-2022 at the Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch.
Results
Median age at the time of diagnosis was 58 years (17-85), the women: men ratio was 2,3. Median time of follow up was 4 years (0-12). 73% of tumours were detected incidentally, on imaging studies. Total thyreoidectomy was performed in 90%. Median diameter of primary tumor was 14 mm (1-100 mm). 68% of tumors were up to 2 cm, 10% $>4$ cm, 2,5% was inoperable due to local invasion or extensive distant metastases. In postoperative material multifocality was found in 10,5%, bilateral tumors in 3%, extrathyroidal invasion in 14%, angioinvasion in 26%. Lymph node metastasis occurred in 28% in the central compartment, in 21% in the ipsilateral lateral compartment and in 4% in the bilateral lateral compartment. Distant metastases were found in 6% at time of diagnosis. The occurrence of metastases in central and lateral neck nodes, and distant sites correlated with primary tumor size, occurring respectively in 10%, 7%, and 2% of tumors $<1$ cm; 30%, 27%, and 8% of 11-20 mm tumors; 41%, 38%, and 15% of 21-40 mm tumors; and 57%, 68%, and 45% of tumors $>4$ cm, ($P < 0.01$). Normalization of serum calcitonine after primary treatment was corelated with CR and achieved in 86% patients with $<1$ cm tumor, 68% 11-20 mm 57% 21-40 mm and 28% of $>4$ cm tumors.
Conclusions
Based on our retrospective data, it seems that in patients with non-hereditary MTC cT1aNoMo (based on preoperative ultrasound and genetic test result), lobectomy with central neck lymph nodes can be considered.

DOI: 10.1530/endoabs.101.PS1-04-07

## PS1-04-08

### Medullary and papillary thyroid carcinoma presenting as a collision tumors in the thyroid: report of seven cases

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Introduction
Collision tumors in the thyroid gland are uncommon entities constituting $<1\%$ of all thyroid tumors. These are defined as two distinct histological types of tumors arising concurrently within the thyroid, with the combination of Medullary Thyroid Cancer (MCT) and Papillary Thyroid Cancer (PTC) being the most common occurrence. PTC and MTC differ in management strategies and clinical courses, highlighting the importance of accurate diagnosis.
Patients and Methods
We conducted a retrospective analysis of patients diagnosed with MCT and PTC collision tumors in the thyroid, who were under follow-up from 2015 to 2021 at our tertiary care department. Among all cases of MTC and PTC during this period (177 PTC and 139 MTC, respectively), collision tumors represented 5.03% of MTC and 3.95% of PTC cases. We identified 7 cases (1 male, 6 females) with an average diagnosis age of 50.57 years (range 25-71 years).
Results
The left thyroid lobe was more frequently involved in both PTC (4/7, 57.1% of cases) and MTC (5/7, 71.4% of cases). 57.1% (4/7) of PTC, and 42.8% (3/7) of MTC were $<1$ cm, including two instances each of multifocal PTC and MTC. On average, MTC tumors, mean size 2.2 cm (0.8-7.7 cm), were more than twice the size of PTC tumors, mean size 0.95 cm (0.15-1.6 cm) - pT1 in three patients, pT2 in one patient, pT3 in three patiens, classified according to the TNM staging at time of surgery, however, all corresponding to pT1 TNM/AJCC 8th edition. The average follow-up period was 7.7 years. Genetic testing for germline RET proto-oncogene mutation was assesed in five patiens: two wild-type cases, two cases with RET polymorphisms linked to hereditary or sporadic MTC, and one case with a mutation in codon 634 (MEN 2 syndrome). Four patients underwent radioactive iodine (RAI) therapy (30-100 mCi); the other 3 patients with microcarcinoma (pT1a) did not receive RAI. Six patients maintained TSH levels between 0.5-2 mUI/l. By the last follow-up, all PTC patients showed excellent biochemical response (mean thyroglobulin levels 0.5 ng/ml, under 119.5 micrograms average dose of levothyroxine), and all patients had normalized calcitonin levels postoperatively except one (with the largest MTC tumor at 7.7 cm and two lymph node metastases, calcitonin levels were 12x upper normal limit). Histopathology analysis revealed focal chronic thyroiditis in two cases.
Conclusion
Collision tumors in the thyroid are not only rare but might also be underreported due to variability in sampling methods, particularly of the apparently unaffected lobe. The incidence rate in our series is similar with that reported in other case series. The aggressiveness of these co-occurring tumors appears similar to that of singular occurrences. However, recognizing this condition is critical for its therapeutic and prognostic significance.

DOI: 10.1530/endoabs.101.PS1-04-08

## PS1-04-09

### Somatostatin analogues treatment in a patient suffering from a sporadic bifocal ret-negative medullary thyroid cancer with extended extra-thyroidal spread after three surgical interventions

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor occurring either sporadically or in a hereditary form that can be cured by complete resection of the tumor and any locoregional metastases, but appropriate treatment remains less clear in patients with residual or recurrent disease. Herein we report the case of a 51-year-old man that was diagnosed with bifocal right-sided medullary thyroid cancer in October 2021 after a fine needle aspiration suggestive of an MTC. The patient underwent the following 3 operations within 2 years: a total thyroidectomy (10/2021), a right central and lateral neck dissection (2/2022), and a right central neck dissection plus right mediastinal lymphadenectomy (7/2022). The histology of the primary operation revealed 2 foci of MTC (max. diameter 4 cm and 1,1 cm) in the right lobe with extrathyroidal extension and 4 infiltrated lymph nodes out of 4 together with an intrathyroidal 0.4 cm large papillary thyroid carcinoma in the left lobe. The histology of the second and third operation revealed five infiltrated lymph nodes out of sixteen, and seven infiltrated lymph nodes out of seven respectively. RET mutation analysis was negative. Calcitonin levels were measured only one month postoperatively when he presented in our clinic and were as high as 3360pg/ml and dropped to 1259pg/ml, and 277pg/ml

after the first, second and third operation respectively. After the first operation, in the $^{18}$F-FDG PET/CT increased uptake was documented in several lymph nodes of the right upper paratracheal space and anterior upper mediastinum, with respective correlate in the cervical MRI. The $^{68}$Ga-DOTATOC PET/CT performed after the second operation documented increased uptake in the right paratracheal region and in the anterior upper mediastinum. In view of the positive $^{68}$Ga-DOTATOC, the revision of the histology demonstrated positive expression of somatostatin receptor (SSTR)2 and SSTR5 (score 3 and 2, according to Volante respectively) and ki-67 3%. A first-generation somatostatin analogue (SSA) treatment was decided with monthly Octreotide LAR 30 mg since an increase of calcitonin to 371pg/ml was observed. Six months later, and as the calcitonin levels did not respond adequately to the treatment (an initial drop of calcitonin levels to from 314pg/ml was followed by an increase to 490 pg/ml). Then medical therapy with monthly Pasireotide LAR 60 mg was initiated and 5 months later (10/2023) the calcitonin levels dropped at 261pg/ml. An antidiabetic therapy was also initiated, probably as side effect of the drug. Somatostatin analogues treatment seems to be a rationale alternative in patients suffering from recurrent and residual sporadic RET-negative medullary thyroid cancer when there is evidence of SSTRs presence by their positive immunohistochemical expression in the tissue and/or by the increased uptake in $^{68}$Ga-DOTATOC PET/CT.

DOI: 10.1530/endoabs.101.PS1-04-09

## PS1-04-10

### Clinical value of preoperative calcitonin for the prediction of distant metastases in patients with medullary thyroid carcinoma

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Introduction
Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor derived from the calcitonin-producing parafollicular C-cells. Calcitonin is the most important tumor marker for MTC both in the diagnostic and follow-up phase. The 2015 ATA guidelines recommend performing additional imaging preoperatively when calcitonin exceeds 500 pg/mL to detect distant metastases. However, this recommendation is based on a single study. Whether this is the optimal cutoff, including other diagnostic parameters, has not been evaluated in other studies. Therefore, the aim of the current study was to investigate the association of preoperative calcitonin and the presence of distant metastases at first clinical evaluation in MTC patients and to find the optimal cut-off.
Methods
We retrospectively collected a cohort of patients treated for MTC in a tertiary care hospital between 1984 and 2023. We included all patients with a preoperative serum calcitonin measurement. The presence of distant metastases was detected by preoperative imaging or biopsy. Performance of calcitonin was visualized by receiver operating characteristic (ROC) curve and analysis of area under the curve (AUC). Diagnostic performance parameters, sensitivity, specificity, positive predicted value (PPV) and negative predicted value (NPV), were calculated for different calcitonin cut-offs.
Results
In total, 123 patients with MTC were included of which 85 were suitable for analysis. Mean age was 55 ($\pm$ 14.4) years, 46% was female ($n$ = 39) and 71% had sporadic MTC ($n$ = 60). Distant metastases at presentation were found in 34% ($n$ = 29) of all patients. They had significantly higher preoperative calcitonin measurements than those without distant metastases (6036 pg/mL, 25-75 range 1367 – 15148.0 vs 695.0 pg/mL, 25-75 range 112.3 – 1835.0, $P <$ 0.001). The AUC for preoperative calcitonin was 0.8 (CI 95% (0.7 – 0.9), $P <$ 0.001). We calculated diagnostic performance parameters for different cut-offs with 350 pg/mL showing the best results (sensitivity: 97%, specificity: 48%, PPV: 49%, NPV: 96%).
Conclusion
To our knowledge, this is the first study investigating the optimal cut-off and its diagnostic accuracy for preoperative calcitonin in detecting distant metastases at first clinical evaluation in MTC patients. In our study, the best diagnostic performance for calcitonin was at a cut-off of 350 pg/mL, suggesting that the currently recommended cut-off of 500 pg/mL could be interpreted as guidance rather than a fixed cut-off. Ongoing analyses aim to further validate our proposed cut-off taking into account the optimal balance between detecting all distant metastases while minimizing unnecessary imaging.

DOI: 10.1530/endoabs.101.PS1-04-10

# Clinical thyroid cancer research-1

## PS1-05-01

### preexisting diabetes and aggressiveness of thyroid cancer: a cross sectional analysis

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Introduction
Insulin resistance and diabetes have been lined to increased tumorigenesis and tumor aggressiveness in a multitude of cancers, but that link seems controversial when it comes to thyroid cancer. The present work aims to characterize the effects of various forms of diabetes [autoimmune = type 1 + LADA = DM1 vs. type 2 diabetes = DM2] on the incidence and features of tumor aggressiveness of thyroid cancers in comparison to the general population (non-diabetes = non-DM).
Methods
We performed a retrospective data collection from patients undergoing thyroid surgery in ten Endocrine Surgery and Endocrinology Clinics in Greece, between 2021-2023. We reviewed the data on pre-existing DM, the DM type, duration and treatment used, preoperative TSH, the surgical pathology report, the use of I-131 therapy and any potential structural recurrence. We compared the aggressiveness of thyroid cancers based on histology among subjects with and without DM and its subtypes.
Results
We studied 808 consecutive patients with thyroid cancer; $n$ = 237 males (29.3%), with a mean age 47.3 $\pm$ 14.3 years, a mean BMI 27.0 $\pm$ 5.0 Kg/m$^2$ and TSH 1.99 $\pm$ 2.21 mIU/l. Out of them, $n$ = 692 had no DM, $n$ = 10 had DM1 and $n$ = 107 had DM2. Surgical pathology consisted of $n$ = 5 poorly differentiated/anaplastic, $n$ = 13 medullary, $n$ = 12 Hürthle cell, $n$ = 17 follicular and $n$ = 773 papillary thyroid cancers (PTC); $n$ = 20 (2.5%) with aggressive histological subtypes of PTC, $n$ = 5 (0.6%) with distant metastases (MET), $n$ = 199 (24.6%) with extrathyroidal extension (ETE), $n$ = 419 (51.9%) with capsular invasion (CI), $n$ = 225 (27.8%) with lymph nodes involvement (LNi) while $n$ = 23 had a structural tumor recurrence (CR) (2.8%). The incidence of aggressive histological types, CR, MET or number of I-131 treatments were not different between groups ($P >$ 0.05). ETE, CI and LNi were found at a significantly higher rate in non-DM compared DM1 and DM2, while gross ETE was more common in DM2 over DM1 and non-DM ($P <$ 0.001).
Conclusions
Autoimmune diabetes seems to confer a protective effect on several features of cancer aggressiveness in affected individuals as compared to DM2 and unaffected patients. Similarly, DM2 seems to significantly promote gross ETE. No statistically significant effects were observed pertaining to the risk for more aggressive tumors or histological subtypes of PTC. Although aggressiveness of thyroid cancer seems minimal in DM1 and potentially lower in DM2, a complex interplay between autoimmunity, hyperglycemia and tumoral biology is present, and requires significantly larger sample size to understand the interconnection between these parameters.

DOI: 10.1530/endoabs.101.PS1-05-01

## PS1-05-02

### Serum anti-thyroglobulin antibody levels following total thyroidectomy are related to the recurrence of papillary thyroid carcinoma

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Backgroud
Thyroid cancer, particularly papillary thyroid carcinoma (PTC), is globally on the rise, driven by increased incidental findings. PTC treatment boasts a commendable 93% 10-year survival rate, yet up to 28% of patients experience locoregional recurrences. Serum thyroglobulin (Tg) serves as a vital marker in post-operative surveillance for differentiated thyroid cancer (DTC). Anti-thyroglobulin antibodies (TgAb) play a crucial role in Tg interpretation, with their interference requiring reliable detection as per American Thyroid Association guidelines. Elevated TgAb levels, more prevalent in recent DTC cases, correlate with increased risks of persistence or recurrence, forming the focus of this study's analysis.
Method
This retrospective study included 15,620 patients from Gangnam Severance Hospital Thyroid Cancer Center who underwent bilateral thyroidectomy for thyroid cancer from March 2004 to December 2022. After exclusions for missing postoperative TgAb results and other carcinoma types, 4434 cases of papillary thyroid carcinoma (PTC) were retrospectively reviewed. Preoperative evaluations involved thyroid ultrasound and fine needle aspiration biopsy for suspicious nodules. TgAb tests, initiated 2 days post-surgery and repeated annually, were stratified into quartiles, and logistic regression analysis revealed a significant association between TgAb levels and PTC recurrence.
Results
The study group comprised 4434 thyroid cancer patients, with 775 males and 3659 females, and a median age of 46 $\pm$ 11.68. In Group 1 (TgAb level less than 20), consisting of 3640 patients, 81.2% were female. Tumor size and cancer recurrence rates increased significantly with higher TgAb levels in each group ($P < 0.001$). The proportion of females was consistently higher across all TgAb groups. Extrathyroidal extension did not exhibit a similar trend. The correlation analysis illustrated a consistent pattern: increasing TgAb levels corresponded to elevated odds ratios and probabilities of papillary thyroid carcinoma recurrence.
Conslusion
In patients who underwent total thyroidectomy for papillary thyroid cancer, serum TgAb levels may be useful in predicting patient recurrence. Previously, the prognosis of PTC patients was considered by dividing them into TgAb positive or negative. Now, by taking advantage of the fact that the higher the serum TgAb level, the higher the recurrence rate, this value alone can be used as a new prognostic indicator regardless of the time of TgAb testing after surgery.

DOI: 10.1530/endoabs.101.PS1-05-02

## PS1-05-03

### Toxicity and quality of life after locoregional radiotherapy in patients with thyroid cancer

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Objectives
To analyze acute and late toxicities and long-term quality of life (QoL) in patients who underwent locoregional external beam radiotherapy (EBRT) for thyroid cancer and to assess the correlation of QoL with treatment characteristics.
Methods
Patients treated with locoregional EBRT for thyroid cancer at University Medical Centre Groningen (UMCG) (2007-2023) were included. Patient/treatment characteristics were extracted from patient files retrospectively. Acute ($<6$ weeks) and late ($\geq 3$ months) toxicities and QLQ-H&N35 results (pre-radiation and 6 months post-radiation), collected as standard part of patient care, were extracted from a prospective database. Additionally, living patients were asked to complete QLQ-H&N43 (renewed QLQ-H&N35 version) and SF-36-RAND-36, allowing a longitudinal comparison. Correlations were evaluated between questionnaire scores and EBRT techniques (IMRT vs VMAT) and other treatment characteristics.
Results
For the retrospective analysis, 66 patients were studied. In a subset of 31 patients that completed the questionnaires during EBRT prospectively, acute toxicities included: dermatitis (93%), pain (74%), hoarseness (71%), dysphagia (67%), tough mucus (56%), xerostomia (52%), change of taste (27%), and mucositis (26%). Late toxicity presented as persisting acute toxicity and fibrosis (65%). After six months, the QLQ-H&N35 domains 'social eating' ($P = 0.031$) and 'dry mouth/sticky saliva' ($P = 0.025$) were impaired, in comparison to pre-radiation. 25 of the 66 patients were alive at time of data collection and 17 of them filled in the two additional questionnaires. Long-term mitigation was not observed for the 10/17 patients that completed both QLQ-H&N35 and QLQ-H&N43. For the treatment characteristics, only VMAT was associated with an improved QLQ-H&N43 score, compared to IMRT ($P = 0.047$).
Conclusion
EBRT causes acute and late toxicities in most thyroid cancer patients and creates a decrease in their QoL. As these patients generally have relative high survival rates, there is a compelling need to minimize toxicities with more refined radiation techniques, such as proton therapy.

DOI: 10.1530/endoabs.101.PS1-05-03

## PS1-05-04

### Reproductive concern and intention in young female patients with differentiated thyroid cancer after thyroidectomy: a prospective cohort study

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Objectives
Thyroid cancer is the common occurring cancer in women of reproductive age. The impact of thyroidectomy on childbearing plans remains unknown. The aim of this study is to longitudinally compare the reproductive concern and intention between young female patients with differentiated thyroid cancer (DTC) and those with thyroid benign disease after thyroidectomy.
Methods
This prospective cohort study enrolled female patients with DTC or thyroid benign disease undergoing thyroidectomy between 18 and 40 years old from Oct, 2019 to Oct, 2021 (registration number: ChiCTR1900027205). Reproductive Concerns After Cancer scale (RCAC) and Fertility Intention Scale (FIS) were evaluated preoperatively and postoperatively at 1, 3, 6, 12, 18, and 24 months, respectively. Pregnancy outcomes after thyroidectomy were also collected.
Results
Of the 482 eligible patients, 402 were diagnosed with DTC (157 underwent total thyroidectomy [TT] and 245 underwent thyroid lobectomy [TL]), and 80 were diagnosed with thyroid benign disease. Compared with the benign group, DTC group had significantly higher RCAC scores from 3 to 24 months postoperatively ($60.1 \pm 6.5$ vs. $58.1 \pm 4.7$, $65.4 \pm 5.3$ vs. $61.4 \pm 8.6$, $66.5 \pm 6.4$ vs. $57.4 \pm 6.3$, $52.6 \pm 8.9$ vs. $50.1 \pm 6.0$, and $53.0 \pm 7.5$ vs. $50.8 \pm 4.5$, respectively). DTC group had lower FIS scores than those with thyroid benign disease at 3, 6, and 12 months postoperatively ($46.9 \pm 8.9$ vs. $49.3 \pm 7.0$, $44.1 \pm 9.2$ vs. $49.0 \pm 6.9$, and $40.8 \pm 6.1$ vs. $50.7 \pm 5.3$, respectively). However, there was no significant difference of FIS scores at 18 and 24 months postoperatively. Among the DTC patients, TT subgroup experienced more reproductive concern and lower fertility intention than LT subgroup from 1 to 18 months postoperatively. However, at 24 months postoperatively, TT subgroup still had significantly higher RCAC scores than LT subgroup, but there was no difference in FIS scores. During follow-up, 79 women became pregnant (59 in DTC group [14.7%] and 20 in thyroid benign disease [25.0%]). The median time from surgery to pregnancy was 12.0 months for DTC and 13.5 months for thyroid benign disease. Seven women (3 in DTC group [5.1%] and 4 in thyroid benign disease [20.0%]) suffered miscarriage in the first trimester, and all of them conceived between 2 and 9 months after thyroidectomy.

Conclusions
It is necessary to take into account the reproductive concern and intention of female patients under child-bearing period after thyroidectomy, especially for those had DTC and underwent TT. Fertility counseling guidance should be provided for all patients after thyroidectomy with fertility intention, regardless of with DTC or thyroid benign disease.

DOI: 10.1530/endoabs.101.PS1-05-04

## PS1-05-05

**Impact of lymph node metastases features on presentation and outcome of patients with differentiated thyroid carcinoma (DTC)**

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Background
The impact of lymph node metastases (LNM) on the outcome of patients with DTC has been reevaluated in the last years. Its relevance is linked not only to the absence/presence of LNM, but also to other features such as number of LNM, dimension and extranodal extension (ENE).
Aim
The aim of this study was to evaluate in a large series of patients with DTC the impact of LNM on the clinical outcome. Patients were divided according to the risk of recurrence outlined by LNM features according to ATA 2015 Guidelines as follows: patients with LNM at low risk (LR-LNM: n $\leq$ 5 + $<$ 0.2 cm), intermediate risk (IR-LNM: $n > 5$ + $<$ 0.2 cm or any number LNM + 0.2-3 cm) and high risk (HR-LNM: any number LNM $>$ 3 cm +/- ENE o ENE +).
Methods
We evaluated 1522 consecutive patients with DTC who underwent total thyroidectomy $\pm$ therapeutic central a/o laterocervical compartment lymph nodes dissection and radioiodine treatment ($^{131}$I) between January 2010 and December 2012. LNM at histology were found in 291/1522 patients (19.1%). Of these, 65/291 (22.3%) patients were excluded because of the absence of complete histologic details about LNM. Overall, 23/226 (10.2%) were LR-LNM, 114/226 (50.4%) IR-LNM and 89/226 (39.4%) HR-LNM. Median follow-up time was 106 months (IQR 48–133).
Results
HR-LNM was more frequently associated with tumors $>$ 4 cm ($P = 0.01$), mETE and N1b ($P < 0.01$), absence of histologic thyroiditis ($P = 0.02$) and more advanced stage at diagnosis ($P = 0.025$). Then, they were more frequently associated with distant metastases at whole body scan ($P < 0.01$). Moreover, during the follow-up HR-LNM patients performed more $^{131}$I courses and consequently higher $^{131}$I total activitiy. At the data lock (March 2024), structural disease was prevalent in HR-LNM (17/89 - 19.1%) than in IR-LNM (11/114 – 9.7%) and LR-LNM (2/23 - 8.7%) group.
Conclusion
HR-LNM, defined by dimension $>$ 3 cm and the presence of ENE at histology, identifies a group of DTC patients with more aggressive disease and a higher risk of persistent/recurrent structural disease. Conversely, in presence of LR-LNM and IR-LNM the risk of persistent/recurrent structural disease is rather low and the need to perform radioiodine treatment in all cases is questionable.

DOI: 10.1530/endoabs.101.PS1-05-05

## PS1-05-06

**Data-driven thyroglobulin cutoffs for low- and intermediate-risk differentiated thyroid cancer follow-up in a real-world setting**

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Background
Thyroglobulin (Tg) plays a crucial role in managing patients with differentiated thyroid cancer (DTC). The utility of Tg in early and long-term follow-up of DTC patients has been well-documented. Although third-generation Tg immunoassays have improved accuracy, limitations persist, such as interference from antithyroglobulin antibodies and variability in measurements. Changes in DTC treatment approaches necessitate reevaluation of Tg thresholds. This study aims to assess the validity of serum Tg testing in the contemporary setting, focusing on two patient populations: those receiving traditional therapy (total thyroidectomy and radioiodine treatment) and those treated solely with thyroidectomy. We *aimed* to identify a data-derived threshold (measured approximately 1 year after initial treatment) based on actual outcomes within the first 5 years of follow-up.
Methods
A total of 540 DTC patients included in the Italian Thyroid Cancer Observatory (ITCO) database meeting specific criteria, were selected, excluding those with anti-Tg antibodies. Serum Tg levels, assessed using highly-sensitive assays, were examined at 1-year intervals post-treatment. Statistical analysis included the determination of the 97th percentile of disease-free individuals to establish potential cutoffs for structural disease.
Results
Serum Tg levels evaluated in 540 patients revealed a consistent distribution across treatment modalities. After excluding 26 patients with structural disease detected at any time point, the median TSH did not differ between patients treated with RRA and those who did not. We identified two potential thresholds (97th percentile of apparently disease-free individuals): 1.97 ng/mL in patients who underwent thyroidectomy alone (lower than proposed by the MSKCC protocol and ESMO Guidelines, but able to reliably rule out malignancy, given its NPV of 98%) and 0.84 ng/mL for patients who received after surgery a radioiodine treatment. Diagnostic performance demonstrated high sensitivity and negative predictive value, validating the potential thresholds in ruling out structural disease.
Discussion
Current guidelines for thyroglobulin (Tg) thresholds haven't been fully validated in the context of contemporary differentiated thyroid cancer (DTC) treatment strategies, which often involve less intensive approaches. Our real-world study support the reliability of serum Tg levels measured one year after treatment across various treatment settings We propose data-driven Tg thresholds that can inform clinical decision-making for patients undergoing total thyroidectomy and radioiodine ablation, as well as those receiving thyroidectomy alone.

DOI: 10.1530/endoabs.101.PS1-05-06

## PS1-05-07

**Thyroidectomized patients on LT-4 therapy with advanced medullary thyroid carcinoma treated with selpercatinib show peculiar variations of thyroid function tests**

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Objectives
In clinical trials assessing efficacy and safety of the highly selective RET inhibitor selpercatinib (Libretto-001 and 531), hypothyroidism was often described. We aimed to evaluate the variation of thyroid function tests (TFTs) in patients with advanced progressive medullary thyroid carcinoma (MTC) treated with selpercatinib at the Unit of Endocrinology of Pisa University Hospital.
Methods
We evaluated clinical and biochemical data of 19 thyroidectomized patients with advanced MTC who started selpercatinib treatment between June 2019 and January 2022. TFTs (fT4, fT3 and TSH) were measured at baseline and at each following evaluation.
Results
Most of the patients were males (68.4%) and, median age at selpercatinib treatment beginning was 54 years. Two patients passed away after 6 and one after 12 months of treatment. During the treatment, all patients showed TFTs alterations. After one month of treatment, in 4/19 (30.8%) patients L-T4 dosage was increased (median 28.5 mg/daily) due to increase in TSH values ($>$15 mUI/mL), and they were excluded from the following analyses. In the remaining 15 patients, after one month of treatment, TSH significantly increased and fT3 significantly decreased compared with baseline, without significant variation in fT4 levels (Table 1). During a median follow-up of 35 months, TSH levels progressively returned in the referral ranges after a median of 5 months of treatment, but this trend was not observed in fT3 levels (Table 1). Of note, levels of fT4 progressively increased (Table 1).
Conclusions
Selpercatinib treatment induces variations of TFTs in all thyroidectomized patients. The typical landscape is characterized by an early increase of TSH and decrease of fT3 levels. In a follow-up of about 3 years, TSH spontaneously

[PS1-05-07]

**Table 1** Trends of TFTs during selpercatinib treatment

| | Baseline ($n = 15$) | 1 month ($n = 15$) | 12 months ($n = 13$) | 24 months ($n = 12$) | 36 months ($n = 8$) |
|---|---|---|---|---|---|
| **TSH mUI/mL (median, IQR)** | 0.67 (0.27-1.55) | 6.68 (3.17-10.5) | 2.57 (0.61-9.4) | 3.06 (0.44-3.83) | 3.05 (0.29-13.79) |
| *p value vs baseline* | - | **< 0.001** | 0.063 | 0.11 | 0.08 |
| **fT3 ng/dL (median, IQR)** | 3.69 (2.96-4.19) | 2.45 (2.1-2.78) | 2.33 (2.05-2.76) | 2.46 (2.25-2.66) | 2.68 (2.40-3.12) |
| *p value vs baseline* | - | **< 0.001** | **< 0.001** | **< 0.001** | **0.016** |
| **fT4 ng/l (median, IQR)** | 1.38 (1.10-1.63) | 1.53 (1.36-1.70) | 1.79 (1.65-2.17) | 2.05 (1.87-2.51) | 1.63 (1.56-2.24) |
| *p value vs baseline* | - | 0.25 | **0.0011** | **< 0.001** | **0.025** |
| fT3/fT4 ratio (median, IQR) | 0.32 (0.31-0.35) | 0.19 (0.16-0.25) | 0.15 (0.13-0.19) | 0.14 (0.13-0.15) | 0.18 (0.15-0.21) |
| *p value vs baseline* | - | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** |

IQR: interquartile range

returned in the normal values, while fT3 levels were slightly below and ft4 levels slightly above the normal ranges. Therefore, a careful follow-up should be performed avoiding a hurried increase in L-T4 and/or L-T3 treatment, which should be reserved only for selected cases.

DOI: 10.1530/endoabs.101.PS1-05-07

## PS1-05-08

### Pediatric differentiated thyroid carcinoma: radioiodine treatment in hypothyroidism or after recombinant TSH?

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Introduction
Pediatric differentiated thyroid carcinoma (DTC) is a rare disease. In the literature, there are limited data for this type of tumor; in particular, it has never been evaluated the efficacy of radioiodine treatment with 131-I after 4-6 weeks from thyroid hormone withdrawal (THW) compared to the use of recombinant TSH (rhTSH); for this reason, the decision is often left to the experience of the team.
Aim
To compare the efficacy and safety of radioiodine treatment after THW or rhTSH.
Patients and Methods
We retrospectively evaluated 337 DTC patients, referred to our institution from 1966 to 2022. Inclusion criteria: age at the time of diagnosis $<18$ year; histologic confirmation of DTC; at least one radioiodine treatment with 131-I. Patients who underwent initial radioiodine treatments in hypothyroidism after THW and subsequent radioiodine treatments in euthyroidism after rhTSH stimulation, were excluded. We divided the patients according to the type of radioiodine treatment: Group A (123 patients treated after THW) and Group B (214 patients treated after rhTSH).
Results
Epidemiological, clinical, and pathological characteristics were similar in the two groups. Group A was submitted to a higher number of 131-I courses ($2.3 \pm 1.8$ sessions vs $1.6 \pm 1.4$) and a higher 131-I cumulative activity than Group B ($201.2 \pm 236.7$ mCi vs $123.3 \pm 176.6$). Despite the higher intensity of radioiodine treatment, due to a longer follow-up ($37.0 \pm 12.7$ years vs $9.8 \pm 7.2$), no significant differences were observed in the last assessment (excellent response: 83.9% vs 74.8%; biochemical incomplete response 12.7% vs 20.5%; structural incomplete response 3.4% vs 4.7; $P = 0.113$) and adverse reactions between the two groups.
Conclusions
This study showed that rhTSH is equivalent to THW. For this reason, and considering the significant benefits, it would be desirable to extend the use of rhTSH in radioiodine therapy to all patients with DTC occurring in the pediatric age.

DOI: 10.1530/endoabs.101.PS1-05-08

## PS1-05-09

### Bone mineral density (BMD), bone turnover markers (BTMS) and evaluation of musculoskeletal system in patients with differentiated thyroid cancer undergoing TSH suppressive therapy

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Background
The effect of L-thyroxine therapy on bone mineral density (BMD) in patients with differentiated thyroid carcinoma (DTC) is still controversial.
Objectives
The aim of this preliminary investigation was to evaluate the role of the evaluation of trabecular bone score (TBS) and body composition in addition to the BMD in a cohort of DTC patients.
Methods
The study involved a total of 104 patients who underwent total thyroidectomy for thyroid cancer, under LT4 therapy, in detail: 64 were females, 38 of them in post-menopausal state, aged $60,2 \pm 14,9$ years (mean $\pm$ SD), *versus* 58 age and sex matched healthy controls (CNT). Bone Mineral Density (BMD, g/cm$^2$) at lumbar spine (L1- L4), total hip and Relative Skeletal Muscle mass Index (RSMI) in whole body composition were analyzed using a DXA scan [Lunar full-Prodigy (GE Lunar, Madison, WI, USA)]; Lumbar spine TBS (TBS iNsight Medimaps) was derived for each spine DXA examination; fasting blood sample were obtained in order to analyse some biochemical parameters namely: calcium, 25(OH) vitamin D, parathormone, TSH, FT3, FT4.
Results
DXA scan was performed a median of 48 months after surgery (2-563 months). At the time of data cut off DTC patients showed a significantly lower bone mass compared with CNT ($P < 0.001$). (Lumbar spine BMD $1.19 \pm 0.24$ vs $1.35 \pm 0.14$ g/cm 2 $P = 0,007$). 42 patients presented suppressed TSH levels ($<0.5$ mU/l) at the time of DXA scan, 37 of them (88%) for more than 12 months. In DTC patients, the T-score for L1-L4 adjusted for TBS was lower than the full T-score L1-L4 (- 1.4 vs -0.25, $P < 0.001$). The concordance between the TBS and the BMD in assessing the diagnosis of osteoporosis was mild ($K = 0,14$). Mean TSH was $2,00 \pm 1.48$ mU/l; FT3 $= 3.29 \pm 1.61$ pg/mL; FT4 $= 13.19 \pm 3.87$ pg/mL, PTH $45.3 \pm 33.1$ ng/l, 25OHvitD $30.6 \pm 10.0$ ng/mL, calcium $9.2 \pm 0.6$ mg/dl. None of these variables proved related to the BMD ($P > 0.10$), while TBS proved related to calcium ($P = 0.014$) and PTH levels ($P = 0.002$). RSMI proved significantly positively related with bone trabecular quality (TBS) ($r = 0.31$; $P = 0.001$) and bone mineral content (BMD) ($r = 0.46$; $P < 0.001$).
Conclusion
This study suggests the usefulness of new diagnostic tools to investigate the effects of TSH suppressive therapy on skeletal mass and bone quality in patients under LT4 therapy after total thyroid ablation for DTC.

DOI: 10.1530/endoabs.101.PS1-05-09

## PS1-05-10

### Differentiated thyroid carcinoma: preliminary results of a randomized clinical trial on the impact of transitioning care to primary healthcare supported by telemedicine

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Introduction
Differentiated thyroid cancer (DTC) has low recurrence rates (2-5%). Despite this, the CDT consensus recommends long-term follow-up with specialists without defining a maximum follow-up time. Telemedicine is a strategy that aims to optimize the transition of care for patients from tertiary care to primary health care (PHC) and can help in the follow-up of these patients.
Objective
To evaluate the impact of the transition of care between specialized care and PHC for patients with DTC supported by telemedicine.
Methods
Patients with DTC and excellent response to initial treatment were randomized to follow-up in-person consultations in a tertiary service or transfer of care with telemedicine support. This support was provided through telephone calls to patients and health units to ensure linkage in PHC and offer support through teleconsultations. The primary outcome was DTC recurrence, assessed in a face-to-face consultation through thyroglobulin measurement and neck ultrasound. Outcomes related to the use of the healthcare system and control of hypothyroidism were also evaluated.
Results
To date, 206 patients have been included, the majority of whom are female ($n = 175$; 85%) and with papillary thyroid carcinoma ($n = 176$; 85.4%). Concerning the ATA risk classification, 110 patients were low risk (54.2%), 91 were intermediate risk (44.8%), and 2 were high risk (1.0%). All patients were treated with total thyroidectomy, 133 (64.6%) received radioactive iodine. The median follow-up before randomization was 6 years (P25-P75 3-12). Both groups have similar demographic and oncological characteristics. One hundred and twenty-nine patients were reevaluated in face-to-face consultations with a median of 31 months (P25-P75 28-35) after randomization, 70 from the intervention group and 59 from the control group. In the intervention group, one patient presented DTC recurrence, and one presented indeterminate response. In the control group, three patients presented indeterminate response. The rates of euthyroidism in the control and intervention groups were 54.2% and 55.7%, respectively ($P = 0.51$).
Conclusion
Transferring care to PHC for patients with DTC with excellent response after initial treatment appears to be safe, not increasing relapse rates or inadequate control of hypothyroidism.
Funding
Departamento de Tireoide da SBEM / Conselho Nacional de Desenvolvimento Científico e Tecnológico.
DOI: 10.1530/endoabs.101.PS1-05-10

## Thyroid cancer treatment

### PS1-06-01

**Intraoperative neuromonitoring does not decrease the risk of vocal cord palsy associated with thyroid cancer surgeries, but cumulative experience over time may**

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Background
The effectiveness of intraoperative neuromonitoring (IONM) in reducing the risk of vocal cord palsy (VCP) after thyroidectomy is controversial. This study aimed to evaluate the impact of IONM on VCP rates, identify risk factors, and assess the trend of VCP rates over time.
Methods
This retrospective observational study included consecutive patients who underwent thyroidectomy for thyroid cancer between March 2014 and June 2022. VCP rates were compared between non-IONM and IONM patients stratified based on the date of surgery. Univariate and multivariate analyses were conducted to identify risk factors associated with VCP, and the prevalence of VCP was observed over time.
Results
A total of 712 patients (485 females and 227 males) were included in the analysis. The mean age was 52.6 years. Final pathology consisted of 688 papillary thyroid carcinomas, 31 follicular thyroid carcinomas, five oncocytic carcinomas, four medullary thyroid carcinomas, two poorly differentiated carcinomas, and two anaplastic carcinomas. Transient and permanent VCP did not significantly differ between non-IONM and IONM groups. Transient VCP occurred in 7/151 (4.6%) patients in the non-IONM group and 24/561 (4.3%) patients in the IONM group ($p = 0.878$). Permanent VCP occurred in 1/151 (0.7%) patient in the non-IONM group and 2/561 (0.4%) patients in the IONM group ($p = 0.607$). Among the nerves at risk in the non-IONM and IONM patients respectively, transient damage occurred in 7/246 (2.8%) and 24/800 (3.0%) cases ($p = 0.901$); and permanent damage occurred in 1/246 (0.4%) and 2/800 (0.3%) cases ($p = 0.688$). Univariate analysis identified N1b stage (odds ratio [OR] 3.038, 95% confidence interval [CI] 1.285 - 7.182, $p = 0.011$) and extrathyroidal extension (OR 2.691, 95% CI 1.064 - 6.805, $p = 0.036$) as significant risk factors for VCP. Multivariate analysis did not reveal any significant risk factors for VCP. There was a statistically significant decreasing trend in VCP rates over time as the cumulative number of cases increased ($p = 0.017$).
Conclusions
IONM did not significantly reduce the risk of VCP. However, the surgeon's experience may have a role in reducing risk, as evidenced by the decreasing trend of VCP rates over time.
Keywords
Intraoperative Neuromonitoring, Risk Factors, Thyroid Cancer, Thyroidectomy, Vocal Cord Palsy
DOI: 10.1530/endoabs.101.PS1-06-01

### PS1-06-02

**Impact of short lenvatinib interruptions in advanced thyroid cancer patients**

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Objectives
Lenvatinib treatment significantly improves the outcome in advanced, radioiodine refractory, differentiated thyroid cancer (DTC) patients. The treatment efficacy relies on maintaining the drug dose intensity, which can be complex due to lenvatinib toxicities. Data from the SELECT study showed that interruptions for over 10% of the treatment period detrimentally affects prognosis. Nevertheless, the increasing knowledge from real-life experiences resulted in improved management of adverse events (AEs), thus reducing the need for prolonged suspensions. The impact of brief lenvatinib withdrawals remains unclear. Short, programmed drug holidays during treatment are reported to improve prognosis, but data are scarce. This study aims to assess the impact of short lenvatinib interruptions in DTC patients.
Methods
We retrospectively analysed 31 patients with advanced DTC treated with lenvatinib in our tertiary care centre. The primary outcome was the effect of short ($<10\%$ of treatment period) lenvatinib interruptions on the treatment efficacy and safety. Efficacy was evaluated as progression-free survival (PFS) and overall survival (OS). Safety was assessed as time to the first dose reduction (TFR), that is the interval between treatment initiation and the first dose reduction due to AEs. Comparison between subgroups was performed by Kaplan-Meyer survival analysis.
Results
For efficacy analysis, we compared PFS and OS of patients who transiently interrupted lenvatinib for $\leq 1\%$ ($n = 16$) and $>1\%$ ($n = 15$) of the time between lenvatinib initiation and either disease progression or death. The two groups were similar according to sex, age, tumour characteristics, metastasis location, follow-up length, and lenvatinib starting dose. Median PFS did not differ between $\leq 1\%$ and $>1\%$ withdrawal groups (39 *vs* 42 months, $P = 0.78$). Median OS was not reached in both groups, with no significant differences ($P = 0.36$). For safety evaluation, we compared TFR of patients who transiently interrupted ($n = 12$) and did not interrupt ($n = 19$) lenvatinib before dose reduction. Groups were similar for most anamnestic and clinical characteristics, including frequency of grade $\leq 2$ (66.7 *vs* 73.7%) and grade $>2$ (26.3 *vs* 33.3%) toxicities ($P = 0.32$). Median lenvatinib starting dose was lower in patients who transiently interrupted lenvatinib before dose reduction (12 *vs* 20 mg, $P = 0.02$). Median TFR was significantly longer in this subgroup (22.4 *vs* 5.5 months, $P = 0.049$). Nevertheless, neither suspensions nor lenvatinib starting dose independently predicted prolonged TFR in Cox regression analysis.
Conclusions
Results from our study demonstrate that short lenvatinib interruptions do not impair DTC patient outcomes. Conversely, they may improve therapy compliance by delaying the need for dose reduction.
DOI: 10.1530/endoabs.101.PS1-06-02

## PS1-06-03

**Risk factors predicting papillary thyroid cancer recurrence: a single-surgeon experience**

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Background
The incidence of thyroid cancer is increasing worldwide. In Korea, the incidence of thyroid cancer increased from 1999 to 2011, but subsequently decreased from 2012 until recently. The most common type of thyroid cancer is papillary thyroid cancer (PTC). Although PTC has an excellent prognosis, a recurrence rate of 30% has been reported.
Methods
This study retrospectively reviewed 2,842 patients who underwent primary thyroidectomy for PTC by a single surgeon between March 2007 and December 2018. Patients with preoperative distant metastasis were excluded.
Results
Among the 2,842 patients, 39 patients (1.4%) experienced disease recurrence during a median follow-up period of 5.0 years (range, 0–12 years). According to univariate analysis, tumor size ($>$ 1 cm), bilaterality, multifocality, extrathyroidal extension, lymphovascular invasion, perineural invasion, T stage ($\geq$ T2), numbers of central and lateral neck lymph node (LN) metastases, stimulated thyroglobulin concentration, and radioactive iodine dose were associated with disease recurrence. According to a multivariate analysis, only the number of central neck LN metastases was associated with disease recurrence (odds ratio 1.144, 95% confidence interval 1.054–1.241, $P = 0.001$).
Conclusion
Patients with clinicopathologic characteristics related to disease recurrence specifically central neck LN metastasis should be followed up carefully.

DOI: 10.1530/endoabs.101.PS1-06-03

## PS1-06-04

**Radiofrequency ablation (RFA) for structural incomplete response (SIR) to therapy in differentiated thyroid cancer (DTC)**

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Objective
SIR may occur in, 2 - 6% of ATA low risk and 67 - 75% of high risk DTC. Regarding locoregional disease, surgery is the optimal therapeutic modality if, the smallest dimension (sd) of the targeted node is $\geq$ 8 or 10 mm (central or lateral compartment). In the presence of, smaller nodes, contraindications or, patient's unwillingness for reoperation, active surveillance or minimally invasive treatments (MIT), may be considered. The purpose of this study is to present 6 DTC cases with locoregional SIR and their response to RFA.
Methods
6 patients (pts) with locoregional SIR following total thyroidectomy with central neck dissection were studied. Persistent or recurrent disease was defined as SIR $\leq$ 3 or $\geq$ 12 months (mos), respectively, after initial treatment. Clinical, histopathological, biochemical data and the therapeutic interventions were recorded.
Results
Pts were followed for 11 - 72 mos (median: 52.5), mean age at diagnosis: 42.2 years (range: 17 - 69). $n = 5$ were classified as ATA intermediate risk, $n = 1$ low risk. $n = 2$, presented aggressive variants (pt X: oncocytic widely invasive, pt Z: follicular with trabecular/insular/solid patterns). Lymphadenopathy was already present at diagnosis in $n = 3$, whereas in all but one radioiodine (RAI) was administrated with the whole-body scan (WBS) revealing minimal uptake in the thyroid bed. Persistent nodal disease was documented in $n = 3$ pts, mean size (sd): 4.88 mm (range: 4 - 6), volume (vol): 0.22 $cm^3$ (range: 0.12 - 0.40) with serum suppressed thyroglobulin (TG): 3.56 - 3.80 ng/ml. RFA was performed and during a follow up of 3 - 33 mos (median: 12) a 75 - 93% (mean: 87.6) vol reduction was documented with subsequent decrease of TG $\leq$ 0.4 ng/ml. Recurrent disease was documented in $n = 3$ pts (including X, Z) 34 - 51 mos after RAI. In pt X, two consecutive locoregional recurrences were documented over a 12-mo period, prior to RFA; he was reoperated twice (with additional RAI) however, a third recurrence was documented 6 mos after previous surgery. Pt Z, due to rising Tg-antibodies and normal neck ultrasound, underwent second RAI, prior to RFA, 31 mos following thyroidectomy, with negative WBS; locoregional recurrence was documented 38 mos after thyroidectomy. Mean size of targeted lesions was (sd): 6.83 mm (range: 4.7 - 9.2) and vol: 0.42 $cm^3$ (range: 0.20 - 0.90). RFA was performed and during a follow up of 3 - 15 mos (median: 9) a 67 - 95% (mean: 84.5) vol reduction was documented. In pt X, new recurrence, 3 mos following RFA, was documented; repeat RFA led to 40% vol reduction. $n = 2$ pts developed Horner syndrome secondary to RFA, which was completely resolved within 1-6 mos.
Conclusions
In DTC with locoregional SIR, RFA may lead to completion of the initial treatment, particularly in persistent disease. In recurrent disease, usually characterizing aggressive variants, RFA may locoregionally restrain disease progression. Larger studies, comparing different therapeutic modalities are needed, towards personalized treatment implementation especially, in intermediate and high-risk DTC.

DOI: 10.1530/endoabs.101.PS1-06-04

## PS1-06-05

**Counselling of thyroid cancer patients, what patient need to know from surgeon about treatment options, complications & follow-up**

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Background
Patients with thyroid swelling, specially advanced thyroid carcinoma shows a poor prognosis, and poses challenges during surgery & with risk of more post-operative complications. For this subset of patients. Important goal is preserving quality of life.
Methods
Different private hospitals & clinics and surgeons involved in thyroid surgery were involved in this survey in revealing the level of knowledge and the application of communication techniques in daily patient care.
Results
Many surgeons, considered that participation of patients & his/her relatives in therapeutic choices is very important. Update knowledge & training of surgeon is of utmost important. Main obstacle to complete and reciprocate communication skill is due to lack of time and staff, so also in the need for greater organization, which goes beyond the multidisciplinary strategy already used.
Conclusions
Proper & pragmatic plan & initiative to train and updating on issues related to counseling can improve communication among the clinicians involved in the treatment of thyroid cancer patients.

DOI: 10.1530/endoabs.101.PS1-06-05

## PS1-06-06

**Molecular profile can influence the PFS in radioiodine-refractory thyroid cancer patients treated with lenvatinib**

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Objectives
Limited and conflicting data exist regarding mutational profiles and clinical responses to tyrosine-kinase inhibitors (TKI) in advanced radioiodine refractory thyroid cancer (RAIR-TC). The role of BRAF/RAS mutational status on progression-free survival (PFS) in patients treated with lenvatinib is controversial. This study aims to assess the impact of genetic profiles on clinical responses to lenvatinib in RAIR-TC.
Materials and methods
We analyzed data from 49 patients with RAIR-TC surgically treated and followed at the University Hospital of Pisa who performed lenvatinib as first-line TKI therapy between 2012 and 2023. Nucleic acids were extracted from FFPE tissues and analyzed using NGS. TERT promoter and TP53 mutations were assessed via digital PCR. Response to Lenvatinib was assessed by CT scans according to RECIST.
Results
Males and females were equally distributed and median age at diagnosis was 60.5 years (IQR 50.7-68.4). PTC and FTC accounted for about 80% of all cases, while 10% had PDTC. About 30% of patients had distant metastases at diagnosis. The median duration of Lenvatinib therapy was 23.1 months (IQR 8-38.5). Genetic alterations were found in 39/49 cases (79.6%). A single driver mutation was found in 10/49 cases (20.4%): BRAF in 3/49 (6.1%), RAS in 6/49 (12.2%), and RET/PTC rearrangement in 1/49 (2%). Twenty-two cases (44.9%) had a driver mutation co-occurring with TERT or TP53 mutations. Seven cases lacked driver mutations but showed TERT mutation in 6/49 (12.2%) cases and TP53 in 1/49 (2%). Median overall survival (OS) was 9.5 years (IQR 6.2-15.2), while median PFS was 16 months (IQR 5.8-29.6). When dividing patients in group 1 (single driver mutation:

point mutations or gene rearrangements), group 2 (driver mutation co-occurring with TERT or TP53) and group 3 (no driver mutations, with or without additional mutations), OS did not significantly differ among the three groups ($P = 0.373$). However, molecular profile significantly influenced PFS. Group 1 had better PFS compared to group 2 and 3 ($P = 0.038$). In multivariate analysis, the absence of driver mutations was the only factor significantly associated with worse PFS (HR 3.095 – 95%CI 1.065-8.998; $P = 0.038$).

Conclusions

In patients with RAIR-TC treated with lenvatinib as first-line TKI, the mutational status did not significantly impact on OS. However, the absence of driver mutations, regardless of TERT or TP53 mutations, was independently associated with a worse PFS.

DOI: 10.1530/endoabs.101.PS1-06-06

## PS1-06-07

### The role of primary non-selective laryngeal reinnervation in the treatment of invasive thyroid cancer

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Introduction

Cases of locally advanced thyroid cancer can lead to spontaneous or irreversible intraoperative damage of RLN. For the correction of dysphonia with OCPS, are used static methods and the physiological reinnervation of the larynx.

Methods

A prospective monocenter study of the results of 61 cases of primary larynx reinnervation in the treatment of patients with invasive forms of differentiated thyroid cancer and initial laryngeal abduction paralysis. Used primary anastomosis of RLN - ansa cervicalis. The control was performed through 3, 6 and 12: laryngostroboscopy, VHI-30, Praat voice analysis 5.1.12. Statistical analysis - Wilcoxon's one-sample test, $P < 0.05$.

Results

Voice improvement was observed 3-6 months after surgery: in 92% of patients were observed medialization of the vocal folds, closure of the glottis during phonation. MTF increased from 7.2 $\pm$ 1.25 sec. up to 20.4 $\pm$ 2.88 sec. The harmonic/noise ratio increased from 14.1 $\pm$ 2.69 dB to 23.3 $\pm$ 1.25 dB, and the frequency of the fundamental tone of the larynx shifted from 188.3 $\pm$ 7.51 Hz to 221.3 $\pm$ 17.86 Hz. VHI-30 results: a decrease in the total score by more than 55 points, $P < 0.05$.

Conclusions

Nonselective primary reinnervation of the larynx does not restore the coordinated mobility of the vocal fold, but improves voice quality.

DOI: 10.1530/endoabs.101.PS1-06-07

## PS1-06-08

### Can nocturnal administration of lenvatinib based on time pharmacology reduce adverse events?

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Purpose

Molecularly targeted drugs are indispensable therapeutic tools for the treatment of unresectable differentiated thyroid cancer. Lenvatinib (LEN) is listed as a preferred regimen in the NCCN guidelines, and is a highly effective anti-tumor agent, but is also associated with a high rate of adverse events (AEs), which may be related to prognosis. AE management is key to LEN therapy. Although there is no recommendation in the package insert regarding the recommended time of LEN administration, A woman in her 30s with lung metastasis of poorly differentiated thyroid cancer who was attending our hospital was accidentally changed to take LEN "before sleep" instead of "after lunch", and her hand-foot syndrome (HFS) and diarrhea of AE were clearly reduced. HFS is said to be aggravated by loading of palms and soles and drug secretion from eccrine sweat glands, and it was assumed that the decrease in LEN blood concentration during the daytime (when palms and soles are loaded) due to pre-sleep medication was a factor in the improvement of HFS. Later, a woman in her 60s who had been suffering from HFS changed the time of her medication to "before sleep," and her HFS decreased as well. We hypothesized that LEN nighttime administration may reduce AEs from a time pharmacological perspective, and examined our patient's case.

Methods

A retrospective study of 44 patients with thyroid differentiated carcinoma of the thyroid, out of 107 patients who received LEN from 1/1/2015 to 9/30/2023, who changed the time of oral administration.

Results

The time of oral administration was changed a total of 55 times. The change to after breakfast, lunch, dinner, and before sleep was 16/5/18/16 times each. 62% (34/55) of the patients changed the time to nighttime, including after dinner and before sleep. The reason for changing the time of administration was to reduce AEs in 25 cases (28 times (1/3/12/12 times after breakfast/lunch/dinner/before sleep), of which 21 times (75%) AEs were reduced. The most common reasons for change in AEs were HFS/fatigue/diarrhea in 12/11/5 cases, and AEs could be reduced only by changing the time of administration in 4/4/3 cases (33/36/60%), respectively. In particular, the diarrhea was thought to be due to the fact that taking LEN at night, when DNA synthesis in the gastrointestinal mucosa is decreased, reduced the damage to normal cells.

Conclusion

Changing the time of LEN administration to nighttime may reduce AEs such as HFS and diarrhea.

DOI: 10.1530/endoabs.101.PS1-06-08

## PS1-06-09

### Surgical management of medullary thyroid carcinoma with tracheal invasion

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Introduction

Tracheal infiltration by thyroid carcinoma causes tracheal stenoses and hemoptysis, which is often fatal. Therefore, surgical treatment of thyroid carcinoma should be performed early to ensure patency of the airway.

Aim

This report deals with the diagnosis and surgical treatment of a patient undergoing resection of the trachea for recurrent thyroid medullary carcinoma infiltrating the trachea in Salah Azeize institute in March 2021.

Observation

A 63-year-old man underwent subtotal thyroidectomy with central lymph node dissection and modified left-sided neck dissection in January 2018 under the diagnosis of medullary thyroid carcinoma. The tumor occupied the entire left lobe and was adherent to sternothyroid muscle and the left recurrent nerve who was sacrificed. The area was subsequently irradiated with 56 Gray. There was no sign of recurrence two years after. Two year and nine months later an occult recurrence was suspected, with elevations of serum calcitonin as the only sign. Control tomography noted a tumor in the trachea. A tracheoscopy showed a tumor obstructing about three-quarters of the lumen of the cervical trachea. A length of about 15 mm of the trachea (three rings) was excised and the defect repaired by primary anastomosis. Laryngeal release was performed simultaneously to reduce the tension on the anastomotic sit. The patient is now well, seven months after the operation, with no signs of recurrence of the tumor.

Conclusion

The prognosis after treatment is better in thyroid carcinoma than in most other carcinomas. However, when a progressive tumor has infiltrated into the surrounding tissues, especially the trachea, the tracheal lumen is narrowed, leading to obstruction and often to fatal hemorrhage.

DOI: 10.1530/endoabs.101.PS1-06-09

## PS1-06-10

### The risk of hypocalcemia in total thyroidectomy with comprehensive mediastinal-recurrent cellular and lymph-node dissection

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Objectives
We aim to correlate the risk of hypocalcemia with mediastinal-recurrent cellular and lymph-node dissection, whether unilateral or bilateral, and incidental parathyroidectomy after total thyroidectomy.
Material and Methods
A retrospective study was conducted over a four-year period from 2020 to 2023 in the Department of Otorhinolaryngology and Cervicofacial Surgery at Salah Azaiz Institute in Tunisia. The study included 85 patients who underwent total thyroidectomy with mediastinal-recurrent cellular and lymph node dissection. The correlation between bilateral and unilateral mediastinal-recurrent cellular and lymph-node dissection and incidental parathyroidectomy and the risk of hypocacalcemia was investigated in the immediate postoperative period, as well as at 1 month and 6 months following surgery. Hypocalcemia was defined as a total serum calcium concentration $< 2.20$ mmol/l. Persistent hypocalcemia was defined as hypocalcemia persisting for 6 months.
Results
85 patients were included, with a sex ratio of 0.2 (17 men, 68 women). The age range was between 9 and 85 years, with a median of 45.6. In the immediate postoperative period, 28 patients (32.9%) showed hypocalcemia, and 12 of those required intravenous supplementation due to severe hypocalcemia. Bilateral mediastinal-recurrent cellular and lymph-node dissection was not associated with a statistically significant increase in the risk of immediate hypocalcemia compared to unilateral mediastinal-recurrent cellular and lymph-node dissection ($P = 0.41$), but the risk was significant at 1 month ($P = 0.02$) and at 6 months. Incidental parathyroidectomy did not significantly increase the rate of early hypocalcemia ($P = 0.28$), but it was associated with a worsening at 1 month ($P = 0.01$) and a higher risk of persistent hypocalcemia.
Conclusion
Hypocalcemia represents one of the most challenging complications following thyroid surgery. Bilateral mediastinal-recurrent cellular and lymph-node dissection may be linked to an increased risk of persistent hypocalcemia, primarily due to the heightened risk of devascularization related to per operative manipulation and incidental parathyroidectomy.

DOI: 10.1530/endoabs.101.PS1-06-10

# Cases reports

## PS1-07-01

### Intrathyroidal osseous metaplasia mimicking thyroid nodule suspicious for malignancy in a female patient with graves' disease- a case report

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Background
Osseous metaplasia (OM) of the thyroid parenchyma and intrathyroidal mature bone formation present rare findings in the pathological evaluation of resected thyroid specimens. Graves' disease is the most common cause of hyperthyroidism and thyrotoxicosis, is mostly characterized by diffuse enlargement of the thyroid gland and occasionally features nodular lesions with a variable percentage of malignant transformation. Herein, we present the case of a female patient with Graves' disease and concomitant diffuse calcifications of the left thyroid lobe with a cytological suspicion of malignancy that turned out histopathologically as benign lesions with osseous metaplasia.
Case report
A 44-year-old female patient presented for endocrinological evaluation due to newly detected hyperthyroidism. The patient reported weight loss of 10 Kg over the past 3 months with persistent heart palpitations, sweating and fatigue. The neck ultrasound revealed an enlarged thyroid gland and an echomorphological pattern typical of autoimmune thyroiditis with diffuse heteroechogenicity and inhomogeneity accompanied by elevated blood flow. The left thyroid lobe featured an area with diffuse micro- and macrocalcifications in the middle zone, as well as a nodular structure with peripheral microcalcifications in the caudal zone (**EU-TIRADS V**). The laboratory evaluation showed a hyperthyroid state with an active thyroid autoimmunity in terms of elevated anti-TPO autoantibodies, as well as TRAb-titers suggestive of Graves' disease. The patient was started on thyrostatic medication with methimazole 15 mg daily combined with propranolol 10 mg thrice daily. Biochemical euthyroidism was restored in 16 weeks and the methimazole dose was progressively reduced to a maintenance dosage of 2,5 mg daily 9 months after diagnosis. A fine needle aspiration biopsy of the above calcified zones was performed which showed cytological findings suspicious for malignancy (**Bethesda class V**). An adjunctive ultrasound of the tracheal lymph nodes revealed no pathological findings. The patient underwent total thyroidectomy, and the histological examination revealed a benign adenomatous nodule with a maximum diameter of 1,1 cm with osseous metaplasia and ectopic bone tissue formation. The patient remained euthyroid under levothyroxine supplementation needing no extra therapeutical procedures postoperatively.
Conclusion
The above case presentation comprises the first official report of osseous metaplasia and ectopic bone formation of the thyroid parenchyma in terms of Graves' disease in Greece. The clinical significance of thyroid ossification should be further investigated as the cases are scarce in the literature. Nevertheless, pathologists should be aware of this rare phenomenon when assessing thyroid specimens with calcified areas harboring a preoperative suspicion for malignancy, as this benign histopathological diagnosis excludes further curative measures for the thyroidectomized patient.

DOI: 10.1530/endoabs.101.PS1-07-01

## PS1-07-02

### Liothyronine and a sudden unexplained death: cause or coincidence?

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Introduction
Levothyroxine monotherapy is the standard treatment for hypothyroidism; it is safe and inexpensive, restores thyroid function tests to within the reference range, and improves symptoms in most patients. However, some patients require Liothyronine (LT3) to improve symptoms, and there is less safety data available for this. Here we report a case of sudden death in a patient using Liothyronine and present a safety data review for Liothyronine and Levothyroxine using national mortality and adverse-drug event records.
Case Summary
A 42-year-old woman was found dead in her house unexpectedly, one morning. She did not have any recent illnesses or significant past medical history and no regular medication was recorded in her general practitioner's record. However, she had previously seen a private practitioner and had been diagnosed with possible chronic fatigue syndrome and an 'under active thyroid'. For these, she took sertraline, clonazepam and liothyronine, bought off the internet and dosed by herself. Post-mortem examination showed no cardiac abnormalities, but did show bilateral pulmonary oedema, focal hepatic necrosis without inflammation, and an atrophic thyroid gland. Serum toxicology was unremarkable. The medical examiner reported the cause of death as "Sudden Unexpected Death in the setting of (chronic) liothyronine use". To set the coroner's conclusion in context, we assessed national statistics for mortality data in Wales over the last 10 years (2013-2022), to determine the overall deaths attributed to 'unknown cause' and to thyroid disease. We found that while deaths due to unknown causes are rare ($n = 681$, 0.185% of all deaths), deaths attributed to thyroid disease (excluding cancer) or thyroid medications, are even rarer ($n = 101$, 0.029% of all deaths). We found no death due to thyroid disease or thyroid medications in the patient's age-bracket. Lastly, we reviewed the number of adverse safety events including deaths due to Liothyronine and Levothyroxine in reports published by the UK medicines regulator, MHRA, via their yellow card reporting scheme since the early 1970s. The MHRA reported 23 deaths associated with Levothyroxine with no reported deaths associated with Liothyronine. Both treatments had similar profiles for other related non-fatal adverse events.
Conclusion
While this case raised concern that LT3 may be associated with sudden death, our safety data review is reassuring, and does not support an association between

Liothyronine and sudden death. Nonetheless, there is a pressing need for systematic studies on LT3 safety in larger populations.

DOI: 10.1530/endoabs.101.PS1-07-02

## PS1-07-03

**Methimazol-induced hepatitis in a patient with graves' disease**

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Introduction
Methimazole is an antithyroid medication which is now considered the first line agent for medical therapy of Graves' disease. Rare complications of methimazole (<1%) include agranulocytosis, aplastic anemia, nephritis and hepatitis. We would like to report the rare case of the patient with Methimazole-induced hepatitis.
Case Presentation
A 46-year-old woman, who complained of fatigue, loss of appetite, nausea, vomiting, jaundice, dark urine and light-colored stools was admitted to the Department of Gastroenterology and Hepatology. She had a history of Graves' disease, which has been diagnosed 20 days ago. At diagnosis, the biochemistry was: thyroid-stimulating hormone <0.001 (0.27–4.20 mU/l), free thyroxine (FT4) 61 (12–22 pmol/l) and free triiodothyronine (FT3) 15.4 (3.1–6.8 pmol/l). She had positive thyroid peroxidase and thyrotropin receptor antibodies. She was started treatment with Methimazol 40 mg daily. After starting treatment, she noticed dark urine, then jaundice and stopped the treatment. Currently lab results: bilirubin 698.5 (<19 µmol/l), indirect bilirubin 509.9 (<15.5 µmol/l), direct bilirubin 188.6 (<5.0 µmol/l), ALT 240 (<32 U/l), AST 180 (<31.0U/l), ALP 590 (<110 U/l) and GGT 40 (<30 U/l). At that time, the thyroid function was TSH <0.005, FT4 64 and FT3 11,3 Hepatitis serology was negative for hepatitis A, B and C. She was also negative for anti-mitochondrial antibody, anti-smooth muscle antibody, anti-parietal cell antibody and anti-nuclear antibody. Iron, Ferritin and Ceruloplasmin levels also were in normal range. She refused a liver biopsy. In the light of negative serological investigations for viral hepatitis and for auto-immune hepatitis, the possibility of drug-induced (methimazol) hepatitis was considered. Anti-thyroid medication was withdrawn and the patient was commenced on Propranolol (β-blocker) to control symptoms and given glucocorticoids (Metipred 32 mg, with gradual dose reduction). Dose adjustments were made with lab tests control. After 3 months lab tests (ALT, AST, Bilirubin, GGT, ALP, TSH, FT4, FT3) were normalized and the patient underwent a total thyroidectomy.
Conclusion
Several direct and indirect mechanisms have been suggested as the cause of liver dysfunction in hyperthyroidism. Summarily, these include direct liver toxicity from prolonged exposure to excessive thyroid hormones, liver cell degeneration from accelerated liver glycogen and protein decomposition, autoimmune-related liver injury, congestive hepatopathy from concomitant thyrotoxic heart failure, previous underlying liver disease and antithyroid medication-related liver toxicity and injury. Based on anamnestic, clinical, laboratory date of our patient, she was diagnosed Drug-induced hepatitis and started not typical therapy for Graves' disease before surgery. Clinicians should maintain a high index of suspicion for underlying hyperthyroidism in patients presenting with unexplained liver dysfunction or unexplained jaundice.

DOI: 10.1530/endoabs.101.PS1-07-03

## PS1-07-04

**Combined immune checkpoint inhibitor therapy and onset of graves' hyperthyroidism followed by seroconversion to autoimmune hypothyroidism: a case report**

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Introduction
Immune checkpoint inhibitors are used as therapy for advanced malignancies. The therapy is based on immune enhancement, thus, autoimmune side effects referred to as immune-related adverse events may occur. Thyroid function abnormalities have been reported, but more evidence is needed to substantiate the main subtypes and course of thyroid disease associated with this treatment.
Case report
A 51-year-old woman with metastatic pancreatic cancer and no previous history of autoimmune disease was referred to the Endocrine Department 4 months following the initial combined therapy with Ipilimumab (anti-CTLA-4) and Nivolumab (anti-PD-1). At the time of referral, the patient had biochemical overt hyperthyroidism with fully suppressed TSH (< 0.01 mIU/l), elevated free T4 (fT4) > 100 pmol/l (reference interval (RI): 12-22 pmol/l), and elevated free T3 (fT3) of 34.6 pmol/l (RI: 3.9-6.8 pmol/l). Despite the markedly biochemical hyperthyroidism, the patients presented with sparse symptoms of hyperthyroidism. TSH-receptor antibodies (TRAb) were negative as were thyroid-peroxidase antibodies, whereas elevated levels of thyroglobulin antibodies were found (993 kU/l). Due to recent CT-scan with contrast, thyroid ultrasound was performed revealing an enlarged, heterogenous hypoechoic gland with increased vascularity. High dose Propylthiouracil (PTU) was initiated with a response in thyroid function parameters (after one week of treatment: fT4: 42.2 pmol/l, fT3: 8.0 pmol/l; after two weeks: fT4: 20.6 pmol/l, fT3: 3.2 pmol/l). After four weeks of PTU treatment, the patient developed biochemical hypothyroidism, thus, treatment with PTU was discontinued, and treatment with Levothyroxine was initiated.
Conclusion
This case report illustrates the onset of autoimmune thyroid disease after combined immune checkpoint inhibitor therapy. The thyroid ultrasound findings and the response with antithyroid drug treatment makes TRAb-negative Graves' hyperthyroidism the most likely initial diagnosis which was followed by seroconversion to autoimmune hypothyroidism. Results highlight the importance of monitoring thyroid function in relation to immune checkpoint inhibitor therapy.

DOI: 10.1530/endoabs.101.PS1-07-04

## PS1-07-05

**Thyroid diagnostic dilemmas**

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We present the case of a 22-year-old male patient who posed a diagnostic dilemma due to discrepancies between his symptoms and biochemical markers in contrast to imaging findings. He reported a 18 month history of on and off neck swelling with associated symptoms of anxiety, tremor, loose stools and dry eyes (no weight loss). Thyroid function tests were normal with a Free T4 (FT4) of 12.4 pmol/l (12-22 pmol/l), TSH 2.75mU/l (0.27-4.2mU/l) and an ultrasound showed an enlarged and hypervascular thyroid gland. Subsequent investigations revealed a Low Free T4 (FT4) of 11.3 pmol/l (12-22 pmol/l), Normal FT3 = 5.1 pmol/l and TSH 1.07mU/l, TSH receptor antibody (TRAb) < 0.8 IU/l, Thyroid peroxidase antibody (anti-TPO) < 9 IU/ml and normal thyroglobulin antibodies at 11 IU/l (range 0 to 115). Subsequent antibody titres showed negative TRAb, Thyroid peroxidase antibody (anti-TPO) < 1.0 IU/ml and undetectable thyroglobulin antibodies. Thyroid ultrasound indicated an enlarged gland with increased vascularity. A Tc-99m pertechnetate thyroid scan showed diffusely increased uptake (13.9%). He responded well to beta-blockade for symptom control (past history of Asthma and mild neutropenia noted). Upon one-year follow-up, the patient continued symptom free with beta-blockade, albeit with subjective eye symptoms but no objective signs of thyroid eye disease. Investigations were repeated at this stage: FT4 remained low 10.9 pmol/l (12-22 pmol/l), FT3 5.8 pmol/l (3.1-6.8 pmol/l), TSH 1.3mU/l (0.27-4.2mU/l). The FT4:FT3 ratio was 1.8 (in keeping with an active process, rather than thyroiditis). Antibodies including anti-TPO, anti-thyroglobulin and TRAb again tested negative. Repeat Thyroid ultrasound revealed a swollen lobulated gland with mildly increased vascularity and pertechnetate thyroid scan showed significant and diffusely increased uptake (23.1%). We thus see no changes in the thyroid status with normal TSH, TRAb, thyroid antibodies in contrast to the radiological evidence of hyperactivity. In conclusion, this case underscores the complexities in diagnosing thyroid disorders with unique differential diagnoses of with a subclinical hyperactive (periodic) Graves', early stage of chronic autoimmune thyroiditis (CAT); or less commonly congenital thyroid hormone synthesis defects or iodine deficiency. Discussion points include a Serial monitoring over two years showed no progression in imaging or uptake characteristics, making CAT less probable. He being symptomatic for less than 2 years makes congenital defects less likely. Use of I-123 and performing a perchlorate discharge test could

identify rare organification defects. Lastly TRAb negative Grave's disease is still a possibility. However serial follow-up has not revealed a worsening picture or signs of abating, which makes this diagnosis less likely.

DOI: 10.1530/endoabs.101.PS1-07-05

## PS1-07-06

**Differential diagnostic challenges for ophthalmic diseases: a case report**

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Introduction
Graves orbitopathy (GO) is the most common extrathyroidal manifestation of autoimmune hyperthyroidism, although it can rarely occur in euthyroid and hypothyroid patients with chronic autoimmune thyroiditis. The eye involvement in GO is frequently bilateral and symmetric. When atypical ocular or incongruent biochemical findings occur, conditions that may mimic GO should be excluded. Immunoglobulin G4 - related disease (IgG4-RD) is a rare, progressive immune-mediated fibrotic disease characterized by tumor-like formations and can affect lacrimal glands, orbits, major salivary glands, pancreas, bile ducts, retro-peritoneum, lungs, kidneys, aorta, pachymeninges and thyroid gland.
Case report
A 36 year old woman has been admitted to our hospital due to right unilateral eyeball protrusion, eyelid swelling and redness, chemosis, conjunctival hyperemia and swelling of the right cheek. She had normal thyroid hormone levels (TSH 1.38 mIU/l, reference range 0.27-4.2mIU/l; fT4 19.1 pmol/l, reference range 12-22 pmol/l,). TSH receptor antibodies levels varied from $<0.8$ to 1.9 IU/l (reference range 0.0-1.8IU/l). Serum IgG4 levels were slightly elevated (IgG4 2.81 mg/dL, reference range 0.03-2.01 mg/dL). An orbital MR imaging showed bilateral increase in the orbital fat volume (predominantly in the right eye), right unilateral proptosis and enlarged two extraocular muscles on the same eye, mimicking GO. The Hertel exophthalmometry implied significant difference in proptosis between eyes (Hertel base 110 mm, right eye 25 mm and left 15 mm). Her past medical history was remarkable for atopy and surgery of the left submandibular salivary gland due to its asymmetrical enlargement with extraction of regional lymph nodes. Revised histopathological findings showed lymphoplasmacytic infiltrate (CD3+ T lymphocytes, activated CD20+ B lymphocytes, rare eosinophils, CD138+ plasmocytes (IgG4/IgG $>$ 40%)) of submandibular salivary gland and lymphadenopathy due to IgG4 infiltrate.
Conclusion
GO and IgG4-RD are conditions with overlapping ocular findings and represent the differential diagnostic challenges, as our case demonstrates. Although clinical findings sometimes suggest GO, IgG4-RD should not be overseen. Biopsy is suggested by some studies for patients who have an unusual clinical course of GO or have clinical characteristics of IgG4-RD.

DOI: 10.1530/endoabs.101.PS1-07-06

## PS1-07-07

**Patient concurrent hashimoto thyroiditis, hypothyroidism and graves orbitopathy**

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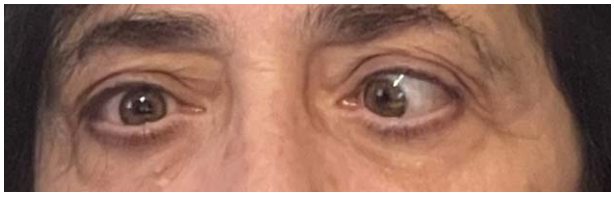
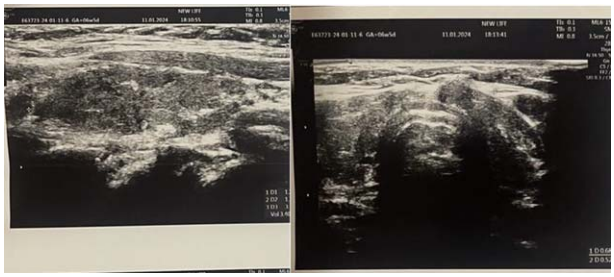
A 58-year-old woman presented left eye twitching, diplopia. irritation and conjunctival and periorbital edema, also left exophthalmos. Her medical history revealed a recent diagnosis of Hashimoto thyroiditis and hypothyroidism, for which she had been prescribed levothyroxine 50 mg daily for one month. Patient present test result, which she made 1 month ago.

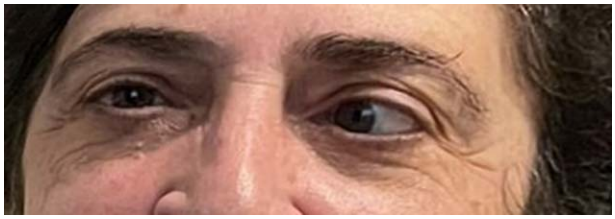


TSH- 8,4266Uu/ml (0,350-5,500)
FT4-8.10 ng/l (7,0-14,8)
FT3-3,15pg/Ml (1,71-3,710)
Anti-tpo- 1736UI/ml $<=5,61$
Anti –tg-5,51UI/ml $<=4,11$
Additionally, she was a tobacco user. She also said that sometimes had tachycardia. Patiens also said that in the evening, exophthalmos appeared in both eyes. Considering the symptoms, repeat the analysis of hormones, antibodies, Also additionally ultrasaund of thyroid and thyrotropin receptor antibodies (Anti-tshr), brain CT, CRP.

Subsequent results indicated: 1. suppressed TSH levels (0.06 IU/ml),
2. Elevated FT3 -4.77 pg/ml, reference range-2,30-4,20 pg/Ml,
3. FT4 -1.38 ng/dl. Reference range -0,89-1,76ng/dl.
4. Anti-thyroid peroxidase antibodies (Anti-TPO) greater than 1300.0 IU/ml
5. Anti-thyroglobulin antibodies (Anti-TG) at 5.90 IU/ml1
6. Anti-TSHR - 16.3. Positive-$>1,5$.
CRP in normal reference range.
Thyroid ultrasound - high blood flow of gland, hyper and hypoechogenic areas, total volume of thyroid -8,5 cm 3, in isthmus one nodule solid and hypoechoic, size-6,8 $\times$ 5,2 MM. TI-RADS 2. Imaging studies, including a CT scan of the brain, showed no abnormalities.
Thyroids ultrasound:



Given the diagnosis of graves diseases, the patient discontinued levothyroxine and commenced treatment with thionamide (thiamazole) 5 mg, beta-blockers, selenium, artificial tears and intravenous glucocorticoid (500 mg weekly for 6 weeks, followed by 250 mg weekly for the next 6 weeks for graves orbitopathy. Smoking cessation was strongly advised. Gave recommendation to after one month control ft4, Tsh. After one month, the patient's symptoms resolved, and follow-up tests showed: elevated **TSH (37.28 IU/ml)** and decreased **FT4 (0.669 ng/dl)**, indicative of hypothyroidism. Thionamide was discontinued, and levothyroxine 50 mg was resumed for two weeks. After two week control, tsh, Follow-up TSH levels were within the target range (**3.07 IU/ml**), stopped take of levothyroxine and intravenous glucocorticoids was continued according to the scheme. Next consultations exophthalmos, diplopia. Irritation, conjunctival and periorbital edema was no presenting. Summary, Hashimoto's thyroiditis and



Graves' orbitopathy are distinct diseases. While it is possible for an individual to have both conditions concurrently, such occurrences are exceedingly rare.

DOI: 10.1530/endoabs.101.PS1-07-07

## PS1-07-08

**Giant paracardial thyroid ectopy causing graves' hyperthyroidism. clinical and histological findings**

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Ectopic Graves' disease and sustained thyrotoxicosis after total thyroidectomy are extremely rare. In this abstract, we report a case of a 34-year-old female, presenting at our department for persistent Graves' disease (GD) despite total thyroidectomy performed at an affiliated hospital 4 months earlier and cessation of thyroid hormone replacement 6 weeks before presentation. She complained of palpitations, nervousness and sweating. Her pulse rate was 82/min, while on propranolol 20 mg td. Free T4 was 65 pmol/l (reference range 12-22 pmol/l), free T3 35 pmol/l (3.1-6.8 pmol/l), TSH <0.005 mU/l (0.3-4.2 mU/l) and TSH receptor antibodies (TSH-R-Ab) 27 IU/l (cut-off <1.5 IU/l, (Elecsys®, Roche Cobas)). Persistent GD in a giant paracardial thyroid was diagnosed by 99mTc-pertechnetate SPECT/CT. In the neck, only subtle pertechnetate uptake was found, while neck ultrasound showed no residual thyroid tissue. Euthyroidism was achieved on antithyroid treatment with methimazole 60 mg/day and methylprednisolone 32 mg (oral) followed by surgical removal of the large ectopic thyroid mass. At thoracotomy, a 13 X 10 X 5.5 cm lesion attached to the pericardium was resected. Nevertheless, binding TSH-R-Ab remained high (21.7 IU/l) and the patient developed active moderate-to-severe Graves' orbitopathy 3 months after mediastinal surgery, requiring IV methylprednisolone according to the 2021 Eugogo guidelines. Currently (1 year and 9 months after mediastinal surgery), she is euthyroid on levothyroxine 100 µg daily (free T4 23.1 pmol/l, free T3 5.6 pmol/l, TSH 0.05 mU/l), while binding TSH-R-Ab remain high (34 IU/l). Serial measurement of the stimulatory TSH-R-Ab, at the accredited and certified JGU thyroid lab, with the help of a novel, CE-marked, ultrasensitive cell-based bioassay (cut-off < 0.024 IU/l) demonstrated the sustained presence of a high concentration of these specific TSH-R-Ab in the patient serum post-thyroidectomy and post-thoracotomy (3.72 IU/l and 3.62 IU/l in December 2023 and March 2024, respectively). Multiple blocks of the eutopic thyroid (35 g) and the large ectopic tissue (408 g) were examined histologically. The eutopic thyroid showed signs of hyperplasia within a nodular structure with variable follicle size. In contrast, the ectopic tissue showed a more diffuse pattern with higher epithelial cells, which is typical for GD. Molecular testing of the giant ectopic tumor (PAX-PPARgamma, BRAF, RET, etc.) was negative for mutations. In conclusion, we present a rare case of persistent GD in a giant ectopic paracardial ectopy, providing to our knowledge the first description of markedly different histological appearance of eutopic *versus* ectopic tissue in the context of GD.

DOI: 10.1530/endoabs.101.PS1-07-08

## PS1-07-09

**A case of thyrotoxic periodical paralysis in a caucasian subject**

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Introduction
Thyrotoxic periodic paralysis (TPP) is characterized by muscle paralysis, hypokalemia and thyrotoxicosis. Mutations occurring in the genes that encode for ion channels (CACNA1S and KCNJ18) are thought to be involved in its onset. TPP mainly affects male subjects (M:F = 26:1), Asian (2% of Asian subjects with thyrotoxic suffer from TTP), while it is rare in Caucasian population (0.1-0.2% of thyrotoxic subjects). Signs and symptoms of thyrotoxicosis are often absent in TPP patients.
Case Report
In February 2023 a 20-year-old Caucasian patient come to our attention because of weakness of the lower limbs and postural instability that had ensued after intense physical activity. He reported that a similar yet milder episode had occurred a few months earlier. The previous event had resolved spontaneously. The patient complained also of fine distal tremors in the previous six months. At physical examination, we observed weakness and hyporeflexia in the lower limbs. Blood tests showed hypokalemia (1.9 mEq/l), ECG sinus tachycardia (105 bpm) and U waves. Neurological symptoms remitted after intravenous infusion of potassium. At laboratory workup, autoimmune hyperthyroidism was diagnosed: fT4 3.62 ng/dL, (nv 0.7-1.7) fT3 14.9 ng/l (nv 2.7-5.7), TSH 0.014 mIU/l (nv 0.4-4), TRAb 5.02 IU/l (nv <1.5). Neck ultrasound showed a diffuse goiter. Treatment with methimazole was started, with restoration of euthyroidism. The patient did not experience further episodes of paralysis thereafter.
Conclusions
If not recognized and treated, TPP can induce respiratory paralysis and potentially fatal cardiac arrhythmias. It is advisable to evaluate thyroid function in case of non-familial hypokalemic paralysis in male subjects, especially if Asian, even in absence of symptoms suggestive of thyrotoxicosis.

DOI: 10.1530/endoabs.101.PS1-07-09

# Hyperthyroidism

## PS1-08-01

**Refractory case of amiodarone-induced thyrotoxicosis in a high cardiovascular risk patient**

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Introduction
Amiodarone is a widely used agent for life-threatening arrhythmias. Although amiodarone is associated with few side effects, including thyroid dysfunction in 15-20% of patients. Amiodarone-induced thyrotoxicosis (AIT) is a major adverse effect that can cause recurrence of arrhythmias and exacerbation of heart failure. It is a challenging diagnosis that affects 0,003% to 10 % of patients taking amiodarone. Type I AIT is seen in patients with preexisting thyroid disease and is generally treated with thionamides, while type II AIT represents a destructive thyroiditis that responds to glucocorticoids. A mixed type exists and is associated with higher mortality, especially in older adults with cardiovascular disease. Thyroidectomy is considered the last resort option for patients intolerant or refractory to medical treatment.
Case report
We present a case of 78-year-old women with a history of atrial fibrillation, essential hypertension and heart failure. She was referred to our hospital because of heart failure exacerbation. Laboratory tests showed suppressed TSH and high level of FT4 and FT3. She endorsed palpitations, excessive sweating, and reported taking amiodarone for 3 years prior to presentation. Thyroid autoantibodies were negative. Thyroid ultrasound showed mild thyromegaly with multiple nodules and normal vascularity. Mixed type AIT was suspected and she was started on methimazole 20 mg and methylprednisolone 32 mg daily. Patient was discharged with improved thyroid hormone results and continued on the same dose of methimazole and steroid. On a follow-up visit after four weeks, thyroid hormones were still on toxic levels. Patient started showing adverse effects of prolonged corticosteroid and methimazole therapy, namely a difficult to control diabetes mellitus, corticosteroid-induced myopathy and hepatotoxicity. She remained thyrotoxic despite using higher doses of methylprednisolone and methimazole without improvement in overall status. Several days after admission, a total thyroidectomy was performed resulting in significant clinical and laboratory improvement and the patient was safely discharged.
Conclusion
This case illustrates the potentially severe consequences of therapeutic medications and the importance of close surveillance of the side effects in several organs. Most cases of AIT are amenable to medical therapy with thionamides and/or glucocorticoids. In the minority of patients who do not respond to these measures or are too critically ill thyroidectomy is a viable option.
Fonseca M, Ferreira M, Paulo J, Neves Z. A Refractory Case of Amiodarone

Thyrotoxicosis. Cureus. 2022 Aug 29;14(8):e28527. doi: 10.7759/cureus.28527. PMID: 36185869; PMCID: PMC9516872.

DOI: 10.1530/endoabs.101.PS1-08-01

## PS1-08-02

**Prevalence of metabolic syndrome and its components in patients with controlled graves' disease**

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Objective
Our aim was to assess the prevalence of the metabolic syndrome (MetS) and its components in patients with controlled Graves' disease (GD).
Methods
This was a cross-sectional study involving 95 consecutive patients with GD referred to our tertiary care inpatient clinical center meeting the following inclusion criteria: controlled hyperthyroidism, treatment with antithyroid drugs, untreated Graves' orbitopathy (GO), if present. Patients' anthropometric parameters were evaluated and laboratory tests were performed with measurement of fasting blood glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, thyroid hormone and antibody levels. The presence of the MetS and its components as defined by the International Diabetes Federation from 2009 were evaluated.
Results
In our patient cohort 82.1% were females, mean age $50.2 \pm 13$ years, with median duration of GD 16.5 months. The MetS was observed in 32.6% of our patients, obesity – in 34.7%, hyperglycemia in 38.9%, arterial hypertension – in 36.8%, low HDL-cholesterol – in 23.2% and hypertriglyceridemia – in 13.7%. At the time of the inclusion in the study 33.7% of the patients were on antihypertensive therapy, 10.5% were on antidiabetic therapy and 6.3% were on antilipidemic therapy. There was not statistical difference neither between the prevalence of the MetS, nor between the prevalence of its individual components in female and male GD patients. The MetS was significantly more frequent in older patients, as well as abdominal obesity, hyperglycemia and arterial hypertension. There was not statistical difference in the frequency of the MetS and its components between GD patients with and without GO, except for waist circumference, which was significantly higher in patients with GO,
Conclusions
The presence of the MetS and its components among GD patients are to great extent similar to those reported in general population, except for dyslipidemia. Both hyperglycemia and dyslipidemia are often underdiagnosed and undertreated in GD patients. There were age-related differences regarding the proportion of GD patients with the MetS, obesity, hyperglycemia and arterial hypertension. The presence of GO does not affect the frequency of the MetS in the population of patients with GD. These findings underline the need for screening for the MetS and its components and their proper treatment in GD patients, especially the older ones.

DOI: 10.1530/endoabs.101.PS1-08-02

## PS1-08-03

**High frequency of mental fatigue after treatment of graves' hyperthyroidism but low rate of sick-leave – report from a longitudinal cohort in sweden**

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Objective
Mental fatigue (MF) is part of the concept of mental illness but is poorly established. Pathological MF occurs in many diseases and greatly reduces both quality of life (QoL) and work capacity. In Graves' disease (GD) that often affects women of working age, about 40% of patients show MF after the acute symptoms have been treated. MF can occur alone, but also in combination with depression or anxiety and women are more than twice as likely as men to be on long-term sick leave with a mental health diagnosis. In MF, life adjustments are needed, but the effect of MF on sick leave and work function in GD is poorly studied. In Sweden, sick-leave is reimbursed from the authority Swedish Social Insurance Agency.
Methods
In a cohort of GD patients ($n = 127$) from the CogThy and ImmunoGraves (IG) studies, patients were evaluated at diagnosis in hyperthyroidism and after 15 months of treatment for sick-leave, MF using the MF scale (MFS), anxiety, depression and clinical activity score (CAS).
Results
At debut 41.1% were on sick leave but 74.8% had MFS $>10$ indicating MF. Of those that were initially on sick leave 92% had MF. At 15 months ($n = 105$) 40.0% had MF but only 3.9% were on sick leave. All these patients had MF at the start of treatment. CAS did not differ between MF and non-MF groups at any occasion. The CogThy included premenopausla women with high FT4 (FT4 $<50$ pmol/l) but the frequency of persistent MF did not differ from the IG study, which included men and women aged 18-65 with overt GD, 39.6% vs 49.4%, respectively.
Conclusion
MF was frequent at follow-up, as we have reported before. Despite its strong correlation to work ability most patients actually worked. Internationally reports on GD patients report a significant number of patients are long-term disabled and many change work. Our result may indicate problems for our patients to have MF approved by the Swedish Social Insurance Agency, as also witnessed by some patients, as MF is not an established complication to MF yet. MF in GD patients needs to visualised and our findings needs further evaluation.

DOI: 10.1530/endoabs.101.PS1-08-03

## PS1-08-04

**Thymic hyperplasia is accurate to detect new onset graves' hyperthyroidism and resolves after restoring euthyroidism**

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Objectives
Abnormal liver blood tests (ALBTs), neutropenia (NEU) and thymic hyperplasia (TH) are new features of Graves' disease (GD). Our objectives were: a) to calculate the accuracy of TH in discriminating between Graves' and non-Graves' thyrotoxicosis, compared to ALBTs, NEU and Graves' orbitopathy (GO); b) to explore the outcome of GD associated TH and non-GD associated TH.
Methods
We prospectively analyzed consecutive adult patients with newly diagnosed thyrotoxicosis from January 2018 to June 2023. TH was detected via neck ultrasound (nUS) then confirmed and followed by magnetic resonance imaging (MRI). For GD vs non-GD clinical sensitivity (SE) and specificity (SPEC), accuracy, positive predictive value (PPV) and negative predictive value (NPV) of GO, TH, ALBTs and NEU were calculated.
Results
264 thyrotoxic patients were included. TH was found in 16.4% (20/122) of GD vs 1.4% (2/142) in non-GD ($p < 0.001$). SE, SPEC, accuracy, PPV and NPV of the four extrathyroidal manifestations of GD were as follows, respectively: GO 26%, 100%, 66%, 100%, 61%; ALBTs 41%, 89%, 69%, 76%, 66%; NEU 5%, 100%, 56%, 100%, 55%; TH 16%, 98%, 61%, 91%, 98%. In 18 of them TH regressed within 12 months after achieving euthyroidism under antithyroid drug therapy, while in the remaining two TH regressed six months after thyroid surgery. In the two non-GD patients with TH thymus disappeared along with euthyroidism.
Conclusions
TH in the hyperthyroidism scenario provides a high PPV for GD. A conservative approach for the diagnostic work-up and initial management of thyrotoxicosis associated TH should be adopted.

DOI: 10.1530/endoabs.101.PS1-08-04

## PS1-08-05

### Trab levels and thyroid volume in graves' disease treated with block-replace therapy *versus* titration regimen

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Context
Graves' disease (GD) is the most common cause of hyperthyroidism, usually affecting women.
Objective
To asses the thyroid function and volume in GD patients treated with anti-thyroid drugs (ATD) in different regimens.
Patients and Methods
The study included 128 adult patients (104 females (F), 24 males (M)) with newly diagnosed or relapsed GD treated medically. Patients were consecutively admitted to a tertiary endocrinology center. Two visits were recorded at a time interval of 2-6 months. Patients with a medical history of radioiodine therapy, those who underwent thyroid surgery, pregnant women and those who were not compliant with medical therapy were excluded. The group was divided into two subgroups according to the ATD regimen used: block-replace (B) and titration (T) regimen. Thyroid hormone levels (free thyroxine ($fT_4$) and total triiodothyronine (TT3)), thyroid stimulating hormone (TSH) and TSH receptor antibodies (TRAb), ATD and levothyroxine ($LT_4$) doses used were registered. Each patient underwent thyroid ultrasound. Thyroid volume was expressed in $cm^3$ and calculated with the formula: sum of anterior-posterior*transverse* longitudinal diameters*0.5233 of each thyroid lobe.
Results
Subgroup B enrolled 53 patients (43 F, 10 M), mean aged $50.4 \pm 11.8$ year-old (y.o) and subgroup T enrolled 75 patients (61 F, 14 M), mean aged $46 \pm 15.2$ y.o., $P = 0.06$. During medical therapy the levels of TSH and $fT_4$ were stable in both subgroups. Also, during medical therapy TRAb levels and thyroid volume decreased in both subgroups but not statistically significant. TRAb levels were statistically significant lower in subgroup B than in subgroup T during both visits: $8.3 \pm 10.8$ UI/l *versus* $14.6 \pm 13.5$ UI/l (visit 1) and $6.7 \pm 10.1$ UI/l *versus* $14.1 \pm 14.2$ UI/l (visit 2) respectively, $P = 0.01$. TRAb levels decreased by 1.51 UI/l 95% CI (-3.23; 6.24) in subgroup B and by 0.52 UI/l 95% CI (-5.51; 6.55) in subgroup T. Thyroid volume was higher in subgroup B than in subgroup T: $25.3 \pm 16.7$ $cm^3$ *versus* $15.5 \pm 15.9$ $cm^3$ (visit 1) and $23.8 \pm 19.5$ $cm^3$ *versus* $11.2 \pm 20.5$ $cm^3$ (visit 2) respectively, $P = 0.002$. Thyroid volume decreased by 1.48 $cm^3$ 95% CI (-5.84; 8.79) in subgroup B and by 4.23 $cm^3$ 95% CI (-2.46; 10.99) subgroup T, respectively. The ATD used was MMI, with lower doses in subgroup B than in subgroup T: $12.21 \pm 6.2$ mg/d *versus* $19.8 \pm 15$ mg/d (visit 1), $P = 0.001$ and $12.09 \pm 7.63$ mg/d *versus* $15.42 \pm 8.61$ mg/d (visit 2), $P = 0.04$. The MMI and $LT_4$ doses used in block and replace regimen were similar during both visits, while in the titration regimen MMI doses were statistically significant lower in the second visit than in the first visit, $P = 0.03$. These results could be explained by the fact that in subgroup B were enrolled more patients with relapsed GD than in subgroup T: 67.92% (36/53) patients *versus* 38.66% (29/75) patients, $P = 0.001$.
Conclusion
Block replace regimen could be suitable for complicated GD with benefits for both TRAb levels and thyroid volume.

DOI: 10.1530/endoabs.101.PS1-08-05

## PS1-08-06

### Healthcare professionals' experiences of caring for patients with gravés disease- an interview study

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Background
Graves' disease (GD) mainly affects women in all age groups. Although most patients improve with treatment, patients still often experience cognitive and psychological symptoms. The ambiguity surrounding these persistent mental symptoms contributes to frustration for both patients and healthcare professionals. The study aims to provide in-depth insights into how healthcare professionals perceive the care of patients with GD. Through interviews, we aim to understand the support needs of this specific group of patients and the requirements of healthcare professionals (HCP). The study aims to provide profound insights into how HCP perceive the care of patients with GD. It also aims to identify ways in which the healthcare system can improve safety and quality of life from a personnel perspective, ultimately improving patient care.
Method
We conducted semi-structured interviews with 12 HCP working with patients with GD (6 nurses and 6 physicians). The interviews were analysed using content analysis according to Graneheim and Lundman.
Findings
The preliminary findings highlight challenges in healthcare and care for patients with GD. These include a shortage of resources, which makes it difficult to provide comprehensive care, and organisational constraints that hinder the efficiency of healthcare services. As a result, it can be challenging to address cognitive and psychological symptoms as thoroughly as necessary. In addition, the predominance of physician-led care and the lack of continuity in patient management are significant barriers to achieving optimal treatment outcomes.
Conclusion
Providing healthcare for patients with GD presents significant challenges, including limited resources, a physician-centred model of care, ambiguity surrounding the role of nurses, and time constraints. To improve the quality of care and address patients' needs, it may be beneficial to include a thyroid nurse in the team. Although medical treatments are available, there is still a need for a more holistic approach to patient care. To effectively address the diverse needs of patients, our previous interviews with patients have shown that an increased allocation of resources, clearer division of roles, and a multidisciplinary approach to care are required.

DOI: 10.1530/endoabs.101.PS1-08-06

## PS1-08-07

### Quality of life in graves disease: does type of treatment matter?

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Introduction
Graves' disease (GD) is the foremost cause of hyperthyroidism, and antithyroid drugs (ATD) are the first line of treatment, with around 40% of relapse after withdrawal. Therefore, radioiodine treatment (RAI) or a second course of ATD is indicated. However, the impact of those treatments on quality of life (QoL) is not well known.
Objectives
Investigate the impact of ATD and RAI in the QoL of relapsed GD patients.
Materials and Methods
Eighty-eight patients with GD relapse were evaluated in the euthyroid state (normal TSH and free T levels), according to the Thy-PRO 39 questionnaire. Group 1($n = 44$, $54 \pm 12$ years; 85% was female) comprised patients on the second course of ATD, and Group 2 ($n = 26$, $56 \pm 11$ years; 96% was female) consisted of RAI-treated patients (and levothyroxine replacement) while remission patients represented Group 3 ($n = 18$, $56 \pm 13$ years; 100% was female).
Results
There was no statistically significant difference ($P > 0.05$ by ANOVA) between the three groups concerning age, sex, and the mean clinical activity score. The

| | Group 1($n = 44$) | Group 2 ($n = 26$) | Group 3 ($n = 18$) | *P*-value |
|---|---|---|---|---|
| FT3 (ng/dL) | 3.54 ± 0.98 | 3.02 ± 0.38 | 2.83 ±0.71 | 0.006 |
| T3T (ng/dL) | 1.34 ± 0.61 | 0.91 ± 0.13 | 1.37 ± 0.78 | 0.001 |
| TT4/TT3 | 0.12 ±0.04 | 0.09 ± 0.02 | 0.14 ± 0.07 | 0.009 |
| TSH (uUI/ml) | 1.96 ± 1.34 | 2.54 ± 1.89 | 2.51 ± 1.27 | NS |
| FT4 (ng/dL) | 1.26 ± 0.38 | 1.39 ± 0.36 | 1.25 ± 0.09 | NS |
| TT4 (ug/dL) | 10.2 ± 3.0 | 10.3 ± 1.8 | 9.7 ± 0.9 | NS |
| CAS | 0.4 ± 0.8 | 0.4 ± 0.6 | 0.4 ± 0.5 | NS |

Group 2 patients had a lower T3T and TT3/TT4 ratio than groups 1 and 3 but no correlation with symptoms in the ThyPro 39 questionnaire.

total of the Thy-Pro 39 questionnaire regarding patient symptoms about goiter, hypothyroidism, hyperthyroidism, eye symptoms, tiredness, cognitive complaints, anxiety, depression, emotional susceptibility, social impact, impact on daily life, and impact on appearance did not show any difference between the three groups either.
Conclusion
Our results indicate that QoL in GD patients on ATD or RAI (with levothyroxine replacement) treatment is similar to remission patients, with patients treated with levothyroxine replacement presenting lower T3T and TT3/TT4 ratio.

DOI: 10.1530/endoabs.101.PS1-08-07

## PS1-08-08

**Contrast-enhanced ultrasound (CEUS) in hyperthyroid diffuse diseases**

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Objective
This study investigates the effectiveness and additional value of contrast-enhanced ultrasound (CEUS) in differentiating between destructive thyroiditis and hyperproduction states in patients with diffuse thyroid disease.
Methods
In this research, 56 patients diagnosed with hyperthyroid diffuse disease underwent evaluation through CEUS, alongside conventional ultrasound and standard diagnostic tests. We focused on qualitative CEUS parameters like perfusion patterns, enhancement intensity, and washout timing, comparing these between the two patient groups: those with destructive thyroiditis and those with hyperproduction-induced hyperthyroidism.
Results
Initial findings revealed distinct CEUS perfusion patterns differentiating between the two conditions. Destructive thyroiditis was characterized by slow wash-in with peak enhancement at median 18s (16-22s) and swift washout median 30s seconds (28-36s), indicative of increased vascular permeability and inflammation. Conversely, hyperproduction states displayed fast wash-in - median 10s (8-12.5s) ($P = 0.01$) and prolonged enhancement, suggesting enhanced thyroid activity and vascularity. CEUS showed high diagnostic accuracy (AUC 0.905) with sensitivity at 91% and specificity at 88.3%. These findings were in alignment with biochemical markers, suggesting the potential of CEUS in augmenting diagnostic accuracy.
Conclusion
CEUS contributes significantly to a deeper imaging-based understanding of pathophysiological differences in hyperthyroid diffuse diseases, aiding in more informed diagnostic and therapeutic decisions.

DOI: 10.1530/endoabs.101.PS1-08-08

## PS1-08-09

**Quality of life after thyroidectomy for benign thyroid disease**

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Objective
βenign thyroid diseases are common and can cause physical and mental symptoms. Although they may not affect a patient's life expectancy, they adversely affect Quality of Life (QoL). Thyroidectomy, even performed for benign thyroid conditions, is an invasive procedure that can further affect QoL. The present study aims to detect changes in thyroid-related QoL in patients with benign thyroid diseases who undergo thyroidectomy.
Methods
A prospective study was conducted on patients who underwent thyroidectomy for benign conditions between June 2018 and January 2020 in Thessaloniki, Greece. The thyroid-related QoL was assessed by a Thyroid-related patient-reported outcomes questionnaire (ThyPRO), recently translated and validated in Greek. The questionnaire consists of 85 items grouped in 14 scales concerning goiter, hypothyroidism, hyperthyroidism and eye symptoms, tiredness, cognitive impairment, anxiety, depression, emotional susceptibility, cosmetic complaints and impaired social, daily and sexual life, as well as overall QoL. Patients were evaluated one day before thyroidectomy and re-evaluated 3 and 6 months after the procedure. Data analysis was performed with IBM SPSS Statistics version 29.
Results
The study initially involved 73 patients, of whom nine were excluded as thyroid malignancy was reported in the histopathology report. Of the remaining 64 patients, 49 were women, and 15 were men aged 47.5 $\pm$ 14.2 years. The most common indication for thyroidectomy was non-toxic multinodular goiter (54.7%) , followed by toxic nodular goiter (21.9%). Patients improved overall QoL three and six months after surgery. Indicatively, goiter symptoms improved from 24.6 $\pm$ 2.6 before surgery to 7.6 $\pm$ 0.9 three months and 3.9 $\pm$ 0.7 six months after surgery ($p < 0.001$). Similar changes were observed in all ThyPRO scales.
Conclusions
Thyroidectomy has a positive effect on the thyroid-related QoL of patients with benign thyroid diseases, regarding goiter, hypothyroidism, hyperthyroidism symptoms and eye-related symptoms, as well as tiredness, cognitive impairment, anxiety, depression, emotional susceptibility, cosmetic complaints, impaired social, daily and sexual life.

DOI: 10.1530/endoabs.101.PS1-08-09

# Nodules

## PS1-09-01

**Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules smaller than 10 mm in the maximum diameter: the efficacy and its correlation with tirads classification**

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Objective
This retrospective study evaluated the effectiveness of ultrasound-guided fine-needle aspiration cytology (USG-FNAc) for diagnosing thyroid nodules less than 10 mm and explored the correlation between the TIRADS classification and USG-FNAc reports.
Methods
This analysis of 344 patients with 407 thyroid nodules less than 10 mm was conducted from June 2022 to July 2023 at the Centre of Endocrinology and Diabetes, Danang Family hospital, Danang, Vietnam. USG-FNAc was performed on all nodules, and cytology was reported according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of USG-FNAc were calculated. Correlation between cytology and TIRADS classification was assessed using Spearman's correlation.
Results
Adequate specimens were obtained in 81% of thyroid nodules after the first FNAc. Cytological diagnoses included 36.6% benign, 12.8% suspicious for malignancy, 1.2% malignant, and 19.7% indeterminate. Among surgically resected thyroid nodules, 78.6% were malignant. USG-FNAc demonstrated moderate sensitivity (80%) and high PPV (92.3%) but lower specificity (75%) and NPV (50%) for malignancy in nodules less than 10 mm in max diameter. A significant positive correlation ($r = 0.24$, $P < 0.001$) was observed between TIRADS classification and TBSRTC.
Conclusion
USG-FNAc offers moderate sensitivity and high PPV for diagnosing malignancy in smaller than 10 mm thyroid nodules, but specificity and NPV are lower. A positive correlation exists between TIRADS classification and cytological outcomes.
Keywords
Ultrasound-guided fine-needle aspiration cytology, thyroid nodules, TIRADS classification, The Bethesda System for Reporting Thyroid Cytopathology

DOI: 10.1530/endoabs.101.PS1-09-01

## PS1-09-02

**Acromegaly and thyroid nodules: a retrospective, single-centre, real-world observational study**

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Objectives
Acromegaly is a rare disease that can cause complications in multiple organs. Although excess IGF-1 may contribute to the development of thyroid nodules, the association between acromegaly and thyroid nodules is still a topic of debate, and the available data are limited and contradictory. The aim of this study was to investigate the potential influence of acromegaly and its treatment on thyroid nodules.
Methods
This is a retrospective, single-centre, real-world observational study on 43 patients with acromegaly (58% female, 42% male, mean age 50 $\pm$ 13 years) who underwent at least one thyroid ultrasound after the diagnosis. 30 patients had at least two years of ultrasound follow-up (median ultrasound follow-up 83 months, IQR 48-122). Information about biochemical data, and local or medical treatment for acromegaly were collected form electronic medical records. Good control of acromegaly was defined by normalization of serum IGF-1 values within the age-specific reference range. A change of at least 3 mm in the size of a thyroid nodule was considered significant.
Results
Thyroid nodules were found in 77% of patients of whom 64% had multinodular goiter (median size of the dominant nodule 10 mm, IQR 6-19). We found a positive correlation between IGF-1 levels at diagnosis and the maximum size of the dominant thyroid nodule ($P = 0.035$ Rho = 0.64) in treatment-naïve patients. At the time of the last thyroid ultrasound, the majority of patients (28 out of 30) achieved good control of acromegaly, either through local treatments (8 patients) or medical treatment (20 patients). We observed a significant growth of the primary thyroid nodule in 9 patients (30%), a decrease in size in 8 (27%) and no significant changes in 13 patients (43%). No association was found between dimensional changes in the dominant thyroid nodule and the type of treatment for acromegaly. The thyroid nodules were classified according to their ultrasound characteristics: 40% were classified as EU-TIRADS-2, 44% as EU-TIRADS-3 and 16% as EU-TIRADS-4. Of these, 38% underwent fine needle aspiration but none were cytologically suspicious, and no patient was diagnosed with thyroid carcinoma.
Conclusions
We confirmed an increased prevalence of thyroid nodules in patients with acromegaly compared to the general population, in accordance with previous studies. The maximum size of the dominant thyroid nodule appears to correlate with the IGF-1 levels at diagnosis. Nevertheless, once achieving good control of acromegaly, the progression of thyroid nodules is comparable to that observed in the general population.

DOI: 10.1530/endoabs.101.PS1-09-02

## PS1-09-03

**Clinical utility of artificial intelligence in follow up of thyroid thermal ablative therapy for benign thyroid nodules**

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Objective
In the last few years, thermal ablative therapies for benign thyroid nodules have emerged strongly and there is increased evidence about its efficacy in improving cosmetic and compressive symptoms. Majority of authors reported in their literature that they follow up their patients by improvement in compressive & cosmetic score and volume reduction ratio (VRR) by ultrasound measurement. The aim of the current study is to assess the clinical utility of artificial intelligence (AI) in follow up of patients with benign thyroid nodules after thermal ablation (TA).
Methods
We included 60 patients in our study (12 of them were males) and their mean age 38y (ranging from 18 to 67 years) who performed TA for benign thyroid nodules (radiofrequency and microwave ablation). All patients were followed by cosmetic scores, compressive scores and VRR by thyroid ultrasound (baseline and 6 months after TA). We used PIUR imaging (PI) software as an example for AI to create 3D images and videos baseline and 6 months after TA for 30 patients. Moreover, 6 months after TA all participants were subjected to Patient Satisfaction Questionnaire Short-Form (PSQ) -to assess patient satisfaction from TA- and Hamilton Anxiety Rating Scale (HAMA-A) to assess anxiety symptoms after TA. Finally, both scores were compared between group (1) (30 patients performed scan using PI software plus conventional ways of follow up) & group (2) 30 patients not performed scan by PI software (as a reference group).
Results
Among group (1) patients, there was statistically significant lower HAMA-A score ($P$ *value* $< 0.05$) in comparison to patients in group (2). Furthermore, there was statistically significant higher PSQ scores in comparison to patients in group (2).
Conclusions
PI software -as an example for AI- is a useful tool for follow up of patients with TA as it increases patient satisfaction from TA and help in reducing anxiety symptoms related to thyroid nodules.

Keywords
Artificial Intelligence; Thyroid Nodules; Patient Satisfaction.
DOI: 10.1530/endoabs.101.PS1-09-03

## PS1-09-04

**Application of shear wave elastography (SWE) in the management of thyroid nodules in children and adolescents**

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Background
Shear wave elastography (SWE) is an ultrasound diagnostic method used to measure tissue stiffness. Since the mechanical properties of tissue involved in the pathological process are changed, SWE might indicate regions of the examined tissue covered by the disease. It is well documented, that SWE helps to differentiate benign and malignant nodules in thyroid gland in adults, however there are still few studies on application of SWE in thyroid diagnosis in children. The purpose of the study was to assess the application of SWE based on Young's modulus expressed in kPa in the management of thyroid nodules in children and adolescents.
Methods
116 pediatric patients (81 girls and 35 boys) with 168 thyroid nodules were enrolled to the study and were qualified to SWE which followed fine needle aspiration biopsy.
Results
According to the result of cytological examination presented in Bethesda system, nodules were qualified as benign (147 nodules with II category according to Bethesda system) and suspected (21 nodules with III, IV and V category according to Bethesda system). Benign cytological diagnosis were nodular goiter, parenchymal goiter, nodular colloid goiter or lymphocytic inflammation. Among suspected nodules 15 were diagnosed as III according to Bethesda system (AUS - Atypia of Undetermined Significance or FLUS - Follicular Lesion of Undetermined Significance in cytology), 1 nodule was diagnosed as IV according to Bethesda system (suspicious for follicular neoplasm - oxyphilic cell tumor) and 5 as V according to Bethesda system (suspicious for malignancy). There were no significant differences between TSH and fT4 concentration between benign and

suspicious group. Patients with benign and suspected thyroid nodules were of comparable age. Mean SWE in benign nodules was statistically significant lower than in nodules with suspected cytology (42.22 ± 16.69 vs. 57.4 ± 24.0 kPa, $P = 0.0004$). Moreover there was a significant correlation between the Bethesda scale and SWE values. 5 patients from suspicious group revealed to be malignant in final histopathological examination.
Conclusion
Our results suggest that SWE is a viable diagnostic method, however it still seems to need some adjustment for pediatric patients.
Keywords
ultrasonography, elastography, nodules, children
DOI: 10.1530/endoabs.101.PS1-09-04

## PS1-09-05

**Predictive factors in patients rejected for radiofrequency ablation of cytologically benign thyroid nodules: an observational cohort study**

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Introduction
Thyroid radiofrequency ablation (RFA) is now recommended as an alternative surgery for symptomatic benign nodules. However, there is some concern that a small but non negligible percentage of such cases can be carcinomas, despite two benign cytology results. Indications for RFA should be validated in a multidisciplinary approach and if feasible during multidisciplinary team meetings (MDTM). The aim of our study is to evaluate the rationale for a systematic validation of the indications by a MDTM and to determine if any clinical and ultrasound (US) features can lead to suspect a malignant histological diagnosis.
Patients and Methods
A retrospective observational study was conducted between January 2019 and December 2023. Patients referred for RFA of a benign nodule with two benign cytology results and whose records were rejected by the MDTM and underwent surgery were analyzed. Data were analyzed using R software.
Results
A total of 573 patients were presented at MDTM. One hundred and thirty-two patients (23%) were considered not eligible for RFA and referred for lobectomy (25% male, mean age 46 ± 14 years-old, mean nodular volume 25 ± 23 mL, 66% classified as EU-TIRADS 3 and 32% as EU-Tirads 4). Forty-nine patients (37%) underwent surgery and eight patients (16%) had a non-benign histology (4 NIFT-P; 1 oxyphilic cell tumor of uncertain malignant potential; 1 minimally invasive follicular carcinoma; 2 follicular variants of papillary carcinomas). Malignancy predictive factors could be associated to male sex, age under 35 years-old (in 75% of cases) and ultrasound nodular appearance (exclusively solid composition in all patients, EU-TIRADS 4 in 63% of cases).
Conclusion
Evaluating the indications for thyroid nodules radiofrequency ablation by a MDTM in an expert center can help to detect tumors not eligible to RFA for histological reasons, despite two benign cytology results. Age, sex and US pattern should be taken into account prior considering RFA of a supposedly benign thyroid nodule.
DOI: 10.1530/endoabs.101.PS1-09-05

## PS1-09-06

**Gender-based disparities in clinical presentation and outcomes of benign thyroid nodules**

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Objectives
Gender has long been recognized as a significant epidemiological variable in the study of thyroid diseases. However, the modern approach of gender medicine introduces new perspectives to this field. The aim of this study was to investigate how gender influences the clinical presentation, volume changes and cytological features of benign thyroid nodules during follow-up
Methods
We conducted a retrospective analysis of 1010 patients (17.1% males and 82.9% females), diagnosed with benign nodular disease, with a median age at diagnosis of 56 years. All patients underwent re-evaluation at a median follow-up period of 3.8 years.
Results
The mean diameter of nodules was 21.4 ± 9.3 mm in females and 25.6 ± 12.1 mm in males ($P < 0.0001$). The mean volume of nodules was 4.1 ± 6.6 ml in females and 9.0 ± 14.2 ml ($P < 0.001$). The rate of thyroid nodules with diameter >4 cm was significantly higher in males (13.3%) than in females (5.5%) ($P = 0.002$). No differences were observed between males and females regarding ATA US risk class ($P = 0.77$) and age at diagnosis ($P = 0.34$). At a median follow-up of 3.8 years, in both females and males the nodule volume was significantly higher than that observed at the diagnosis ($P < 0.0001$ and $P < 0.0001$, respectively). The rate of patients with nodule volume increased, according to ATA criteria, was 38.1% in males and 47.0% in females ($P = 0.02$). In females group the rate of nodules with increased of volume was significantly higher in female younger than 45 years (106/200, 53% *versus* 288/636, 45.2%, $P = 0.01$). On the contrary no correlation between age and the risk of increased volume was observed in males ($P = 0.36$). At FNAC repetition (3.8 years after diagnosis) the change in cytological features (from Thy 2 to Thy3-4-5) was observed in 3.3% of females (28/837) and in 3.5% of males (6/173) without differences ($P = 1.0$).
Conclusions
These findings suggest that gender influences not only the initial presentation but also the subsequent evolution of benign thyroid nodules. Further studies exploring the underlying mechanisms driving these gender-specific differences are warranted to optimize patient management strategies tailored to individual needs.
DOI: 10.1530/endoabs.101.PS1-09-06

## PS1-09-07

**Active surveillance of bethesda iv nodules**

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Objective
Treatment decision-making for Bethesda IV nodules remains challenging. Active surveillance(AS) is now a well-established strategy for low-risk, differentiated thyroid carcinoma. Since most of the Bethesda IV nodules are operated on unnecessary basis, and molecular testing is costly and is not available in a lot of centers. We started AS for the clinically low-risk Bethesda IV nodules, which would be a practical option, and hereby we are sharing our preliminary results.
Methods
Thirty-four patients with a nodule with a long axis of less than 30 mm, having no sonographically detectable high-risk features (HRF) or only with one HRF and < 1 cm (EU-TIRADS), no extrathyroidal extension and no detected lymph nodes suggestive of metastasis, with Bethesda IV (2017) has been found eligible for AS. Patients were monitored with ultrasound(US) at 6-12 months intervals. A 30% volume increase with regard to the baseline measurement was considered as significant nodule growth, whereas a 100% volume increase, the long axis exceeding 30 mm, or identification of pathological lymph node(s) were defined as surgical indications.

Results
Of the patients, 24/34 (70.6%) were female, and the median (min-max) age at diagnosis was 47 (range 18-79) years. The median (min-max) follow-up period was 24(6-108) months, and 29/34(85 %) patients had a follow-up of 1 year or more. The long diameter of the nodules on baseline ultrasound(US) was mean ± sd 13.23 ± 5.43 mm, median(min-max) 14(3-24)mm, and baseline median nodule volume (min-max) was 0.72(0.01-4.84) ml. According to the EU-TIRADS, 8/34 (24%) were classified as EU-TIRADS-3, 22/34(65%) as EU-TIRADS-4, and 4/34(12%) as EU-TIRADS-5 (i.e. all <1 cm, 3 markedly hypoechogenic, one with microechogenities). At the last US, the long diameter was mean ± s.d 14.26 ± 6.12 mm with a median(min-max) of 14(4-30)mm, and median nodule volume (min-max) was 0.6(0.03-14.13)ml. When the volume change of the nodules during follow-up was analyzed, it was observed that the volume change was less than 30% in 14/34 (42%) patients, while the number of patients with volume increases and decreases was equal in 10/34 (29.41%) for both. None of the patients developed pathologic lymphadenopathy in the neck.
Conclusions
The first results of our AS group revealed that Bethesda IV patients, who were found to be eligible for AS, showed no signs of significant tumor progression or metastasis after a median follow-up of almost two years.

DOI: 10.1530/endoabs.101.PS1-09-07

## PS1-09-08

**Natural course of benign thyroid nodules**

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Objective
Thyroid nodules (TN) are extremely common in the general population. Data on long-term follow-up of benign nodular thyroid disease are limited. The aim of our study was to evaluate the changes in ultrasound features in a group of patients with TN.
Methods
We retrospectively collected data about ultrasound features of 228 nodules from 153 consecutive patients with mean age 54.73 ± 11.55 years [125 F (81.7%), 28 M (18.3%)], followed for a median period of 5 years in the Endocrinology Unit of Pisa Hospital. Nodule volume (V) was calculated using the ellipsoid formula. Nodules smaller than 0.065 $ml^3$ were excluded and, according to the initial V, were divided in 2 groups: A if $V \leq 1$ ml and B if $V > 1$ ml.
Results
138/153 (90.2 %) patients had normal serum TSH values (0.4-4 mUI/l), 5/153 (3.3%) had TSH < 0.4 mUI/l and 10/153 (6.5%) had TSH > 4 mUI/l. 84/153 (54.9%) patients had positive thyroid autoantibodies (TAb), while 69/153 (45.1%) had negative TAb. Table 1 shows the thyroid nodules % volume variation (%V) compared to the initial volume. %V was not significative different in the whole group, while a significative increase was observed in subgroup B. Nodules were considered increased or reduced if their final V was higher or lower, respectively, of at least 30% compared to the initial V. At the end of follow-up, in group A, 53/148 (35.8%) nodules remained stable, 61/148 (41.2%) showed an increased V, 34/148 (23.0%) a reduced V; in group B 31/80 (38.8%) nodules remained stable, 24/80 (30.0%) showed an increased V and 25/80 (31.3%) a reduced V. The age of patients with increased V nodules (50.8 ± 12.4 years) was significative lower compared to patients with stable nodules (57.8 ± 9.7 years) ($P < 0.05$). The frequency of stable, increased, and reduced TN was not significantly different when sex, TAb positivity, mean serum TSH values, and the presence of single or multiple nodules were considered.
Conclusions
During follow-up, we observed an increased volume of TN with an initial V > 1 ml, while smaller TN did not show significative differences, probably due to the high variability in ultrasound measurements of small TN. TN growth was higher in younger patients and was not significantly associated with sex, TAb positivity, mean serum TSH values, and the presence of single or multiple nodules.

**Table 1** Thyroid nodules % volume variation compared to the initial volume during follow-up (25°-75° percentile)

| Median %V (25°-75° percentile) | 24 months | 24-48 months | 48-72 months | >72 months | p |
|---|---|---|---|---|---|
| **All TN** | -8.7 (-40.4;47.9) | 12.5 (-21.1;54.2) | 8.9 (-19.9;58.7) | 12.6 (-40.6;116.4) | NS |
| **Group A** | 45.4 (-6.2;330) | 21.7 (-11.9;83.3) | 0 (-20.9;66.6) | -2.2 (-35.4;63.1) | NS |
| **Group B** | -33.1 (-51.8; 11.1) | -23.1 (-42.9;14.5) | 10.7 (-15.1;49.0) | 43.2 (-43.6;137.2) | 0.027 |

DOI: 10.1530/endoabs.101.PS1-09-08

## PS1-09-09

**Role of elastography in the differentiation of thyroid *versus* parathyroid lesions**

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An accurate localization diagnosis in parathyroid disease using ultrasound assessment remains a challenge in many instances. The objective of this study is to investigate the diagnostic effectiveness of bidimensional shear wave elastography 2D SWE as a supplementary method for differentiating superficial structures, namely thyroid and parathyroid lesions.
Methods or Background
In this study, a total of 140 cases were assessed, including patients with coexisting benign thyroid nodules and enlarged parathyroid glands due to primary hyperparathyroidism. Final pathology report was used as golden standard of diagnostic. Ultrasound evaluation = multi-parametric ultrasound, SUPERSONIC ULTRAFAST Mach 30 Aixplorer, 3rd software version, with a multifrequency linear probe 5-18MHz.
Results or Findings
There was a statistically significant difference observed for the mean elasticity index between thyroid and parathyroid lesions (15 kPa vs.4.8 kPa, $P < 0.001$). A cut-off value of 7.5 kPa was established in order to differentiate thyroid from parathyroid tissue (AUC 0.950, Se 93%, Sp 91%), with greatly improved diagnostic performance compared to ultrasound alone (AUC 0.830, Se 71%, Sp 62%). Parathyroid elasticity was correlated negatively and weakly with serum calcium values (r=-0.360, $P < 0.001$) and positively and weakly with PTH values ($r = 0.250$, $P = 0.035$). Our data suggests that 2D-SWE cut-off values can improve diagnostic specificity and sensitivity for correctly diagnosing thyroid nodules and parathyroid lesions.
Conclusion
Differentiating these lesions non-invasively could improve clinical results, diagnostic costs, evaluation time, and invasive treatments.

DOI: 10.1530/endoabs.101.PS1-09-09

## PS1-09-10

**Changes of thyroid volume after iodine supplementation: preliminary data**

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Background
the iodine supplementation introduced from 2005 by a nationwide program of iodine prophylaxis on a voluntary basis led to iodine sufficiency in Italy. Aim of the present work was to evaluate the modification of thyroid volume (TV) according to the change of iodine status.
Methods
We retrospectively revised 400 subjects submitted to neck ultrasound, with no history of thyroid diseases. We measured TV according to the ellipsoid formula, BMI and TSH. Exclusion criteria were: an inhomogeneous ultrasound pattern or nodular lesions; TSH $<0.6$ and $>4.5$ mU/l; obesity and treatment with drugs affecting thyroid function. Non-normally distributed data are expressed as median (95% CI) and normally distributed values as mean $\pm$ SD.
Results
We preliminary analyzed data about 200 subjects (100 F, 100 M), with normal median TSH levels of 1.6 (range 1.5-2.2) mU/l, aged 42 (42-46.3) years, with males significantly older than women ($P < 0.01$). Overall median TV was 8.5 (8.6-9.5) ml. Median TV was significantly higher in males [10.1 (range 10-11.2) ml], compared with females [7 (range 6.8-7.9) ml], ($P < 0.0001$), leading to the following reference range: 2.9-11.1 ml for females and 4.6-15.97 ml for males, respectively. Overall, median BMI was 22.5 (range 22.3-23.5) kg/m$^2$, and higher in males compared with females [21.5 (21.2-22.7) vs 23.9 (23.3-25) kg/m$^2$, $P <$ 0.0001]. A significant positive correlation (Spearman r, 95%CI) was found in both groups between TV and age (r 0.26, 0.1-0.38), weight (r 0.6, 0.47-0.71), height (r 0.53, 0.39-0.65) and BMI (0.47, 0.32-0.6) ($P < 0.001$).
Conclusions
Iodine supplementation in the population appears to have led to a mean reduction of about 2 ml in TV compared with a previous Italian study (1) which reported a mean volume of $12.9 \pm 3.6$ in males and $9.2 \pm 2.9$ ml in females. The positive, although weak, correlation with age strengthen this hypothesis, as older people have been exposed to a mild iodine deficiency during childhood and adult age, possibly leading to increased thyroid size. We are now recruiting more individuals in order to obtain normative data for different age groups.
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DOI: 10.1530/endoabs.101.PS1-09-10

## Poster Session 2
## Intracellular effects of thyroide hormone

### PS2-10-01

**Type 3 deiodinase is a negative prognostic marker for hepatocarcinoma**
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Background
Recent reports have suggested a link between the thyroid hormone (TH) signalling pathway and liver disease, including hepatocellular carcinoma (HCC). Deiodinases are enzymes responsible for the peripheral metabolism of TH. Although the expression of deiodinases type 1 (D1) and 3 (D3) has been shown to change during induced liver injury, their role in hepatocarcinogenesis is still poorly understood.
Aims
To evaluate the role of deiodinases and their regulation in liver carcinogenesis and to investigate whether and how TH homeostasis affects HCC phenotype and patient outcome.
Methods
This is an ongoing monocentric prospective case-control study. We enrolled 49 patients who underwent liver surgery for HCC (31 cases) or for other non-neoplastic liver diseases in a non-cirrhotic context (18 controls). We evaluated genes and protein expression of the TH signaling pathway (D1, monocarboxylate transporter 8 -MCT-8-, thyroid receptors alpha and beta -TRα, TRβ- and Kruppel-like factor 9 - KLF9-) by RT-PCR and Western blot analysis in HCC, and for D3 also by immunohistochemistry of cirrhotic and healthy liver samples.
Results
RT-PCR analysis showed a progressive statistically significant decrease in DIO1 ($P$ 0.004), MCT-8 ($P$ 0.001) and TR β ($P$ 0.02) mRNA expression from healthy liver to HCC. There was a corresponding decrease ($P$ 0.03) in the expression of KLF9, which is involved in cell differentiation and proliferation. Western blot analysis showed a decrease in the expression of D1 protein in all cirrhotic samples and HCC samples ($P$ 0.01), whereas D3 protein was increased in 55% of the HCC samples ($P$ 0.02). In patients with HCC, D3 expression was associated with a higher degree of liver stiffness (32 kPa, IQR 23.47-35.5, $P$ 0.002) and a higher BMI ($P$ 0.004). A statistically significant difference in overall survival (OS) was observed between D3-positive and D3-negative HCC patients (log rank $P$ 0.003), with a median OS of 17.9 (IQR 15.5-18.7) months for D3-positive *vs* 41.3 (35.1-43.8) months for D3-negative patients. In addition, a shorter progression-free survival and an increased recurrence rate were observed in D3-positive patients, although not statistically significant. Interestingly, D3 expression was associated with higher tumour grade.
Conclusions
These preliminary data showed that D3 expression may define a more severe phenotype of HCC and could be used in clinical practice as a negative prognostic biomarker for patient outcome. Our exploratory findings need to be applied to a larger sample size to be confirmed.
DOI: 10.1530/endoabs.101.PS2-10-01

### PS2-10-02

**Non-genomic effects of thyroid hormones on the breast cancer microenvironment**
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Objective
Mesenchymal stem cells (MSCs) are central players and the most abundant cell type in the breast cancer tumor microenvironment and own a well-recognized role in tumor initiation, progression, invasion, metastasis, angiogenesis as well as resistance to treatment, making them attractive novel targets for anti-tumor therapy. There is increasing evidence for an association between thyroid function and breast cancer risk, and thyroid hormone- mediated effects through the αvβ3 integrin are proposed as a pathophysiologic link.
Methods
To evaluate the migration behavior of MSCs in the presence or absence of thyroid hormone treatment in response to tumor-derived signals, a 3D migration assay was performed MSCs pretreated with T3 (1nM) or T4 (1μM) with or without tetrac (100nM) (T4 analog, specific inhibitor of αvβ3 integrin-mediated thyroid hormone action) for 24 h were subjected to a gradient between serum-free medium and serum-free conditioned medium (CM) from five different types of breast cancer cells (T47D, MCF7, BT-474, MB-231, MB- 453).
Results
MSCs subjected to a gradient between CM derived from each breast cancer cell line and serum-free medium showed a directed chemotaxis towards tumor-CM with significantly increased forward migration index (FMI) and center of mass (CoM). This migratory behavior was significantly enhanced upon treatment with T3 or T4. Except for T47D-CM, the additional treatment with tetrac inhibited the effects of T3 and T4 on MSC migration, demonstrating that this effect is mediated through αvβ3 integrin.
Conclusion
Our preliminary *in vitro* data on the effects of thyroid hormones T3 and T4, and thyroid hormone metabolite tetrac on MSC migration suggest an important role of non- genomic, integrin αvβ3-mediated thyroid hormone action on MSC biology within the breast tumor microenvironment that warrants further investigation.
DOI: 10.1530/endoabs.101.PS2-10-02

## PS2-10-03

**Thyroid hormone receptor α is involved in pro- and anti-inflammatory properties of murine macrophages**

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Macrophages are phagocytic immune cells with many functions, including fighting infections and wound healing. As a result, they are also involved in many diseases, such as metabolic syndrome, neurodegenerative disorders and cancer. Macrophages have been identified as thyroid hormone (TH) target cells, but the link between TH and the immune system is not yet fully understood. The active thyroid hormone triiodothyronine (T3) exerts its action through the nuclear thyroid hormone receptor (TR), of which the TRα is the dominant receptor in macrophages. The role of the TRα in macrophage function was investigated using bone marrow derived macrophages (BMDMs) from transgenic mice with a mutation in the T3 binding domain of the TRα (TRαPV, a dominant negative variant, resulting in resistance to thyroid hormone). BMDMs from these mice and corresponding wild types (WT) were polarized into a pro-inflammatory M1 or immunomodulatory M2 phenotype using either LPS + interferon gamma or IL-4 respectively. Pro- and anti-inflammatory cell surface marker expression was measured with flow cytometry. In addition, immunometabolism of the macrophages was measured using Seahorse analysis. The results of three consecutive cultures are described, further analyses are ongoing. After polarization into an M1 phenotype, expression of the M1 surface markers CD80 and CD86 decreased in TRαPV macrophages compared to WT macrophages, while the M2 cell surface marker CD206 showed an increasing trend in TRαPV M2 macrophages. Additionally, M2 TRαPV macrophages tend to increase their oxygen consumption, indicating increased oxidative phosphorylation, which is a hallmark of M2 macrophages. RNA sequencing analysis will be performed in order to unravel the molecular mechanisms involved. In conclusion, a dominant negative mutation of the TRα results in decreased pro-inflammatory marker expression in M1 cells, increased expression of an immunomodulatory marker in M2 cells, accompanied by elevated oxidative phosphorylation. These results indicate that impaired TRα function could alter macrophage phenotype and function.

DOI: 10.1530/endoabs.101.PS2-10-03

## PS2-10-04

**Unravelling the role of MCT8 in early brain development**

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It has long been known that thyroid hormones (TH) are essential to orchestrate the correct development of the brain. For many years it has also been recognised that TH need of transporter proteins to access target tissues and cells. Moreover, in the last 20 years the Monocarboxylate transporter 8 (MCT8) has emerged as a TH transporter of great physiopathological importance, as mutations in MCT8 lead to severe neurological alterations already from prenatal stages. Despite the importance of TH action during brain development and the pathophysiological relevance of MCT8, its role during brain development has not been fully addressed. Previous studies in mice lacking MCT8 have suggested its deficiency leads to a transient state of brain hyperthyroidism during development, although increased expression of alternative TH transporters in the brain has hindered the interpretation of these findings. The aim of this study is to elucidate the role of MCT8 during early mouse brain development. Firstly, we have delineated the anatomical expression of MCT8 in the mouse brain during early development. Furthermore, we have investigated the different types of neural cells expressing MCT8 during perinatal stages of brain development. Using a mouse model with a point mutation in MCT8, we have demonstrated that these mice also present a transient state of brain hyperthyroidism. Importantly, this hyperthyroidism occurs without an increase in alternative TH transporters, indicating that the perinatal brain hyperthyroidism is not due to enhanced TH transport through other transporter proteins. Moreover, we have further explored this state of perinatal state of brain hyperthyroidism running RNAseq analysis and RNAscope in mice brain samples and digital PCR in human brain samples of a 30th gestational week foetus with a mutation in MCT8.

DOI: 10.1530/endoabs.101.PS2-10-04

## PS2-10-05

**Exploring the molecular mechanisms underlying radiation-induced thyroid damage using an organoid model**

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Head and neck cancer (HNC) represents one of the most diagnosed cancer types. To date, radiotherapy is among the main approaches for the HNC treatment. Radiation of tumors unavoidably results in off-side effects on the surrounding tissues, such as the thyroid, causing hypothyroidism. Previous studies have revealed that radiation can damage thyroid cells directly, impair their mitosis, or induce an auto-immune response. Here, we investigate thyroid stem-like cells' faith following radiation damage by exploiting mouse-derived thyroid organoids. It was shown that irradiation-induced damage of single cells isolated from mice thyroid glands impairs their ability to grow organoids in a dose-dependent manner, compromising their stemness. Furthermore, irradiation of formed thyroid organoids increases cell death and decreases cell stemness, inducing an *in vitro* differentiation process, as observed by gene expression analysis. This also revealed that, following irradiation, several interferon-related genes mainly involved in the innate immune response to viral infections are activated, such as cytokines, chemokines, and pattern recognition receptors (PRRs). Sequencing data from irradiated thyroid organoids gave a hint about the dysregulated processes to deepen in order to unveil potential targets to exploit to prevent this side effect. The molecular events observed underline the radiation-dysregulated pathways, factors leading to tissue damage and misfunctioning, giving more information about the causes underlying hypothyroidism. Knowing the molecular mechanisms responsible for healthy tissue damage occurring with radiotherapy is fundamental to counteract them and prevent side effects, improving the patient's post-cancer treatment quality of life.

DOI: 10.1530/endoabs.101.PS2-10-05

## PS2-10-06

**The role of thyroid hormone receptor A1 (TRA1) signaling in parvalbumin-expressing interneurons in the central regulation of the cardiovascular system and anxiety-like behavior**

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Thyroid hormones (TH) play a regulatory role in growth and development as well as cardiovascular function and thermogenesis. Furthermore, an excess of TH can cause anxiety and nervousness in hyperthyroid patients. While the direct effects of an imbalance in the TH system on peripheral organs like the heart and the liver are well studied, there is evidence of a central component of regulation. In this project, we aim to understand the contributions of the central nervous system in the T3-dependent regulation of the cardiovascular system and anxiety-like behavior. Using a Cre transgenic mouse line in combination with a stereotaxic injection of an AAV carrying the gene for a dominant negative TRα1, we generated mice with impaired TRα1 signaling in the parvalbumin-expressing population of hypothalamic and hippocampal GABAergic neurons, respectively. Given the impact of parvalbumin neurons in the **hypothalamus** on cardiovascular parameters such as blood pressure and heart rate frequency distribution, the model allowed us to investigate the contribution of central TRα1 signaling to the regulation of cardiovascular function. Continuous radiotelemetry recordings of heart rate and body temperature as well as ECG measurements were utilized in this study. Using the animal model with an impaired **hippocampal** TRα1 signaling in parvalbumin neurons, we investigated the TH-dependent effects of this hippocampal cell population on anxiety-like behavior as well as memory

function and metabolism. Our findings demonstrate that this AAV-based method can be utilized to elucidate the consequences of a cell-specific hypothyroidism in targeted neurons, shedding light on the role of local thyroid hormone action in parvalbumin neurons in the regulation of behavior and cardiovascular functions.

DOI: 10.1530/endoabs.101.PS2-10-06

## PS2-10-07

### Brain abnormalities in young mice harboring combined NKX2-1 and PAX8 gene mutations

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Objectives
It has been extensively demonstrated that hypothyroidism can profoundly disrupt the ontogenesis and functions of the brain, leading to impairments in cognitive abilities and psychosis. This can occur due to an imbalance induced by hypothyroidism in the physiologically programmed formation of neurons within specific time windows and brain regions. It is unclear whether mutations in the mammalian thyroid morphogenic genes Pax8 and Nkx2-1 may directly or indirectly collaborate in causing adult brain abnormalities. It is also unknown if these potential changes may involve the mitochondrial compartment. Such uncertainty primarily stems from the fact that mitochondria are organelles highly susceptible to alterations in thyroid activity and the fundamental basis for brain functions.
Methods
In this study, we examined brain features in 3 month-old single or double heterozygotes for Nkx2-1- and Pax8-null mutations (DHTP) mice under different human-like dysthyroidisms. We focused on potential alterations of specific neurotransmitter systems, expression of markers of pre- and post-synaptic function and, given the physio-pathological role mitochondria have in controlling the bioenergetic status of neurons, of mitochondrial dynamics and oxidative balance. An integrated approach was employed by combining transcriptomic, proteomic, functional and histology techniques.
Results
Compared to Wt controls, DHTP mice, bearing both systemic and brain hypothyroidism, showed altered expression of synaptic markers, generic and cholinergic (corroborated by immunohistochemistry in caudate, putamen, hippocampus, and basal forebrain) and glutamatergic-ones. Addittionally, they showed reduced expression of key proteins related to synaptic plasticity potency and several glutamate receptor isoforms. DHTP mice brains also exhibited imbalanced mitochondrial dynamics. Nkx2-1+/- mice displayed dopaminergic neuron-specific alterations, morphologically, more evident in the substantia nigra of DHTP mice. Nkx2-1+/- mice also exhibited enhanced mitochondrial biogenesis and oxidative capacity likely as a global response of brain to Nkx2-1 haploinsufficiency and/or to their elevated T3 circulating levels. Pax8+/- euthyroid mice showed reduced transcription of both tyrosine hydroxylase and dopamine transporter, indicating dopaminergic dysfunction, possibly at an early stage, but consistent with observed deregulated glucose homeostasis in such animals.
Conclusions
Overall, this study provides new insights into the impact of Pax8 and NKx2-1 haploinsufficiency on various neuroanatomical, molecular, and neurochemical aspects of the brain. These findings offer new perspectives for targeting brain alterations and dysmetabolism in managing overt and subclinical thyroid dysfunctions, potentially preventing or counteracting neurological abnormalities that may predispose to dementia, cognitive disturbances, and behavioral alterations.

DOI: 10.1530/endoabs.101.PS2-10-07

## PS2-10-08

### Regulation of hepatic mitochondrial quality control system by 3,5-diiodo-l-thyronine (3,5-t2) in a mouse model of high-fat diet-induced nafld

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Objective
Non-alcoholic fatty liver disease (NAFLD) is emerging as one of the main hepatic metabolic alterations, often associated with elevated high-fat diet (HFD) consumption. Hepatic lipid accumulation may progress in metabolic alterations involving increased production of reactive oxygen species (ROS). The main intracellular source of ROS are mitochondria, which are also responsible for lipid metabolism. Thus, alterations of mitochondrial machinery are widely recognized as central players in the development of liver steatosis. Thyroid Hormones (TH) are master regulators of energy and lipid homeostasis: 3,5,3′-triiodo-L-thyronine (T3) is known to prevent HFD metabolic side effects by modulating, among several pathways, mitochondrial dynamics, biogenesis and mitophagy, collectively known as mitochondrial quality control (MQC). Recent studies in rodents revealed that 3,5-diiodo-L-thyronine (3,5-T2), a naturally occurring TH metabolite, elicits hypolipidemic effects by increasing the resting metabolic rate without being thyrotoxic. However, until now, literature has been lacking of studies that correlate directly 3,5-T2 to MQC. Here, using a mouse model of HFD-associated NAFLD, we aim to characterize the role of 3,5-T2 administration by focusing on the liver MQC system in a context of metabolic alterations.
Methods
Male mice were fed a 60% fat diet for 19 weeks. During the last 10 days of treatment, 3,5-T2 or T3 were injected at the dose of 200 µg and 15 µg for 100 g body weight, respectively. Factors linked to mitochondrial biogenesis (mtDNA copy number, PGC1α) dynamics (for fusion MFN2 and for fission DRP1) and mitophagy (PINK1 and PARKIN) were investigated. Moreover, analysis of mtDNA oxidative damage and mitochondrial base excision repair (BER) system were performed.
Results
HFD mice developed obesity and liver steatosis. Moreover, they showed a significant accumulation of mtDNA oxidative damage and a downregulation of the BER system. Both iodothyronines showed hypolipidemic actions and reverted the HFD-induced mtDNA damage by stimulating the BER system. As far as the MQC is concerned, only T3 stimulated mitochondrial biogenesis. Both iodothyronines modulated mitochondrial dynamics, with 3,5-T2 stimulating fusion while T3 pushed dynamics balance towards fission. Finally, both iodothyronines strongly increased the PINK1 and PARKIN expression, indicating an activation of mitophagy.
Conclusions
Results represent a first step to shed light on how 3,5-T2 modulates the MQC. Further efforts are needed as 3,5-T2's ability to regulate these mechanisms could be used for the treatment of HFD-induced hepatic metabolic dysfunctions in the near future.

DOI: 10.1530/endoabs.101.PS2-10-08

## PS2-10-09

### Exploring the role of DIO2 in the control of proliferation and cell fate determination in adult neural progenitors

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Thyroid hormones (THs) are pivotal in orchestrating neurodevelopment and regulating adult brain function. Recent investigations into rodents have unveiled the potent effects THs have in adult neurogenic niches, particularly in the subventricular zone (SVZ), the brain's largest neural stem cell (NSC) niche. THs

influence neurogliogenesis, finely controlling processes such as cell cycle and progenitor determination, directing either neuronal or oligodendroglial commitment. Among the intricate network of regulators modulating TH availability and action in the SVZ, the role of type two deiodinase (DIO2), the primary T4-activating enzyme, remains unexplored. DIO2, is mainly expressed in astrocytes and tanycytes, regulating local T3 production in the brain and hypothalamic-pituitary axis. Although no inactivating mutations in the DIO2 gene have been documented in humans, DIO2 gene polymorphisms correlate with conditions such as mental retardation, bipolar disorder, and insulin resistance. Here, our study aimed to investigate DIO2 function in regulating NSC behavior in the adult SVZ, notably proliferation, determination. In particular, we will analyze in more detail a potential function of DIO2 in the release of NSC from quiescence, a process for which underlying molecular mechanisms are still far from being elucidated. Using single-cell RNA sequencing analysis in young adult mice SVZ, a strong association between DIO2 expression and NSC quiescent state was revealed. Subsequent RNAscope analysis was performed to assess DIO2 expression pattern in the different SVZ cell types not only in the SVZ but also along the RMS-OB axis. Moreover, we tested the effects of administering exogenous deiodinase inhibitors ex vivo, using neurosphere assay. to better analyze the action of DIO2 on NSC proliferation and neuron/glia determination. Altogether, these data revealed an intriguing role of DIO2 in the tight control of NSC proliferation, notably on NSC activation Moreover, functional implications of DIO2 were assessed through behavioral tests on DIO2-lacking mice (Dio2 KO), using olfactory memory and odor discrimination tests as non-invasive biomarkers of SVZ status. Dio2 KO mice displayed impaired odor memory, suggesting a functional role of DIO2 in adult SVZ-neurogenesis In sum, we highlight the contribution of DIO2 as a key regulator of adult SVZ neurogliogenesis. Our findings also point towards the need for further experiments, specifically focusing on regulating DIO2 expression *in vivo*, that will help shedding light on its implications in brain function and pathology.

DOI: 10.1530/endoabs.101.PS2-10-09

## PS2-10-10

**Impact of triiodothyronine (T3) on differentiation and T3-responsive characteristics in ipsc-derived hepatocyte-like cells to study energy and lipid metabolism**

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Background
The increasing global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) emphasizes its significant health implications, including liver inflammation, cirrhosis, and malignancy. Thyroid hormones (TH) play a vital role in hepatic energy metabolism, and their reduced local availability in the liver is associated with MASLD development. This study presents the comprehensive characterization of functional components of the TH system in human hepatocyte-like cells (HLCs), a refined hepatic model derived from human induced pluripotent stem cells (iPSCs).
Methods
A robust differentiation protocol was developed to efficiently generate hepatocyte-like cells from three iPSC donor lines. Consistent and comparable culture qualities were achieved through a 28-day differentiation period. A publicly available human iPS cell line from the Allen Cell Collection was also successfully differentiated with comparable results. RNA sequencing and network analysis from enriched gene set data examined maturation under continuous 5 nM T3 exposure compared to control differentiation media containing basal T3 concentrations $\leq$ 1 nM. Critical components of the TH system were identified by radioactive T3 uptake and DIO1 enzyme activity assays. Hepatocyte functionality was evaluated by assessing liver-specific enzyme activities (ALAT, ASAT, GPX1, CYP3A4) and secreted proteins (ALB, TTR, SELENOP). Additionally, exposure to 300 µM oleic and palmitic acid (1:1) for five days mimicked fatty acid accumulation.
Results
Transcriptomics revealed a refined hepatocyte model following T3 exposure, with increased THRB expression, reduced AFP levels, and an expression shift towards less DIO2/3 and more DIO1. Gene set enrichment analysis indicated T3-dependent downregulation of Hedgehog and NOTCH4 signaling, marking a more mature hepatocyte state. Decreases in extracellular matrix-receptor interactions and the PI3K-AKT pathway were associated with altered hepatic glucose supply. Increased ribosomal and proteasomal activities, along with enhanced oxidative phosphorylation, suggested cellular restructuring and heightened energy turnover associated with T3 exposure. Liver-specific enzyme activity and the secretion of binding proteins were in the comparative range of two hepatic cancer cell lines. The accumulation of lipid droplets after exposure to free fatty acids was also achieved.
Conclusions
This thoroughly characterized HLC model, expressing an intact and functional TH system, serves as an ideal platform for investigating T3-associated treatments and mechanisms involved within the context of MASLD.

DOI: 10.1530/endoabs.101.PS2-10-10

# Basic Thyroid Cancer Research-1

## PS2-11-01

**Anti-proliferative and anti-migratory activity of licorice extract and glycyrrhetinic acid on papillary thyroid cancer cultures**

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Papillary thyroid cancer (PTC) is the 8th most common cancer among women overall. Licorice (Li) contains over 300 active compounds and many of them with anti-cancer properties. Glycyrrhetinic acid (GA) is a major component of Li and a mineralocorticoid receptor agonist. The aim of this study was to investigate the potential anti-proliferative effects of Li and GA on PTC cell cultures. Li extract (LE) was produced from the root and tested on BCPAP and K1 cell lines, as well as GA. We used the MTT test to investigate the anti-proliferative activity, the wound healing test for the migratory activity, and finally we analyzed cell cycle distribution, apoptosis and oxidative stress after LE or GA incubation. Both LE and GA reduced cell viability at 48 h and cell migration at 24 h in both PTC cultures. LE and GA induced cell cycle arrest in the G0/G1 phase in the BCPAP cell line, while only LE induced it in the K1 culture. GA, but not LE, increased the apoptosis rate in both cell lines, whereas LE, but not GA, increased oxidative stress in both cultures. We produced the first evidence in the literature of the *in vitro* anti-proliferative and anti-migratory activity of LE and GA on PTC. In the future, a better understanding of the molecular pathways associated with LE and GA action on cancer cells will provide new molecular targets, especially in thyroid cancer treatment.

DOI: 10.1530/endoabs.101.PS2-11-01

## PS2-11-02

**Maldi-ms imaging in niftp diagnosis: an alternative approach**

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Objectives
This project, funded by a Ministerial Finalized Research grant, investigated the pathogenesis of follicular thyroid lesions using a combined genomic-proteomic

approach (NGS and MALDI-MS) to recognize and characterize *Non-invasive follicular thyroid neoplasms with papillary like nuclear features* (NIFTPs) [1] and their potential clinically targetable proteogenetic targets.
Methods
A total of 95 patients undergoing thyroidectomy at IRCCS San Gerardo (Monza, Italy) were enrolled in the study. Real-time PCR and NGS were used for genomic profiling, while MALDI-MSI was employed for proteomic analysis [2,3].
Results
Results showed that nodules with *RAS* mutations exhibited a distinct protein signature compared to *RAS* wild-type nodules, which, conversely, showed similarities with hyperplastic lesions. Among the putative markers identified through proteomic analysis, an exploratory study on cyclophilin A was conducted.
Conclusions
In conclusion, this study allowed the development of an original and innovative protocol enabling the monitoring of *RAS* mutational status through the spatial visualization of proteins interacting with *RAS*, as well as opening up new ways for the application of mass spectrometry imaging technique to the study of other oncogenes, which could be deciphered from a proteomic perspective within their interactome context.
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DOI: 10.1530/endoabs.101.PS2-11-02

## PS2-11-03

**Generation of medullary thyroid cancer ex-vivo cellular models**
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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from parafollicular C-cells. Differently to other neuroendocrine tumors, the information on MTC tumor microenvironment and its role in in therapy resistance are scanty, mainly because of the lack of reliable *in vitro* models. We hypothesized that, similarly to other cancers, MTC cells may have a certain degree of plasticity that could be modulated by variable microenvironmental factors. The main aim of this study was the establishment of patient-derived MTC *in vitro* models that can be grown in different tridimensional conditions and conserve the ability to shift toward a more mesenchymal stem-like phenotype. We successfully established 8 patient-derived primary MTC lines derived from tumors harboring different genetic backgrounds and with variable aggressiveness. We characterized their phenotype and response to different microenvironmental conditions and targeted therapies through Western Blot, Confocal Microscopy, ELISAs, ELDAs, RT-qPCR and proliferation assays. Interestingly, these cells may be grown at high passage numbers without losing their plasticity when cultivated in stem-promoting conditions. In differentiation media, they conserve the ability to secrete high levels of the MTC markers, calcitonin and CEA. When cultured in tridimensional conditions they all show a significant increase in the stem and neuroendocrine precursor markers such as SOX2, OCT4, EPAS1, TUJI and FOXA1 and a shift between the Epitelial-to-Mesenchimal Transition markers, E-cadherin and Vimentin, that occurs in a spatial-dependent manner. These variations in the behavior of MTC lines partially recapitulate several of the alterations that were detected in MTC tissue samples. Moreover, changes in culture conditions, as the induction of a pseudo-hypoxic state or growth in adhesion-free environment, have a great impact on the cell lines phenotypes and their response to the anticancer drugs available for MTC treatment, such as Pralsetinib, Selpercatinib, Cabozantinib, Lenvatinib and Vandetanib. In conclusion, we report here the generation of an unprecedented valid patient-derived *in vitro* model that can provide further insight in MTC biology complexity and will allow future translational studies, including those aiming to understand the mechanisms underlying the onset of therapy resistance.
DOI: 10.1530/endoabs.101.PS2-11-03

## PS2-11-04

**Downregulation of MIR-346 affects the expression of nuclear receptor-interacting protein 1 (NRIP-1) and estrogen receptors in follicular thyroid cancer**
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Objectives
Evidence exists that estrogen receptor alpha (ERα) and beta (ERβ) may be involved in the pathogenesis of thyroid cancer. miR-341, a potent biomarker that distinguishes follicular thyroid cancer (FTC) from adenoma, has shown proliferative and metastatic effects in various cancers by regulating nuclear receptor-interacting protein 1 (NRIP1), which forms complexes with ERα. Thus, we investigated the role of miR-346 on estrogen-associated pathogenesis of FTC.
Methods
Human follicular thyroid carcinoma cell lines (FTC-133, RO82-W-1) were used. To examine the effects of estrogen and miR-346 on behavioral traits and estrogen-associated pathogenesis of FTCs, FTC-133 and RO82-W-1 were treated with 100 or 200nM of estradiol-17 β (E2) and transfected with the inhibitor targeting human miR-346. Cell migration and invasion assays were performed after the cells were transfected with either the inhibitor or the control; gene and protein levels of NRIP1, ERα, and ERβ were examined by qPCR and western blot, respectively.
Results
The expression of miR-346 was significantly higher in FTC-133 and WRO-82-1 compared to Nthy-Ori-3-1. In miR-346-downregulated FTC-133 and WRO-82-1, the trans-well assay showed that $E_2$, *in dose-dependent manner*, significantly decreased the number of invaded cells in both cell lines. Downregulation of miR-346 itself also had significant protective effects on invasion in both FTC-133 and WRO-82-1; and $E_2$ significantly intensified these effects in both cell lines. The similar pattern was observed in cell-migration assays. Downregulation of miR-346 significantly decreased the protein expressions of NRIP1 and ERα while increasing protein expression of Erβ. These resulted in the decreased ratio of ERα to ERβ in WRO-82-1. $E_2$ treatment increased the protein expression of ERβ, and downregulation of miR-346 augmented $E_2$-induced ERβ increase.
Conclusions
The inhibition of miR-346 resulted in the increased expression of NRIP1 and ERβ and decreased migration and invasion of FTC cells, which augmented by E2. Considering the facts that NRIP1 is the direct target of miR-346 and NRIP1 is a cofactor of ERβr, their interactions may be involved in the pathogenesis of FTC.
DOI: 10.1530/endoabs.101.PS2-11-04

## PS2-11-05

**Fusion partner agnostic approaches improve detection of targetable gene fusions in thyroid cancers**
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Point mutations constitute the majority of thyroid cancer mutations. Depending on screening strategy and patient populations, however, rearrangements also serve as oncogenic drivers for roughly one-in-five tumors. This underscores the importance of a comprehensive molecular approach that extends beyond assessment of single nucleotide variants (SNV). Receptor tyrosine kinases (RTK) feature prevalently within the described gene fusions in thyroid entities. Such fusions impart a constitutively active phenotype that deregulates multiple signaling cascades. RTKs are highly indiscriminate, both in their fusion partners

and the underlying genomic mechanism of rearrangement, which can fall below the detection limit of conventional diagnostic approaches. As a consequence, targeted multiplex amplicon sequencing has emerged as a preferred method for characterizing thyroid neoplasia. However, such approaches require *a priori* knowledge of fusion partners and/or breakpoints. Therefore, it was hypothesized that gene partner and/or breakpoint agnostic approaches might impart improved clinical sensitivity. To assess this hypothesis in a primary sample across four marketed thyroid sequencing panels (ThyroSPEC, Oncomine Focus Assay (OFA), Illumina TruSight Fusion Panel (IFP), and Archer FusionPlex CLT), we performed an *in silico* analysis on $n = 20$ unpublished cases of fusion-driven thyroid carcinomas identified using retrospective FusionPlex sequencing, between 2022-2023. To supplement this data, we identified 16 publications reporting at least five thyroid cancer fusion-driven cases, however, 13/16 (81%) were excluded due to lack of transcript or genomic reference IDs and 1/16 (6%) was excluded due to utilization of a targeted multiplex amplicon approach, for a final total of $n = 168$. Sensitivity analysis was performed through stratification via the five most common RTK fusion partners/families: RET, NTRK1-3, BRAF, ALK, and MET. Proportions tests were used to evaluate significance, with multiple hypothesis correction. We observed that FusionPlex could identify 100% of the 168 described fusions, compared to a detection frequency of 57%, 60%, and 65% for ThyroSpec, IFP, and OFA, respectively ($P = 1.11e-20$). Subset analysis revealed similar significance for BRAF ($P = 7.36e-19$), NTRK1-3 ($P = 3.69e-7$), and MET ($P = 0.023$), however RET and ALK did not reach significance. Collectively, these findings demonstrate the critical importance of panel selection for identifying fusion-driven thyroid cancers and that a gene partner and/or breakpoint-agnostic approach to fusion discovery has improved clinical sensitivity. Additional work will need to quantify the diagnostic utility of agnostic sequencing approaches against both broad scale and hot-spot panels as they relate to metrics of cost-effectiveness and theranostic consequence.

DOI: 10.1530/endoabs.101.PS2-11-05

## PS2-11-06

**The autonomic system balance and integrin AVB related molecular markers in patients with papillary thyroid carcinoma**

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Objectives
Differentiated thyroid cancer (DTC) accounts for over 95% of thyroid malignancies. It has been reported that integrin αvβ3, fractalkine, and CX3CR1 expression were upregulated in patients with papillary thyroid carcinoma (PTC). L-thyroxine (T4) is the principal ligand of the thyroid hormone analogue receptor on the extracellular domain of integrin αvβ3. In patients with DTC, thyroid hormone suppression therapy (THST) with T4 has been associated with a higher risk of cardiovascular mortality. The purpose of this study was to assess a possible association between molecular markers and sympathetic-parasympathetic balance assessed via heart rate variability (HRV), both at baseline and under THST, in patients newly diagnosed with PTC with no significant comorbidities.
Methods
This prospective study included 36 PTC and 14 benign nodular goiter (BNG) patients who were euthyroid preoperatively. Molecular markers assessments included the following parameters: integrin αvβ3, fractalkine, and CX3CR1. The analysis of HRV included both time-domain parameters and frequency-domain parameters. After at least 6 months of THST, patients with PTC were reassessed for molecular markers and HRV parameters.
Results
PTC and BNG groups were similar in terms of age, gender, and BMI ($P = 0.184$; $P = 0.705$; $P = 0.749$, respectively). Serum integrin αvβ3 level was significantly higher in the PTC group ($24.27 \pm 8.01$ ng/ml; $17.25 \pm 7.27$ ng/ml; $P = 0.006$). Other serum molecular marker levels were similar in both groups. Significant decreases were observed in HRV parameters including HF, LF, VLF, SDNNi, rMSSD, SDSD, and pNN50 under THST. In the PTC group, frequency-domain HRV analysis showed the following correlations: 1) lower HF values with higher CX3CR1 ($r = -0.42$, $P = 0.011$); 2) lower LF values with higher CX3CR1 ($r = -0.45$, $P = 0.007$); 3) lower VLF values with higher CX3CR1 ($r = -0.35$, $P = 0.034$). In multivariate regression, CX3CR1, and integrin αvβ3 were revealed to be independently related to the LF/HF ratio ($B = 0.002$, $P = 0.003$; $B = -0.107$, $P = 0.026$; $B = 0.256$, $P = 0.026$, respectively) in patients with PTC baseline. Under THST, only CX3CR1 was found to be associated with an LF/HF ratio independent of TSH level ($B = 0.001$, $P = 0.036$).
Conclusions
The study showed that serum integrin αvβ3 levels were significantly higher in patients with PTC compared to the BNG. There was a relationship between sympathetic-parasympathetic balance assessed via HRV and molecular markers particularly CX3CR1 and integrin αvβ3 in patients with PTC. We found that CX3CR1 was an independent marker of autonomic nervous system dysfunction in patients with PTC under THST.

DOI: 10.1530/endoabs.101.PS2-11-06

## PS2-11-07

**Effects of crizotinib in strn-alk anaplastic thyroid cancer in primary culture *in vitro***

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Anaplastic thyroid cancer (ATC) is one of the aggressive and fatal human cancers, and accounts for <2% of thyroid carcinomas. Anaplastic lymphoma kinase (ALK) rearrangements are associated with tumor growth and considered a target for the treatment of ATC. Crizotinib is an oral small-molecule tyrosine kinase inhibitor of ALK, MET, and ROS1 kinases, approved in ALK-positive non-small cell lung cancer. The effect of crizotinib in primary human ATC (pATC) cells in transforming striatin (STRN)-ALK fusion has not yet been demonstrated in the literature. The aim of this study is to obtain pATC with STRN-ALK *in vitro* and investigate the antineoplastic effect of crizotinib. We obtained thyroid surgical samples from 12 ATC patients and 6 controls who were undergone to parathyroidectomy: 10/12 with pATC, 2 with transforming STRN-ALK fusion (17%). In 3/10 pATC (2 with/one without STRN-ALK), overall in those with STRN-ALK, crizotinib was able to inhibit proliferation, migration, invasion, while increased apoptosis. In addition, crizotinib was also significantly able to inhibit the proliferation of AF cells, a continuous cell line obtained by primary ATC cells. Finally, results obtained from these preclinical studies in human pATC (with STRN-ALK) *in vitro* will help to better understand the anticancer activity in ATC and pave the way to future clinical evaluations in these patients.

DOI: 10.1530/endoabs.101.PS2-11-07

## PS2-11-08

**TSHR variants in benign and malignant thyroid tumors**

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Background
Variants of the *TSHR* gene occur in different types of thyroid tumors. The importance of their molecular testing and the clinical impact is unclear. The aim of this study was to detect *TSHR* variants in a large cohort of malignant, low-risk and benign thyroid tumors and correlate them with clinical and histopathological data.
Methods
The cohort consisted of 885 fresh frozen thyroid tumor samples (455 malignant tumors, 52 low-risk neoplasms and 378 benign tumors) from 148 pediatric (under 18 years) and 736 adult patients. DNA extracted from the samples was analyzed for the presence of *TSHR* variants (NM_000369.5) in exon 10 using the Nextera XT DNA Library Prep Kit and next-generation sequencing (MiSeq, Illumina).
Results
A total of 14 types of *TSHR* variants were found in 38 thyroid tumors from 37 patients (32 females, 5 males). The histology of *TSHR* -positive thyroid tumors was as follows: 30/378 (7.9%) benign tumors, 4/390 (1.0%) papillary thyroid carcinomas (PTCs), 3/52 (5.8%) low-risk neoplasms and 1/20 (5.0%) follicular thyroid carcinomas (FTCs). One-third 13/37 (35.1%) of patients with *TSHR* -positive thyroid tumor were pediatric patients. In pediatric patients, almost all (11/13) *TSHR* -positive thyroid tumors were benign, 1/13 was a low-risk neoplasm, and 1/13 was a PTC that was positive for the *NCOA4/RET* fusion gene and the *TSHR* variant K340N was found to be germline. In other PTC from an adult patient, the *TSHR* I541V variant was also found to be of germline origin. In the remaining three *TSHR* -positive thyroid carcinomas, peripheral blood from patients was unavailable. Overall, the most common variant was the *TSHR* M453T detected in eight samples with different histology (5× benign tumor, 1× low-risk neoplasm, 1× PTC, 1× FTC). The second most common variants detected in five cases each were D633Y and F631L. Both variants were identified only in benign tumors and interestingly, the D633Y variant was found only in pediatric patients. Other *TSHR* variants that were repeatedly detected only in benign tumors were: S425I in four cases, D633H in three cases, and T632I, I568T, and D619G each in two cases.
Conclusion
*TSHR* variants were detected at a higher frequency in thyroid tumors from pediatric (8.8%) than from adult (3.3%) patients. Most *TSHR* -positive thyroid tumors were benign and some of the variants found were associated only with benign histology.
*Supported by AZV NU21-01-00448 and MH CZ RVO 00023761.*
DOI: 10.1530/endoabs.101.PS2-11-08

## PS2-11-09

**Dual agonism of sodium iodide symporter function *in vivo***

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Objectives
New approaches are urgently needed to enhance radioiodide (RAI) ablation of aggressive and metastatic thyroid cancer. Our previous experiments revealed that valosin-containing protein inhibitors (VCPi), such as disulfiram, markedly increase sodium iodide symporter (NIS) activity to promote RAI uptake. Recently, disulfiram was reported to inhibit NPL4 activity – a critical VCP cofactor – via its copper bound diethyldithiocarbamate metabolite $Cu(DDC)_2$. We hence hypothesised that disulfiram and its metabolites increase RAI uptake by interfering with ER-Associated Degradation (ERAD) via a VCP/NPL4 pathway, permitting more NIS protein to be trafficked to the plasma membrane. Here, our aim was to understand the mechanistic impact of $Cu(DDC)_2$ on NIS function in thyroid cells, as well as to investigate the clinical relevance of $Cu(DDC)_2$-gene interactions.
Methods
We utilised RNA-Seq to identify transcriptional pathways altered by $Cu(DDC)_2$. Technetium-99m pertechnetate ($^{99m}$Tc) uptake after intravenous administration was used to evaluate NIS function in wild-type BALB/c mice. TCGA was appraised to investigate $Cu(DDC)_2$-gene interactions with recurrence in RAI-treated papillary thyroid cancer (PTC).
Results
$Cu(DDC)_2$ increased RAI uptake in a dose-dependent manner across multiple thyroid cancer cell lines (mean ~3.4-fold). Subsequent RNA-Seq analysis revealed potent transcriptional changes in 8505C cells treated with $Cu(DDC)_2$, including dysregulation of 357 genes encoding transcription factors. TaqMan RTPCR confirmed induction of transcription factors with key roles in regulating NIS expression, such as PAX8 and CREM, in multiple thyroid cell lines and human primary thyrocytes. In support, $Cu(DDC)_2$ was unable to induce NIS mRNA expression or $^{125}$I uptake when PAX8 was depleted in primary thyrocytes and thyroid cancer cells. Importantly, significant induction of thyroidal $^{99m}$Tc-uptake (~30%;$n = 7$;5 mg/kg dose;$P < 0.05$) in wild-type BALB/c mice treated intravenously with $Cu(DDC)_2$ was associated with increasing PAX8 (1.4-fold;$P < 0.05$) and CREM mRNA (1.6-fold;$P < 0.01$) expression. Surprisingly, $Cu(DDC)_2$ retained activity in the absence of NPL4 but not VCP in thyroid cancer cells and primary thyrocytes. Thus, $Cu(DDC)_2$ required functional VCP but not NPL4 expression to enhance RAI uptake. We further appraised TCGA with LASSO regression analysis identifying a 22-gene riskscore classifier based on $Cu(DDC)_2$-associated transcription factors, which showed a significantly worse prognosis for high-risk RAI-treated PTC [Hazard Ratio (HR) = 11.6;95%CI 5.8-23.31;$P < 0.001$;$n = 256$].
Conclusions
We have identified a new dual agonist of RAI uptake dependent on the distinct functionalities of PAX8 and VCP, with the potential to directly impact RAI therapy for patients with aggressive thyroid cancer. Our bioinformatic analyses validated the clinical relevance of $Cu(DDC)_2$-associated genes in RAI-treated PTC, enabling construction of a risk score classifier for predicting recurrence.
DOI: 10.1530/endoabs.101.PS2-11-09

## PS2-11-10

**Exploring the genetic links between voltage-gated potassium channels and familial non-medullary thyroid carcinoma: a family study**

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Introduction
Our team identified a family where 5 elements developed thyroid cancer between the ages of 26 and 38. Since no syndromic form of the disease was found, the diagnosis was of familial non-medullary thyroid carcinoma (FNMTC). Our team employed Whole-Exome Sequencing (WES) and identified a new potentially pathogenic germline mutation in the *KCNB2* gene [ *p.(Gly106Arg)*]. *KCNB2* encodes a voltage-gated potassium channel (vgKCN), and the detected missense mutation is localized in the tetramerization domain of the protein, possibly affecting its assembly and $K^+$ efflux. Since $K^+$ efflux by the cell is a necessary condition for cellular homeostasis, channel disruption can impact the function of other ion channels nearby. Mice studies showed that *KCNE2* disruption indirectly impairs sodium-iodide symporter (NIS) function, and therefore iodide uptake by the cell, resulting in hypothyroidism or follicular nodular disease.
Hypothesis
By indirect effect on NIS function vgKCN mutations may increase predisposition to thyroid cancer and interfere with radioiodine (RAI) therapy response.
Methodology
We conducted *in silico* studies using two different NGS databases, TCGA and one in-house oncocytic tumors database (513 and 18 patients, respectively). Alterations in 59 genes were searched for copy-number variation, point mutations and other genetic alterations. *in vitro* assays using the FRTL-5 cell line are being performed. FRTL-5 cells were transfected with overexpression vectors containing either *KCNB2* wild-type or *KCNB2* mutated sequences, and the empty vector (EV) as a negative control. Expression of thyroid markers (e.g. NIS, TSH receptor, Thyroglobulin and TPO) was evaluated by qPCR and cell viability by PrestoBlue assay. Protein expression of thyroid markers will be assessed by Western blot. Cell cycle and apoptosis through flow cytometry, cell morphology by phalloidin assay, and cell colony formation by crystal violet. Transformed cells will further be treated with Guangxitoxin-1E, a potent *KCNB1* / *KCNB2* inhibitor.
Results
Our *in silico* results show that vgKCN mutations are rare events in thyroid cancer [19/488 (4%) in TCGA; 3/18 (17%) in our in-house database]. *BRAF* and *NRAS* alterations are frequent events in vgKCN altered tumors (58% and 16%, respectively). No *KCNB2* pathogenic mutations were observed. vgKCN mutations were not correlated with patient prognosis. Our *in vitro* preliminary results show that *KCNB2* mutated cells present higher expression of the channel than *KCNB2 wild-type* cells. No differences in cell viability were found between *KCNB2* wild-type and mutated cells.
Conclusions
If confirmed, vgKCN mutations may identify patients with altered RAI response, serving as thyroid cancer markers and potential pharmacological targets.

DOI: 10.1530/endoabs.101.PS2-11-10

## Diagnosis of Thyroid Cancer-1

### PS-12-01

**The clinical significance of markedly elevated preoperative serum thyroglobulin levels**

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Objectives
Any condition involving increased follicular cell mass may raise serum thyroglobulin levels. However, we occasionally encounter patients with markedly elevated preoperative thyroglobulin levels, indicating thyroid cancer with substantial metastatic burden. We aimed to investigate the clinical significance of markedly elevated preoperative serum thyroglobulin levels.
Methods
From 2019 to 2021, we analyzed patients underwent thyroid surgery for papillary thyroid cancer (PTC) or benign, with a focus on preoperative thyroglobulin levels $\geq$500ng/ml.
Results
In 7,737 PTC cases and 781 benign cases, 84 in each group had preoperative thyroglobulin levels $\geq$500ng/ml. Forty (48%) had the BRAF V600E mutation, and 11 (13%) had the TERT promoter mutation in PTC. In the 24 cases with a cancer size $>$4 cm, 3 (13%) showed distant metastasis, and 1 (4%) had another nodule $>$2 cm; none had diffuse thyroid disease (DTD). In the 32 cases with a cancer size $>$2 cm but $\leq$4 cm, 4 (13%) showed distant metastasis. 4 (12%) had another nodule $>$2 cm, and 3 (9%) exhibited DTD; two had both conditions. In the 28 cases with a cancer size $\leq$2 cm, 1 (4%) showed distant metastasis. 15 (53%) had another nodule $>$2 cm, and 9 (32%) exhibited DTD; two had both conditions. In benign, for 50 cases with size $>$4 cm, multinodular, 1 (2%) exhibited DTD; for 12 cases with size $>$2 cm but $\leq$4 cm, 3 (25%) cases showed DTD; and for 22 cases with size $\leq$2 cm, no focal lesion, 22 (100%) cases exhibited DTD. Even with preoperative thyroglobulin $\geq$1000ng/ml, a similar pattern persisted.
Conclusions
In cases with markedly elevated preoperative thyroglobulin levels, a high cancer burden is often observed. However, it can also occur in cases with large benign nodules or DTD. Therefore, additional research is needed to determine the clinical utility when excluding such cases.

DOI: 10.1530/endoabs.101.PS-12-01

### PS2-12-02

**Performance of eu-tirads, ATA and AACE/ACE-AME ultrasound risk stratification system (RSS) in pediatric patients with thyroid nodules**

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Objectives
Thyroid nodules in patients $\leq$18 years are less frequent than in adults, however several studies showed a higher rate of malignancy. The aim of the present study is to analyze the ultrasound (US) features of nodules in patients $\leq$18 years and to test the ability of the main US risk stratification system (RSS) in identifying malignancy. Moreover, we also evaluated the potential correlation between the results of US RSS and cytology.
Methods
We analyzed the US reports and cytology results of series of a consecutive thyroid nodules in patients $\leq$18 years diagnosed in our department for the first time, between 2016 and 2022. The nodules were classified according to EU-TIRADS, 2015-ATA, and AACE/ACE-AME while the cytology was classified according to Italian Consensus.
Results
The whole study group consisted of 271 nodules in 221 patients. Most patients were females (74.2%), and the median age at cytology was 16 years (IQR 14-17). The median nodule diameter was 1.9 cm (IQR 1.4-2.9). Cytology result was TIR5 in 9.3%, TIR4 in 4%, TIR3b in 8.8%, TIR3a in 19.5%, TIR2 in 32.7%, TIR1C in 13.6% and TIR1 in 12.1% of cases. Ultrasound features were available in 216/271 nodules (79.7%). The thyroid was multinodular in 34.3% of cases. The nodules were mostly solid (74.1%), isoechoic (49.1%), "wider than tall" (80.6%) with well-defined margins (82.9%) and without calcifications (77.8%). Approximately one third of the nodules had a high suspicion of malignancy in accordance with the 3 RSS evaluated [EU-TIRADS 5: 35.2%; 2015-ATA High Suspicion 30.6%; AACE/ACE-AME High-risk: 35.2%]. The rate of cytology suspicious for malignancy (TIR4 and TIR5) was 23.7-27.3% in the high and 10.5-11.4% in the low/intermediate ultrasound risk.
Conclusions
Our data show a lower performance of US RSS in thyroid nodules for pediatric patients compared to adults. However, in patients $\leq$18 years, the 3 main US RSS were able to identify about 75% of the nodules as low/intermediate suspicious for malignancy of which about 90% were not suspicious for malignancy by cytology.

Therefore, in these cases a careful approach and a conservative management should be a viable option.

DOI: 10.1530/endoabs.101.PS2-12-02

## PS2-12-03

**Differences and analogies in thyroid cancer discovered incidentally or by thyroid related screening: a multicenter study**

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Objective

The prevalence of Thyroid-Cancer (TC) has increased worldwide and an association with metabolic and cardio-vascular disorders has been reported. Nevertheless, an increasing percentage of patients are currently diagnosed incidentally through non-thyroid related imaging for other clinical conditions. Our aim was to assess the prevalence of Thyroid-Related (TD) *vs* Incidental (ID) reason leading to TC diagnosis and to compare the two groups in terms of clinical characteristics, size and severity of TC at presentation and rate of non-thyroid cancers and cardiovascular/metabolic comorbidities.

Methods

We performed a retrospective cohort study in three high-volume hospital-based centers for thyroid diseases (Pavia, Latina and Messina) in Italy. Consecutive patients with TC were enrolled, collecting data on reason leading to TC diagnosis, age, sex, BMI, presence of cardio-metabolic comorbidities and non-thyroid cancer.

Results

Among the 356 enrolled subjects the US diagnosis of TC was prompted by thyroid-related reasons in 283 (79.5%, TD group) and incidental in 73 (20.5%, ID group). The ID group patients were more frequently males, significantly older and with a higher BMI than the TD group ones, they had a higher rate of non-thyroidal cancers and cardiovascular/metabolic comorbidities. No significant differences could be observed in terms of TC histotype, cancer size, extra-thyroidal extension, lymph-node metastases, AJCC Staging or ATA Risk stratification.

Conclusions

Biological features of TC are similar in the TD and ID groups, but patients in the two groups display significant differences as to their clinical features.

DOI: 10.1530/endoabs.101.PS2-12-03

## PS2-12-04

**Markers of aggressiveness in radioiodine-refractory thyroid cancer**

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Introduction

Most differentiated thyroid cancers (DTC) have a good response to treatment. However, about 5% of DTC exhibit resistance to radioiodine (RAI), thus having a poor prognosis. Resistance to RAI occurs as a result of losing thyroid differentiation. Immunohistochemical analysis of thyroid cancers shows a substantial ability to predict cancer recurrence and its resistance to RAI.

Case reports

The first case is a of a 66-year-old female, known with total thyroidectomy and bilateral laterocervical lymphodissection for papillary thyroid carcinoma. At the last assessment, whole body scintigraphy showed lung metastasis and an iodine fixing area in the right paratracheal region for which 140 mCi RAI was administered. Tissue section from the lateral and lower tracheal tumor block was subjected to immunostaining (TTF1, PAX8, Thyroglobulin, CK19 were positive in tumor cells, Ki67 15%) which confirmed the local secondary determination of poorly differentiated carcinoma originating in papillary carcinoma with clear and tall cells with weak affinity for capturing RAI. The second case is of a 77-year-old female, known with poorly DTC with trabecular pattern and outstanding areas of sclerohyalising type, with areas of capsular angioinvasion. Immunohistochemical markers (TTF1, PAX8 and Thyroglobulin positivity over 80%, Ki67 3%) indicated the possibility of response to radiotherapy, but with high risk of distant metastases. The third case is of a 45-year-old female, known with total thyroidectomy for poorly DTC and pulmonary and supradiaphragmatic lymph node metastases. Increased value of thyroglobulin (5141 ng/ml, N:3.5-77), the cumulative dose of 240 mCi RAI, the lack of iodine capturing images on anterior cervical region and whole body scintigraphy, as well as positive immunohistochemical markers (TTf1, PAX8, Thyroglobulin, CK19, Ki67 25%) for poorly DTC may suggest a decrease in the chances of response to future radiotherapy.

Conclusion

The case series highlights the predictive capabilities of the immunohistochemical analysis concerning the dedifferentiation of thyroid cancers and their resistance to RAI.

DOI: 10.1530/endoabs.101.PS2-12-04

## PS2-12-05

**Comparative analysis of thyroid cytopathology preparation: conventional smear, liquid-based preparation, and their combination**

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Objectives

Fine-needle aspiration biopsy (FNA) is the preferred preoperative pathological diagnostic method for thyroid nodules. Processing methods for FNA samples mainly include conventional smear (CS) and liquid-based preparation (LBP). There is still debate as to which method or their combination is better. This study aims to compare the diagnostic accuracy of the two methods and their combined usage.

Methods

We included thyroid cytopathology data from nine medical centers between 2013 and 2023. We identified a total of 35006 samples, of which 1049 samples used CS, 9677 samples used LBP, and 24280 samples used both CS and LBP. Among the samples utilizing both methods, 22472 had only a final cytological diagnosis based on two methods, while 1808 samples from prospective cohort had the diagnosis of CS, LBP and their combination, respectively. According to the Bethesda reporting system, we calculated the distribution of diagnostic categories for different methods and compared the diagnostic uncertainty (category III and IV). For category II, V, and VI samples with histological diagnosis, we compared the diagnostic accuracy of the different preparation methods. For the prospective cohort samples, we performed consistency analysis and compared the diagnostic performance of different preparation methods.

Results

Overall, the rate of diagnostic uncertainty (category III and IV) of CS was higher than that of LBP and combined CS and LBP (21.63% vs 14.01% vs 14.10%). 744 samples using CS, 4022 using LBP and 7270 using both methods under category II, V, or VI samples had definitive histological diagnosis. Their sensitivities (97.34% vs 98.84% vs 98.47%) and accuracies (95.83% vs 97.66% vs 95.82%) were comparable, while the specificity of LBP (79.34%) was higher than that of CS (60.00%) and their combination (67.58%). For the satisfactory samples (category II-VI) in the prospective cohort, the concordance rate between CS and

| | Overall data | | | Prospective cohort | | |
|---|---|---|---|---|---|---|
| | CS $n = 744$ | LBP $n = 4022$ | CS&LBP $n = 7270$ | CS $n = 531$ | LBP $n = 550$ | CS&LBP $n = 546$ |
| Sensitivity | 97.34% | 98.84% | 98.47% | 97.88% | 96.79% | 97.74% |
| Specificity | 60.00% | 79.34% | 67.58% | 58.33% | 75.00% | 66.67% |
| Accuracy | 95.83% | 97.66% | 95.82% | 96.99% | 96.00% | 96.89% |
| PPV | 98.30% | 98.68% | 97.01% | 99.03% | 99.03% | 99.05% |
| NPV | 48.65% | 81.36% | 80.50% | 38.89% | 46.88% | 45.45% |

LBP was 94.20%. The sensitivities (97.88% vs 96.79% vs 97.74%) and accuracies (96.97% vs 96.00% vs 96.89%) of three methods were comparable, while LBP showed higher specificity (75.00%) than CS (58.33%) and the combined methods (66.67%).
Conclusions
The diagnostic uncertainty rate of CS was higher than that of LBP and combined usage. The diagnostic accuracy of CS and LBP was comparable, and the combination of CS and LBP did not improve the diagnostic accuracy. Therefore, it is not suggested to combine CS and LBP in routine cytological diagnosis.

DOI: 10.1530/endoabs.101.PS2-12-05

## PS2-12-06

**A comparative study between the old and the new version of a microrna and dna-based molecular classifier for indeterminate thyroid nodules in real-world samples**

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Background
In 2018 we presented the first version (v1) of our microRNA-based algorithm for indeterminate thyroid nodules classification (mir-THYpe full), which was used in real-world clinical routine until recently, when an new optimized version (v2) was released using new machine learning techniques and combinating microRNA and DNA data.
Objective
Our aim was to simulate and analyze what the performance of v2 algorithm would have been, if it had been used in the classification of the same samples originally classified by the v1.
Methods
The cohort of this study was composed of microRNA and DNA data extracted from thyroid FNA smear slide of 1.718 nodules (from 1.687 patients who payed for the test) (945 Bethesda 3 and 773 Bethesda 4) that were originally classified by the v1 in real-world clinical routine and now were re-analyzed and classified by the new optimized v2 algorithm. The molecular analysis performed in the samples consisted of microRNA profile and DNA mutation analysis (BRAF V600E and pTERT C228T/C250T). From those, anatomopathological data was available for 329 nodules (112 benign and 217 malignant) and used to evaluate the performance of the v2. Due to the unrealistically high disease prevalence (66.0%), a real-world adjusted prevalence (32%) was performed based on Bayeś theorem.
Results
When comparing the results of the v1 with the v2 version of the algorithm, 979 vs 1.175 samples were classified as negative for malignancy (Benign Call Rate/BCR - 57.0% vs 68.4%) and 739 vs 543 samples as positive. In this simulation, the real-world performance of the new v2 would be: 94.5% of sensibility, 75.9% of specificity, 64.8% of positive predictive value (PPV), 96.7% of negative predictive value (NPV) and 81.8% of accuracy.
Conclusion
The results show an BCR improvement in performance of v2 compared to v1, resulting in an increment of the number of cases that would have benefited from the test avoiding unnecessary diagnostic surgeries. The v2 also showed high PPV and NPV, suggesting that real-world performance for future tests will also be optimized.

DOI: 10.1530/endoabs.101.PS2-12-06

## PS2-12-07

**Molecular profiling of thyroid nodules: insights from the mir-thype full trial in brazilian patients**

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Background
Thyroid nodules are prevalent in up to 60% of the adult population, occurring in a ratio of 4:1 woman/man. Using fine needle aspiration, approximately 25-30% of cases are categorized as "indeterminate": Bethesda 3 (B3) or Bethesda 4 (B4). In these cases, molecular tests, such as mir-THYpe full, can assist in diagnosis and prognosis, utilizing microRNA profiling and DNA analysis of mutations including BRAF V600E, pTERT C228T/C250T, RET M918T, C634Y/R, and V804L/M.
Objective
To evaluate by a retrospective analysis, the molecular profile data of Brazilian patients submitted to the mir-THYpe full test.
Methods
Molecular data from 3164 nodules (1812 B3 and 1352 B4) were analyzed, stratified by age (using a cut-off at 55 years), sex, mutation prevalence, and correlated with anatomopathological reports (APR) of patients who underwent surgery subsequent to the molecular test.
Results
Out of the total 3164 nodules, 64.2% (2032/3164) were classified negative and 35.8% (1132/3164) as positive for malignancy by mir-THYpe full test, being 75.5% (2389/3164) from female and 24.5% (775/3164) from men. In the negative results cohort, no mutations were detected, of which 20 patients underwent surgery and in 18 benign lesions were confirmed by APRs. In contrast, in the molecular positive results cohort, mutations were detected in 22.4% (254/1132) of the total cases, being: 232 BRAF V600E, 19 pTERT C228T, two RET M918T, and one RET C364R mutation. The pTERT C228T mutation was found in 5.2% (17/329) of the positive tests in individuals $\geq$55 years, compared to only 0.2% (2/803) in those $<$55 years ($P < 0.0001$). Regarding the BRAF V600E mutation, it was detected in 17.9% (59/329) of individuals $\geq$55 years, compared to 21.5% (173/803) in those $<$55 years ($P = 0.17$). Of all patients in the positive cohort, 207 APRs were accessible, confirming 127 cases of cancer/NIFTP.
Conclusion
In our cohort, many clinical parameters were aligned with what is found in other cohorts from other countries, like woman/man ratio, BRAF V600E mutation prevalence (including distribution by age or in all cohort) and prevalence of TERT C228T over C250T. Interestingly, the TERT positivity rate when divided by age showed an increased rate in the $\geq$55 years Brazilian patients with indeterminate cytology, suggesting acts as a risk factor for the occurrence of this mutation on indeterminate thyroid nodules.

DOI: 10.1530/endoabs.101.PS2-12-07

## PS2-12-08

**Appropriately positioned molecular testing for cytologically indeterminate thyroid nodules in an optimized thyroid nodule diagnostic pathway has incremental impact in addition to clinical assessment, cytology and ultrasound malignancy risk**

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Objective
Molecular test (MT) of cytologically indeterminate thyroid nodules (ITNs) needs to be appropriately focused on clinical situations where it can influence decision making. We therefore evaluated MT as an adjunct to an optimized integrated interdisciplinary thyroid nodule diagnostic pathway.

Methods
1024 consecutive ITNs were included, each underwent reflexive ThyroSPEC MT between July 30, 2020, and October 30, 2023. A multivariate regression model was built to assess the rates of malignancy (ROM) for ThyroSPEC MT categories and other clinical variables. A nomogram was generated based on the model as a graphical tool to compute the overall ROM in clinical practice.
Results
The model achieved a cross-validated AUC of 0.83. Patients with high-risk mutations or malignant molecular markers exhibited significantly higher odds (152.8 times) of malignancy compared to those with mutation-negative or benign molecular marker results. The ThyroSPEC MT demonstrated a negative predictive value of 92% [CI 84-97%] for ATA low suspicion or TR3 category and 89% [CI 83-94%] for ATA intermediate suspicion or TR4 category. Mutation was the predominant reason for surgery in 55% of patients with intermediate-risk mutations and in 100% of patients with malignant molecular marker and high-risk mutations. 40% of patients opted against surgery despite positive mutation results (64 intermediate-risk mutation, 4 malignant molecular marker or high-risk mutation) due to patient preference based on informed, shared decision-making. However, among patients with a benign mutation, 38% of cases were under surveillance because of the benign mutation, while 19% of cases under surveillance were due to patient preference.
Conclusions
High-risk mutations or malignant molecular markers were associated with significantly higher odds of histological malignancy and always impacted clinical management. For the most frequent intermediate-risk mutation nodules, integrating the ROM of the MT results with the ROM of additional clinical variables may further improve clinical decision making. Overall, these results highlight the importance of appropriately positioning and interpreting MTs as an adjunct to an optimized integrated interdisciplinary thyroid nodule diagnostic pathway to further improve diagnostic impact.
Model result

| Covariate | OR (95% CI) | P |
|---|---|---|
| ThyroSPEC High-risk Mutations or Malignant molecular markers (vs. Mutation Negative or Benign Molecular Marker) | 152.8 (18.8, 1245.0) | <0.0001 |
| ThyroSPEC Intermediate-risk Mutations (vs. Mutation Negative or Benign Molecular Marker) | 5.7 (3.2, 10.1) | <0.0001 |
| Max nodule size >5 (vs. 0-2) | 4.3 (1.6, 11.5) | 0.003 |
| Bethesda Nuclear Atypia (vs. no atypia mentioned) | 4.3 (2.2, 8.3) | <0.0001 |
| USMR 5 (vs. 1-3) | 2.9 (1.3, 6.4) | 0.009 |
| USMR 4 (vs. 1-3) | 1.8 (1.0, 3.4) | 0.063 |
| Palpation Discovery yes (vs. no) | 1.8 (1.1, 3.2) | 0.033 |
| Bethesda BIV (vs. BIII) | 1.6 (0.8, 3.0) | 0.161 |

USMR 1-3: ATA benign–low risk, ACR-TIRADS 1–3
USMR 4: ATA intermediate risk, ACR-TIRADS 4
USMR 5: ATA high risk, ACR-TIRADS 5

DOI: 10.1530/endoabs.101.PS2-12-08

## PS2-12-09

**A combined approach TI-RADS and ceus in detecting thyroid cancer**

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Objective
This study aims to assess and suggest improvements to the Thyroid Imaging Reporting and Data System (TI-RADS), incorporating both classical ultrasound (US) features and contrast-enhanced ultrasound (CEUS) patterns, to refine malignancy risk categorization in thyroid nodules.
Methods
In this study, 250 solid thyroid nodules, all subsequently confirmed by thyroidectomy and pathology, were evaluated using European TI-RADS guidelines and qualitative CEUS. This approach aimed at achieving more accurate risk stratification crucial for effective clinical management.
Results
Out of the examined nodules, 71 were malignant. The conventional TI-RADS showed a diagnostic performance with an area under the curve (AUC) of 0.720, sensitivity of 84.3%, and specificity of 45.2%. In contrast, CEUS demonstrated superior diagnostic efficacy, particularly when identifying benign nodules through homogeneous enhancement and peripheral rings (AUC = 0.800 and 0.830). Markers such as inhomogeneous enhancement and unenhanced areas were strong indicators of malignancy (AUC = 0.850 and 0.740). The combined use of TI-RADS and CEUS (TI-RADS + CEUS model) significantly enhanced diagnostic accuracy (AUC = 0.885; sensitivity 92.7%; specificity 74%), suggesting a more effective risk categorization system.
Conclusion
The integration of CEUS into the European TI-RADS provides a more comprehensive diagnostic tool, improving the precision of thyroid cancer diagnosis and malignancy risk assessment.

DOI: 10.1530/endoabs.101.PS2-12-09

## PS2-12-10

**A multi-center study of malignancy risk stratification of indeterminate thyroid fine needle aspiration cytologies based on mirna expression**

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Objectives
Fine needle aspiration (FNA) cytology of highly prevalent thyroid nodules results in an indeterminate cytopathologic diagnosis in approximately 20% of cases. To better triage patients for diagnostic *vs* definitive thyroid surgery or to avoid diagnostic surgery, low-cost gene panels can be used as a rule-in molecular test. However, there remains a need to pre-surgically diagnose indeterminate thyroid nodules where somatic mutations are not identified. The extent of this need is dependent on the comprehensiveness of the respective gene panel. In this study, direct digital counting of miRNA expression was used to identify miRNAs that are significantly differentially expressed between benign and malignant thyroid tumors. Discriminator and stably expressed miRNAs were selected to create a real time PCR (TaqMan) panel. Indeterminate FNAs were analyzed on the TaqMan panel, and classifiers were trained and validated to risk stratify for malignancy.
Methods
A retrospective cohort study was conducted. A discovery cohort of thyroid nodule FNAs and FFPEs with no common somatic mutations was analyzed for 798 miRNAs on the Human v3 miRNA panel (nCounter). A panel of differentially expressed and stably expressed miRNAs was selected from the discovery cohort and the literature. Air-dried smear and liquid cytology FNAs with no common somatic mutations were analyzed on the custom TaqMan panel, and miRNA expression levels were used to train and validate malignancy risk classifiers in both sample types.
Results
Based on the discovery panel and the literature, a 16-miRNA panel was developed and validated in 127 air-dried smear indeterminate thyroid FNA cytology specimens and 157 liquid thyroid FNA cytology specimens. A gradient boosting classifier achieved sensitivity of 100% and specificity of 83% in the air-dried smear sample type. However, miRNA expression was completely overlapping between benign and malignant tumors in the liquid FNA cytology specimens.
Conclusions
This study presents a novel, highly accurate miRNA expression classifier that could be used to incrementally risk stratify indeterminate air-dried smear FNA cytologies where common somatic mutations have been ruled out. This study also presents novel data indicating methanol-based preservation of thyroid liquid FNA cytology may hinder use of miRNA expression levels for molecular diagnostics, this finding requires further investigation.

DOI: 10.1530/endoabs.101.PS2-12-10

## Medullary Thyroid Cancer-2

### PS2-13-01

**Clinical and molecular analysis of a MEN2A kindred harboring the rare RET variant p.ser904phe**

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Introduction
Medullary thyroid carcinoma (MTC) is a rare malignant tumor that originates from the thyroid C cells. MTC may occur sporadically (75%) or as part of cancer syndrome (hMTC). hMTC is associated with germline mutations in the RET proto-oncogene. The pathogenic variants at codon 634 were the most prevalent (30-50%). Other pathogenic variants were found in less than 10% of MEN2A subjects. The rare RET variant p. Ser904Phe has been reported in only 3 kindreds worldwide and is currently classified as likely pathogenic. Objectives: To characterize the clinical and molecular features of the MEN 2A kindred with a variant at codon 904 and investigate its penetrance and risk of progression.
Methods
Ascending, collateral, and descending relatives of subjects with p. Ser904Phe variant were invited to participate in this study. Molecular analysis was performed by Sanger sequencing of RET exon 15.
Results
Of the 48 individuals screened, 31 (64.5%) harbored the mutation: 17 (54%) were women, and the median age was 34.4 $\pm$ 15.7 years. Thyroid ultrasound was performed on 24 subjects, revealing a nodule in 12 of them (0.8 $\pm$ 0.46 cm). All participants with thyroid nodules had high calcitonin levels (reference value up to 5ng/l). Twelve patients underwent total thyroidectomy (7 women and 5 men): 10 presented MTC (mean 1.06 cm), 1 had mixed MTC and papillary carcinoma carcinoma (1.2 cm), and 1 had C cell hyperplasia with amyloid deposits (0.1 cm). Gene carriers without any evidence of clinical disease are being monitored. Twelve relatives are awaiting sample collection for molecular screening. Conclusions: This large hereditary MTC kindred with rare RET variant p. Ser904Phe indicate that this variant is associate with low aggressive tumor. Furthermore, the strong genotype-phenotype association indicate that it must be reclassified as pathogenic variant rather than likely pathogenic. Follow-up of these subjects will be necessary for a better understanding of the long-term behavior of the disease in carriers of this rare variant.

DOI: 10.1530/endoabs.101.PS2-13-01

### PS2-13-02

**Basal calcitonin needs the help of stimulation test for the diagnosis of sporadic medullary thyroid cancer (MTC) only in selected cases**

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Background
Calcitonin (CTN) is the main marker for the diagnosis and follow-up of patients with MTC. Its value, either basal (bCTN) or stimulated (sCTN) after calcium stimulation test (Ca-Test) is used in clinical practice for the diagnosis of patients with suspicious MTC. The aim of our study is to evaluate the performance of bCTN and sCTN in patients undergoing surgery with suspicion of sporadic MTC.
Methods
We evaluated 158 consecutive patients (Jan 2018-Oct 2023) with suspicious sporadic MTC who performed Ca-Test, having either bCTN and sCTN evaluated with the same assay (sensitive IMA) at the same laboratory, and subsequently treated by surgery.
Results
57% were males, and the median age was 56.5 years (IQR 45-63). Histology was benign in 21 (13.3%), PTC in 28 (17.7%) of whom 21 with associated C-Cell Hyperplasia, MTC in 109 (69%) cases. The bCTN and sCTN values with improved sensitivity/specificity ratio for the diagnosis of MTC in the whole study group were 28.15 ng/l (AUC 0.907 - sens: 81.7%, spec: 89.8%) and 310.5 ng/l (AUC 0.809 - sens: 72.5%, spec 81.6%), respectively. In males these values were 33.2 ng/l (AUC 0.901 - sens 81.5%, spec 91.7%) and 341.5 ng/l (AUC 0.801 - sens: 74.1%, spec: 80.6%) while in females 22.1 ng/l (AUC 0.94 - sens: 87.3%, spec 92.3%) and 311.5 ng/l (AUC 0.897 - sens: 67.3%, spec: 100%). Seventeen out of 62 (32.2%) cases had an MTC in males and females with bCTN $\leq$ 33.2 and $\leq$ 22.1 ng/l, respectively. Of these, all were $<$1 cm, 88.2% N0 (11.8%, $n = 2$ were N1a, with micrometastases) and none had distant metastases. Conversely, only 4 patients did not have MTC if bCTN was $>$ 33.2 ng/l in males and $>$ 22.1 ng/l in females. In the 3 males, bCTN showed a median value of 40.2 ng/l while in the only female was 28.4 ng/l.
Conclusions
In our series, bCTN was more accurate than sCTN for the diagnosis of sporadic MTC. The values with better sensitivity and specificity were 33.2 ng/l and 22.1ng/l in males and females, respectively. MTCs diagnosed below these thresholds were all $<$ 1 cm, with very few cases of CC lymph node micrometastases, without any distant metastatic case. Conversely, the few cases who did not have MTC having bCTN values slightly above the thresholds, could benefit of the Ca-Test.

DOI: 10.1530/endoabs.101.PS2-13-02

### PS2-13-03

**Role of procalcitonin in unmasking false hypercalcitoninemia**

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Introduction
Calcitonin (Ct) is the most sensitive serological marker of medullary thyroid carcinoma (MTC). Its assay however is plagued by numerous interferences with consequent high risk of false diagnoses and unnecessary thyroidectomy. Numerous studies have been conducted to identify potential alternative MTC serum markers, among which the most promising one is procalcitonin (proCt). This work aims to present the possible use of proCt in unmasking cases of false hypercalcitoninemia (hyperCt).
Case reports
4 adult patients were referred to us for recent and incidentally finding of hyperCt. The first patient was a woman with autoimmune thyroiditis, the second one was a smoker woman with multinodular goiter, the third one was a man with rheumatoid arthritis and the last one was a thyroidectomized woman with pancreatic lesion. Calcitonin assay (Immunolite 2000 automated platform, Siemens, Healthcare Diagnostics), calcium gluconate stimulation test (Ca-test) and proCt assay were performed in all patients. Ct after 1:2 and 1:4 dilution, precipitation on PEG and heterophilic Ab test (HBT) were performed in patients #1 and #2. Ct assay on another automated platform (LIAISON Diasorin) was performed in all patients except for patient #4. In patient #1, #2 and #3, Ct assays during Ca-test were substantially unchanged, basal Ct value was lower using a different automated platform and proCt was always undetectable. In patients #1 and #2 the value of basal and stimulated Ct after serial dilution (1:2 and 1:4) were lower than the values obtained in toto. Similar results were also obtained after precipitation on PEG and HBT. Based on this data, we concluded for false hyperCt caused by laboratory interferences. On the contrary, patient #4 presented increased Ct values after the Ca-test, detectable ProCt value and frankly increased Ct values

| Patient | Basal Ct (pg/ml) | Ct post Calcium gluconate (pg/ml) | Ct post-dilution (1:2/1:4) (pg/ml) | ProCt (ng/l) | Ct assay on other automated platforms (pg/ml) | Final Diagnosis |
|---|---|---|---|---|---|---|
| #1 | 175 | 190 | 21/<2 | <0.1 | <1 | False hyperCt in patient with autoimmune thyroiditis |
| #2 | 118 | 196 | 29/<2 | <0.1 | <3 | False hyperCt |
| #3 | 189 | 192 | | <0.1 | 30 | False hyperCT due to rheumatoid factor interference |
| #4 | 376 | 461 | | 0.6 | 130 | Pancreatic calcitonin-secreting NET |

performed on pancreatic lesion eluate, so we concluded for a pancreatic calcitonin-secreting neuroendocrine tumor (NET) (Table 1)
Conclusion
Undetectable proCt values in patients with hyperCt are suggestive of false hyperCt. ProCt could help clinicians in unmasking cases of spurious hyperCt, without the need to perform dilution, precipitation or HBT.
DOI: 10.1530/endoabs.101.PS2-13-03

## PS2-13-04

**Sporadic medullary thyroid carcinoma: about 17 cases**
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Purpose
To Study the clinical, paraclinical and therapeutic features of medullary thyroid carcinomas (MTCs)
Methods
Retrospective study of 17 patients treated for MTC over a period of 6 years [2016-2022]
Results
The mean age was 52.6 years and Sex-ratio was 0.88. Clinically, the thyroid nodule was hard (5cases) fixed (2cases) associated with adenopathy in 6 cases and recurrent paralysis in 4 cases. Ultrasound showed nodules classified Eutirads 5 (12cases) and Eutirads 4 (5cases). The mean value of calcitonin was 1061 pg/ml. Five patients had distant bone metastasis, pulmonary metastasis in 2 cases and hepatic metastasis in 2 cases. Total thyroidectomy was performed in 15 cases associated with central lymph-nodes dissection in 12 cases and lateral lymph-nodes dissection in 8 cases. A radical lymph-nodes dissection was necessary in 2 cases. A tracheal resection and anastomosis were performed in one patient. For two patients, only a thyroid biopsy was performed. On final histology exam, multifocality was found in 4 cases. The average tumor size was 2.96 cm. Lymph-node involvement was found in 6 cases. Postoperative radiotherapy was performed in 8 cases. After a mean follow-up of 2.4 years, five patients presented a metastatic recurrence. Three patients received targeted therapy.
Conclusion
MTC is a rare neuroendocrine tumor. The increasing knowledge about diagnostic and therapeutic strategies has been leading to better prognosis.
DOI: 10.1530/endoabs.101.PS2-13-04

## PS2-13-05

**Molecular characterization of circulating tumor cells (CTCS) in sporadic medullary thyroid carcinoma (SPMTC) patients**
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Objectives
Distant metastases (DM) and/or biochemical persistent disease (BPD) in MTC, adversely affect disease prognosis. Calcitonin and CEA doubling-times (DTs) are the main prognostic indicators for disease progression. Liquid biopsy based on CTCs enrichment and characterization seems to be an intriguing non-invasive tool providing information about tumor biology and molecular identity. The aim of this study was the molecular characterization of CTCs in spMTC patients with DM and/or BPD using epithelial, mesenchymal as well as MTC-specific markers.
Methods
Nine spMTC patients (DM:3, BPD:6) carrying somatic mutations in *RET* ($n = 7$) and *HRAS* ($n = 2$) were included. Peripheral blood (20mL-EDTA) was obtained every six months. Using identical blood draws for 31 PB-samples, CTCs enrichment was directly compared by EpCAM-based positive immunomagnetic selection (EpCam-IMS) and the size-based Parsortix microfluidics system (Angle PLC, UK). The EpCam-IMS was superior in terms of sensitivity since a significantly higher percentage of identical PB-samples was found positive at the gene expression level ($P < 0.05$) while specificity was not affected. CTCs gene expression analysis was based on RT-qPCR for epithelial (*CK-8, CK-18, CK-19*), mesenchymal (*Vimentin-VIM*), MTC-specific (*Calcitonin-CALCA*) and chemokine-receptor markers (*CXCR4*). Calcitonin and CEA DTs were calculated, and disease status was determined according to the RECIST criteria.
Results
Calcitonin and CEA DTs were > 2 years in all but one patient (mean: 11.28 and 9.23 years, respectively). No structural disease progression (SDP) was documented except for one patient with *HRAS* mutation (pt-X). Interestingly, Calcitonin and CEA DTs of pt-X were 5.08 and 3.00 years, respectively, although there was an upward trend in CEA while serum Calcitonin levels were significantly elevated one month after SDP. Overexpression of *CALCA* was detected in one sample, related to pt-X, at a time-point set 60-days before marked serum calcitonin increase and 30-days before SDP was documented. *CXCR4* was strongly expressed in 3 samples related to pt-X; *CXCR4* expression was absent only at the final time-point of pt-X, when disease stabilization (biochemical and structural) was documented, after changing systemic treatment. Epithelial markers were not expressed in any of our samples while *VIM* was overexpressed in most of them ($n = 20/31$ samples).
Conclusions
EpCAM-IMS seems to be a better method for CTCs isolation in MTC patients with DM and/or BPD. Expression of *VIM* in most of our patients advocates towards an epithelial to mesenchymal transition (EMT) process possibly occurring in progressive MTC. *CALCA* and *CXCR4* expression in CTCs, along with other epithelial and mesenchymal markers, should be studied in larger patients' series and for longer follow-up periods.
DOI: 10.1530/endoabs.101.PS2-13-05

## PS2-13-06

**The impact of preoperative calcitonin screening on the prognosis of patients with medullary thyroid cancer: a retrospective multicenter cohort study**
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Objectives
There is still controversy in different guidelines regarding the necessity of routine preoperative calcitonin (Ctn) testing in medullary thyroid cancer (MTC). The impact of Ctn screening on surgical decision and clinical outcomes remains debated.
Methods
This retrospective multicenter-cohort study involved 149 MTC patients from 6 centers between 2013 to 2023. Clinical characteristics, surgical procedure and clinical outcomes were compared between Ctn-screened and Non-screened group. Kaplan-Meier method was used to estimate recurrence-free survival (RFS) and overall survival (OS).
Results
In total, 127 MTC patients with preoperative Ctn screening and 22 MTC patients without screening were analyzed. MTC patients with preoperative Ctn screening underwent more radical surgical procedures including total thyroidectomy and lymph node dissection, compared to those without screening (84.3% vs. 68.2% and 91.3% vs. 72.7%, respectively). The rate of recurrence and death were lower in the Ctn-screened group (16.1% vs. 36.4%, 0.8 % vs. 18.2 %, respectively). The survival curve showed a significantly better overall survival in Ctn-screened group than Non-screened group (HR:17.932, 95% CI 1.888-170.294, $P$-value = 0.001), while no significant difference was observed of RFS between two groups (HR:1.6, 95% CI 0.645-3.966, $P$-value = 0.307).
Conclusions
Preoperative Ctn screening can prompt surgeons choosing more radical initial surgical treatment for MTC patients, potentially leading to better long-term outcomes. Further evaluation of the cost-effectiveness of routine Ctn screening in thyroid nodule patients is warranted.
DOI: 10.1530/endoabs.101.PS2-13-06

## PS2-13-07

### Unraveling the prevalence and clinical behavior or sporadic apparently non-invasive medullary thyroid carcinoma

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Background
Medullary thyroid carcinoma (MTC) is a malignant tumor originating from C-cells producing calcitonin (CTN). Most of the MTC are sporadic and can potentially metastasize to lymph nodes and distant sites. High pre-operative CTN values and larger tumor dimension are usually associated with metastatic disease. However, anecdotal cases of large sporadic MTC with high pre-operative CTN values, without lymph nodes metastases, and completely cured after surgery have been described configuring a picture of non-invasive MTC (niMTC).
Aim
The aim of our study was to evaluate the prevalence and clinical behavior of these niMTC in a large series of sporadic MTC followed at the Unit of Endocrinology of the University of Pisa (2000- 2020).
Results
From a prospectively maintained database we evaluated data of 674 sporadic MTC patients. We excluded patients with lymph nodes and distant metastases at diagnosis, those with tumor diameter $<2$ cm and without controls after surgery. Then, 63 cases were included. Median age at diagnosis was 53 years. Pre-operative median CTN values were 730 ng/l (IQR 349-1890) and tumor median dimension at histology was 3 cm. All patients were N0 with a median of 8 removed lymph nodes (IQR 4-12). At first post-operative evaluation (median 4 months), most of patients (58/63-92%) were cured, conversely 5 (8%) showed detectable CTN values but negative imaging. After a median follow-up of 74 months (IQR 36-120), 77.8% ($n = 49$) remained cured. Conversely, 9 (14.3%) had biochemical disease, 3 (4.8%) had metastatic lymph nodes and 2 (3.2%) distant metastases. After a median of 100 months (IQR 64-181) of follow-up, two patients died for the disease. When evaluating the potential differences between cured and not cured (biochemical/metastatic) patients, no differences were highlighted in age at diagnosis, pre-operative CTN values and tumor dimension. However, patients not cured had more frequently histologic desmoplasia ($P = 0.03$), while although slightly different nor Ki-67 ($P = 0.1$) neither number of mitosis ($P = 0.08$) raised the significance. Lastly, in a subgroup ($n = 34$) in which somatic mutations were performed, no differences in the presence of RET somatic mutation were highlighted between cured and not cured patients ($P = 0.9$).
Conclusions
In our series, the presence of sporadic niMTC was 9.3%. Despite high pre-operative CTN levels and large tumors, most of these patients did not show metastatic lymph nodes at diagnosis and are cured early after surgery. However, few cases can develop metastatic disease also after several years, therefore follow-up should be careful pursued over time.

DOI: 10.1530/endoabs.101.PS2-13-07

## PS2-13-08

### Usefulness of extensive germline ret testing in apparently sporadic medullary thyroid cancer

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Introduction
Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor that originates from the parafollicular thyroid cells (C cells); MTC occurs as both a hereditary disease (25% of all cases), when MTC in a manifestation of multiple endocrine neoplasia type 2 or 3 (MEN 2/3) and as sporadic disease. The hereditary type is a consequence of germline mutation in the rearranged during transfection (RET) proto-oncogene, which can undergo oncogenic activation through both cytogenetic rearrangement and activation of point mutation. Other types of mutations are acquired (or somatic), found in up to 55% of patients with sporadic MTC and are associated with disease aggressiveness. Patient's genotype influences the clinical management for themselves as well for their families. Thyrosine kinase inhibitors (TKIs) were approved for advanced MTC cases with RET alterations.
Patients and methods
We performed genetic testing for germline RET mutations on 82 subjects (58 complete gene analyses and 24 targeted analyses). Genomic DNA was extracted from peripheral blood, and mutational screening was performed according to a standard algorithm approved by the American and European MTC management Guidelines. In addition, genomic DNA was extracted from tissue samples using fresh or formalin-fixed, paraffin-embedded tumor for somatic RET mutation. In patients with detected germline RET mutation, somatic status was assumed to be identical, and the test was not repeated on tumour DNA.
Results
A germline RET variant was identified in a total of 31/82 (37.8%) patients. From them, all cases with positive family history 24/24 (100%) and 7/58 (12.06%) cases initially considered sporadic were diagnosed as hereditary MTC. Five different RET variants, were identified in our sample. The most common RET proto-oncogene alteration was found in exon 11, codon 634 in 14/31 (45.16%) cases. From a total of 8 patients tested for somatic RET mutations, 6/8 (75%) were found positive. Among those, the most common mutation, 5/6 cases, was M918T mutation, and in one case C634A mutation. We observed a more aggressive disease (metastatic, progressive) in all patients with somatic RET mutation, requiring treatment with TKIs, vandetanib or cabozantinib.
Conclusion
Mutational screening is mandatory in all patients with MTC, allowing the detection of germline mutations in initially "so-called" sporadic MTC, which could trigger family genetic screening. Precision genetic-based oncology with targeted treatment, such as TKIs, could improve survival in advanced medullary thyroid cancers.

DOI: 10.1530/endoabs.101.PS2-13-08

## PS2-13-09

### Index cases of familial medullary thyroid carcinoma show different clinical presentation and outcome compared to sporadic cases

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Objectives
Medullary thyroid carcinoma (MTC) is a rare neoplasm that occurs in sporadic (75%) (sMTC) or familial (25%) (fMTC) form, the latter caused by germinal mutations of the *RET* gene. In fMTC, cases can be distinguished into index cases, the first case who were diagnosed in a specific family, then apparently sporadic at the time of surgery, and gene carriers identified through *RET* screening starting from the index case. The aim of this study was to evaluate potential differences in clinical presentation and outcome between patients with sMTC and index cases of fMTC.
Methods
We performed a retrospective observational study through a prospectively collected database of 671 sMTC and 116 fMTC index case patients followed at the Unit of Endocrinology of the University Hospital of Pisa from 2000 to 2021.
Results
At diagnosis, patients with fMTC were younger than sMTC (median age 44 vs. 55 years, $P < 0.001$), without difference in gender (males 39% vs. 44%, $P = 0.3$). Median tumor dimension did not differ between fMTC and sMTC (1.2 vs. 1.4 cm, $P = 0.3$). Conversely, fMTC patients showed higher prevalence of aggressive histologic features compared to sMTC, such as minimal extrathyroidal extension (37.3% vs. 19.1%, $P < 0.001$), tumor with T stage $> 2$ (21.6% vs. 13%, $P = 0.03$), lymph node metastases (59% vs. 43%, $P = 0.002$) mainly in the central compartment (59% vs. 39%, $P = 0.005$). However, no difference in rate of distant metastases (11.8% vs 8.9%, $P = 0.37$) and stage IV disease (27.5% vs 28.9%, $P = 0.82$) were highlighted between fMTC and sMTC. After a median follow-up of 10 years in fMTC and 6.8 years in sMTC, at last follow up excellent response was lower in fMTC than sMTC (33.9% vs 54.2%, $P < 0.001$).
Conclusions
In our series, index cases of fMTC and patients with sMTC showed a different clinical presentation being more aggressive in fMTC. This evidence is reflected also in the clinical outcome at last follow-up characterized by lower rate of excellent response in fMTC. Therefore, the possibility of having fMTC in relatively young patients with an aggressive MTC and apparently negative familial history should not be overlooked.

DOI: 10.1530/endoabs.101.PS2-13-09

## PS2-13-10

**Pathological and molecular characterization of peritumoral desmoplasia in medullary thyroid carcinoma**

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Background
Medullary thyroid carcinoma (MTC) has a high predisposition to neck lymph node involvement, which correlates with worse outcome. Peritumoral stromal desmoplasia, defined as the presence of a newly formed stroma surrounding tumor cells, is a strong predictor of lymph node metastases in MTC.
Objective
The main purpose of the present study is to characterize peritumoral stromal desmoplasia in MTC, through the identification of other associated histopathological features and their possible molecular basis.
Methods
We performed a retrospective observational study on patients with histologically proven MTC diagnosed at our Institution from 2010 to 2024. Paraffin-embedded thyroid tumor tissue was collected for each patient for histopathological analysis. The selected patients' medical records were revised up until the last follow-up visit in order to assess their disease status at the end of the study.
Results
The study population included 51 patients (32 female, 19 male), of which 44 with sporadic MTC. Desmoplasia was observed in 49% of patients (Table), who did not differ in age, sex and duration of follow-up compared to cases without desmoplasia. Desmoplasia was significantly associated with higher basal calcitonin and procalcitonin levels ($P = 0.001$ and 0.019, respectively), primary tumor size ($P = 0.007$), lymph node metastases ($P = 0.014$) and angioinvasion ($P = 0.007$). There was no significant association with grade of intratumoral fibrosis (12.5% vs 8%), necrosis (12% vs 7.7%) and tumor capsule invasion (88.9% vs 61.5%), although these features were more represented in MTCs with desmoplasia. In cases with available molecular analysis ($n = 20$), somatic *RET* mutations were identified both in MTCs with and without desmoplasia (57.1% vs 66.7%), and there were no differences in the distribution of the type of mutation detected (M918T, C634 or others). At the end of follow-up (median 40.8 months), desmoplasia was significantly associated with a higher prevalence of disease persistence ($P = 0.05$).
Conclusions
Desmoplasia in MTC is associated not only with lymph node metastases but also with angioinvasion and increased tumor size, regardless of the presence and type of *RET* mutation. Further studies on larger series may clarify whether desmoplasia is associated with other pathological factors with a negative prognosis.

| | Desmoplasia $n = 25$ (49) | Non desmoplasia $n = 26$ (51) | p |
|---|---|---|---|
| *RET* somatic mutation, n | 8/14 | 6/9 | ns |
| Calcitonin (pg/ml), median [IQR] | 466,5 [118-2861,3] | 73,8 [20,9-1132] | 0,001 |
| CEA (ng/ml), median [IQR] | 21,5 [7,1-44,8] | 5,6 [4,4-76] | ns |
| Procalcitonin (ng/ml), median [IQR] | 3,6 [0,8-33,7] | 0,4 [0,1-5,5] | 0,019 |
| Primary tumor size (mm), median [IQR] | 12 [8-21] | 8 [6-10,3] | 0,007 |
| Angioinvasion, n (%) | 10 (40) | 2 (7,7) | 0,007 |
| Lymph node involvement, n (%) | 9 (36) | 2 (7,7) | 0,014 |
| Persistence at last follow up, n (%) | 11 (44) | 5 (19,2) | 0,05 |
| Follow-up period (months), median [IQR] | 35,9 [11,2-52,8] | 24,1 [10,8-40,8] | ns |

DOI: 10.1530/endoabs.101.PS2-13-10

# Clinical Thyroid Cancer Research-2

## PS2-14-01

**High concordance in intuitive *vs* standardized assessment of whole-body scintigraphy after radioiodine therapy for thyroid cancer**

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Objective
In patients with differentiated thyroid carcinoma, whole-body scans (WBS) are usually assessed 48 h after radioiodine administration. The aim of the study is to correlate the intuitive assessability after different time points with the standardized diagnostic algorithm.
Methods
Data were available from 35 consecutive, prospectively treated (97% exogenous TSH stimulation) patients in whom WBS were acquired at up to 6 time points (6, 24, 48, 72, 98 and 168 h). Blinded reading of WBS was done by to three experienced observers regarding diagnostic quality. After one year of latency, the whole-body scintigraphies were re-evaluated using a standardized Likert scale (Van Nostrand criteria). The qualitative ranking was determined intuitively, the standardized quality was determined using a predefined scale (1 to 5 points) for 10 parameters (max. 50 points).
Results
The intuitive ranking of the three observers was consistent in terms of the best scan after 24 h (average rank 1.76), followed by 48 h (rank 2.27), 6 h (rank 2.77) and 72 h (rank 3.48); only the last two scans after 96 and 168 h were discordantly ranked 5th (rank 4.55) and 6th (rank 4.58) respectively. After using the standardized evaluation criteria, all observers had the same ranking, only one observer rated 4 and 48 h scans on average as equivalent (31.66 vs. 31.32 points).
Conclusions
There was a high concordance in the intuitive *vs* standardized assessment of the diagnostic value of the whole-body scans and between the investigatores. The diagnostic performance of the scans after 24 h (rank 1; 39.52 points) is comparable to that after 48 h (rank 2; 34.73 points); for radiation protection reasons, a preference for the 48 h scan is advisable.

DOI: 10.1530/endoabs.101.PS2-14-01

## PS2-14-02

**Tracking dynamic evolution of low- and intermediate-risk differentiated thyroid cancer. identification of individuals at risk of recurrence**

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Purpose
The generally good prognosis of low- and intermediate-risk differentiated thyroid cancer (DTC) underscored the need to identify those few patients who relapse.
Methods
Records of 299 low- or intermediate-risk DTC patients (mean follow-up 8.2 $\pm$ 6.2 years) were retrospectively reviewed. The sample was classified following the American Thyroid Association (ATA) Dynamic Risk Stratification (DRS) system.
Results
After classifying patients according to DRS at the first visit following initial therapy (FU1), structural recurrence occurred in 2/181 (1.1%), 5/81 (6.2%) and 13/26 (50.0%) with excellent, intermediate, and biochemical incomplete response to treatment, respectively. All relapses but one happened within 5 years from FU1. Univariate analysis comparing excellent, indeterminate and biochemical incomplete with structural incomplete responses at the end of the follow-up (FUe), identified tumour size ($P < 0.001$), T status ($< 0.001$), positive lymph nodes (N) ($P < 0.01$), multifocality ($P < 0.004$), need of additional radioiodine (RAI) ($P < 0.0001$), and first DRS status ($P < 0.0003$) as risk factors of recurrence. In the multivariate analysis, only RAI remained statistically significant ($P < 0.02$). Comparison between excellent and indeterminate with biochemical and structural incomplete responses, identified tumour size ($P < 0.0004$), T ($P < 0.01$), N ($P < 0.0001$), bilaterality ($P < 0.03$), first DRS status ($P < 0.0001$), and RAI ($P < 0.001$) as recurrence risk factors. T ($P < 0.01$) and first DRS ($P < 0.0006$) were confirmed in the multivariate analysis.
Conclusions
Patients with DTC classified as low- or intermediate-risk of recurrence with excellent response to treatment at FU1 rarely develop structural disease and this occurs almost exclusively in the first 5 years. Initial DRS status is an accurate tool for determining the risk of recurrence.

DOI: 10.1530/endoabs.101.PS2-14-02

## PS2-14-03

### Impact of presence of psammoma bodies on long-term prognosis in papillary thyroid carcinoma cases

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Aim
Papillary thyroid carcinoma (PTC) is a malignancy originating from the follicular epithelium of the thyroid gland. Psammoma bodies (PBs), structures characterized by concentric layers surrounding a calcified focus, are a pathognomonic finding in PTC. The precise mechanism of PB formation, as well as their association with clinical presentation and prognosis, remains an area of active investigation. This study aimed to elucidate the influence of PB presence on histopathological and clinical findings at the time of diagnosis and on recurrence status during long-term follow-up in patients with classical-type PTC.
Method
A cohort of 102 patients diagnosed with classical papillary thyroid carcinoma at the Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolic Diseases (2010-2022) was retrospectively analyzed. Inclusion criteria were surgical treatment prior to 2019 and availability of pathology data. Existing pathology specimens were re-evaluated for the presence of psammoma bodies.
Results
A total of 102 patients with classical-type papillary thyroid carcinoma were included (77 female [75.5%], 25 male [24.5%]; mean diagnostic age 40.4 $\pm$13.9 years). Pathology specimen re-examination identified psammoma bodies in 66 patients (64.7%). Patients were grouped according to PB presence for further analysis. No significant intergroup gender differences were observed, however the PB-positive group exhibited a significantly lower mean diagnostic age ($P$ = 0.015). Tumor histopathology, including size, capsular invasion, extrathyroidal extension, and presence of non-tumor lymphocytic thyroiditis or nodular goiter, showed no significant difference between groups. The PB-positive group had a higher incidence of lymph node metastasis at diagnosis ($P$ = 0.001). While the PB-positive group displayed a numerically higher long-term recurrence rate, this difference did not reach statistical significance ($P$ = 0.532).
Conclusion
This study suggests a potential association between psammoma PBs in classical-type papillary thyroid carcinoma and lymph node metastasis at diagnosis. While not statistically significant, a higher recurrence rate was observed in PB-positive patients during long-term follow-up. The presence of psammoma body in patients with papillary thyroid carcinoma may be a guide for central lymph node dissection.
Keywords
papillary thyroid carcinoma, psammoma body
DOI: 10.1530/endoabs.101.PS2-14-03

## PS2-14-04

### Subcutaneous neck metastases from thyroid cancer: a series of six cases diagnosed and followed-up in a single center

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Introduction
Cutaneous metastases are a rare event in thyroid cancer (TC), generally occurred in the context of a metastatic and progressive disease and generally represents a poor prognostic factor. In the subgroup of skin metastases, very rare are the subcutaneous localizations to the thyroidectomy scar, described only in few papillary (PTC) and follicular TC (FTC) cases. We reported a series of 6 cases of PTC/FTC patients with subcutaneous metastases localized both on thyroidectomy scar and/or near thyroid bed, discovered incidentally during follow-up.
Methods
We looked for DTC cases with subcutaneous metastases among all patients with PTC/FTC followed at the Endocrine Unit of the University Hospital of Pisa in the last 20 years. Six cases were identified among a total of about 10.000 patients followed at our center. An ultra-high frequency Ultrasound (UHFUS) examination using 70 MHz probe was performed in 4/6 patients before surgical excision. All subcutaneous metastases from TC were treated by dermatologists and endocrine surgeons of University of Pisa and analyzed by the same anatomo-pathological team.
Results
In 4/6 cases, the subcutaneous metastases were incidentally discovered by the patient himself as a small, palpable, rounded, and blue papule localized in the neck region, while in 2/6 cases there were incidentally detected during other therapeutic or diagnostic exams. In 4/6 patients, the subcutaneous metastases were localized near/above the thyroidectomy's surgical scar, while in the remaining ones in the right suprajugular region of the neck. In almost all patients, after the first discovery, subsequent subcutaneous relapses were found during follow-up. UHFUS was very useful in the detection and follow-up of the subcutaneous metastases, especially the subclinical ones, and a quite perfect correspondence was found between the ultrasonographical appearance of the lesion and the histologic one. The median time between the thyroidectomy and the first discovery of subcutaneous metastases was 8.5 years. No patient had distant metastases at the diagnosis. All patients are still alive after a median follow-up of 13.5 years and only one has distant metastases.
Conclusions
We reported a series of six cases of subcutaneous skin metastases from TC at the thyroidectomy surgical scar. The diagnosis was always incidental, and no symptoms have been reported with these lesions. The UHFUS is very useful in the identification, differential diagnosis, monitoring, surveillance of these subcutaneous lesions and to identify subclinical lesions and to precisely delimitate the lesion margins in case of surgery. These local skin lesions, at variance with distant cutaneous metastases, do not impair the patient' survival.
DOI: 10.1530/endoabs.101.PS2-14-04

## PS2-14-05

### Real life experience of a single center in the treatment of metastatic rai refractory (RAI-R) differentiated thyroid carcinoma (DTC)

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Objectives
The majority of DTC cases has excellent prognosis; approximately 5% may develop metastatic disease not responding to radioiodine treatment (RAI-R DTC). There are few reports of real-life experience concerning their clinical course.
Methods
We conducted a retrospective study in metastatic RAI-R DTC patients focusing on the clinical characteristics at diagnosis, the location and time interval of the appearance of metastatic lesions, the treatment modalities performed (local therapies and/or systemic treatment), the response to therapy and the disease progression rate.
Results
95 metastatic RAI-R patients (46.3% men, age-at-diagnosis 55.24$\pm$13.6years) were followed up for median 8yrs (2-50). The median time from diagnosis to metastases appearance was 3yrs (0-39); 40% underwent $\geq$3 cervical surgeries and received median cumulative RAI activity 400mCi (100-1250), 28.4% underwent cervical EBRT, 6.3% cervical RFA. 14.7% had a second neoplasia. Local therapies for distant metastases were performed in 40(42.1%) while stabilization was achieved in 33.7%. TKI was administered in 45(47.4%). The median time interval from metastases appearance to TKI administration was 2.5yrs (0.3-20). 18(40%) underwent local therapies while receiving TKI, 18(40%) received multiple TKIs. Patients not treated with TKI (compared to those treated with TKI) had less frequently soft tissue invasion, mediastinum lymph-nodes, more frequently classical-PTC or FTC and underwent less frequently local procedures ($p \leq 0.03$). No significant differences were observed in the outcome between groups. *Sorafenib* was administered to 30 (29 as first-line therapy), with median-interval from metastases appearance to sorafenib 3years (range 0.2-12). Overall response was PR 2/30(6.7%), SD 3/30(10.0%), PD 22/30(73.3%), 8(26.7%) discontinued due to SAE, 21/30 underwent SAE-related dose reduction.

*Lenvatinib* was administered to 31 (16 as first-line therapy), with median-interval from metastases appearance to lenvatinib 4years (0.1-15). Overall response was PR 8/31(25.8%), SD 8/31(25.8%), PD 14/31(45.2%), 1(3.2%) discontinued due to SAE, 29/31 underwent SAE-related dose reduction. *Cabozantinib* was administered in 7 patients (2 as second-line TKI, 5 as third-line treatment). Overall, the final outcome was: PR 7/95(7.4%) SD 38(40%) PD 50(52.6%), 34/95(35.8%) died of disease progression, 7/95(7.4%) died of unrelated causes. Twenty-three are still under TKIs treatment. In Cox-proportional-hazard analysis, for the total follow-up period, when age-at-diagnosis, TKI, local therapies, local surgeries, soft-tissue invasion, tumor size and histology were included in analysis, the age-at-diagnosis and the administration of local therapies were predictors of more favorable overall and cancer-specific survival ($P < 0.02$).

Conclusions

In metastatic RAI-R DTCs younger age at diagnosis and the implementation of local therapies are associated with a more favorable outcome.

DOI: 10.1530/endoabs.101.PS2-14-05

## PS2-14-06

**Postoperative basal serum thyroglobulin and need for radioiodine in patients with low to intermediate-risk papillary thyroid cancer**

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Background

The use of radioiodine treatment (RAI) in cases categorized as low to intermediate risk papillary thyroid cancer (PTC) is still uncertain. Current guidelines recommend a selective use of RAI based upon the clinicopathologic features of each case. In this context, postoperative serum thyroglobulin (pTg) could be useful but the predictive role for recurrence and the optimal cut off value to be applied is not clearly established.

Objectives

To determine the predictive value of postoperative Tg and the optimal cutoff to avoid radioactive iodine therapy in patients with low to intermediate-risk PTC

Methods

We selected patients with low to intermediate risk PTC diagnosed between 2009-2015 with available data on histology, follow-up and laboratory tests. All patients had TSH $\leq$3.5 mU/l and negative AbTg. Tg was measured by a second-generation assay (Abbot Architect).

Results

We selected 200 patients followed in our institution. RAI was performed in 100 of 200 patients (50%), 15 individuals (13,3%) displayed biochemical or structural disease after a median duration follow-up of 17.5 months. At univariate analysis, factors associated with recurrent disease were male sex, RAI, pTg tumor size, mETE, lymph node MTS. The factor independently associated with recurrence, identified through multivariate COX proportional hazard analysis, was pTg (HR: 1.2, 95%CI: 1.07-1.34, p: 0.01). The optimal basal pTg to identify recurrence was 0.5 (AUC: 0.74, 95%CI: 0.61-0.89). When evaluating the combination of tumor size and pTg, Tg $<$0.5 ng/ml and size $<$1.5 cm had a NPV of 95.5%. When considering RAI, propensity score-based matching was performed, and no significant differences were found between treated and non-treated patients.

Conclusions

The study suggests that the combination of postoperative Tg and tumor diameter is a critical factor in low to intermediate PTC that should be routinely integrated into RAI decision-making and could be easily applied in clinical practice to manage PTC patients.

DOI: 10.1530/endoabs.101.PS2-14-06

## PS2-14-07

**Differentiated thyroid cancer in children: a single institution experience of 7 years**

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Objectives

Differentiated thyroid cancer (DTC) is rare in childhood and adolescence. However, its incidence increases by 1.1% per year, rendering it the most common pediatric endocrine neoplasia, representing 3% of all pediatric malignancies. The aim of the study is to present the data of pediatric patients with DTC followed in our institution.

Methods

Patients with DTC who were diagnosed and treated in our division between 2017 and 2024 were enrolled in the study. All patients were under 18 years old. Data regarding demographics, treatment, and follow-up outcomes were retrospectively collected.

Results

Thirty-one patients with a median age at presentation of 13 years (range, 7 to 17) were recruited [9 boys (29%)/ 22 girls (71%)]. According to BMI z score 52% had normal weight, 35% were overweight and 13% obese while the respective distribution in the general pediatric Greek population is 27,5% normal weight, 37.5% overweight and 35% obese. Most of our them (93%) originated from central and South Greece while 35% (11/31) had a positive family history for thyroid cancer. Total thyroidectomy, with central and/or lateral neck dissection, when needed, was performed. Histological examination revealed DTC in all patients, 25 of whom with classic variant of PTC and 5 an aggressive type of PTC. Data is missing in one patient. 84% of our cases were treated with RAI therapy according to histological findings while one is still pending. A total of 7 patients were lost to follow-up while 5 patients were diagnosed within the last year. 54% of the patients (13/24) with a follow-up of $>$1year had an excellent outcome. Three patients (12%) underwent a second RAI therapy due to persistence of the disease, while 4 (17%) had a closer follow-up due to persistence of thyroglobulin levels between 0.2 and 1 ng/ml and/or persistence of anti-TG positivity albeit with stable or declining levels during follow-up.

Conclusions

Our study confirms the increasing incidence of DTC among children and adolescents during the last years with an average of 4.4 new cases yearly albeit with an excellent outcome. Further studies are needed to identify possible causes and risk factors. Total thyroidectomy followed by RAI, only when indicated, is the recommended treatment for patients with pediatric DTC in terms of reducing relapse rate and improving surveillance for recurrent disease without increasing the risk of long-term complications of RAI treatment in young patients who will not benefit of a higher-intensity treatment approach.

DOI: 10.1530/endoabs.101.PS2-14-07

## PS2-14-08

**Needle tract seeding of thyroid cancer after biopsy of distant metastasis: a retrospective cohort study**

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Objective

Imaging-guided percutaneous core needle biopsy (PCNB) is currently the most common technique for the investigation of potentially malignant bone lesions. It

allows precise needle placement and better visual guidance, leading to improved diagnostic accuracy. Needle tract seeding (NTS) is a rare complication of biopsies in general, and its true incidence remains unknown. This study aimed to assess the risk of NTS in patients with thyroid cancer who underwent bone biopsy.
Methods
For our cohort, we extracted data from the electronic medical record (EMR) at the Mayo Clinic in Rochester, MN. Inclusion criteria included patients with a history of thyroid cancer who underwent biopsy for bone metastasis between 1/1/2014 and 10/1/2023.
Results
We identified a cohort of 20 patients that fit our inclusion criteria. Of these 20 patients, 2 patients developed NTS after CT-guided bone biopsy. Cases of seeding had a larger tumor size, a more aggressive histopathological presentation, significantly shorter duration between cancer diagnosis and bone metastasis and underwent more tumor manipulation procedures such as biopsy and RFA, in contrast to those without seeding.
Conclusions
Our study identified NTS to have an incidence of 10% after biopsies of bone metastasis related to thyroid carcinoma. These are likely the result of an interplay of risk factors, including tumor biology, penetrated tissues, and procedural technical details. Further studies with larger sample sizes are needed to confirm our findings and identify strategies to mitigate NTS.

DOI: 10.1530/endoabs.101.PS2-14-08

## PS2-14-09

**Predictive factors determining incomplete response to initial radioiodine therapy in patients with papillary thyroid microcarcinoma**

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Objective
The aim of this study was to evaluate the response to initial postoperative radioactive iodine therapy (I-131) in patients with papillary thyroid microcarcinoma.
Methods
This was a retrospective study including 123 patients treated for papillary thyroid microcarcinoma with low to intermediate-risk, between 2012 and 2020. These patients underwent total thyroidectomy followed by radioactive iodine therapy (I-131). Clinical examination, thyroglobulin (Tg) levels measurement, ultrasound, and cervico-thoracic scintigraphy (CTS) were performed.
Results
The mean age was $44.4 \pm 14.1$ years with a female predominance (86.2%). All patients received adjunctive I-131 therapy following total thyroidectomy. The most frequently observed tumor stage was T1aNx, accounting for 31.7% of tumors. Baseline Tg levels measurement and CTS were performed before the first treatment. Response assessment was performed at a median of 6 months following the first treatment. Based on clinical, biological, and radiological criteria, 95 patients (77.2%) were responders to treatment, while 28 patients (22.8%) were non-responders. Therapeutic response significantly varied according to baseline Tg levels and postoperative CTS results ($P < 0.001$). There was no statistically significant difference in response to the initial treatment regarding patients' epidemiological, clinical, and therapeutic data.
Conclusion
Baseline Tg levels $>$10ng/ml, intense cervical uptake on postoperative CTS, and associated histological lesions are predictive factors of poor response to initial radioiodine therapy. Multicenter studies are warranted to establish a clear consensus regarding the strategy for adjunctive radioiodine therapy administration

DOI: 10.1530/endoabs.101.PS2-14-09

## PS2-14-10

**Are we able to preoperatively predict low-risk thyroid cancer? a retrospective analysis of preoperative ultrasound in large group of patients**

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Recently, we have witnessed an increase in the number of new thyroid cancer (TC) cases and thyroid surgeries. Both the ATA 2015 and 2022 Polish guidelines allow sparing treatment in low-risk TC. Nevertheless, most patients are qualified for total thyroidectomy. The aim of the study was to analyze the possibility of preoperative diagnosis of low-risk TC based on ultrasound examination (US).
Material and method
A retrospective analysis involved 1043 patients diagnosed with TC between 2019 and 2021, among them 962 patients with differentiated TC. All patients underwent fine-needle aspiration biopsy and preoperative neck ultrasound, which assessed tumor diameter, margins, vascularization, signs of extrathyroidal invasion and evaluated neck lymph nodes. Total thyroidectomy was carried out in 967 (92.7%) patients. Postoperatively, low-risk, intermediate-risk, and high-risk TC was diagnosed in 527 (50.5%), 367 (35.2%), and 149 (14.3%) patients.
Results
Nodule diameter $\geq$17 mm is significantly correlated with the risk of angioinvasion, extrathyroidal extension, neck lymph node metastases and the number of metastatic lymph nodes. The presence of extrathyroidal invasion in the US significantly increased the risk of extrathyroidal extension in histopathological examination (HP) (OR 2.32 [95% CI 1.38-3.82]. Increased vascularisation in the nodule was related to a significantly higher risk of angioinvasion in HP (OR 2.83 [95%CI 1.53-5.17]. The presence of suspected lymph nodes (LN) in the US significantly increases the risk of LN metastases in HP (OR 12.98 [95%CI 8.05-21,42]. In univariate analyses, the presence of ill-defined nodule margins, thyroid capsule invasion, microcalcifications, and suspected LN in the US significantly increases the risk of recurrence. Suspected lymph nodes and thyroid capsule invasion were the only factors significantly increasing the risk of recurrence in multivariate analysis. Considering these results, 468 patients (44.9%) could be qualified based on the preoperative US for thyroid lobectomy as a sufficient surgical procedure.
Conclusions
Some features observed in preoperative neck ultrasound may be helpful in preoperative thyroid cancer risk stratification and planning the adequate extent of primary surgery.

DOI: 10.1530/endoabs.101.PS2-14-10

# Translational Thyroid Cancer Research-1

## PS2-15-01

**Development of a molecular quantum chemistry-based pipeline combined with publicly available datasets and robust open-source bioinformatics tools that indicate variations in redox balance genes that may have diagnostic and prognostic significance in thyroid cancer**

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Thyroid cells possess a strong reduction-oxidation (REDOX) mechanism that protects DNA from oxidative stress caused by elevated reactive oxygen species resulting from the synthesis of thyroid hormones and iodides derived from the iodination of thyroglobulin. SOD1, SOD2, GPX-1, G6PD, and CYBA encode important proteins involved in REDOX reactions. Their crucial roles in the promotion and progression of various types of cancers as well as their influence on pathways frequently activated in thyroid cancer are widely recognized. However, studies of thyroid tumors have yielded controversial results. To identify potential biomarkers and therapeutic targets, our group developed a strategy for a thorough analysis of the entire coding region of these genes by combining open-source bioinformatics techniques, publicly accessible datasets, and molecular quantum chemistry with multiple analysis algorithms, including 13 tools. In addition, we investigated the frequency of genetic alterations and their association with protein expression levels, and validated our results using large cancer biological databases (cBioPortal, OncoPrint, and PrognoScan). We collected 1.885 nsSNPs from the dbSNP database, including 223 for SOD1, 593 for SOD2, 324 for GPX1, 389 for G6PD, and 356 for CYBA. Eleven nsSNPs (8 in SOD1, 1 in GPX1, 1 in G6PD, and 1 in CYBA) consistently exhibited deleterious predictions across all 13 tools, demonstrating potential changes in protein function, structure, and stability, which can lead to perturbations in the REDOX

balance. We further investigated the protein interaction network and signaling pathways observing a robust interaction between G6PD and other genes. G6PD expression positively affects the expression of TP53 and HRAS, making the gene a promising candidate for targeted therapy. Investigation of the frequency of genetic alterations and their association with protein expression levels has been hindered by the low mutation rate found in samples from patients with thyroid tumors in the CBioPortal database. Clinical databases indicate that SOD1, SOD2, GPX1, G6PD, and CYBA are associated with worse prognosis in several types of cancer, but our analysis did not reveal any significant impact on the survival of patients with thyroid cancer. Investigation of mRNA expression levels in the GEPIA database also did not show any impact of these genes on the overall survival of patients with thyroid cancer. In conclusion, we confirmed the important role of ROS in thyroid cancer etiopathogenesis, demonstrating that our bioinformatics pipeline is useful and may identify potential biomarkers of the risk and/or prognosis of thyroid cancer, as well as new therapeutic targets. One nsSNP, whose MAF is $>0.5$, may become a useful biomarker and is currently being validated in a large population of patients with thyroid cancer.

DOI: 10.1530/endoabs.101.PS2-15-01

## PS2-15-02

### Expression of HSA-MIR-139-5P as a clinically feasible prognostic marker for thyroid cancer

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Introduction

Patients with advanced differentiated thyroid cancer are often radioiodine refractory and present worse outcome with increased mortality[1]. Early identification is critical for the appropriate disease management and follow-up[2]. In this regard, we previously found that hsa-miR-139-5p (miR139-5p) down-expression is associated with recurrent/persistent disease[3]. Furthermore, miR139-5p down-expression has recently been associated with refractoriness to radioiodine therapy[4].

Objectives

Here, we evaluate miR139-5p expression in a retrospective long-term follow-up thyroid cancer series enriched with poor prognosis cases to validate the prognostic value of miR139-5p expression and estimate a threshold to dichotomize the cases. In addition, we explore the feasibility of incorporating miR139-testing into the clinical setting using an automated *in situ* hybridization (ISH) technique.

Methods

DNA and RNA were extracted from formalin-fixed paraffin-embedded tissue sections of normal thyroid tissue, thyroid tumors and metastases (when available) from 60 patients with either progressive/persistent disease (DP/PD) or an excellent response (ER) to primary treatment. The tumor series was analyzed for recurrent tumor driver mutations and *TERT* promoter (*TERT* prom) mutations. MiR139-5p expression was measured by qPCR and the geometric mean of 4 housekeeping miRNAs was used as a normalizer. An ISH assay for pre-miR139 detection was optimized by CNIO Histopathology Unit to test miR139 expression in whole tissue sections, using the Discovery ULTRA platform (Roche). Spatial expression of pre-miR139 was quantified and correlated with the prognostic immunohistochemical marker Ki-67 by quantitative image analysis (QuPath v0.5.0).

Results

Paired tumor/normal data analysis confirms a statistically significant miR139-5p expression reduction in tumors, which is more significant in DP/PD-related primary tumors and metastases than in ER-related primary tumors. Furthermore, the distribution of miR139-5p expression in ER- and DP/PD-related primary tumors reveals that extreme expression intervals are disease outcome specific. Notably, 4 of the 8 tumors correctly classified as DP/PD according to miR139-5p expression intervals are negative for *TERT* prom mutations, a known prognostic marker. Finally, ISH assays support the results observed by qPCR and reveal heterogeneous pre-miR139 expression, which inversely correlates with that of Ki-67.

Conclusion

Our results validate miR139-5p expression analysis as a prognostic marker in thyroid cancer, which may add sensitivity to the prognostic power of *TERT* prom mutations. In addition, this study underscores the clinical feasibility of incorporating miR139-testing into the clinical practice.

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DOI: 10.1530/endoabs.101.PS2-15-02

## PS2-15-03

### Genomic profiling of metastases from papillary and poorly differentiated thyroid carcinomas

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Objective

While the genetic repertoire of papillary thyroid carcinomas (PTCs) and poorly differentiated thyroid carcinomas (PDTCs) is well documented, there is a considerable lack of molecular profiling in the metastases of these tumors. Hence, we aim at performing a meticulous molecular profiling of metastatic PTCs and PDTCs.

Methods

We retrieved and analyzed the molecular and clinical features of 136 metastatic PTCs and 33 metastatic PDTCs subjected to targeted DNA sequencing, from the cBioPortal database. The clinicopathological data included the number and location of the metastases, and relevant genomic data included somatic mutations, structural variants, copy number amplifications and homozygous deletions, tumor mutational burden and fraction of the genome altered (FGA).

Results

Bone metastases from PTCs had a significantly lower frequency of *BRAF* hotspot mutations than the lymph node metastases (LNMs) (43% vs 85%, $P < 0.01$) and head and neck metastases (43% vs 89%, $P < 0.05$), and a significantly higher frequency of *RBM10* and *NRAS* mutations than the LNMs (21% vs 3% for both genes, $P < 0.05$). In addition, the FGA of the bone metastases was found to be significantly higher when compared to the FGA of the head and neck, and lung metastases (5.6% vs 0.1% and 5.6% vs 1.3%, $P < 0.05$, respectively). The frequency of *RET* translocations was significantly higher in the lung metastases from PTCs when compared to the LNMs (15% vs 4%, $P < 0.05$). The LNMs from PTC patients harboring $\geq 4$ distant metastases (DMs) had a significantly higher frequency of *TERT* promoter and *ATM* pathogenic mutations than the LNMs from PTC patients harboring $<4$ DMs (95% vs 63%, $P < 0.001$, and 13% vs 0%, $P < 0.05$, respectively). Moreover, copy number amplifications affecting *SDHA* were significantly more frequent in the bone metastases from PDTCs when compared to the LNMs (38% vs 0%, $P < 0.05$).

Conclusion

The metastases from PTCs and PDTCs harbor clinically relevant alterations associated to distinct body locations, such as *BRAF* and *RBM10* mutations, *RET* translocations and *SDHA* amplifications that may be explored therapeutically.

DOI: 10.1530/endoabs.101.PS2-15-03

## PS2-15-04

### Usefulness of metabolomic analyses in the pre surgical evaluation of thyroid nodules

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Objectives
Metabolomic is a newly emerging technology with great diagnostic potential in the oncology field. Several studies have evaluated the usefulness of the metabolomic approach in the diagnosis of differentiated thyroid carcinoma (DTC), but most of them analyzed ex vivo samples. High-field nuclear magnetic resonance (NMR), a versatile and quantitative technique, allows the analysis of complex mixtures with minimal sample preparation, identifying molecules in a wide range of molecular weights. The aim of our study was to evaluated the feasibility of metabolomic's approach *in vivo* samples and to identify those metabolites able to discriminate between benign and malignant nodules.
Methods
we selected 41 samples of thyroid nodules submitted to fine needle aspiration (FNAC) preserving a minimum portion for NMR analysis. Twentythree/41 (56.1%) were classified Thy2, while 18/41 (43.9%) Thy5.
Results
The multivariate analysis between benign and malignant samples highlighted a significant differentiation of the two groups, with a lower relative concentration of citrate, a metabolite already associated with the progression and invasiveness of tumors, which was 8 times lower in the Thy5 compared to Thy2 ($P = 0.0002$). Another significant lower concentration of metabolites in Thy5 was observed for serine ($P = 0.02$), while creatinine was significantly higher ($P = 0.03$).
Conclusions
These data demonstrates the usefulness and feasibility of using high-field NMR in the analysis of thyroid samples *in vivo*, identifying and quantifying 60 metabolites, and indicating citrate as the most discriminating metabolite between benign and malignant nodules. These results, although preliminary, could play a crucial role especially in the diagnosis of nodules with indeterminate cytology, selecting more accurately those patients to be sent for surgery.

DOI: 10.1530/endoabs.101.PS2-15-04

## PS2-15-05

### BRAF mutation is associated with tumor volume doubling time of thyroid microcarcinoma during active surveillance

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Introduction
Active surveillance (AS) is proposed as an option for the treatment of papillary thyroid microcarcinoma (PTMC), considering the indolent nature of papillary thyroid cancer. However, ongoing discussions are needed regarding the selection of target patients and long-term safety.
Methods
We enrolled patients who delayed surgery for more than one year after being diagnosed with PTMC from 2014 to 2021 at a single center, and they followed until 2023. Primary end-point was delayed surgery, and the secondary end-point was the progression of disease. Based on the tumor volume doubling time of PTMC, progression was grouped as rapid-growing disease if less than 3 years, slow-growing disease if it was between 3 and 10 years, and stable disease if it was more than 10 years.
Results
A total of 75 patients were analyzed. Their mean age was 50 years, and 57 patients (76%) were female. The patients were followed up for a median time of 4.5 years, of which 21 (28%) patients underwent surgery after a median time of 3.2 years. Lymph node metastasis was identified in 7 patients (33%) of the delayed surgery group. When the primary end-point was analyzed using multivariable Cox-regression, the characteristics of patients who underwent surgery during the follow-up period were those with a baseline maximal diameter of 0.7 cm ($P <$ 001) or more or those in the rapid-growing group ($P <$ 001). For secondary end-points with multivariable logistic regression, we found that BRAF mutation was associated with rapid-growing disease, and sonographic feature without echogenic foci were associated with stable disease.
Conclusions
PTMC in this cohort who voluntarily chose AS reported stable disease for a considerable period of time. BRAF mutational status may help to predict rapid growing disease during AS of PTMC. [This research was supported by the Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (RS-2023-00245534).]

DOI: 10.1530/endoabs.101.PS2-15-05

## PS2-15-06

### Methionyl-trna synthetase 1 expression as a diagnosis and prognosis factor in papillary thyroid cancer

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Background
Methionyl-tRNA Synthetase 1 (MARS1) is a critical enzyme in translation initiation, responsible for catalyzing transfer of Met to the initiator tRNA. In this study, we aimed to examine whether MARS1 expression is different between normal cells and cancer cells in thyroid tissue and if it can supplement the limitations of general cell staining methods currently performed for diagnosis of cancer.
Methods
Initially, 103 patients were included in this study to compare MARS1 expression of cancer cells and normal cells. Next, 100 patients were selected to compare MARS1 expression using immunohistochemical analysis in patients with and without lateral neck metastasis. Lateral neck metastasis was found in 50% of the patients.
Results
The average MARS1 expression of cancer cells was 2.59 and that of normal cells was 1.28. MARS1 expression of the two groups showed statistically significant differences ($p = 0.000$). There was a significant difference in the average MARS1 expression grade of cancer cells between the metastasis and non-metastasis groups ($p < 0.05$). In addition, a significant difference was observed in the average MARS1 expression grade between the lymph node of metastasis group and the cancer cells of non-metastasis group ($p < 0.05$).
Conclusions
In this study, we found that MARS1 could be used as a complementary method to the current fine needle aspiration biopsy tissue staining method. Additionally, MARS1 could be a predictor of the prognosis of papillary thyroid carcinoma.

DOI: 10.1530/endoabs.101.PS2-15-06

## PS2-15-07

### Analysis of the impact of oncocytic cells on the performance of the thyroid molecular classifier based on micrornas and DNA: results from the optimized version of the MIR-thype test

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Background
In thyroid nodules, the presence of oncocytic cells poses a diagnostic challenge for both cytology and molecular analysis. This challenge arises from the distinctive morphological characteristics and molecular profile of these cells, making it difficult to differentiate between benign and cancerous conditions.
Objective
To evaluate the performance of the v2 algorithm version of a microRNA and DNA-based molecular classifier test (mir-THYpe full) in oncocytic subtypes of thyroid nodules.
Methods
The molecular data for nodule classification was obtained from preoperative FNA samples of 59 thyroid nodules (58 patients) (26 Bethesda-III; 32 Bethesda-IV; 1 Bethesda-V) with known post-surgery oncocytic lesions (45 oncocytic adenomas; 14 oncocytic carcinomas). The analysis of microRNA and DNA mutational data (BRAF V600E and pTERT C228T/C250T) were performed by qPCR.
Results
The molecular test correctly classified as negative for malignancy 38/45 (84.4%) oncocytic adenomas (two false-positives had TERT C228T mutation) and as positive for malignancy 10/14 (71.4%) oncocytic carcinomas (four true-positives

had TERT C228T mutation). Forty-eighth out of the 59 oncocytic samples were correctly classified (81% accuracy). The performance of the algorithm was: 71% of sensibility, 84% of specificity, 59% of positive predictive value, 91% of negative predictive value at 23.7% disease prevalence.
Conclusion
Despite the diagnostic challenge imposed by oncocytic cells, the results showed that v2 version of the microRNA and DNA-based molecular test mir-THYpe full has an acceptable performance to early identification of benign and cancer oncocytic subtypes, when compared to Afirma and Thyroseq, that showed only 20% PPV on oncocytic lesions. Therefore, the molecular test has the potential to enhance prognostic insights by assessing pertinent mutations, thereby aiding in the prediction of patient outcomes.

DOI: 10.1530/endoabs.101.PS2-15-07

## PS2-15-08

**How (respiratory) air can complement the diagnosis of thyroid changes - a pilot study using ion mobility spectrometry**

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The aim of this pilot study is to establish a technique that can be used to detect thyroid abnormalities at an early stage, to assess the severity of these changes and to determine whether it can be used as an adjunct to other commonly used tools such as sonography, scintigraphy, fine needle aspiration biopsy and surgery. The study included 39 subjects with no identifiable thyroid changes and 86 subjects (patients) with sonographic and/or laboratory abnormalities. In the patients with thyroid changes, a histological report was available after the assessment. Only subjects $>$ 18 years, able to give informed consent and with good expiratory capacity were included in the pilot study. Potential subjects with inflammatory processes and elevated CRP, previous malignant disease, and poor general health (ECOG 1 or higher) were excluded. Subjects were not allowed to eat or chew gum for two hours prior to measurement. A 500 ml sample for ion mobility spectrometry (IMS) with an upstream multicapillary gas chromatography (MCC) column was used to collect the exhaled air and measure the metabolites, the "volatile organic compounds" (VOCs). The last 10 ml were used for MCC-IMS and analysed after histopathological findings were available. Thyroid cancer was diagnosed in 15 people and benign findings were found in 71 people. According to the different number of cases per group, the group size was randomly adjusted to 15 cases and subgroups (control, benign and malignant groups) were formed. After evaluation, at least two peaks could be identified to differentiate these subgroups (malignant vs benign) and interestingly show a sensitivity of almost 100% and a specificity of up to 87%. The determination of VOCs in MCC-IMS seems to be a promising diagnostic procedure in the context of thyroid abnormalities for the assessment of dignity (benign vs. malignant) and thus represents an excellent and complementary investigational tool.

DOI: 10.1530/endoabs.101.PS2-15-08

## PS2-15-09

**Impact of genomic biomarkers on treatment decisions and clinical outcomes in patients with radioiodine-refractory thyroid cancer and treatment with multi-tyrosine kinase inhibitors – a multi-center registry analysis**

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Background
In differentiated thyroid cancer (DTC) *BRAF* mutations are oncogenic drivers in ~60% of cases. This mutation confers downstream MEK-ERK activation resulting in radioiodine (RAI)-refractory disease. Dedifferentiation towards poorly differentiated (PDTC) and anaplastic thyroid cancer (ATC) comes with additional mutations in *TP53* or the *TERT* promoter. Activating alterations of *RAS* and *RET* are the most frequent alternative oncogenic events. Next generation sequencing (NGS) plays a crucial role to identify these somatic alterations as basis for precision thyroid-oncology. Here, we aimed to determine the frequency and impact of genetic biomarkers on treatment decisions and outcomes in patients with RAI-refractory DTC in a real-world setting.
Patients Methods
In this interim analysis, 97 patients treated with multi-tyrosine kinase inhibitors (MKIs), or selective inhibitors from7 German referral centers were included. Tumor samples of all patients were tested for targetable mutations by NGS testing. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.
Results
Ninety-seven patients were included with follicular (FTC) histology in 40 (41%), papillary (PTC) histology in 32 (33%), and PDTC in 25 (26%). Median patient age was 71 years (range 31 – 82 years), and NGS was performed most frequently early during treatment (median 2 treatment lines, range 0 – 5). Thirteen samples ($n$ = 97, 13%) were tested positive for $BRAF^{V600E}$, and one $BRAF^{K601E}$ variant ($n$ = 97 1%) was found. Seven cases ($n$ = 69, 10%) had activating *RAS* mutations (*N-RAS* [4/69; 6%]; *H-RAS* [2/69; 3%]; *K-RAS* [1/69, 1%]. Two *NTRK* ($n$ = 69, 3%), 2 *ALK* ($n$ = 42, 5%), and 3 *RET* fusions ($n$ = 45, 7%) were detected. Remaining alterations included *TP53* (13/50, 26%), *PTEN* (10/50, 20%), and *TERT* promoter (2/50, 4%). 42% had no druggable target. First line therapy was Lenvatinib in 70 patients (72%) and sorafenib in 14 patients (14%). Seven patients (7%) were treated with selective inhibitors (alectinib [2/7, 29%], larotrectinib [1/7, 14%], dabrafenib [2/7, 29%], and selpercatinib [2/7,29%]). Median PFS from time of initiation of systemic treatment with MKI was 119 months (95% confidence interval [CI], not reached [NR]) and median OS was 48 months (95% CI, 30.6 – 65.4). Median PFS and OS from time of initiation of systemic treatment with selective inhibitors was NR (95% CI, NR).
Conclusion
Our real-world clinical data indicate that *BRAF* mutations are relatively rare in patients with RAI-refractory DTC compared to published data, which may be explained by the histologic subtypes in our cohort. MKIs/selective inhibitors are effective treatment options in the majority of patients with RAI-refractory DTC, and we found median OS to be comparable with published data sets. To be able to target druggable mutations within an individualized therapy concept, we highly recommend timely molecular analysis of tumor tissue in patients with RAI-refractory DTC.

DOI: 10.1530/endoabs.101.PS2-15-09

## PS2-15-10

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.PS2-15-10

# Diagnostics and Populations Studies

## PS2-16-01

**A review on impediments related to the legislation and implementation regarding iodine deficiency disorders in pakistan; a lesson for other nations**

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The success of any health endure relies on commitment towards the outcome. Pakistan having already affected by the myth with iodized salt; posing a challenge for the legislative system to legislate and regulate the iodine supplementation. Iodine deficiency control bill 2009 is still pending for approval from national assembly since then. With this background we aimed to assess the challenges faced for legislation and implementation of the programme. After 18$^{th}$ amendment in constitution there is a power devolution from federal government to provincial states; which holds the responsibilities for health, health related regulations and implementations. In part, there were some successes claimed in terms of legislation and implementation by provinces but still iodine deficiency remains a huge challenge for Pakistani population. Data is obtained from online databases and organizational reports, including NGOs, health ministries, the iodine global network (IGN), and other related organizations exploring topics like salt usage and household nutrition supplementation, IDD regulation and implementation, assessment of legislation and IDD program. After critical review the potential factors for impeding achieving legislation goals are lacking political commitment, impact of religious groups on political system, unawareness related to salt iodization and iodine supplementation, lacking uniform legislation across the country, outdated acts and laws in provinces, legislative gaps, unclear roles among government and international agencies involved in regulatory efforts. While implementation issues remains simultaneous hindrance including lack of monitoring and regulation, shift in the dietary patterns, unknown Iodine Levels, regulatory compliance and resource allocation. These issues underscore the importance of effective implementation strategies, regulatory oversight, and continuous monitoring to ensure the success of iodine legislation in combating iodine deficiency disorders. A recent EUthyroid consortium highlighted similar issues for not reaching to success in spite of the Krakow declaration stressing upon such political commitments. Without overcoming these gaps sustainable control of iodine deficiency disorders in Pakistan and around the globe would still remain an unachievable dream.

DOI: 10.1530/endoabs.101.PS2-16-01

## PS2-16-02

**Increased psychological distress among patients with thyroid diseases during COVID-19 pandemic: the epitome study**

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Background
Psychological distress is elevated in patient with chronic diseases during pandemics such as the COVID-19 outbreak. Data of the impact of common endocrinopathies including thyroid abnormalities on psychological status of patients during pandemics are lacking so far.
Objectives
To compare psychological distress about COVID-19 pandemic, between patients with thyroid diseases and patients with non-endocrine diseases (controls) in the outpatient clinics of the University Hospital, Heraklion, Crete, Greece, using data from a cross-sectional study, the Epitome study in Crete.
Methods
One hundred and eight endocrine patients with thyroid disorders seen at the outpatient Endocrine clinic and two hundred and four controls without endocrinopathies seen at the Dermatology and Vascular Surgery outpatient clinics completed questionnaires about demographics, need for information, sources of information worries about the COVID-19 pandemic and the Greek version of the DASS-21 for psychological distress questionnaire. The levels and prevalence of stress, anxiety, and depression about the COVID-19 pandemic between the two groups were compared after controlling for age, gender, education, residence, employment status and ever diagnosed with psychiatric disease in multiple linear regression models. Ethical approval was obtained by Institutional Review Board.
Results
Mean age of patients with thyroid diseases was 49,8 years and controls 45.7 years ($P = 0.007$), with predominance of women in both groups ($P = 0.006$). Patients with thyroid diseases. reported significant mean score increase in DASS-21 stress scale (b-coef:2,25; $P = 0,053$), compared to controls. Interestingly patients with thyroid disease and one or more additional endocrinopathy reported significantly increased prevalence of stress symptoms (b-coef:4,09; $P = 0,018$). We found no differences in anxiety and depression symptoms between the two groups, which showed low rates of both.
Conclusions
The current study highlights the increase in stress symptoms among patients with thyroid diseases and concurrent endocrinopathies during Covid-19 pandemic. These results are relevant when designing policies on information on pandemics and supportive measures for endocrine patients in General Hospitals.

DOI: 10.1530/endoabs.101.PS2-16-02

## PS2-16-03

**Management of central hypothyroidism in geriatric patient with panhypopituitarism due to pituitary apoplexy**

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Indroduction
Central hypothyroidism is a rare cause of hypothyroidism, consequence of various disorders affecting pituitary (secondary) or hypothalamus (tertiary hypothyroidism). Difficulties in the diagnosis and management of patients are due to the nontypical clinical picture, frequent combination with impaired function of other pituitary hormones, difficulties in laboratory assessment in high TSH levels or low - normal T4 free levels. Diagnosis is based on a confirmed decrease in the level of free T4 with a low or normal level of TSH. The standard treatment for hypothyroidism of any etiology remains monotherapy with levothyroxine, which allows to restore the euthyroid state in most patients. The criterion for the effectiveness of therapy is to maintain the level of T4 free in the upper half of the reference norm interval.
Case report
71 y/o male patient presented in our clinic with complaints of severe fatigue, decreased appetite, myalgia and weakness in April of 2023. In February of 2021 he was hospitalized in NYC, Brooklyn, with a diagnosis of pneumonia, antibiotic therapy was initiated. His medical history revealed pituitary microadenoma with apoplexy without proper functional status assessment. Patient demonstrated progressive weakness, low blood pressure, especially for the last month. He was evaluated by the cardiologist and referred to us. Laboratory work-up revealed secondary adrenal insufficiency and secondary hypothyroidism. Patient was prescribed hydrocortisone and levothyroxine and resulted in significant improvement of the patient's condition. On the follow up visit patient demonstrated muscle weakness, difficulty getting up from the chair, headache and knee pain, the feeling of numbness variations in blood pressure. Laboratory tests revealed low normal T4 level. The patient was instructed to adjust the dosage of levothyroxine, which resulted in significant clinical improvement.
Conclusion
Central hypothyroidism is a rare and heterogeneous disorder that is characterized by a defect in thyroid hormone secretion in an otherwise normal thyroid gland due to insufficient stimulation by TSH. The disease results from the abnormal function of the pituitary gland, the hypothalamus, or both. Achieving optimal thyroid hormone replacement is more difficult in TSH deficiency compared to primary

hypothyroidism because of the inability to be guided by serum TSH levels.A combination of clinical symptoms and free thyroxine levels are typically used to make a diagnosis and monitor replacement.

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DOI: 10.1530/endoabs.101.PS2-16-03

## PS2-16-04

### Association of thyroid peroxidase antibodies and high-sensitivity c-reactive protein in men and women: a cross-sectional analysis from the elsa-brasil study

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Objective
Previous studies have suggested that increased thyroid peroxidase antibody (TPOAb) levels are a low-grade inflammatory marker. However, limited research has investigated its association with high-sensitivity C-reactive protein (hs-CRP). We aimed to explore the association between TPOAb levels and elevated hs-CRP levels in men and women, using data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).
Methods
We included participants with information on hs-CRP, TPOAb, and covariates, hs-CR$P < 10$ mg/l; and, without previous cardiovascular disease or stroke ($n = 5{,}476$ men, $51.5 \pm 9.1$ years old; $n = 6{,}575$ women, $51.7 \pm 8.8$ years old). Fasting serum levels of hs-CRP and TPOAb were measured. Elevated hs-CRP was defined as values between 3 and 10 mg/l. TPOAb was categorized as undetectable ($\leq 5.00$ IU/ml), low detectable (5.01-14.99 IU/ml), high detectable (15.00-33.99 IU/ml), and positive ($\geq 34.00$ IU/ml). Logistic regression models assessed hs-CRP as the dependent variable (reference: not elevated) and TPOAb as the independent variable (reference: undetectable). Univariate and adjusted models (Model 1 adjusted for sex, age, race, log-TSH and log-FT4 levels; Model 2 adjusted for model 1 plus diabetes, hypertension, dyslipidemia, smoking, eGFR$<$ $<$60 ml/min/1.73 $m^2$ and BMI $\geq 30$ kg/$m^2$) were performed. For the sensitivity analysis, we excluded individuals (181 men and 819 women) with clinical thyroid diseases.
Results
The prevalence of elevated hs-CRP levels was 19.6% and 27.9% for men and women, respectively (chi-square test, $P < 0.001$). Men with low and high TPOAb detectability were more likely to have elevated hs-CRP than the undetectable group in the univariate (low: OR:1.40; 95%CI: 1.00-1.95; $P = 0.050$ and high: OR:1.50; 95%CI: 1.05-2.14; $P = 0.027$) and fully adjusted models (low: OR:1.41; 95%CI: 1.00-1.99; $P = 0.048$ and high: OR:1.48; 95%CI: 1.03-2.14; $P = 0.035$). For women, there was no statistically significant association between TPOAb categories and elevated hs-CRP levels (low: OR: 0.98; 95%CI: 0.73-1.32; $P = 0.941$; high: OR:1.19; 95%CI: 0.87-1.64; $P = 0.278$; positivity: OR:1.08; 95%CI: 0.78-1.50; $P = 0.637$). After excluding participants with clinical thyroid diseases, the results remained similar. However, for men, only the high detectable group showed statistically higher odds of having elevated hs-CRP (OR:1.46; 95%CI: 1.00-2.11; $P = 0.048$). The associations for low detectable and positive TPOAb were marginal (low: OR:1.40; 95%CI: 0.99-1.98; $P = 0.058$ and positive: OR:1.50; 95%CI: 0.98-2.31; $P = 0.062$).
Conclusion
We found an association between TPOAb and hs-CRP levels among men, which persisted even when thyroid function was considered. These findings corroborate previous literature showing the potential relevance of TPOAb detectability as an indicator of low-grade inflammation, particularly in the male population.

DOI: 10.1530/endoabs.101.PS2-16-04

## PS2-16-05

### Nadh fluorescence in the skin is a novel biomarker of hypothyroidism-associated impairment of energy metabolism

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Background
Hypothyroidism (HT) is characterized by decreased overall energy expenditure and the basal metabolic rate. The reduced form of nicotinamide adenine dinucleotide (NADH) fluorescence in the tissue was shown to provide important information on the metabolic state of the mitochondria in terms of energy production. We hypothesize that the intensity of skin NADH fluorescence is associated with impaired energy metabolism in HT. The aim of this study was to evaluate the parameters of NADH fluorescence in the skin as potential biomarkers of impaired energy metabolism in HT.
Methods
We conducted a prospective controlled clinical experimental study. Twenty one patients with HT (7 with newly diagnosed and 14 with decompensated HT) along with sex - and body mass index (BMI) - matched 21 healthy controls (HCs) were recruited. Body temperature ($T_{body}$), local skin temperature ($T_{skin}$), HR (heart rate), thyroid stimulating hormone (TSH) and free T4 (FT4) were measured in all subjects. Skin NADH fluorescence was assessed by laser fluorescence spectroscopy (365 nm radiation source) on the dorsal forearm at rest ($NADH_{rest}$) and during local heating up to 35°C ($NADH_{heat}$). The difference between $NADH_{heat}$ and $NADH_{rest}$ ($\Delta NADH_{heat}$) was also calculated. To compare values between the HCs and the HT groups, the Student's t-test or Mann-Whitney U test were used when appropriate. Data are presented as the mean ± SD.
Results
The results of the study are presented in the Table.

| Variable | Healthy controls | Hypothyroidism | *P*-value |
|---|---|---|---|
| BMI, kg/$m^2$ | 24 ± 4 | 25 ± 5 | 0,765 |
| $T_{body}$, °C | 36,3 ± 0,5 | 36,2 ± 0,4 | 0,382 |
| $T_{skin}$, °C | 27,2 ± 2,3 | 27,2 ± 2,3 | 0,636 |
| HR, 1/min | 76 ± 10 | 76 ± 12 | 0,746 |
| TSH, mIU/l | 1,6 ± 0,8 | 27,95 ± 21,28 | **<0,001** |
| FT4, pmol/l | 16,24 ± 1,64 | 12,31 ± 4,13 | **<0,001** |
| $NADH_{rest}$ | 0,642 ± 0,237 | 0,865 ± 0,364 | **0,02** |
| $NADH_{heat}$ | 0,583 ± 0,209 | 0,708 ± 0,281 | 0,11 |
| $\Delta NADH_{heat}$ | -0,059 ± -0,059 | -0,157 ± 0,11 | **0,003** |

$NADH_{rest}$ and $\Delta NADH_{heat}$ were significantly higher in the HT group compared with HCs, with no differences in $NADH_{heat}$ between the groups.

Conclusion
HT is characterized by an increase in the intensity of skin NADH fluorescence at rest and its increased utilization during a thermal test. These variables can be used as new promising markers of impaired energy metabolism in hypothyroidism.

DOI: 10.1530/endoabs.101.PS2-16-05

## PS2-16-06

### Very low rates of thyroid function testing in human studies evaluating basal metabolic rate

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Objective
Because thyroid hormones positively regulate basal metabolic rate (BMR), one would expect that researchers systematically evaluate thyroid function in studies focused on BMR or resting energy expenditure (REE). The persent study aimed to document the percentage of human metabolic studies that find a difference in BMR/REE following an intervention and subsequently go on to evaluate whether thyroid function is altered.
Methods
A literature search was conducted in PubMed for human studies where BMR is measured by indirect calorimetry; the keywords "energy expenditure" or "metabolic rate," and "indirect calorimetry" were utilized. There was no restriction on the publication date. Articles written in English with full-length text availability were reviewed. Studies were excluded if they were not human studies, if indirect calorimetry was not utilized to measure BMR, if there was no specific intervention, or if the results did not show an increase or decrease in BMR following the intervention. The full-text articles of selected studies were analyzed to determine if thyroid function was evaluated, and, if so, to contextualize the implications of the measurements.
Results
3652 human studies that mentioned BMR or REE were identified. When the keyword "indirect calorimetry" was added, 671 articles were retained. Of the reviewed articles, roughly 50% identified a difference in BMR measured by indirect calorimetry following an intervention. Of those studies, less than 10% evaluated thyroid function. Those that did evaluate thyroid function were

primarily assessing pharmacological interventions with thyroid hormones, including 3,5-diiodo-L-thyronine (T2) and levothyroxine (T4), or with growth hormone. Other studies evaluated thyroid function because their study populations comprised patients with hyperthyroidism.

Conclusions

Despite the crucial impact of thyroid hormones on BMR, the present study highlights a striking gap in research methodology. Among the reviewed studies observing changes in BMR following interventions, only a small minority proceeded to evaluate thyroid hormone levels. This oversight underscores the need for greater attention to thyroid function assessment in metabolic research, as it could offer valuable insights into the mechanisms underlying metabolic regulation and inform more targeted interventions for metabolic disorders. Thyroidologists should strive to raise awareness of the impact of thyroid hormones on BMR and to bridge the apparent gap with the metabolic research community.

DOI: 10.1530/endoabs.101.PS2-16-06

## PS2-16-07

### Iodine intake and thyroid diseases in adult subject from different geographical regions of croatia

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Objective

Croatia is iodine sufficient country due to universal salt iodization as documented by epidemiological studies with urinary iodine measurement in schoolchildren and pregnant women, as well as women of reproductive age. However, high salt intake is present and program for reduction of salt intake in Croatia is initiated. The epidemiological project funded by Croatian science foundation EHUH2 was carried out to investigate prevalence of hypertension and related risk factors, salt intake as well as iodine intake and thyroid diseases in the population. The aim of the study was to assess iodine and salt intake and thyroid diseases in adult population from different regions of Croatia. SUBJECTS: The study enrolled 1146 adult subjects (819 females and 327 males), median age 58 (18-90) years.

Methods

Questionnaire, serum and 24-hour urine samples were collected for thyroid function tests and urinary iodine (UIC), sodium and creatinine measurement. All subjects underwent thyroid ultrasound (US) (GE Healthcare Logiq eR7 device with 12 MHz linear transducer) for assessment of thyroid volume and nodularity. UIC was measured by modified Sandel-Kolthoff method using microtiter plate technique.

Results

There were 115 (10.0%) (100 female and 15 male) subjects on L-T4 therapy due to hypothyroidism, 5 (0.4%) subjects on methimazole therapy due to hyperthyroidism. A total of 13 (1.1%) subjects underwent thyroid surgery due to benign thyroid conditions, and 8 (0.7%) subjects due to differentiated thyroid cancer. Ectopic sublingual thyroid was recorded in one subject. Thyroid nodules were detected in 550 (48.0%) subjects: 117 (21.3%) males and 433 (78.7%) females, with increasing prevalence with age and highest prevalence in rural areas with elderly population. An overall median UIC in adult population of Croatia was 131.1 μg/l. There were 29.3% of samples with UIC $<$ 100 μg/l, 66.7% of samples between 100-300 μg/l, and 4.0% of samples with UIC $>$ 300 μg/l. Furthermore, there was no difference in UIC medians between males and females and no significant difference between coastal and continental regions of Croatia (UIC medians around 130 μg/l). CONCLUSIONS: Present study confirms sufficient iodine intake in adult subjects in all investigated areas of Croatia according to medians of UIC. Interestingly, similar median UIC around 130 μg/l was recorded in most regions, with no difference between males and females. High prevalence of thyroid nodules and hypothyroidism on L-thyroxine therapy was recorded in female subjects in all geographical regions. The highest prevalence of thyroid nodules was recorded in rural areas with predominantly elderly female population.

DOI: 10.1530/endoabs.101.PS2-16-07

## PS2-16-08

### Acquired hypothyroidism, iodine status and hear impairment in adults

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Objectives

Hearing impairment is mainly described in congenital hypothyroidism and iodine deficiency in children. Hearing impairment has a major impact on behavior, educational attainment, social status and quality of life. In connection with thyroid disease, little attention is paid to hearing impairment. The incidence of hearing impairment in congenital hypothyroidism reaches 35-50%. The pathogenesis, incidence and severity of hearing impairment is even less known in acquired hypothyroidism with a reported incidence of 25%. The aim of our study was to evaluate hearing in acquired hypothyroidism.

Methods

30 patients with untreated and newly diagnosed peripheral hypothyroidism (H) and a control group of 30 healthy probands (C) were enrolled into the study. Biochemical examinations were performed including the determination of median iodine urine concentration (IUC) μg/l established by 3 morning urine samples. The hearing examination included subjective complaint assessment, otomicroscopy, tympanometry, transitory otoacoustic emission (TOAE), tone and verbal audiometry, and brainstem auditory evoked potential (BERA) examinations. Mann-Whitney U test, Fisher's Exact test and multivariate regression (a method of orthogonal projections to latent structure, OPLS) were used for statistical analysis.

Results

The H and C groups were significantly different in thyroid hormones levels (medians with 95% CI) TSH mU/l 13.3 (8.1, 19.3) vs. 1.97 (1.21, 2.25) $P = 0$, fT4 pmol/l 10.4 (9.51, 11.1) vs. 15 (13.8, 16.7) $P = 0$, anti-TPO IU/ml 335 (164, 520) vs. 28 (4.78, 31) $P < 0.01$, and thyroid volume (mL) 11.9 (10, 13.2) vs. 9.38 (8.6, 10.5) $P = 0.019$. The H and C groups were not different in age 39 (34, 43) vs. 41 (36,44) $P = 0.767$, BMI 25.6 (24,28.3) vs. 23 (21.6, 23,9) $P = 0.080$, and IUC 142 (113, 159) vs. 123 (101, 157) $P = 0.814$. The hear examinations as otomicroscopy ($P = 1$), tympanometry ($P = 1$), TOAE ($P = 1$), audiometry ($P = 0.179$), and BERA ($P = 0.505$) were not different between H and C groups.

Conclusions

We did not observe any hear impairment in patients with acquired hypothyroidism. We have to conclude that our study did not show any associations between hear impairment and severity of hypothyroidism or iodine status.

DOI: 10.1530/endoabs.101.PS2-16-08

## PS2-16-09

### Thyroid function and incidence of increased carotid intima-media thickness: results from elsa-brasil cohort study

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Introduction

Recent literature highlights the intricate link between thyroid function and atherosclerosis, particularly emphasizing its influence on carotid internal media thickness (cIMT). However, the studies yielded contradictory results, with some of them showing that subclinical hyper or hypothyroidism, may influence atherogenesis and increased cardiovascular risk, while others not showing such effect.

Objective

We aimed to investigate the association between thyroid function (TSH and FT4 quintiles) and incidence of increased carotid intima-media thickness (cIMT) in

men and women, euthyroid or with subclinical conditions, from the ELSA-Brasil study.
Methods
This is a prospective cohort study using baseline and 8y-follow-up data of men ($n=$ 2,057, 48.1 $\pm$ 7.9 years old) and women ($n$ = 2,857, 48.8 $\pm$ 7.7 years old), without history of cardiovascular disease. Fasting serum TSH, FT4, and FT3 were determined (Roche Diagnostics) and quintiles were calculated. We included in the main analysis euthyroid participants (TSH 0.4-4.0 mIU/l and no use of levothyroxine and anti-thyroid medication), and participants with subclinical conditions (TSH any level and 0.93 < FT4 < 1.70 ng/dL). Baseline levels of cIMT $\geq$ 0.68 (75th percentile) were classified as "increased cIMT". Incidence of increased cIMT was defined as baseline cIMT < 0.68 and follow-up CIMT $\geq$ 0.68. We performed sex-stratified Cox regression models, univariate and adjusted (for age, race, BMI, smoking, diabetes, hypertension, dyslipidemia), to determine hazard ratio (HR) and 95% confidence intervals (CI). Sensitive analyses were done 1) excluding those who were taking medications that interfere on thyroid function; and 2) plus excluding participants with subclinical thyroid function.
Results
The incidence of increased cIMT was 26.0% ($n$ = 535) for men and 21.5% ($n$ = 614) for women. Men in the second quintile of FT3, compared to the third quintile, showed higher risk for incident cIMT in univariate (H$r$ = 1.51, CI = 1.13-2.02, $P$ = 0.005) and fully adjusted model (H$r$ = 1.49, CI = 1.11-1.99, $P$ = 0.007). For women, the lowest levels of TSH (H$r$ = 1.33, CI = 1.03-1.72, $P$ = 0.028) and FT3 (H$r$ = 1.26, CI = 1.00-1.58, $P$ = 0.046) were associated with cIMT incidence in the univariate after adjustment for confounder variables. No association was seen between FT4 titers and cIMT. Results remained the same in the sensitivity analyses, except for the association between FT3 and incident cIMT for euthyroid women.
Conclusions
Individuals, especially women, with lower levels of TSH and FT3 were associated with higher risk of developing increased cIMT. The findings may suggest an influence of thyroid function on the atherosclerotic process.
DOI: 10.1530/endoabs.101.PS2-16-09

## PS2-16-10

**Diagnostic role of thyroid elastography in graves' disease**
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Objectives
Distinguishing between a healthy thyroid and autoimmune thyroid disease can sometimes be challenging. In addition to clinical and laboratory tools, as well as thyroid ultrasound, additional diagnostic tool is the elastographic assessment of thyroid tissue. With our research, we aimed to determine if we could differentiate between thyroid tissue in patients with Graves' disease (GD) and subjects with a healthy thyroid using ultrasound shear wave elastography (SWE).
Methods
In our prospective study, we evaluated 95 participants, comprising newly diagnosed GD patients and healthy individuals. GD diagnosis relied on clinical presentation, biochemical hyperthyroidism, positive antibodies against TSH receptor (TSHRAb), and a hypoechoic inhomogeneus ultrasound pattern of the thyroid gland. Healthy participants exhibited euthyroidism, negative thyroid autoantibodies, and an isoechoic homogeneous ultrasound thyroid appearance. SWE was employed in all participants to measure shear wave velocity ($v_{sw}$) and calculate the elasticity expressed in kPa. We utilized ROC analysis to assess the effectiveness of the SWE method, expressing its accuracy through AUC measurement.
Results
The GD group consisted of 42 patients (16.7% males and 83.3% females) with a mean age of 40.9 $\pm$ 12.8 years. The healthy group comprised 53 individuals (22.6% males and 77.4% females) with a mean age of 46.3 $\pm$ 15.7 years. In the GD group, the median $v_{sw}$ was significantly higher compared to healthy participants (2.80 m/s (range, 1.26–4.17) vs 2.11 m/s (range, 1.39–3.42), $P < 0.001$). This corresponds to the median calculated elasticity of the thyroid gland, which was 23.1 kPa (range, 4.75–52.20) in the GD group and 13.3 kPa (range, 5.83–35.0) in the healthy group ($P < 0.001$). Furthermore, the determined optimal cut-off point for $v_{sw}$ was 2.65 m/s, yielding a specificity of 92.5%, sensitivity of 66.7%, and an AUC of 0.804. Regarding calculated elasticity, the optimal cut-off point was found to be 18.48 kPa, with a specificity of 90.6%, sensitivity of 71.4%, and an AUC of 0.814.
Conclusions
The stiffness of thyroid tissue is significantly higher in patients with GD than in healthy subjects. Our results indicate that SWE elastography represents a useful tool that allows differentiation of thyroid elasticity between GD and a healthy thyroid with excellent specificity and adequate sensitivity.
DOI: 10.1530/endoabs.101.PS2-16-10

# Non- Surgical Treatment

## PS2-17-01

**Predictive factors for success of radioactive iodine treatment in graves' disease**
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Objectives
Correction of 131I dose for thyroid gland size is one of the methods used to determine radioactive iodine (RAI) activity for patients with Graves' disease (GD), but the predictive factors for its clinical outcome are still unclear. This study aimed to investigate which factors influence its success in a real-world cohort.
Methods
Observational and retrospective study of RAI treatments in a terciary referral center in Almada, Portugal, carried out between 2014 and 2022. Therapeutic success was defined as achieving eu- or hypothyroidism within 12 months of 131I administration. The data was analysed using SPSS® and Excel®.
Results
A total of 119 patients (103 females; mean age 48 years), with a mean estimated thyroid gland size of 58g, underwent 124 RAI treatments with a mean RAI dose of 11mCi. Four patients needed more than one 131I administration. A year later, success was reported in 89 (72%) treatments (group 1) with a 28% ($n$ = 35) rate of therapeutic failure (group 2), with no difference in age and sex between groups. In group 1, 84% of patients were hypothyroid and 16% were euthyroid. In the pre-treatment analyses, group 1 had significantly lower TRAbs titers than group 2 (9 vs 15 IU/l; $P$ = 0.01), as well as free T3 (7 vs 9 pg/ml; reference range 2-4.4; $P$ = 0.039). Despite group 1 having shorter disease (57 vs 79 weeks) and antithyroid treatment duration (32 vs 40 weeks), as well as higher TSH levels (0.19 vs 0.03mU/l) and lower thyroid gland size (55 vs 64g) and mean administrated RAI dose (11 vs 12mCi), no association between these variables and treatment success was found. Smoking habits, presence of orbitopathy, corticosteroid therapy, 24h RAI uptake and prior antithyroid therapy were also not identified as risk factors for treatment failure.
Conclusion
With a success rate similar to previous studies, the present study found that lower titers of free T3 and TRAbs are strongly associated with treatment efficacy.
DOI: 10.1530/endoabs.101.PS2-17-01

## PS2-17-02

**Efficacy of radioactive iodine treatment in graves' disease using a calculated 131i dose in a portuguese cohort**
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Objective
To evaluate the success of administration of $^{131}$Iodine adjusted for thyroid gland size in the treatment of hyperthyroidism in Graves' disease.
Methods
All patients with Gravés hyperthyroidism who underwent therapeutic administration of $^{131}$I in a referral center in Portugal, from 2014 to 2022 were selected. Values of estimated thyroid gland size, administrated doses of $^{131}$I and 24h radioactive iodine uptake (RAIU) prior to therapy were collected. Thyroid function was evaluated 3, 6 and 12 months after administration. The goal of RAI treatment was to achieve eu- or hypothyroidism within 12 months.
Results
This study included 135 $^{131}$I administrations in a total of 130 patients (84% female, mean age 47 years) with a mean time since diagnosis of 63 years. 132 patients (98%) had been previously treated with antithyroid medications (86% with methimazole and 12% with propylthiouracil) and 4 underwent more than one RAI treatment. The mean estimated thyroid gland size was 57.7g, range 14-172g. Mean RAIU was 54.1%, range 19-75%, with RAI administrated doses ranging

from 4 to 23mCi, with a mean dose of 11.4mCi. Three months after $^{131}$I administration, hyperthyroidism was documented in 47 patients (38%), euthyroidism in 38 (30%) and hypothyroidism in 40 (32%). At 6 months, 7% of the individuals who had hyperthyroidism at 3 months recovered, with a total of 40 patients with hyperthyroidism. Also, by this time, 20 patients (16%) had euthyroidism and 68 (53%) were hypothyroid. Twelve months later, the decreasing tendency of hyperthyroidism was maintained, with a total of 35 (28%) patients remaining hyperthyroid. Additionally, 14 individuals (11%) had euthyroidism and 75 (61%) were hypothyroid.
Conclusion
The overall Graves' disease treatment success rate obtained with $^{131}$I administration adjusted for thyroid gland size at our institution was 72%, similar to previous studies.

DOI: 10.1530/endoabs.101.PS2-17-02

## PS2-17-03

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.PS2-17-03

## PS2-17-04

**Efficacy of intrathyroidal dexamethasone injection in steroid-dependent subacute thyroiditis – preliminary report of dlisat study**

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Objectives
Steroid-dependent subacute thyroiditis (SAT) is a challenging clinical problem. Long-term treatment and high cumulative doses of systemic steroids are associated with high risk of steroid-related complications. The DLISAT study aims to evaluate the efficacy and safety od intrathyroidal dexamethasone injections in chosen groups of patients, comparing the outcomes with standard oral steroid therapy. This paper presents the preliminary results focusing on two patients with steroid-dependent SAT.
Methods
Steroid-dependent SAT was defined as recurrent symptoms upon at least three attempts of steroid dose reduction. Patients with inadequately rapid dose reduction were excluded from the study. The included patients underwent four (Patient 1) and five (patient 2) attempts of dose reduction during 7 and 8 months, respectively. Intrathyroidal injections of 4 mg of dexamethasone (1 ml of solution), with or without 1 ml of 2% lidocaine, were administered into the affected thyroid lobe under ultrasound guidance. Doses were repeated every 2-7 days based on the obtained results. Parameters including pain severity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and thyroglobulin (Tg) were measured before and after injections. Ultrasound image and shear wave elastography results were analyzed before and after each injection, as well as after therapy completion. Total recovery criteria included resolution of symptoms, normalization of ESR, CRP and thyroid hormones, along with significant reduction of SAT-related thyroid lesions in ultrasound examination.
Results
Excellent response to therapy was observed in both patients, with rapid pain release after the first dose. No side effects except for injection-related discomfort was reported. Complete recovery was achieved after 6 and 7 injections into the affected lobes in Patient 1 and Patient 2, respectively. The whole therapy duration was 27 for Patient 1 and 29 for Patient 2. The dose of dexamethasone required for the total therapy was 24 mg in Patient 1 (one lobe affected) and 56 mg in Patient 2 (both lobes affected).
Conclusion
Intrathyroidal dexamethasone injections demonstrated excellent efficacy and safety in patients with oral steroid-dependent SAT, resulting in rapid symptom relief, short therapy duration, and low steroid doses. This approach seemed to be a great therapeutic tool in patients with symptoms recurrence during reduction of oral steroid dose, and may be considered a first line treatment, especially in patients with high risk of steroid-related complications.

DOI: 10.1530/endoabs.101.PS2-17-04

## PS2-17-05

**J-131 therapy in patients with autonomously functioning thyroid nodules and normal FT4 blood level**

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Objective
The purpose of this study was to evaluate the results of radionuclide therapy with iodine-131 (I-131) in patients (pts) with autonomously functioning thyroid nodules (AFTNs) and a normal thyroid hormone (FT4) blood level.
Methods
In this study 131 cytological benign AFTNs in 116 pts (100 female and 16 male) with normal FT4 level have been treated with a fixed I-131 doses (370 MBq). Clinical exam, ultrasonography with color Doppler (US), fine needle aspiration biopsy (FNAB), TSH, FT4, FT3, anti-TPO, anti-Tg, anti-TSH receptor and thyroid scan (scintigraphy) have been performed in all pts before and 6 months after I-131 therapy.
Results
The median age of the pts was 61 (range 35 - 90) years. AFTNs were located more frequently in the right thyroid lobe (73 nodules) than in the left lobe (58 nodules). In 19 pts a solitary AFTN has been found on ultrasonography and the other 97 patients had AFTNs in multinodular goiter. 15 pts had two AFTNs. On post I-131 therapy thyroid scan in 80 AFTNs complete therapy effect has been observed, but in 51 AFTNs a scintigraphycally partial effect has been noted. Statistical analysis showed a significant reduction in the thyroid ($P$ = 2,8179E-24) and AFTNs ($P$ = 4,0351E-06) volume after J-131 therapy. TSH value significantly increased ($P$ = 3,0081E-05) and FT4 value significantly decreased ($P$ = 3,1438 E-05) after I-131 therapy. FT3 ($P$ = 0,3757), anti-TPO ($P$ = 0,7615) and anti-Tg ($P$ = 0,1412) and anti-TSH receptor ($P$ = 0,1182) values did not change significantly.
Conclusion
This study shows that radionuclide therapy with I-131 in pts with AFTN and normal FT4 blood level is a very effective modality. The effect of the I-131 therapy on AFTNs can be evaluated with a thyroid scan 6 months after I-131 therapy.

DOI: 10.1530/endoabs.101.PS2-17-05

## PS2-17-06

**Proficiency in performing radiofrequency ablation procedure for non-functioning benign thyroid nodules: a qualitative rather than quantitative matter**

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Objective
Radiofrequency ablation (RFA) is an emerging non-surgical treatment for benign thyroid nodules (BTN). Despite its proven safety profile, data on the learning curve (LC) required to achieve proficiency are still lacking.
Materials and methods
The first 179 RFA procedures performed by a single operator in patients with non-functioning BTN were retrospectively analyzed. Six-month nodule volume reduction rate (VRR) $\geq$ 50% was regarded as reflection of proficiency. Multiple

linear regression analysis has been performed to determine the relationship between the VRR and clinical variables. Cumulative sum (CUSUM) charts were plotted to assess LCs for all consecutive procedures and in relation to basal nodule size. In details, Group 1 (G1): 57 patients with small nodules ($<10$ ml); Group 2 (G2): 87 patients with intermediate nodules (10 – 25 ml); Group 3 (G3): 35 patients with large size ($>25$ ml).
Results
LC of all 179 procedures showed 3 phases: initial learning (1-39 procedures); consolidation (40-145 procedures); and experienced period (146-179 procedures). For G1 and G2 proficiency is achieved starting from the 10th procedure within the group (or 37th considering consecutively all procedures) and from the 59th procedure within the group (or 116th considering consecutively all procedures), respectively. LC of G3 did not detect operator proficiency.
Conclusion
Specific LCs exist concerning the basal size of the nodule treated with RFA. In nodules with baseline volume $>25$ ml suboptimal VRR has to be expected. Previously achieved experience on small-intermediate nodules does not seem to provide advantages in terms of higher VRR in the treatment of large nodules. Other potential and non-modifiable factors likely play a key role in the final volume reduction independently from the increased skill of the operator.

DOI: 10.1530/endoabs.101.PS2-17-06

## PS2-17-07

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.PS2-17-07

## PS2-17-08

**Laser thermal ablation for benign thyroid nodules: a single polish centre experience**

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Introduction
Percutaneous laser thermal ablation is a minimally invasive method of shrinking benign thyroid tumors (also used in selected cases of papillary thyroid cancer or primary hyperparathyroidism). Pressure symptoms and a cosmetic defect are main indications for this procedure.
Aim
The aim of the study was to present the results of percutaneous laser thermal ablation for benign thyroid nodules performed in a single Polish center.
Material and Methods
Between 2022-2024, 175 laser thermal ablation procedures were performed (in 160 patients) using the Elesta EchoLaser X4® and the ModiLite® application at the tertiary referral center. From this group, 65 patients with at least one year follow-up were included in the analysis. Thyroid ultrasound was performed immediately before and 12 months after the procedure with the Esaote MyLab Omega ® ultrasound device.
Results
The study group comprised 10 males and 55 females (median age 47 years). Indications for the procedure were compression symptoms in 57 patients (87.7%), a cosmetic defect in 13 patients (20%), subclinical hyperthyroidism in 4 patients (6.2%) and a recurrent cyst in one patient (1.5%). 31 (47.7%) of ablated lesions were predominantly solid with $<50\%$ of the fluid component, 24 (36.9%) - solid, 9 (13.8%) - predominantly liquid with $>50\%$ of the fluid component, and one (1.5%) was a pure cyst. 56 patients underwent one procedure, 6 patients - two procedures, and 3 patients - three procedures. The median tumor volume before ablation was 10.85 mL (range 2.86-92.67 mL). Median deposited energy was 5004.9 J (range 1203.0-18285.0 J). The median tumor volume after ablation was 4.21 mL (range 0.38-41.8 mL). The median percentage reduction in tumor volume was 59.87% [4.93-93.47]. The most frequent side effects reported within 7 days after procedure were: pain (22 patients – 33.8%), weakness (13 patients - 20%), flu-like symptoms (11 patients – 16.9%), and neck swelling (10 patients – 15.4%). Longer-lasting complications included: hematoma in 4 patients (6.2%), subacute thyroiditis in 1 patient (1.5%), and a transient recurrent laryngeal nerve palsy in 1 patient (1.5%). Subclinical hyperthyroidism was not resolved in any of four patients despite the reduction in tumor size.
Conclusions
Laser ablation is an effective method of reducing the size of benign thyroid nodules. To authors' knowledge this is one of the first Polish reports on effectiveness and safety of the procedure.

DOI: 10.1530/endoabs.101.PS2-17-08

## PS2-17-09

**Safety and efficacy of ultrasound-guided thrombin injection for pseudoaneurysms arising after ultrasound-guided biopsy of thyroid nodules**

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Purpose
Iatrogenic pseudoaneurysm is a rare but potentially fatal complication of thyroid biopsy. However, the standard management strategy for thyroid pseudoaneurysm is not established. In this study, we aimed to evaluate the incidence, imaging features, clinical manifestations of pseudoaneurysms occurring after thyroid biopsy and to evaluate the efficacy and safety of US-guided percutaneous thrombin injection for pseudoaneurysm.
Materials and Results
From January 2020 to September 2023, 7,256 patients underwent thyroid nodule biopsy in a single institution. We assessed the number of pseudoaneurysms that occurred after thyroid biopsy and were treated with percutaneous thrombin injection. Baseline patient characteristics, imaging features, treatment efficacy, and complication rates were evaluated.
Results
A total of seven cases of pseudoaneurysms developed after biopsy despite more than 30 minutes of manual compression. All cases were associated with core needle biopsy. All patients presented with persistent neck swelling and tenderness after manual compression. Except for one case which showed obliteration following manual compression, the remaining six aneurysms (0.08%) refractory to manual compression were managed with US guided TI. All pseudoaneurysms (100%) were successfully occluded after US guided TI. After TI, no cases required further surgical repair. There were no major complications. Five pseudoaneurysms were located at the thyroid capsule, and two case was located intrathyroidally. The average size of pseudoaneurysms was 0.72 cm (range 0.2-1.3 cm). All pseudoaneurysms (100%) were successfully occluded with less than 500 IU doses of thrombin. After thrombin injection, no cases required further surgical repair. One patient (15%) developed transient loss of consciousness with involuntary movement of the upper extremity after thrombin injection, which spontaneously resolved during observation. The average cost for thrombin injection was $5.72.
Conclusion
US-guided percutaneous thrombin injection is an effective, relatively safe, less invasive method for the management of iatrogenic pseudoaneurysms after biopsy of thyroid nodules.

DOI: 10.1530/endoabs.101.PS2-17-09

## PS2-17-10

**Prevalence and ultrasonography features of thyroglossal duct cyst in adults according to radioactive iodine ablation**

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Objectives
This study aimed to assess the prevalence and US features of TGDCs in adults on ultrasonography (US), and to assess whether the prevalence or size of TGDCs increases after RIA.
Methods
A total of 2820 patients underwent thyroid or neck US examination between July and December 2018. Among them, 54 patients were excluded owing to young age (< 19 years; $n = 52$) and a history of radiation ther¬apy to the neck ($n = 2$). Eventually, 2766 patients (2148 women and 618 men, mean age ± SD: 53.4 ± 11.9 years, age range: 19–91 years) were included. The pres¬ence or absence, location, largest diameter, and shape of the TGDCs were prospectively investigated on real-time US.
Results
The prevalence of TGDC was 5.8% ($n = 160$) on US (mean size: 0.9 ± 0.4 cm, range: 0.3–3.3 cm). There was no significant difference in size of TGDCs between RIA history (+) and RIA history (–) groups (mean size: 0.92 ± 0.41 cm and 0.86 ± 0.45 cm, respectively, $P = 0.684$). There was no significant difference in patient age, gender, reason for thyroid/neck US, type of thyroid surgery, and session number and application/no application of RIA between the TGDC (+) and (-) groups ($P > 0.05$). TGDCs were more common in the suprahyoid neck (77.5%) and the common shapes were flat-to-ovoid (43.8%) and round (41.9%).
Conclusions
RIA may not be associated with the prevalence or enlargement of TGDCs.

DOI: 10.1530/endoabs.101.PS2-17-10

## Pregnancy

### PS2-18-01

**Changes of central sensitivity to thyroid hormones during pregnancy**

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Introduction/Aim
Central sensitivity to thyroid hormones refers to the sensitivity of the hypothalamic-pituitary-thyroid (HPT) axis to changes in circulating free thyroxine (fT4). The relationship between fT4 levels and iodine intake is complex. The aim of the present study was to assess central sensitivity to thyroid hormones in pregnancy against iodine intake.
Materials & Methods
Data were collected from 138 pregnant women (with a mean age of 29.8 years) during singleton pregnancies; women with known/diagnosed thyroid disease were excluded. Specifically, TSH and fT4 and 24-hour urinary iodine excretion (UI) were measured in each trimester. The Thyroid Feedback Quantile-based Index (TFQI) was calculated to assess central sensitivity to thyroid hormones. For the statistical analysis of TFQI by trimester, analysis of variance (ANOVA) was used, while Pearson's correlation was used to assess TFQI *vs* UI.
Results
The mean TFQI index ranged from -0.08 (first trimester) to +0.23 (second trimester, p: 0.01) ending in -0.06 (third trimester), while UI was 134, 167 and 132 μg/l, respectively. The TFQI correlation was positive (Pearson r: + 0.39, p: 0.02), only for UI values between 100 μg/l - 250 μg/l, in the third trimester.
Discussion
TFQI is a new index reflecting central sensitivity to thyroid hormones. Lower TFQI indicates higher sensitivity to thyroid hormones, and in our sample this was noted in the first trimester (the critical period of organogenesis) and the third trimester (when it also appeared to be related to iodine intake). Thus, the observed changes in TFQI may reflect different ways of central action of thyroid hormones, according to the phase of pregnancy. The positive association between maternal TFQI (indicative of central sensitivity to thyroid hormone) and urine iodine levels during the third trimester may reflect the combined influence of maternal and fetal thyroid function. Our results are intriguing and have the potential to enhance our comprehension of the changes in the HPT axis' function via variations in central sensitivity to thyroid hormones and its interplay with nutritional iodine status during pregnancy.

DOI: 10.1530/endoabs.101.PS2-18-01

### PS2-18-02

**Iodine status in pregnant women with hashimoto's thyroiditis: is iodine supplementation needed?**

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Objective
No consensus has been reached yet on whether iodine supplementation should be recommended also in pregnant women with Hashimoto's thyroiditis who are receiving levothyroxine (LT4) therapy. We aimed to evaluating the iodine status in a sample of pregnant women residing in the Veneto region of Italy and suffering from autoimmune thyroiditis. Here we present our preliminary results.
Methods
81 pregnant women with Hashimoto's thyroiditis, whether or not undergoing LT4 therapy, were consecutively enrolled. Inclusion criteria were women aged more than 18 years old, resident in Veneto and agreeing to participate in the study; exclusion criteria were non-autoimmune hyperthyroidism or iatrogenic hypothyroidism. Data on participants' dietary habits, iodine containing supplements (IS) use and social status were collected through a questionnaire. Serum TSH and FT4 and an early-morning spot urine sample to determine the iodine to creatinine concentration ratio (UI/Creat) were taken. Children's' anthropometric data, gestational age at birth, sex and neonatal TSH value were collected.
Results
a median UI/Creat value of 276 μg/g and a more than adequate level of UI/Creat (≥ 250 μg/g) was found in 57.1%, while in 27.2% a state of iodine deficiency (< 150 μg/g) was observed. Patients on LT4 therapy accounted for 92.6% and, in this group, the median UI/Creat value was 286 μg/g. Iodized salt was consumed by 82.7% but was not associated with median UI/Creat. UI/Creat was, associated with regular cheese consumption (364 μg/g *vs* 238 μg/g, $P = 0.03$). Median UI/Creat was 289 μg/g in IS-users and 124.5 μg/g in non-users ($P = 0.054$), with iodine deficiency in 66.7% of the latter *vs* 23.9% in the former ($P = 0.02$). A positive weak correlation, at the limit of significance ($P = 0.057$, $r = 0.22$) was found between daily L-T4/Kg and UI/Creat. At multivariate analysis the supplement intake was the only independent variable for adequate UI/Creat (OR: 6.35; CI: 1.07-37.8; $P = 0.04$). Higher neonatal weight was associated, at the limits of statistical significance ($P = 0.056$), with an UI/Creat ≥ 250 μg/g and higher neonatal TSH values (2.5 mIU/l *vs* 1.2 mIU/l) were found in the group of women taking the supplement.
Conclusions
Although the intake of LT4 and supplementation contributed to the elevation of median iodide levels, failure to use it resulted in a tendency to iodine deficiency. Iodine supplementation resulted in in higher neonatal TSH values, although in the normal range. A moderate iodine supplementation in women with autoimmune thyroiditis undergoing LT4 therapy should be taken into consideration, also based on their L-T4 dose.

DOI: 10.1530/endoabs.101.PS2-18-02

### PS2-18-03

**Thyroid function in pregnancy in normal weight and obese women without thyroid diseases**

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Objectives
The association between thyroid function variations and body mass index (BMI) has been described in the adult population in several studies: higher TSH values and lower FT4 values, while still within reference range, have been correlated

with higher BMI values. The aim of the study was to assess thyroid hormones variations in relation to body weight in pregnant women without thyroid diseases.
Methods
In this prospective study, thyroid function of 601 pregnant consecutive women without thyroid disease was examined based on pre-pregnancy weight and weight gain at the end of the gestation. In particular, 141 women (23.5%) had a pre-pregnancy BMI $<20$ kg/m2, 335 (55.7%) had a BMI between 20-25 kg/m2, 88 (14.6%) had a BMI between 25-30 kg/m2 and 37 (6.2%) had a BMI $>30$ kg/m2. The difference in the mean age between normal weight (34 $\pm$ 5.18 DS) and obese patients (33 $\pm$ 5.87 DS) was not statistically significant. Throughout each trimester, thyroid function (TSH, FT4 and FT3 values), the presence of anti-thyroid antibodies (AbTg and AbTPO), thyroid ultrasound and patients' anthropometric and hormonal data were assessed.
Results
Comparing thyroid function based on pre-pregnancy BMI, significantly higher TSH values (1.54 mUI/l [1.17 IQR] vs 1 mUI/l [1.02 IQR], $P = 0.034$) were observed in obese women in the first trimester of pregnancy compared to normal-weight women. Furthermore, women who gained more than 15 kg during pregnancy had significantly lower FT4 levels at the end of pregnancy compared to women who gained less weight. This finding is significant in the overall population of women (0.75 ng/dL [1.83 IQR] vs 0.82 ng/dL [0.17 IQR], $P = 0.000$) or, when divided by BMI at the beginning of pregnancy, in women who were normal weight in the early first trimester (0.73 ng/dL [0.17 IQR] vs 0.82 ng/dL [0.15 IQR], $P = 0.000$), while it was not significant in patients who were overweight or obese at the beginning of pregnancy.
Conclusions
In conclusion, higher TSH levels were observed in women with obesity in the first trimester of pregnancy. Lower FT4 levels were highlighted in women with greater weight gain during pregnancy, particularly in patients who were normal weight in the early first trimester.

DOI: 10.1530/endoabs.101.PS2-18-03

## PS2-18-04

**Mild & moderate iodine deficiency in pregnant women from sub-himalayan regions of india: impact on thyroid status**

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It is well established that due to enhanced iodine/thyroxine requirement during pregnancy women with inadequate iodine intake are at high risk of iodine deficiency (ID). However, the relative impacts of mild & moderate ID are yet debated. General population inIndia has been declared iodine-sufficient (93%, *vide* WHO) but we found 70-90% pregnant women from 3 States, iodine-deficient(UIC $<150$ mg/l).
Objective
To assess the extent of ID and its impact on TSH & FT4 in pregnant women. Methods. Study design: Epidemiological observational survey. Study subjects drew from rural Himalayan foothills of Uttarakhand, UK ($n = 120$ longitudinal) & Bihar, BR ($n = 432$ crisssectional). Blood & urine collected from women 18-45years. Only eligible subjects were included. IEC approval & informed consent were obtained. Using UIC as biomarker of iodine-sufficiency (IS $>150$ mg/l, WHO) pregnant women were categorised into IS, mild ID($<150$-100 mg/l), moderate ID($<100$-50 mg/l) and severe ID($<50$ mg/l). TSH(mIU/l) and FT4(pmol/l) were determined and compared across categories and States.
Results
UK and BR, both populations attest to complete success of USI outreach in India(Iodised salt usage UK, 97% and BR, 100%, both over 10-20 years). But iodisation was adequate only in 17% of study population in BR. BR population also constituted predominantly moderate to severe ID (UIC $<100$ mg/l, 56.2%,70%,69.7% in 1st, 2nd, 3rd trimester respectively) as compared to UK which was mostly mildly iodine deficient (UIC $<150$-100 mg/l, 93%,93%,66% in 1st, 2nd, 3rd trimester respectively). TSH & FT4 did not vary significantly among ID categories. But significantly higher median values and upper IQR cut-offs of TSH were observed in almost all categories of ID, in almost all trimesters in BR population, as compared to UK (due to space restriction only 2 categories are shown in Table 1).

TABLE 1 UK: UIC $<100$ mg/l vs BR: UIC $<100$ mg/l UK: UIC $>150$ mg/l vs BR: UIC $>150$ mg/l

| | | | | |
|---|---|---|---|---|
| Tri1 TSH median(IQR) | 1.2(0.6-2.4) | 2.1(1.5-3.5) | 2.5(1.7-2.9) | 3.1(2.1-3.4) |
| Tri2 TSH median(IQR) | 2.1(1.7-2.8) | 3.4(2.7-5.1) | 3.1(2.6-3.5) | 4.0(3.0-5.0) |
| Tri3 TSH median(IQR) | 3.4(2.8-4.1) | 4.2(3.2-5.1) | 3.3(insufficient no.) | 4.1(3.1-5.0) |

However, all TSH and FT4 values remained within normal range for the population (2.5-97.5 percentile TSH 0.43-5.9mIU/l) based on 2000 data points from our cohorts. The TSH/FT4 correlation was significantly higher in BR women ($r = 0.6$-0.8) as compared to UK ($r = 0.1$-0.4) indicating greater sensitisation of hypothalamo-hypophyseal-thyroid axis.
Conclusion
USI outreach in India is a total success but lacks in iodine fortification. Moderate ID does not impair thyroid function and resultant TSH increase may be physiological homeostasis to achieve euthyroidism, rather than pathophysiological.
Acknowledgement
NABL, NABH, DSIR certified lab facilities of SRHU & Apeejay Stya Group & research grant from SRHU is gratefully acknowledged. SLT is a UGC-Rajiv Gandhi fellowship awardee.

DOI: 10.1530/endoabs.101.PS2-18-04

## PS2-18-05

**Trimester specific thyroid hormone reference range in mild iodine deficiency compared to normal iodine nutrition**

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Objective
Pregnant women worldwide are at risk for mild iodine deficiency (ID) due to transfer of iodine through placenta, increased glomerular filtration of iodine and higher maternal thyroid hormone production for foetal needs. Studies show that mild ID involves normal thyroid hormone levels but may lead to increased thyroglobulin levels resulting from an increased maternal thyroid volume through changed thyroid metabolism. When assessing thyroid hormones during pregnancy, reference ranges should preferably be based on a pregnant population. It is also internationally recommended that trimester-specific reference ranges should be established in an iodine-sufficient population, which may be difficult to achieve in countries where pregnant women typically suffer from mild ID. It is also unknown whether mild ID affects the upper and lower limits of the reference ranges. In the SWIDDICH study (www.swiddich.se, **NCT02378246** clinical trials.gov), a large randomised controlled multicentre trial in Sweden, blood samples from each trimester were analysed to evaluate how trimester-specific reference ranges were affected by iodine supplementation in a mild ID pregnant population resulting in normal iodine levels (previous pilot data urinary iodine concentration (UIC) in the intervention group had UIC 136 (91-211) µg/l vs 65 (39-108) µg/l in the non-intervention group $P < 0.001$ $n = 158$).
Methods
Women without known thyroid disease, with singleton pregnancy were included during first trimester ($n = 368$: age range 18 – 40 years) and randomised to use a daily supplement with/without iodine (150 µg/day). Blood samples were collected at the maternal health care centre during all trimesters. TSH, free T4, free T3 and anti-TPO were measured using the Roche Cobas method; individuals with increased anti-TPO according to the reference range from the manufacturer was excluded. The limits of the reference ranges were analysed and compared between the two groups for each trimester.
Results
There was no significant difference between the two groups in the upper and lower limits of the reference ranges for FT4, FT3, TSH in any of the trimesters. There was a significant difference in all thyroid hormones between the different trimesters -except for FT3 comparing trimester 2 and 3. The reference range for FT4 (including all trimesters and both groups) were lower compared to a non-pregnant adult population.

Conclusion
Appropriate trimester-specific reference ranges are of major importance when treating women with thyroid dysfunction during pregnancy. These data shows that they can be established not only in iodine sufficient, but also in mildly ID pregnant populations. This data may impact future international guidelines and benefit healthcare for women worldwide.

DOI: 10.1530/endoabs.101.PS2-18-05

## PS2-18-06

**Iodine status in a population-based cohort study of a multiethnic pregnant women in norway**

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Context
Iodine is an important mineral essential for thyroid function and for normal development of the fetus. There is growing evidence that iodine insufficiency is still a major health issue globally.
Objective
The main aim of this study was to look for ethnic differences in iodine status in pregnant women based on urinary iodine concentration (UIC) and food frequency questionnaires (FFQ). Furthermore, we assessed the influence of iodine status on thyroid function.
Methods
Data from the STORK Groruddalen study, a population-based cohort of healthy women ($n = 823$) with multiethnic background residing in Groruddalen, Oslo, Norway was used. Fifty-two % of participants were of ethnic minority background. Based on a spot sample of morning urine collected in week 15 ($n = 654$), we calculated weight corrected iodine intake $CII_{UIC}$ (UIC µg/l x weight (kg) x 0.0235) to estimate iodine status. We also computed an estimated iodine intake score based on data from a semi-quantitative, interviewer administered FFQ in week 28, ($n = 727$). Combined UIC and dietary data was available for 601 participants.
Results
Median UIC was 89 µg/l (IQR 51; 127). The estimated iodine intake ($CII_{UIC}$) was 131 µg/d (IQR 84;217). Based on $CII_{UIC,}$ the proportion of women with severe iodine insufficiency ($CII_{UIC}$ <50) was 4-15% in different ethnic groups, and high/excessive (>500) in 4-13%. However, no significant difference was seen between different ethnic groups. Based on FFQ, the median iodine intake was 144 µg/d (IQR 75;219). The lowest iodine intakes were found in Middle East women and the highest levels in South Asian women ($P < 0.084$). Dairy items contributed to 31% and Fish 29% of the total iodine intake, both with significant differences between ethnic groups (respectively $P < 0.019$ and $P = 0.033$). Seventeen percent of the participants reported regular use of iodine containing supplements. We observed higher levels of free thyroxin at week 28 in groups with moderate and highest iodine intake ($P < 0.004$). However, no significant differences were seen in TSH levels.
Conclusion
Based on US Institute of Medicine's recommended equation to estimate daily iodine intake in pregnancy, our results indicate that a large group of pregnant women present mild iodine insufficiency. However. The estimated urinary or dietary iodine status did not affect thyroid function consistently, and no significant differences were found between ethnic groups. Larger studies are needed to confirm these findings, and further to assess the effect of mild iodine insufficiency on development of the fetus.

DOI: 10.1530/endoabs.101.PS2-18-06

## PS2-18-07

**An innovative method to better understand thyroid function changes: longitudinal trajectories of gestational thyroid function**

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Background
Pregnancy causes significant changes in regulation of the hypothalamus-pituitary-thyroid (HPT) hub and extrathyroidal thyroid chemical digestion. Thus, after effects of thyroid capability tests contrast in pregnant ladies contrasted and nonpregnant ladies, and trimester-explicit reference scopes of TSH and free T4 (fT4) have been proposed. Most studies of thyroid function changes during pregnancy use a cross-sectional design comparing means between groups rather than similarities within groups. A unique method for examining longitudinal changes that offer a dynamic knowledge of the connection between thyroid status and progressing pregnancy is latent class growth analysis (LCGA).
Objective
To examine the longitudinal changes that offer a dynamic knowledge of the connection between thyroid status and progressing pregnancy using latent class growth analysis, or LCGA.
Design
Prospective observational study with repeated assessments.
Setting
General community in collaboration of Health directorate, Govt of Haryana India
Subjects
Three hundred seven healthy pregnant women were included at 10 weeks' gestation. Main Outcome Measures: The presence of both free T4 (FT4) and TSH trajectories throughout pregnancy determined by LCGA.
Results
When taking into account the effect of age as a predictor variable, the results obtained from LGCA analyses a considerable fluctuation in TSH, FT4, and UIE levels with time. The foundation of these methods is structural equation modeling. A negative covariance (m = -0.802) is seen for TSH between the slope and the intercept, indicating that a higher baseline TSH value will result in a slower rate of growth in trimesters over time. Comparably, for FT4, a negative covariance (m = -0.747) is found between the intercept and slope; for each successive length, this covariance is predicted to drop by 3.72 points (from a baseline value of 24.35). The projected trimester for UIE is anticipated to drop by 3.81 points from a baseline value of 130.36, following a similar pattern. Additionally, there is a negative covariance for UIE.
Conclusion
Unique trajectories of longitudinal variations in women's TSH, FT4, and UIE levels throughout pregnancy were shown by LCGA. These trajectories were associated with parity and showed patterns that may indicate that multiparous and multiparous women.

**Research facility from Swami Rama Himalayan University & Apeejay Stya University are gratefully acknowledged**

DOI: 10.1530/endoabs.101.PS2-18-07

## PS2-18-08

**Iodine availability from prenatal supplements in portugal**

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Introduction
Iodine supplementation is recommended for populations at risk in countries without sufficient iodized salt coverage, as Portugal. Pregnancy is a time of particular susceptibility to malnutrition. In Portugal, despite the recommendation (issued in 2013 by the health authorities) to supplement iodine during preconception, pregnancy and lactation, pregnant women are still iodine deficient.
Objectives
To characterize the nutritional composition of prenatal supplements regarding iodine, iron, selenium, and folic acid. To evaluate iodine availability from iodine-

containing supplement sales in Portuguese pharmacies. To assess iodine supplementation coverage from pharmacy dispenses.
Methods
Data from iodine supplement sales since 2008 in Portuguese pharmacies was provided by CEFAR-ANF (Centre for Health Evaluation and Research, National Association of Pharmacies). Product information was complemented with INFOMED (human medicinal products database) and Web search. Iodine, folic acid, and iron content was obtained through the label information. Pharmacy dispenses of iodine supplements between 2019 and 2021 were collected from a sample of female consumers, identified with at least one prescription associated to one fiscal number.
Results
Iodine-containing supplements represented 72% of prenatal supplement sales in 2023. Of 30 identified prenatal supplements, only 67% have the recommended iodine content. All the iodine-containing supplements also have folic acid, 87% iron and 83% selenium. Units of iodine-containing supplements sold increased over the years from 2008 ($F(1,12)=211$, $P < 0.001$, $R2=0.94$). When considering all sales (pharmacies and outside pharmacies [(that represent 11% total sales)]), the amount of iodine available from prenatal supplements reached 114 mg per birth, per day. From a sample of 86012 women with pharmacy dispenses between 2019 and 2021, mean duration of supplementation was 4.5 months ($sd=3.8$). Less than one percent is covered for the advisable period of 18 months.
Conclusion
Iodine-containing supplements represent a considerable percentage of prenatal supplement sales aligning with the usage reports by pregnant women in the literature. However, estimated duration of supplementation is below recommendations. These findings are in accordance with reported urinary iodine levels in the Portuguese pregnant population, prompting studies evaluating compliance, and verifying nutritional composition. Additional measures are needed for the promotion of women adherence to recommendations, to incite healthcare professionals to inform on iodine relevance, and for health authorities to implement policies to ensure iodine sufficiency to the population (universal salt iodization).

DOI: 10.1530/endoabs.101.PS2-18-08

## PS2-18-09

**Maternal urinary iodine concentration and thyroid function in the offspring: preliminary results of an italian multicenter study**

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Background and objectives
In the period 2022-2023, a multicentre study coordinated by the Italian National Observatory for Monitoring Iodine Prophylaxis (OSNAMI), was launched in 8 Italian regions representative of the Northern (Lombardy, Veneto, Liguria), Central (Tuscany, Lazio) and Southern Italy and Islands (Sicily, Calabria, Sardinia) with the aim of evaluating iodine nutrition in pregnant women ($n$ = 400/region) and thyroid function in the offspring. Here we present results of a preliminary analysis conducted in 2,473 pregnant women and concerning the use of iodized salt (IS) and/or iodine-containing supplements (ICS) during pregnancy, urinary iodine concentration (UIC) at the 3rd trimester, and neonatal TSH in the offspring.
Subjects and Methods
Pregnant women were recruited at the last visit before delivery ($n$ = 1242 Northern, $n$ = 262 Central, $n$ = 969 Southern Italy-Islands). Women with thyroid diseases were excluded from the study. A questionnaire was administered to collect information on the use of IS and/or ICS. A morning spot urinary samples was also collected for the measurement of UIC. In the offspring, data on TSH in at term newborns (>=37w) were obtained thanks to a mandatory nationwide newborn screening program for congenital hypothyroidism active in Italy.
Results
We found that 70% of the recruited women used IS. Among the IS users, 88% were using IS since at least 2 years. Specifically, 25% of the pregnant women used IS-only, 44% IS+ICS, 18% ICS-only, and 12% NO-IS/NO-ICS. Overall, a median UIC of 101 μg/l ($Q1=61$, $Q3=166$) was found. According to the use of IS and/or ICS, the median UIC was significantly higher in IS+ICS group (118 μg/l) than in ICS-only (108 μg/l), IS-only (84 μg/l), and NO-IS/NO-ICS (77 μg/l) groups ($P < 0.001$). The median value of neonatal TSH was significantly higher in IS+ICS and NO-IS/NO-ICS groups (both 2.2 mIU/l), than in ICS-only (1.8 mIU/l) and IS-only (1.9 mIU/l) groups ($P < 0.01$).
Conclusions
These preliminary data show that the use of IS+ICS during pregnancy significantly increases UIC, although pregnant women are still iodine deficient in our country. Our data also suggest that the contemporary use of IS and ICS during pregnancy is associated with higher neonatal TSH values in comparison with the use of IS or ICS alone. Further studies are needed to verify this association and to better understand relationships among iodine intake during pregnancy, maternal UIC, and neonatal TSH.

DOI: 10.1530/endoabs.101.PS2-18-09

## PS2-18-10

**Thyroid and fertility: a survey on the clinical practice among endocrinologists belonging to the italian thyroid association (AIT)**

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Increase of patients submitted to assisted reproduction techniques (ART) and to the high prevalence of thyroid disorders in the fertile age, this survey aimed to evaluate the current management of these women by the Italian thyroidologists. A short questionnaire was sent to all members of the AIT. The questions concerned the out-patients management of women of childbearing age with thyroid diseases. According to our results, there is a clinic dedicated to the management of patients with thyroid diseases planning conception or during pregnancy in about 50% of the centers, but 97.4% of the endocrinologists investigate the possible desire for pregnancy during the visit and more than 70% of them follow patients during ART. The iodine supplementation when planning a pregnancy is suggested by 70% of the endocrinologists and precise indications about the need of TSH and FT4 measurement are given by more than 95% of participants. Concerning the L-T4 therapy, a “blind increase” of 30% in case of pregnancy positive test is suggested in slightly less than 60%, 15% of whom only if pregnancy is achieved by ART. A thyroid screening in women planning conception is recommended by almost all the participants (94%); similarly, TSH screening if largely recommended in women with PCO (90%). According to the recent ETA guidelines, 87.3% of endocrinologists starts L-T4 treatment in case of TSH >2.5 mU/l in case of positive thyroid autoimmunity; moreover, therapy is suggested also in the absence of autoimmunity in women with previous miscarriage by about 60% of participants. L-T4 therapy is often already started by gynecologist, as referred in our survey by 83.8% of endocrinologists. After ovarian stimulation,

TSH levels are measured by 68% of participants, 72% of whom in all patients, while 17% and 11%, respectively, only in case of positive autoantibodies or in hypothyroid women already on L-T4 replacement therapy. As far as the timing of the TSH check, the majority of endocrinologists (75%) suggests to perform it at the time of HCG measurement, while almost everyone else at the oocytes pick-up (25%). Although only 50% of the centers have a thyroid clinic program dedicated to pregnancy, almost all the Italian thyroidologists are involved in the management of infertile/pregnant women. This survey identified a discordant application of ETA guidelines dedicated to the infertile women submitted to ART.

DOI: 10.1530/endoabs.101.PS2-18-10

## Thyroid Eyes Disease

### PS2-19-01

**Analysis of thyroid stimulating immunoglobulins vs conventional TSH-receptor antibodies in clinical practice**

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Objectives
Our purpose was to determine the value of thyroid stimulating immunoglobulin (TSI) in comparison to TSH receptor antibodies (TRAb) in clinical practice. The specific aims were 1) to evaluate the sensitivity and specificity of TSI, TRAb and its combination at diagnosis 2) to determine corresponding TSI cut-offs in the "Graves' Recurrent Events After Therapy" (GREAT) score in patients with Graves' disease (GD), and 3) to determine the predicting potential of TSI and TRAb for recurrent disease measured at the end of the anti-thyroid drug (ATD) treatment.
Methods
During 3 months, all clinical TRAb samples ($n = 672$) from the Thyroid and Radioactive iodine units were frozen for later analysis of TSI. Data was collected on thyroid hormones, TRAb, date of start/withdrawal of ATD and recurrency when applicable. Files were reviewed by two independent raters to determine the final thyroid diagnosis taken the full course of disease in consideration.
Results
At diagnosis of hyperthyroidism, 13 samples (10.7%) were positive for TSI but not TRAb, thereof only one was assessed as falsely positive. The area under the curve was 0.82 for TRAb and 0.90 for TSI. The potential of TRAb and TSI to diagnose GD are presented (value [95% confidence interval]) in the table. TRAb and TSI combined did not give additional value compared to TSI alone. The TSI values corresponding to the TRAb cut-offs 6 and 20 in the GREAT score were 4.8 and 21.7, respectively. At the end of the ATD treatment, TRAb had sensitivity 0.18 (0.04-0.43) and specificity 0.86 (0.68-0.96) and TSI had sensitivity 0.59 (0.33-0.82) and specificity 0.72 (0.53-0.87) in predicting recurrence.

| | **Sensitivity** | | **Specificity** | |
|---|---|---|---|---|
| | TRAb (IU/l) | TSI (IU/l) | TRAb (IU/l) | TSI (IU/l) |
| At diagnosis of hyperthyroidism ($n = 122$) | 0.63 (0.50-0.75) | 0.83 (0.71-0.91) | 1.00 (0.94-1.00) | 0.98 (0.91-1.00) |
| Overt hyperthyroidism ($n = 49$) | 0.78 (0.62-0.90) | 0.97 (0.86-1.00) | 1.00 (0.74-1.00) | 1.00 (0.74-1.00) |
| Subclinical hyperthyroidism ($n = 46$) | 0.43 (0.18-0.71) | 0.71 (0.42-0.92) | 1.00 (0.89-1.00) | 0.97 (0.84-1.00) |
| Subclinical hyperthyroidism with TSH $<$ 0.1 IU/l ($n = 34$) | 0.46 (0.19-0.75) | 0.77 (0.46-0.95) | 1.00 (0.84-1.00) | 0.95 (0.76-1.00) |
| Subclinical hyperthyroidism with TSH 0.1-0.3 IU/l ($n = 12$) | 0.00 (0.00-0.98) | 0.00 (0.00-0.98) | 1.00 (0.79-1.00) | 1.00 (0.79-1.00) |

Conclusions
Our results suggest a more general use of TSI in future guidelines and we have therefore calculated the corresponding levels of TSI in the GREAT score, which needs to be evaluated in future studies. However, in subclinical hypothyroidism the interpretation of TRAB/TSI shall be cautious.

DOI: 10.1530/endoabs.101.PS2-19-01

### PS2-19-02

***In vivo* and *in vitro* evidence for a protective role of autoantibodies against the insulin-like growth factor-1 receptor (IGF-1R) in graves' orbitopathy**

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The insulin-like growth factor-1 receptor (IGF-1R) is involved in the pathogenesis of Graves' orbitopathy (GO) and a possible protective role of autoantibodies against IGF-1R (IGF-1R-Abs) has been suggested. We conducted a cross-sectional study to investigate IGF-1R-Abs serum levels in 147 consecutive patients with Graves' disease (GD), with ($n = 92$) or without ($n = 55$) GO (primary outcome). Secondary outcomes were: 1) relationship between IGF-1R-Abs and GO features; 2) effect of IGF-1R-Abs on cell proliferation in primary cultures of orbital fibroblasts. IGF-1R-Abs were measured by ELISA. Serum IGF-1R-Abs levels were higher (29.3 ng/ml, IQR 17.4-36.6) in patients without GO than in those with GO (19.8 ng/ml, IQR 11.2-29.8; Mann Whitney U 1,819, $P = 0.00509$). The prevalence of IGF-1R-Abs levels above a previously established cut-off value of 55 ng/ml did not differ statistically between the two groups, in spite of a trend to a greater prevalence in patients without GO (9 vs 3.2%). Within GO patients, IGF-1R-Abs did not correlate with GO features, namely proptosis, clinical activity score, eyelid width and visual acuity, whereas there was a correlation with diplopia. Thus, IGF-1R-Abs were lower in patients with the most severe degrees of diplopia (Omega square = 0.0123, $P = 0.035$). Incubation of a thyroid cell line (FRTL-5 cells) with IgGs purified from a pool of sera with IGF-1R-Abs $>$ 55 ng/ml increased cell proliferation in a dose-dependent manner (Omega square = 0.965; $P < 0.0001$), presumably reflecting TSH-receptor stimulating antibodies, whereas proliferation was reduced in a dose-dependent manner in orbital fibroblasts from GO patients (Omega square = 0.747; $P < 0.0001$), suggesting a role of IGF-1R-Abs. Overall, our findings suggest that IGF-1R-Abs are present only in a minority of patients with GD and seem to play a protective role on GO development and features.

DOI: 10.1530/endoabs.101.PS2-19-02

### PS2-19-03

**The association of the cholesterol metabolic profile and fatty acid content with the clinical phenotype of graves' orbitopathy**

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Background
Graves' orbitopathy (GO) is an autoimmune orbital disease of insufficiently defined pathogenesis. Hyperlipidemia has been recognized as a risk factor for GO, while statin therapy may reduce its incidence. Since statins inhibit cholesterol synthesis, a potential link between cholesterol metabolism and the ocurence of GO is possible, but still unexplored. Alongside lipid-lowering, the anti-

inflammatory effects of statins may also contribute to their beneficial impact on GO. Therefore, our study aims to investigate the patients' basic lipid profiles, cholesterol synthesis and absorption status, and fatty acid content, all in relation to GO clinical phenotype.

Material and methods

The study included 89 consecutive patients with GO of varying degrees of activity and severity. We analyzed plasma concentrations of non-cholesterol sterols (NCS): cholesterol synthesis markers (desmosterol and lathosterol) and cholesterol absorption markers (campesterol, stigmasterol, and β-sitosterol) using a Gas Chromatography Flame-Ionization Detection (GC-FID) method. Lipid parameters were assessed in serum by routine biochemical methods on the Olympus AU400 analyzer. Fatty acids were also quantified in plasma using GC-FID (Agilent Technologies 7890A). Stimulating thyrotropin receptor antibodies (TSAb) were quantified using a cell-based bioassay (Thyretain®, Quidelortho, San Diego, CA, USA).

Results

The analysis of basic lipid parameters showed that patients with active GO had significantly lower HDL-C compared to inactive GO patients ($P = 0.032$). The ApoB/ApoA1 ratio was significantly higher in moderate-to-severe and sight-threatening GO ($P = 0.029$) and predicted the development of a more severe form of the disease (O$r = 5.253$, CI% (1.136-24.283), $P = 0.034$). Also, a positive correlation between LDL-C and TSAb levels ($\rho = 0.255$, $P = 0.019$) was observed. Concerning NCS, there were no significant differences between groups, except for lathosterol, which exhibited a significant increase in more severe GO cases ($P = 0.045$). However, cholesterol synthesis-to-absorption ratio was significantly higher in patients with sight-threatening GO compared to patients with mild GO ($P = 0.013$). Furthermore, this ratio also showed a borderline-significant association with GO activity ($P = 0.058$) and positively correlated with CAS score ($\rho = 0.232$, $P = 0.048$). Content of monounsaturated oleic fatty acid (18:1 n9) was significantly lower in active compared to inactive GO ($P = 0.009$). Oleic acid correlated negatively with CAS score ($\rho = -0.241$, $P = 0.025$) and TSAb ($\rho = -0.245$, $P = 0.019$).

Conclusions

Alterations of patients' lipid profile and the status of cholesterol synthesis and absorption markers were associated with a worse clinical phenotype of GO. Furthermore, our results indicate the potentially protective role of oleic acid in GO pathogenesis.

DOI: 10.1530/endoabs.101.PS2-19-03

## PS2-19-04

### Analytical performance of a novel bioassay for blocking thyrotropin receptor antibodies

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Background

Blocking thyrotropin receptor (TSH-R) autoantibodies (TBAb) are present in 10-15% of patients with autoimmune thyroid disease (AITD). TBAb are functional and affect thyroid function. Analytical performance of a novel bioassay for TBAb was evaluated.

Methods

Serum samples from AITD patients were tested with a CE market cell-based TBAb blocking reporter bioassay (Thyretain®, Quidelortho, USA) with expression of a Luciferase transgene as readout and a new "Turbo™" TBAb bioassay (Quidelortho) with a readout that is based on a cyclic AMP-activated luciferase. All serum samples were also run on two TSH-R binding immunoassays (Cobas e411, Roche, Germany and ALINITY i Immunoassay-System, Abbott Germany). A Passing-Bablok regression, a Bland Altman plot, as well as user and lot comparisons were performed. Additionally, a dose-response curve was fitted for the TBAb Turbo and Thyretain bioassays via serial dilution and IC50 / IC80 values were compared.

Results

Of 1011 unselected, consecutive AITD patients, 131 patients (212 samples) were TBAb positive. Of 212 samples, 149 (70.3%), 47 (22%) and 16 (7.5%) were hypothyroid, euthyroid and hyperthyroid, respectively. The four TSH-R-Ab assays were negative in 90 control subjects devoid of autoimmune thyroid and endocrine disorders. In contrast, the Turbo™ cAMP TBAb, Luciferase TBAb and the binding assays detected TBAb in 212 (100%), 168 (79%) and 138/180 (65%) samples, respectively (Chi-square test $P < 0.001$). The Turbo™ TBAb bioassay highly correlated with thyroid function (Mann Whitney U test (MWU) $P < 0.001$). Furthermore, the magnitude of percentage inhibition in both Turbo™ and Luciferase TBAb bioassays correlated with TSH-R-Ab binding assay positivity (both MWU $P < 0.001$). The two TBAb bioassays correlated (Spearman's $r = 0.8$, $p < 0.001$) and the Bland-Altman plot displayed no significant bias (0.24). Values scatter with slight systemic deviation between TBAb mean values of 10–50% Inhibition with higher Turbo™ TBAb than Luciferase TBAb results. Intra-assay validation demonstrated adequate precision with very low coefficient of variation (CoV) (average CoV 0.054) and lower CoV values with samples with high inhibitory effect ($CoV_{Average} = 0.017$ for a sample with 95% Inhibition Luciferase TBAb). CoV did not differ between users ($p_{CoV} = 0.35$) and lots ($p_{CoV} = 0.121$). IC50 / IC80 values were 1.7 ng/ml / 0.76 ng/ml and 6.76 ng/ml / 2.48 ng/ml) for Turbo and Luciferase TBAb bioassays demonstrating the markedly higher sensitivity of Turbo™.

Conclusions

The novel, easy-to-perform, rapid and reliable Turbo™ TSH-R blocking bioassay detected significantly more TBAb than the established immunoassays emphasizing its higher analytical performance and clinical utility in the management of patients with AITD.

DOI: 10.1530/endoabs.101.PS2-19-04

## PS2-19-05

### Lymphocytes' immunophenotype guided treatment in a thyroid eye disease patient successfully treated with rituximab

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Introduction

Rituximab is an anti-CD20 monoclonal antibody used as second-line treatment for patients with moderate-to-severe and active Thyroid Eye Disease (TED) and resistant to i.v. Methylprednisolone (ivMP). Rituximab induces B-cells depletion in the peripheral blood and in target organs of patients with TED. We report on a case of a patient with active TED successfully treated with two doses of Rituximab 500 mg i.v. after immunophenotypic characterization by flow cytometry of lymphocytes derived from blood and ultrasound-guided-fine-needle aspiration (US-FNA) of thyroid and neck lymph nodes (LNs). Analysis and immunophenotyping of retro-orbital tissue were also performed after decompression surgery.

Case report

A 55-year-old man with a history of TED, presented with activation of the right eye in January 2021 (CAS 4/10) that was treated with ivMP, resulting in disease inactivation (CAS 0/10), with residual marked proptosis. After 18 months he presented with active TED in the left eye (CAS 5/10). We performed a first

immunophenotypic analysis which showed elevated count of CD19+ B-cells in the blood, thyroid and LNs. We then decided to treat him with a dose of Rituximab 500 mg i.v.. After 4 weeks, we detected no CD19+ B-cells in the blood and thyroid while, unexpectedly, we found a certain degree of residual infiltration in LNs. Treatment appeared to be ineffective (CAS 6/10). Based on the immunophenotype findings, we decided to administer a second dose of Rituximab 500 mg i.v., which led to complete and lasting inactivation of TED (CAS 0/10) and total B-cells depletion also in LNs. We also observed a progressive reduction of follicular T helper lymphocytes (Tfh) and Germinal-Center (GC) Tfh in LNs of the patient. After treatment CD4+ T lymphocytes showed a reduction of CD69 and CD40L expression, both in LNs and blood. Tissue obtained from orbital decompression 6 months after Rituximab therapy was characterized by B-cells infiltration with a reduction of naive B-cells and an increase of memory B-cells, when compared to orbital tissue from chronic TED.
Conclusions
We have shown the feasibility of personalized therapy in a patient with TED otherwise resistant to ivMP. Effectiveness of Rituximab was associated with reduction of B-cells in the blood, thyroid and cervical LNs. Our results also show that Rituximab not only predictably depletes B-cells, but also influences T-cells, with changes of subsets (Tfh and GC-Tfh cells) and modifications of the activation/co-stimulation status (CD40L and CD69 expression), which suggests a more complex mechanism of action.

DOI: 10.1530/endoabs.101.PS2-19-05

## PS2-19-06

**Graves orbitopathy, does all the patients evolve in the same way?**

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Introduction
Graves' orbitopathy (GO), represents the main extrathyroid manifestation of Graves' disease, with a wide variety of clinical presentations. According to Rundle's curve, GO is characterized by an Initial phase inflammatory phase, a severity peak followed by a stable plateau phase (fibrotic phase).
Objectives
To identify and describe GO patterns distinct from the Rundle's curve.
Methods/Case Presentation
Five hundredn and sixty six patients with GD were included in the study, with 197 patients developing GO during the 60 months follow-up as determined by the clinical activity score (CAS) and evaluated every six months over 60 months. Serum TSH, FT4 and thyroid stimulating hormone receptor antibody (TRAb) positivity were also determined. The relationship between the patterns identified and the two main treatment alternatives was also evaluated. Group 1 ($n = 115$) consisted of patients that followed the Rundles' Curve pattern and group 2 ($n = 82$) consisted of patients with GO evolution characterized by periods of worsening and improvement of inflammatory signs of GO.
Results
In Group R, mean age and standard deviation (SD) was 39 $\pm$ 10 years, and 75% of patients were female, mean initial TSH was 0.018 $\pm$ 0.03 uUI/ml, mean initial FT4 was 4.46 $\pm$ 2.10 ng/dL, 85% were TRAb-positive, and 48% smoked. In Group NR, mean age was 40 $\pm$ 11 years, and 80% of patients were female, mean initial TSH was 0.018 $\pm$ 0.03 uUI/ml, mean initial FT4 was 3.87 $\pm$ 1.81 ng/dL 84% were TRAb positive, and 38% were smokers.
Conclusion
This study described a group of patients with GO evolution different than Rundle's curve characterized by periods of worsening and improvement of inflammatory signs of GO, suggesting that GO is a recurrent chronic disease.

| Mean CAS | Grup R | Group NR | P value |
|---|---|---|---|
| T0 | 1.27 $\pm$ 1.27 | 2.19 $\pm$ 1.49 | $P < 0.005$ |
| T6 | 0.96 $\pm$ 1.04 | 1.71 $\pm$ 1.67 | |
| T12 | 0.95 $\pm$ 0.99 | 1.31 $\pm$ 1.29 | |
| T18 | 0.80 $\pm$ 0.89 | 1.61 $\pm$ 1.41 | |
| T24 | 0.70 $\pm$ 0.91 | 1.23 $\pm$ 1.28 | |
| T36 | 0.66 $\pm$ 0.76 | 1.28 $\pm$ 1.37 | |
| T48 | 0.40 $\pm$ 0.65 | 1.20 $\pm$ 1.45 | |
| T60 | 0.36 $\pm$ 0.58 | 0.94 $\pm$ 1.10 | |

DOI: 10.1530/endoabs.101.PS2-19-06

## PS2-19-07

**Duration of treatment for thyroid eye disease**

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Purpose
The duration of treatment thyroid eye disease (TED) varies substantially between cases, this reflects the understanding that the active phase of the condition can last from 6 to 24 months. This study considers the treatment duration for a number of common symptoms of TED.
Subjects
746 patients, 155 males and 591 females with mean age 47.7 $\pm$ 15.2 years (9-92 years), who first visited Olympia Eye Hospital in 2018 and underwent anti-inflammatory or surgical treatment for TED. Data was examined between 2018-2023.
Methods
Treatments performed over a 5-year period were examined retrospectively. Treatment duration (time from first visit to last anti-inflammatory treatment or surgery) was quantified for patients who underwent subcutaneous triamcinolone acetonide injection (SCTA) for levator palpebrae superioris muscle inflammation, subtenon triamcinolone acetonide injection (STTA) for extraocular muscle inflammation, methylprednisolone pulse therapy for multiple extraocular muscle inflammation, and surgery.
Results
SCTA was performed in 469 cases, STTA in 252 cases, pulse therapy in 210 cases, and surgical treatment in 122 cases (32 orbital decompression in 32, 81 strabismus, and 24 eyelids). The average duration of treatment was 5.1 $\pm$ 7.9 months for SCTA only (270 patients), 4.7 $\pm$ 9.3 months for STTA only (60 patients), and 8.2 $\pm$ 11.0 months for pulse therapy only (52 patients). In those with multiple treatments, cases with pulse therapy, STTA and strabismus surgery had the longest average duration of 19.9 $\pm$ 15.8 months. The mean follow-up period was 39.7 $\pm$ 24.1 months; 134 patients (17.7%) had been attending the hospital for more than 5 years, with one patient still on anti-inflammatory treatment.
Conclusion
The duration of treatment was shorter in cases in which inflammation could be eliminated by local treatment alone, and longer in cases in involving inflammation of multiple muscles or when strabismus surgery was required. Treated cases had an average follow-up of about 3 years. These treatment durations can help identified those who are refractory to current treatments and might be considered for treatment with new drugs

DOI: 10.1530/endoabs.101.PS2-19-07

## PS2-19-08

**Management of thyroid eye disease (TED) related strabismus in euthyroid patient with with negative anti thyroid antibodies**

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Introduction
The thyroid eye disease (TED) is an autoimmune disorder. Diagnosis is based on recognition of clinical features and may be supported by serologic tests of thyroid function, immune testing, and orbital imaging. Clinical orbital signs include eyelid retraction, proptosis, compressive optic neuropathy signs, eyelid erythema, chemosis, caruncular edema, and restrictive strabismus. The laboratory tests include thyroid-stimulating hormone-receptor (TSH-R) antibody, thyroid-stimulating immunoglobulin (TSH), thyroid-binding inhibitory immunoglobulin (TBII), and anti-microsomal antibody. The typical feature in orbital imaging is enlargement of extraocular muscles. The majority of TED patients have hyperthyroidism (90%), 6% of the patients are euthyroid, 1% have hypothyroidism, and 3% are affected by Hashimoto's thyroiditis at the time of diagnosis. Strabismus may occur in 15% of all patients with TED. Diplopia is a common symptom of the strabismus, which can interfere with the daily activities of the patient. Strabismus and diplopia management remains challenging.
Case presentation
We present a case of 42 y/o male who was referred to our endocrine department in February of 2024 by the ophthalmologist. Patient had complaints of diplopia,

internal strabismus and eye movement restriction, periodic headache and palpitations since 10.2023. He was diagnosed with autoimmune thyroiditis at that time. MRI done in 10.2023 revealed lateral rectus muscle swelling and increased thickness. Unfortunately, patient did not receive appropriate assessment and recommendations. We ordered laboratory tests, which revealed increased FT3, normal TSH, FT4, patient was instructed to initiate IV methylprednisolone infusions and selenium intake. After 3 weeks, on the follow up visit, patient demonstrated significant clinical improvement, the degree of strabismus and diplopia, swelling and facial redness were also decreased. FT3 normalized, TSH and FT4 remained within normal limits. Patient is given corresponding recommendations to continue his treatment and further diagnostic assessment.
Conclusion
Abnormalities in thyroid hormonal tests and/or the presence of thyroid specific antibodies help to support the diagnosis, but they are not essential, and their absence does not exclude the diagnosis. Systemic glucocorticosteroids, rituximab, and tocilizumab have been shown to be effective in improving ocular motility and diplopia in these patients. Strabismus related to thyroid eye disease presents many challenges to the ophthalmologist. Management of these patients is classified into non-surgical and surgical approaches. Multidisciplinary approach, appropriate patient selection and available therapies guide the treatment.

DOI: 10.1530/endoabs.101.PS2-19-08

## PS2-19-09

**A marker of inflammatory state and the clinical outcome of active go to parenteral glucocorticoids**

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Oxidative stress (OX) is relevant in the pathogenesis of Graves' ophthalmopathy (GO) an inflammatory- autoimmune disease. Hypercholesterolemia is one of the most relevant clinical conditions related to OX and it has been demonstrated to be involved in clinical presentation and activity of GO. Low density lipoproteins cholesterol (LDLc) levels evaluated before parenteral glucocorticoids (GC) administration are related to GO clinical outcome to GC. Monocyte to high-density lipoprotein cholesterol (HDL) ratio (MHR), is a putative inflammatory biomarker and it seems to be relevant to the clinical outcome of cardiovascular diseases. Aim of our study was to evaluate the role of MHR to the clinical outcome of active moderate to severe GO (MSGO) to parenteral glucocorticoids respect to some conditions related to OX.
Methods
we studied n 115 patients, n 86 females, n 29 males, with active MSGO that were treated with a cumulative dose 47.5 (DS 17.4) mg/kg in 12 weeks of parenteral metilprednisolon. GO clinical activity and the clinical outcome of GO to GC was evaluated by seven points Clinical Activity Score according to EUGOGO suggestions. LDLc, age, sex, early response to GC, BMI, TRAbs levels and MHR were evaluated by univariate analysis and as covariates respect the outcome by some multivariate analysis models.
Results
90 GO patients were responders and 25 were non responders at weeks 12. Baseline MHR was significantly increased in patients non responders respect to responder: MRH 0.0091 (0.0069-0.0122) responders vs MRH 0.0115 (0.0073-0.0155) non responders $P = 0.043$ (Mann -Whitney U test) According to univariate analysis there were differences respect to LDLc between the two groups of GO patients LDLc 115.8 mg/dl (94.9-135.2) responders vs 135.9 mg/dl (108.7-162.4) non responders, $P = 0.019$ (Mann -Whitney U test). Female gender was associated to Improved outcome at week 12 (83.7% vs 62.1%, females vs males, $P = 0.015$, Chi square test). No statistical differences were found for age, BMI, TRAb, thyroid hormones, History of Hypertension (HoH). By a multivariate analysis model (M1) baseline MRH and baseline LDL were significantly and independently related to the clinical outcome of GO to GS at 12 weeks: $P = 0.024$ and $P = 0.012$ respectively.
Conclusions
Some clinical conditions related to OX can modulate the clinical outcome of GO to GC, MRH might be an additive marker of the inflammatory state that could modulate the clinical outcome of GO to GC.

DOI: 10.1530/endoabs.101.PS2-19-09

## PS2-19-10

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.PS2-19-10

# Poster Session 3 Thyroid Function, Feedback & Disruptors

## PS3-20-01

**A new mouse model to better decipher the minimum proportion of active follicles required to sustain normal thyroid function**

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Objectives
Hypothyroidism is successfully treated by T4 replacement. Nevertheless, T4 treatment is not always well-tolerated. Regenerative medicine using thyroid follicular cells (TFCs) constitutes a very attractive alternative therapy; however, the minimal number of TFCs that have to be fixed remains unknown.
Methods
The severe hypothyroid phenotype of DUOXA$^{-/-}$ mice will be rescued using targeted expression of the $H_2O_2$; enzymatic complex DUOX2/DUOXA2. The proportion of functional thyroid follicles necessary to recover a healthy thyroid function will be evaluated in triple transgenic animals (3TA: DUOXA$^{-/-}$/Tet:D2DA2$^{+/-}$/TG:CreER$^{+/-}$) following doxycycline (DOX) induction and intraperitoneal injection with reduced doses of tamoxifen (TAM) to reactivate a restricted number of TFCs. Moreover, the proportion of active TFCs required in a follicle for TH synthesis will be evaluated by combining TH staining with RNAscope detection of the DUOX2 transcript as a marker of CreER$^{T2}$-mediated recombination.
Results
To evaluate how quickly TH synthesis resumes in 10 mg TAM-injected 3TA, thyroids have been collected 0 to 7 days after DOX induction. Four days after T4 withdrawal, reduction of the colloidal lumen was clearly observed in DUOXA$^{-/-}$/Tet:D2DA2$^{+/-}$ animals (2TA) and further enhanced at Day-7. In contrast, a preserved follicular structure was present in 3TA. Despite maximum induction of transgenes 2 days after DOX initiation, 3TA as well as 2TA showed elevation of TSH-dependent genes at Day-3. Meanwhile, iodinated thyroglobulin (TGI) starts to be detected in 3TA in a limited number of small follicles mainly localized in the center of the thyroid tissue. 24h later, staining of positive TGI increased to 89% of thyroid follicles together with a significant reduction of Nis, Tpo and TSHr expression. At Day-7, 95% of thyroid follicles were TGI positive. Next, animals were injected with various doses of TAM (10 to 0.1 mg) before DOX supplementation during 1 week. The vast majority of thyroid follicles were functional (TGI$^{+}$) in 3TA injected with TAM from 10 to 0.5 mg. In contrast, injection with 0.25 or 0.1 mg of TAM resulted in hypothyroid phenotype with Nis, Tpo and TSHr overexpression and altered thyroid follicular structures. Concomitantly, these mice presented a clear reduction of TGI$^{+}$ follicles below 50%. Finally, detection of the DUOX2 transcript confirmed the reduced number of recombined TFCs upon restricted TAM injection, but revealed that a very few number of active TFC would be sufficient to reconstitute a functional thyroid follicle.
Conclusions
These preliminary experiments clearly demonstrated that iodination of TG resumes very rapidly, as fast as 24h, after the restoration of the TFC function. Moreover, these data suggested that more than 80% of active follicles are required to support healthy thyroid function, but this could be achieved via a more limited proportion of active TFC suitable for TH synthesis.

DOI: 10.1530/endoabs.101.PS3-20-01

## PS3-20-02

**Overview of traditional chinese medicine for hashimoto's thyroiditis: focus on selenium and antioxidant phytochemicals**

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Objective
Hashimoto's thyroiditis (HT) is not only the most frequent autoimmune thyroid disease (AITD), but it also has a significant impact on patients' health-related quality of life (HRQoL), and it has been variably associated with differentiated thyroid carcinoma. Even though its pathogenesis is still incompletely understood, oxidative stress is believed to play an important role. Hypothyroidism related to later stages of HT can be treated with levothyroxine substitution therapy; various approaches such as selenium supplementation and iodine-restricted diets have been proposed as disease-modifying treatments for earlier stages; and even thyroidectomy has been suggested for refractory cases of painful HT. Nevertheless, many patients still report suboptimal HRQoL, highlighting an unmet medical need in this area.
Methods
The concepts and approaches of traditional Chinese medicine (TCM) in treating HT are not broadly known in the West. Here, we provide an overview of TCM for HT, including combinations of TCM with selenium. We encompass evidence from clinical trials and other studies related to complex TCM prescriptions, single herbs used in TCM, and isolated phytochemicals; wherever possible, we delineate the probable underlying molecular mechanisms.
Results
The findings show that the main active components of TCM for HT have commonly known or presumed antioxidant and anti-inflammatory activities, which may account for their potential utility in HT.
Conclusions
Further exploring the practices of TCM for HT and combining them with evidence- and mechanism-based approaches according to Western standards may help to identify new strategies to alter the clinical course of the disease and/or to better treat patients' symptoms and improve their HRQoL.

DOI: 10.1530/endoabs.101.PS3-20-02

## PS3-20-03

**Variable sensitivity of thyroid hormone feedback in different zebrafish models of thyroid dysfunction**

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The thyroid hormone (TH) feedback is the principal mechanism contributing to maintain the circulating levels of thyroid hormones within the physiological limits that are required for an adequate action at the tissue level. Therefore, circulating TSH determination is considered the most accurate parameter to diagnose a disorder of thyroid function. Several defects are known to be associated with the disruption of such mechanism, but their intimate understanding is still limited. Over the past few years, we generated various zebrafish models that faithfully reproduce the biochemical signature described in patients with the aim to obtain insights into the specific alterations of TH feedback. CH is typically characterized by low THs and elevated TSH, but the TSH normalization requires abnormally higher L-T4 doses in several cases (e.g., *GLIS3* mutations), thus representing a challenge for clinicians. Interestingly, zebrafish knockdown model for *glis3* (glis3KD) displays thyroid dysgenesis associated with low THs and high pituitary *tshb* signal. In comparison with euthyroid and PTU-induced hypothyroid controls, glis3KD larvae require L-T4 doses of 10- and 3.5-fold higher, respectively, to fully suppress the expression of pituitary *tshb*. Intriguingly, zebrafish models for SECISBP2 (both mutant and morphant fish) are characterized by normal thyroid development, high T4 and low T3 levels and mild increment of *tshb* that require a 4-fold higher dose of L-T4 than euthyroid controls for suppression, as likely consequence of D2 activity. Even more complex scenarios emerge with mutations in thyroid hormone receptors (TRs). Zebrafish embryos expressing mutant thrb isoforms, along with those overexpressing the human TRβ2 variants (e.g. E464X), develop an enlarged thyroid gland, elevated T4 and T3 levels, and increased pituitary *tshb*, which are completely resistant to L-T4 suppression. Remarkably, the overexpression of other TRβ2 variants (e.g., R243Q) exhibits similar biochemical abnormalities, although *tshb* can be suppressed with L-T4 doses that are 5- and 3-fold higher than those required for euthyroid and PTU-induced hypothyroid controls, respectively. The specificity of TRβ2-dependent regulation of TSH expression is further validated by the absence of defects in the HPT-axis functions in all zebrafish models for RTHα, even when mutant THRA transcripts are injected at the stage of 1-2 cell embryos. However, when a mutated chimeric construct, in which the N-terminus domain of TRα1 is replaced with that of TRβ2, is overexpressed in zebrafish, the levels of *tshb* and THs appear comparable to those observed in RTHβ. In conclusion, we generated several zebrafish models faithfully reproducing the thyroid function test signatures and refractoriness to TH feedback exhibited by patients with these rare thyroid disorders. The mechanisms contributing such refractoriness are indeed variable and include alterations of TH metabolism or in the TR structures.

DOI: 10.1530/endoabs.101.PS3-20-03

## PS3-20-04

**Identification of eukaryotic translation initiation factor 4b as a novel candidate gene for congenital hypothyroidism**

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Congenital hypothyroidism (CH) is the most common endocrine disorder in neonates, but its etiology is still poorly understood. To identify novel genes, we performed whole exome sequencing in 98 CH patients not harboring known CH candidate genes. Through bioinformatic analysis, eukaryotic translation initiation factor 4B (EIF4B) was identified as the most promising candidate gene. The EIF4B gene was inherited in an autosomal recessive model, and one patient with thyroid dysgenesis carried EIF4B biallelic variants (p.S430F/p.P328L). Functional analysis was performed using morpholino (which is defined as a synthetic oligomer molecule that contains 25 DNA bases on a methylene morpholine backbone) antisense oligomers in zebrafish and CRISPR—Cas9-mediated gene knockout in mice. In zebrafish, the knockdown of eif4ba/b expression caused thyroid dysgenesis and growth retardation. Thyroid hormone levels were significantly decreased in morphants compared with controls. Thyroxine treatment in morphants partially rescued growth retardation. In mice, the homozygous conceptuses of Eif4b+/- parents did not survive. Eif4b knockout embryos showed severe growth retardation, including thyroid dysgenesis and embryonic lethality before E18.5. These experimental data supported a role for EIF4B function in the pathogenesis of the hypothyroid phenotype seen in CH patients. Our work indicated that EIF4B was identified as a novel candidate gene in CH. EIF4B is essential for animal survival, but further studies are needed to validate its role in the pathogenesis of CH.

DOI: 10.1530/endoabs.101.PS3-20-04

## PS3-20-05

**Investigating the safety and NRF2 activation of a sulforaphane-generating supplement through drinking water in mice across thyroid and other tissues**

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Background and objectives
Sulforaphane is one of the best studied Nrf2-activating compounds. In preclinical studies, it is usually administered either intravenously or via gavage. While these administration methods are efficacious in activating Nrf2 in target tissues, they have certain disadvantages: (i) they are invasive and thus not optimal from the perspective of the 3Rs (Replacement-Reduction-Refinement), notably regarding Refinement; (ii) their invasive nature may potentially affect certain molecular or

behavioral readouts; (iii) they are labor-intensive for the personnel working with the experimental animals and require proper training to avoid injury to the animals; (iv) they do not recapitulate the preferred mode of administration of drugs to humans (i.e., oral intake). An oral sulforaphane-producing supplement (Avmacol®) in the form of a pill is on the market for human use. Each pill supplies broccoli seed extract that contains the sulforaphane precursor glucoraphanin as well as an active myrosinase enzyme that converts glucoraphanin into sulforaphane in the small intestine. Studies in humans have supported that this supplement can effectively activate Nrf2 *in vivo*. The main objective of the present study was to test whether oral administration of the supplement to mice via the drinking water is safe and efficacious in activating Nrf2 in various target tissues.

Methods

First, the supplement was dissolved in water and the capacity of the resulting solution to activate Nrf2 was tested by treating cells stably transfected with an ARE-luciferase construct. Dose-dependent Nrf2 activation was consistently observed. Maintaining the solution at room temperature for up to 7 days before treating the cells had no effect on its capacity to activate Nrf2 *in vitro*. Next, male and female adult mice were treated with the supplement, which was dissolved in their drinking water. The mice had continuous access to the supplement solution, which was their only source of drinking water. The solution was changed every 2-3 days, and the mice were treated for a total of 3 months. No adverse events or altered behavior were observed during this period. The mice were then sacrificed, and various tissues were harvested for molecular and histological analyses.

Results

A mild induction of Nrf2 activity was observed in the liver and other tissues, as reflected in an increase of Nqo1 mRNA expression levels. At the histological level, no signs of tissue damage were observed.

Conclusions

These data demonstrate that administration of a commercially available sulforaphane-producing supplement to mice via the drinking water over 3 months is safe and efficacious in activating Nrf2. This method is then suitable for preclinical studies in the field of Nrf2-related research.

DOI: 10.1530/endoabs.101.PS3-20-05

## PS3-20-06

**Optimization of the spatial transcriptomics technology to explore the combined effect of a perinatal exposure to TBBPA and western diet at adult age on the unique transcriptomic signature of the different hypothalamic NUCLEI**

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The growing obesity rate is not only the result of sedentary lifestyle and Western diet, but environmental exposure to endocrine disrupting chemicals (EDCs) may also contribute to this global phenomenon. Some EDCs called obesogens target central pathways regulating food intake and energy expenditure, in particular in the hypothalamus. Indeed, this brain region is the central regulator of many functions including thyroid axis and metabolism. It consists of various nuclei, each having a unique role in regulating these functions. Organisms are especially vulnerable to EDCs during the perinatal period when hormonal signaling orchestrates the setup of endocrine and metabolic axes. In this context, we explored the combined effect of perinatal exposure to the flame-retardant tetrabromobisphenol A (TBBPA), an EDC well known to perturb thyroid hormone signaling, and high fat-high sucrose diet (HFHS, mimics Western diet) at adult age, on the hypothalamic transcriptome. We compared the responses to these treatments on two mouse strains with different metabolic and thyroid status, the C57BL/6J mice and the WSB/EiJ mice. Pregnant dams received 10 mg/kg/d TBBPA or vehicle for 4 weeks (last week of gestation through lactation). The progeny followed a HFHS diet from 2 to 6 months of age. We compared four groups for each strain: vehicle + control diet, vehicle + HFHS diet, TBBPA + control diet and TBBPA + HFHS diet. We used the cutting-edge technology of spatial transcriptomics (10X Genomics), which add a spatial localization to total transcriptome analyses. We measured the whole transcriptome activity, mapped to the relevant hypothalamic regions to identify the specific transcriptional pathways regulated in each hypothalamic nucleus. We first had to optimize this technology in order to adapt the analysis workflow to the specificity of the physiological regulations that we were looking for. This optimization step allowed us to identify different clusters which were exactly aligned with the hypothalamic nuclei identified by histology. We were thus able to identify a specific transcriptional signature for each hypothalamic nucleus. The second step was to establish a workflow to compare these transcriptional signatures between the different study groups within and between each strain. The spatial transcriptomics analysis overcomes the low-resolution of bulk RNAseq in a complex tissue-context and resolves the spatial origin of the signal as opposed to single cell RNAseq. This powerful technology allows us to identify the molecular pathways specifically affected by the different treatments in the different hypothalamic nuclei involved in the regulation of thyroid axis and metabolism. This will unravel the mechanisms by which the perinatal TBBPA exposure coupled to HFHS diet interfere with the setpoint adjustment of the thyroid axis or other hormonal pathways, and therefore alter the adult's ability to cope with metabolic challenges.

DOI: 10.1530/endoabs.101.PS3-20-06

## PS3-20-07

**Dissecting oxidation-dependent and oxidation-independent components of thyroid autoregulation**

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Objective

The autoregulatory response of thyroid follicles to excess iodine involves different steps and processes, most notably the acute inhibition of thyroglobulin (Tg) iodination called the Wolff-Chaikoff phenomenon, and the subsequent downregulation of the sodium-iodide symporter (NIS) during the so-called escape from the Wolff-Chaikoff phenomenon. The molecular mechanisms involved in these phenomena are still incompletely understood. In previous studies, we have found paradoxical autoregulatory responses in mice with altered redox signaling. Specifically, mice lacking the ubiquitous transcription factor Nrf2 that mediates the transcriptional antioxidant response show increased levels of thyroidal iodinated Tg (Tg-I) at baseline compared to wild-type (WT) mice, as well as a paradoxical increase in thyroidal Tg-I in response to iodine excess. We aimed to test the dependence of autoregulatory responses on the oxidative status of follicles.

Methods

WT and Nrf2 KO mice were treated (or not) via the drinking water for 2 weeks with N-acetyl-cysteine (NAC) that promotes scavenging of intracellular oxidants. During the second week, half of the mice were treated with excess iodine (sodium iodide 0.05%) in the drinking water (total of $8 \times 8 = 64$ mice). Mice were then sacrificed, and the thyroid, pituitary and serum were harvested for analysis.

Results

Iodine treatment increased pituitary beta-TSH mRNA levels in all mice compared to respective untreated controls. Iodine-treated Nrf2 KO mice showed significantly higher pituitary beta-TSH mRNA levels than respective WT mice; this difference was completely abolished by NAC treatment. Iodine-treated Nrf2 KO mice were also the only group in which NAC treatment did not decrease the levels of Tg-I compared to no NAC treatment. In contrast, the response of NIS to excess iodine was independent of both genotype and NAC treatment.

Conclusions

Thyroid autoregulation in response to excess iodine comprises an oxidation-dependent component (inhibition of Tg iodination) and an oxidation-independent one (NIS downregulation).

DOI: 10.1530/endoabs.101.PS3-20-07

## PS3-20-08

**Exposure to an EDC mixture disrupts thyroid function in mice in a sex specific manner**

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Background
Recent studies in France have shown a 1.4-fold increase in the incidence of congenital hypothyroidism (CH) due to gland *in situ* over the last four decades. CH was previously thought to follow a monogenic model. In recent years, however, evidence has emerged for a more complex genetic cause involving multiple genes and external factors. Our hypothesis is that environmental factors such as endocrine disrupting chemicals (EDCs) may lead to altered thyroid development and function during prenatal and postnatal life. Approximately 30 anthropogenic chemicals have been identified in American women, 15 of which are ubiquitous, including in pregnant women. A mixture of these 15 EDCs affects thyroid hormone signaling and thus early brain development in the Xenopus model. In addition, the human foetus is also exposed to sodium fluoride (NaF), which crosses the placental barrier and has been recognized as an EDC. This latter does cause a reduction in thyroid hormone secretion, but the underlying mechanism remains unknown.
Objectives
Study the effects of long-term exposure to EDC on thyroid function before mating and throughout the life of the mice.
Methods
Parental exposure two weeks before mating and offspring exposure from birth to 10 months of age to EDC mixture and EDC-NaF mixture. The thyroid phenotype was analyzed and compared with phenotype of unexposed mice, taking into account the sex difference male/female. Histological sections of thyroid glands were performed at adult stage (1 month and 10 months) to analyze tissue structures and size. Quantitative PCR was performed to look for disturbances in the expression of thyroid transcription markers, differentiation markers and oxidative stress markers.
Results
In exposed female mice to EDC-NaF, the thyroid gland was significantly 20% smaller than in non-exposed females ($P < 0.05$). In addition, increased expression of *Pax8, Nkx2-1, Foxe1, Nis, Tg, Duox2, Dio1* and *Dio2* expression was observed in the thyroid suggesting an hyperactivity of the gland ($P < 0.05$). The male thyroid gland showed a decrease in *Tpo* at 1 month and a strong increase in *Dio2* and *Nox4*, respectively by a factor of 3 and 2 ($P < 0.01$) at 10 months, indicating oxidative stress.
Conclusions
Exposure to EDC leads to long-term thyroid dysfunction with a strong difference between males and females. Actions of NaF and EDC were potentialized in female mice thyroids. Action of EDC mixture in males gave a strong impact on oxidative stress. Further studies are needed to elucidate the exact mechanism of these disturbances in two sexes.

DOI: 10.1530/endoabs.101.PS3-20-08

## PS3-20-09

**Identification of markers for thyroid signaling disruption by transcriptomic analysis in teleost fish and amphibian**

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Environmental pollution is a major concern in households and ecosystems, many of which interfere with the homeostatic balance of living systems. Endocrine disruptors affect many biological pathways including thyroid axis. The identification of Thyroid Disruptor Chemicals and of their effects on organisms is a challenge for both regulators and industry. As thyroid signaling is highly conserved in vertebrates, zebrafish and amphibian embryos are alternative models for studying both physiological regulations and disruption. We designed a transcriptomic analysis where embryos of both species are exposed to reference compounds alone or in combination with thyroid hormones ($T_3$ and $T_4$) following the Fish Embryo Test (OECD guideline, No.236) or the Xenopus Eleutheroembryonic Thyroid Assay (OECD guideline, No.248). We selected four reference compounds: Iopanoic acid, Sodium Perchlorate, Tetrabromobisphenol A and Propylthiouracil based on their different modes of action on the thyroid signaling pathway. We analyzed their transcriptomes by RNA sequencing together with ad hoc bioinformatic pipelines. Lists of differentially regulated genes are classified in several clusters, each corresponding to a type of biological response. Despite a great diversity of biological responses, differentially regulated genes can be further classified into three categories: solely chemical dependent, solely Thyroid Hormone dependent and crosstalk responses. We first found major effects with chemicals alone, but virtually no effect with THs alone in zebrafish and the opposite in Xenopus. Second, co-treatments revealed for both species potential thyroid signaling disruption. The crosstalk responses represented a significant number of patterns in all conditions. The biological processes affected are related to metabolism (mainly related to lipid and carboxylic acid metabolism) in zebrafish and cell proliferation (covering cell cycle, DNA repair and cell division processes) in Xenopus. Stratification of the datasets with system biology uncovered additional processes affected linked to nervous and immune systems. Finally, we provide a list of candidate thyroid signaling disruption markers. In conclusion, our data provide a set of genes that represent a potential list of biomarkers of thyroid signaling disruption, and the associated effects.

DOI: 10.1530/endoabs.101.PS3-20-09

# Thyroid Cancer Case Reports-2

## PS3-21-01

**A rare thyroid cancer – case report of a follicular thyroid lymphoma**

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Introduction
Thyroid and cervical nodules are a common pathology that require a complex management. However, thyroid lymphoma is a rare entity which can be challenging to diagnose. It represents less than 5% of all thyroid malignancies and no more than 2,5% of all lymphomas. We aim to report the case of thyroid lymphoma and a review of the literature.
Clinical Report
We describe the case of 63 year-old women with no relevant personal or family history that presents to our endocrine surgery unit with a quickly enlarging cervical mass over the last 4 months, causing mild compressive symptoms. No other symptoms were present. Laboratory tests showed normal thyroid function. The ultrasound revealed a 5 × 5 cm solid hypoecogenic nodule classified as EU-TIRADS 4, on the left lobe and several cervical adenopathys. Fine needle aspiration biopsy revealed a Bethesda category V – Suspicious for malignancy with small dispersed lymphocytes suggesting a small-cell non-Hodgkin lymphoma. The CT-scan evidenced right traqueal and esophageal deviation, extensive adenopathys in the III and IV cervical levels bilaterally as well as in the supra-clavicular and upper mediastinic space. Cervical Lymph nodule biopsy confirmed the diagnosis of folicular lymphoma with low grade follicular pattern CD20+, CD10+ BCL6+, BCL2+, CD3-, CD5- CD23 e Ciclina D1-. The patient was referenced to the onco-hematology unit and started chemotherapy. The surgical team kept an expectant strategy for worsening of the compressive symptons.
Discussion and Conclusion
The follicular lymphoma is a rare thyroid lymphoma, representing only 12% of all thyroid lymphomas. Is is staged based on the Ann Arbor criteria. The presence of autoimmune chronic lymphocytic thyroiditis is associated with increased risk. Our case is classified as a IIE and no previous diagnosis of Hashimoto's thyroiditis was known. Unlike other forms of thyroid cancer, surgery is not the first line of treatment and should be reserved for selected cases. Treatment lies mainly in a chemotherapy regimen with or without radiotherapy. The optimal treatment remains controversial given the limited evidence available and lack of large prospective trials. The treatment for thyroid lymphoma and prognosis is broadly divided according to the lymphoma subtype.

DOI: 10.1530/endoabs.101.PS3-21-01

## PS3-21-02

**A case of bilateral chylothorax after a total thyroidectomy and left sided modified radical neck dissection for papillary thyroid cancer**

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Introduction
Chylous leaks after neck dissections occur in 1-2% of patients. However, bilateral chylothorax after neck dissections for thyroid carcinoma is extremely rare. We report the case of a bilateral chylothorax after a total thyroidectomy and left sided modified neck dissection for thyroid carcinoma and management of chylous leak.
Case Report
A 39-year-old patient presented with a two-week history of a palpable tumor measuring 3 × 3 cm in the left thyroid lobe. Cytology was suspicious for papillary thyroid carcinoma. Ultrasound (US) guided fine-needle aspiration biopsy of the lymph node lateral to the left carotid artery was performed, which revealed a metastasis of papillary thyroid cancer. The patient underwent a total thyroidectomy, left sided central and lateral neck dissection. In the morning of the second postoperative day (POD), left side of the neck was swollen and an ultrasound examination suspected a hematoma. During surgical revision no free fluid was present and only edema of tissues was found. However, the patient complained of dyspnea and chest discomfort in the afternoon of the same day. Because pulmonary embolism was suspected, a computed tomography of the chest was performed, which revealed massive bilateral pleural effusions. Bilateral thoracic drainages were inserted and about 1,5 L of milky white fluid were evacuated. The patient had a total parenteral nutrition for the following eight days. The patient was re-operated on POD 5 due to persisting chylous thoracic discharge. The thoracic duct was prepared in a length of 5 cm and a yellow spot with a diameter of 3 x 2 mm was found on the front side, from which there was no outflow of lymph during the operation. The thoracic duct was ligated. The thoracic drains were removed on POD 10 and a regular diet was started again. The patient was discharged on POD 11. Histology showed a papillary thyroid carcinoma stage pT4N1b. Two months after surgery postoperative external beam radiotherapy to the neck and superior mediastinum with 50.5 Grays was performed and five months after surgery the patient had ablation of thyroid remnant with 103 mCi of radioiodine. The patient has no evidence of disease 14 years after initial treatment of thyroid carcinoma.
Conclusions
A bilateral chylothorax is a potentially life-threatening condition. A bilateral chylothorax was diagnosed with a computed tomography of the chest and treated with bilateral thoracic drainage, a total parenteral nutrition and ligature of damaged thoracic duct.

DOI: 10.1530/endoabs.101.PS3-21-02

## PS3-21-03

**Autonomous thyroid hormone production in metastatic follicular cancer – a case report**

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Introduction
Differentiated thyroid cancer (DTC) accounts for 90% of all thyroid cancers. The majority of DTC have a favourable outcome, but 5–10% of the patients will develop metastatic disease. Functioning metastases of differentiated thyroid cancer are very rare and their pathogenesis is still not fully understood.
Case report
We present the clinical course and management of a 71-year-old woman diagnosed with subclinical non-autoimmune hyperthyroidism. A nodule in the left thyroid lobe with high risk ultrasound features was found and fine needle biopsy (FNB) was performed with a cytological result of Bethesda category 3. Considering the ultrasound characteristics of the nodule the patient was referred for a lobectomy. The surgical treatment was postponed by the patient for personal reasons. Three months later, a MRI study was done for back pain and disseminated bone metastases were found, initially interpreted as being with pulmonary origin because of a coexisting pulmonary mass. Subsequently, a PET/CT and a bone biopsy with immunohistochemical staining suggested thyroid origin. The repeated FNB and cytology of the same nodule yielded a follicular lesion – Bethesda category 4. The bone findings were interpreted as metastatic thyroid cancer and a total thyroidectomy was done. The pathology report described invasive follicular thyroid cancer. The patient was referred for radioiodine ablation. Suppressed TSH and high FT4 were found just before the intake of radioiodine despite the discontinuation of oral levothyroxine for one month. The post-therapeutic whole body scan (WBS) showed multiple foci of increased uptake in the bones. The hyperthyroidism persisted after the radioiodine ablation. The patient underwent a second radioiodine therapy after rhTSH stimulation. The post-therapeutic WBS revealed persistence of the foci with increased uptake in the skeleton. A reduction of T3 and T4 was observer three months later. A third radioiodine therapy is scheduled.
Conclusion
Functional metastatic thyroid cancer is a rare phenomenon and must be considered when evaluating thyroid cancer with concurrent hyperthyroidism. The presented case illustrates the diagnostic and therapeutic challenge posed by autonomous hormone production from metastatic FTC.

DOI: 10.1530/endoabs.101.PS3-21-03

## PS3-21-04

**Papillary thyroid carcinoma arising within a mature ovarian cystic teratoma: a case report**

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Introduction
Mature cystic teratoma is the most common germ cell tumor of the ovary and is known to be benign tumors containing well-differentiated cells from three germ layers. However, malignant transformation of the various tissue components within mature ovarian teratomas, such as the occurrence of papillary thyroid carcinoma, is extremely rare.
Case Report
During a check-up, a 62-year-old asymptomatic woman, was found to have a 5-cm hyperechoic lesion with an internal cystic component in her left ovary, suspected to be a mature teratoma. Consequently, a total hysterectomy with bilateral salpingo-oophorectomy was performed, during which an unruptured thin-walled ovarian tumor was removed. Gross pathology revealed an uniloculated solid-cystic lesion with smooth serosa. The solid part showed homogenous soft tan appearance with hair. There was no ascites or papillary projection adhesion between tumor, omentum, and uterus. The pathology report showed a 2-cm classic subtype papillary thyroid carcinoma arising in a 4.7-cm mature teratoma, without lymphovascular invasion and no involvement of the ovarian surface. Her thyroid ultrasound and thyroid function tests were normal. There was no evidence of metastasis on imaging. The role for a total thyroidectomy and radioactive iodine ablation was discussed. After reviewing the pathology and confirming the absence of aggressive behavior in the papillary thyroid carcinoma, shared decision-making was made not to pursue further management. Following a one-year follow-up, there was no recurrence or metastasis of the tumor.
Conclusions
We presented a case report describing the rare occurrence of incidentally discovered papillary thyroid carcinoma arising in a mature ovarian teratoma. Currently, there is a lack of consensus on postoperative management. After a careful evaluation to determine the aggressive behavior of the ovarian tumor and to exclude metastasis, the option of not undergoing thyroidectomy and radioactive iodine ablation may be considered.

DOI: 10.1530/endoabs.101.PS3-21-04

## PS3-21-05

### Massive thrombosis of the internal jugular vein by a thyroid gland carcinoma

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Objectives
The purpose of our study is to describe the management of the a neoplastic internal jugular vein thrombosis secondary to a vesicular thyroid gland carcinoma that was not accessible through a cervical approach.
Materials and methods
We described the case of a vesicular thyroid gland carcinoma that resulted in an enormous neoplastic thrombosis of the internal jugular vein that was managed in our department using a cervico-thoracic approach.
Results
A 64-year-old female was referred to our department for a right thyroid gland nodule. It was classified as EU TIRADS V at the ultrasound and was associated to clinically and radiologically suspicious lymph nodes. Peri-operatively, we noted a thyroid gland mass was indurated at palpation. It also infiltrated the internal jugular vein massively. The latter invasion was located beyond the sternal notch and its resection was juged as not accessible using a cervical approach. Frozen-section examination confirmed a vesicular thyroid gland carcinoma. Thus, we performed a total thyroidectomy, with a bilateral central and lateral neck dissection that included the II, III and IV neck lymph nodes sectors. Since the right jugular vein was invaded by a thrombus that reached the level of the superior mediastinum, we performed a manubriotomy to reach the totality of the thrombosis and to ensure a carcinological and total resection of the invaded portion of the internal jugular vein. No post-operative complications were recorded and the patient received radioactive iodine treatment.
Conclusion
A neoplastic invasion of the internal jugular vein by a differentiated thyroid gland carcinoma is a very rare occurrence and is associated to a worse prognosis. The pre-operative diagnosis of such an occurrence is important in order to plan its management modality and the surgical procedure.

DOI: 10.1530/endoabs.101.PS3-21-05

## PS3-21-06

### Metastasis to the thyroid gland: a rare etiology of thyroid nodules associated with malignant neoplasms

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Background
Non-thyroid metastases to the thyroid (NTMs) are rare, representing approximately 1.4%-3% of cases among malignant thyroid tumors.
Methods
A research of anatomopathological and cytological reports was carried out, from the years 2008 to 2023 of patients with NTMs, previously carried out in the Department of Pathological Anatomy at a tertiary hospital. Only two patients were found. Aims: we describe the clinical presentation, the demographic profile, the prognosis and the forms of treatment of NTMs.
Case reports
We describe two cases of secondary neoplastic involvement of the thyroid. The first case, female, 82 years old, history of primary hypothyroidism, systemic arterial hypertension, type 2 diabetes mellitus, breast cancer treated with mastectomy 39 years ago, as well as left nephrectomy for clear cell renal carcinoma 28 years ago. During oncological follow-up, she presented metastases to the pancreatic stump, supraclavicular lymph node on the left, as well as the appearance of two thyroid nodules on the left in a cervical ultrasound examination, classified as TIRADS-3. Thyroid aspiration puncture (FNA) was performed, suggesting secondary involvement due to renal neoplasia. The second case, male, 59 years old, diabetic and smoker for 80 pack years, diagnosed with supraglottis squamous cell carcinoma 4 years ago, treated with cordectomy, already with multiple metastatic pulmonary foci, presented 3 years after diagnosis with complaints of hoarseness and cervical bulging due to large thyroid nodule on the right shown on computed tomography, whose FNA showed poorly differentiated carcinoma with a basaloid pattern.
Conclusion
the appearance of thyroid nodules in patients with a history of malignant neoplasms should prompt investigation of a possible metastatic focus, aiming to reduce the morbidity and mortality that accompanies the underlying disease.

DOI: 10.1530/endoabs.101.PS3-21-06

## PS3-21-07

### An innovative way of administration of radioactive iodine in an 11 years' old girl with intellectual disability after total thyroidectomy for differentiated thyroid cancer

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Differentiated thyroid cancer (DTC) in children and adolescents is a rare disease, however its incidence is rising worldwide, rendering it the most common pediatric endocrine neoplasia, representing 3% of all pediatric malignancies. Total thyroidectomy is the treatment of choice in pediatric DTC aiming a more recurrence-free and disease-free survival. Based on the presence of local or distant metastases, $^{131}$I radioiodine treatment is quite often required post-surgery. The radioiodine $^{131}$I is shallowed in a single capsule and is quickly absorbed in the gastrointestinal tract to enter the bloodstream. It is then concentrated to the iodine avid residual thyroid and metastatic tissue to fully eliminate the disease and decrease the risk of recurrence. An 11-years' old girl with intellectual disability and a palpable neck mass was referred to our hospital for further investigation. Thyroid ultrasound revealed a solid, hypoechoic nodule of 34 × 17 × 21 mm in size, in the right thyroid lobe with calcifications, accompanied by Infiltrated local lymph nodes. The ultrasound-guided fine needle aspiration (FNA) confirmed the presence of papillary thyroid cancer (PTC), BETHESDA VI. The patient underwent a total thyroidectomy with central and bilateral lymph node dissection and the pathology showed classic PTC with infiltration of 20 of the 54 excised lymph nodes. Therefore, higher-intensity treatment with $^{131}$I radioiodine (RAI) was indicated. Due to the patient's history of intellectual disability with behavioral difficulties and denial in swallowing, the success of iodine treatment with oral administration was doubted. A multi-disciplinary team (MDT) meeting, consisting of pediatric endocrinologists, nuclear radiologists, gastroenterologists, surgeons and anesthesiologists, concluded to gastroscopy-guided RAI administration as the most effective way for RAI treatment. The patient was sedated and the iodine capsule 45mCi $^{131}$I was inserted via endoscope by the gastroenterologist to the stomach. The procedure was completed without iodine diffusion in the local environment. No further complications were recorded, and the patient was discharged after 24 hours. 7 days-post treatment whole body scan showed the

expected iodine accumulation in the thyroid bed. Herein we describe for the first time in children an alternative way of RAI administration with endoscopy in patients with intellectual disability treated for advanced DTC. In our case this method was carried out successfully with a favorable outcome.

DOI: 10.1530/endoabs.101.PS3-21-07

## PS3-21-08

**Epidural metastases revealing differentiated thyroid cancer: a case report**

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Introduction
Follicular thyroid cancer (FTC) is the second most common type of differentiated thyroid cancer (DTC). It is more likely to metastasize to the bone compared to papillary types, primarily through blood spread. Bone involvement is seen in 6-12% of FTC cases, with the spinal column being the most affected area. However, spinal metastases most often appear in the late stages, making their presence as an initial revelation of the disease extremely rare.
Case report
A 58-year-old woman presented the neurosurgery department with complaints of low back pain and severe right leg pain and numbness for 6 months. Hypoesthesia was noted on the right S1 dermatome during physical examination. Computed tomography showed an osteolytic heterogeneous tumor involving the S1 vertebral body. The spinal MRI showed osteolytic lesions hypointense on T1-weighted images and heterogeneous hypo- and hyperintense on T2-weighted images with marrow replacement of the S1 vertebral body, extending into the epidural space. Lumbar biopsy was performed. Histopathological and immunohistochemistry studies confirmed the diagnosis of FTC. The patient underwent decompressive radiotherapy followed by total thyroidectomy and bilateral mediastinal-recurrent lymph node dissection. Pathological examination revealed follicular carcinoma. She was subsequently treated with iodine-131 ablation.
Conclusion
Spinal metastasis unveiling FTC is exceptionally uncommon. However, this diagnosis should be considered, particularly in cases where routine cancer screening fail to identify the primary tumor s site. Furthermore, imaging modalities for thyroid evaluation should be included in the diagnostic approach

DOI: 10.1530/endoabs.101.PS3-21-08

## PS3-21-09

**Papillary thyroid cancer (PTC) Coexisting with thyroid tuberculosis: about cases**

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Introduction
Association of Thyroid tuberculosis with thyroid cancer is a very rare entity. To the best of our knowledge, only six cases of thyroid TB and papillary thyroid cancer have been reported in the literature. The purpose of our work is to present the diagnostic and therapeutic modalities of this association.
Methods
Retroceptive study conducted on 4 patients followed and treated for papillary thyroid carcinoma associated with thyroid tuberculosis between 2019-2023.
Results
All our patients were women. The average age was 50 years. They all consulted for anterior neck swelling. History of diabetes and dysthyroidism in the family were noted in 1 case. There were none of the common TB symptoms such as low fever, fatigue, night sweats, emaciation or loss of appetite. None of the 4 patients had any history of pulmonary or extrapulmonaryTB. A clinical examination revealed multinodular goiter in 3 cases. There was no palpable lymphadenopathy in the neck. Thyroid function tests showed an euthyroidism state in all cases. Thyroid B-mode ultrasonography revealed a multinodular goiter in 3 cases eutirads IV, and a single nodule located in the left thyroid lobe in 1 case Eutirads IV. The chest X-ray was normal in all cases. A total thyroidectomy was performed in one time associated with central neck dissection. The intraoperative histological evaluation revealed papillary cancer. The final diagnosis was established by definitive histopathological examination. The histopathological examination of the dissected cervical lymph nodes showed the absence of TB, and metastasis. There were no post-operative complications. RadioIodine therapy and quadritherapy antituberculosis was prescribed in all cases. During the subsequent regular follow-up examinations there were no signs of disease recurrence.
Conclusion
Association of tuberculosis with thyroid papillary carcinoma is a very rare and implicated the possible role of mycobacterial infections in the tumorigenesis of PTC. Diagnosis of this association requires histological examination, which is usually made postoperatively. Further accumulation of cases and experience in the future would improve the diagnosis and treatment strategies of this entity.

DOI: 10.1530/endoabs.101.PS3-21-09

## PS3-21-10

**Atypical metastasis of follicular thyroid carcinoma**

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Introduction
Primary cancers most likely to metastasize to the mandible. We report a case of mandibular metastasis of follicular thyroid carcinoma.
Case Report
A 68-year-old patient with gingival lesions that invaded the mandible. The mandibular tumor occurred two years after a papillary thyroid carcinoma treated by total thyroidectomy. Pathological examination of a gingival sample revealed metastasis of papillary thyroid cancer. The gingival and mandibular lesions disappeared four months after radioiodine therapy. After 20 months of follow-up, we found no sign of recurrence.
Discussion – Conclusion
If follicular thyroid carcinomas metastasize hematogenously, papillary carcinomas will rather remain intrathyroidal or will give rise to lymph node metastases. Very few cases of mandibular metastases from papillary thyroid carcinoma are reported in the literature. Metastatic papillary tissue could arise from aberrant thyroid embryological remains. Mandibular metastases from papillary thyroid carcinoma should be included in the list of differential diagnoses of tumors of the oral region. The survival of the patient depends on the early diagnosis and treatment.
Key word
follicular thyroid carcinoma, mandibular metastasis.

DOI: 10.1530/endoabs.101.PS3-21-10

# Diagnosis of Thyroid Cancer-2

## PS3-22-01

**Ultrasonographic features predicting lateral cervical lymph node metastases in patients with papillary thyroid microcarcinoma**

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Background
Papillary thyroid microcarcinoma (PTMC) is characterized by its favorable prognosis and potential for active surveillance (AS) as a management option. However, the presence of cervical lymph node (LN) metastasis, especially lateral LN metastasis, significantly impacts both management and prognosis. This study identified predictors of lateral LN metastasis by analyzing pre-operative ultrasonographic findings alongside clinicopathological factors.

Methods
A retrospective review of medical records was conducted for patients with PTMC who underwent surgery at Chonnam National University Hwasun Hospital between 2004 and 2013. This is a case-control study that compared patients with lateral LN metastasis to age and sex-matched patients without LN metastasis.
Results
The study included 90 PTMC patients with lateral LN metastasis (N1b) and 268 age and sex-matched patients without LN metastasis (N0). Structural recurrences of 4.4% (4/90) were observed in the N1b group only. The N1b group exhibited a higher frequency of upper lobe tumor location as compared to the N0 group. A higher proportion of non-parallel shape was observed in the N1b group than the N0 group (80.0% vs. 66.0%, $p = 0.013$). In multivariate analysis, independent risk factors for lateral LN metastasis included extra-thyroidal extension (ETE), multiplicity, upper lobe tumor location, and non-parallel shape.
Conclusions
Lateral cervical LN metastasis is a significant risk factor for structural recurrence in PTMC patients. Detailed ultrasound examinations, evaluation of tumor location, number, orientation, and the presence of ETE, are crucial in accurately predicting lateral LN metastasis. These assessments can help guide the decision between active surveillance and immediate surgery in patients with PTMC.

DOI: 10.1530/endoabs.101.PS3-22-01

## PS3-22-02

**Fine needle aspiration cytology in the diagnosis of thyroid nodules**

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Introduction
Thyroid nodules are a frequent and mostly benign pathology. Failure to recognize a cancer remains a major concern for any physician confronted with this pathology. Fine needle aspiration cytology (FNAC) is the key to diagnosis. The aim of our study was to describe the results of cytological examination in determining the histological nature of thyroid nodules.
Methods
We conducted a cross-sectional, retrospective, and descriptive study, spread over a 5-year period from January 2016 to December 2020.
Results
The median age of the 200 patients was 46 years. Female predominance was evident, with a sex ratio of 0.09. All our patients underwent FNAC followed by surgical excision. FNAC was non diagnostic in 8 cases (4%) and benign in 53 cases (20.50%). It revealed atypia of undetermined significance in 33 cases (16%) , a follicular neoplasm in 45 cases (21.50%) and a malignant suspicion in 47 cases (22.50%). FNAC was malignant in 22 cases (10.5%). Pathological examination showed malignancy in 115 cases. FNAC has an overall sensitivity of 84% and a specificity of 71.6% in predicting thyroid nodules diagnosis.
Conclusion
Combining clinical and ultrasonographic criteria with cytological results improves the sensitivity of thyroid carcinoma screening.

DOI: 10.1530/endoabs.101.PS3-22-02

## PS3-22-03

**Cost-effectiveness of diagnosis by ultrasound for asymptomatic thyroid cancer in south korea**

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Background
Thyroid cancer can be detected in early stage using ultrasonography, but there are also questions about the necessity of screening tests due to its relatively high survival and low recurrence rate compared to other cancers. In this study, a cost-effectiveness analysis of thyroid cancer was conducted for better patient selection with cases diagnosed by ultrasound, as well as cases diagnosed through the presence of symptoms.
Methods
For the analysis, Markov decision chain model were used. The post-diagnosis process for patients followed the guidelines recommended by the Korean Thyroid Association. Recurrence rates and death rates were analyzed based on 25,000 patients from our institution. The cost calculations for diagnosis and treatment followed the regulations set by the South Korean Ministry of Health and Welfare. Deterministic and probabilistic sensitivity analyses were performed to account for uncertainty in the model's variables.
Results
The average cost of diagnosis and treatment for patients diagnosed with asymptomatic thyroid cancer using ultrasound was ₩2,730,997 for 5 years and ₩3,970,652 for 10 years after diagnosis. In the case of patients diagnosed based on symptoms, the average cost was ₩3,970,652 for 5 years and ₩5,116,628 for 10 years. In sensitivity analysis, the cost range for patients diagnosed using ultrasound was ₩2,661,955 to ₩2,758,116, while for patients diagnosed based on symptoms, it ranged from ₩3,785,588 to ₩3,877,687 for 5 years. The maximum incremental cost was ₩1,215,732. A slight increase was observed in the maximum incremental cost between patients diagnosed using ultrasound and those diagnosed based on symptoms for 10 years, at ₩1,274,846 (₩3,901,609-₩4,025,078 for patients diagnosed using ultrasound and ₩5,060,500-₩5,176,455 for patients diagnosed based on symptoms).
Conclusion
Diagnosis using ultrasound for asymptomatic thyroid cancer offers advantages in terms of cost-effectiveness when compared to symptom-based diagnosis in Korea. Cost-effectiveness can vary due to differences in the cost of diagnosis and treatment in each country, making it essential to establish an optimized thyroid screening strategy for a specific population.

DOI: 10.1530/endoabs.101.PS3-22-03

## PS3-22-04

**The value of acr, european, korean and ATA ultrasound risk stratification systems combined with ras mutations for detecting thyroid carcinoma in cytologically indeterminate and suspicious for malignancy thyroid nodules**

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Objectives
The aim of this study was to evaluate the diagnostic value of four commonly utilized ultrasound (US) RSSs (the American College of Radiology [ACR], European [EU], Korean [K] TI-RADSs and American Thyroid Association [ATA] US-based RSS criteria) in combination with activating point mutations of the RAS genes (NRAS, HRAS, and KRAS) for detecting thyroid carcinoma in cytologically indeterminate and suspicious for malignancy thyroid nodules.
Methods
We retrospectively analyzed cytologically "indeterminate" and "suspicious for malignancy" thyroid nodules which underwent US, molecular testing and surgery between September 1, 2018, and December 31, 2023. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC, 95% confidence interval [CI]) was calculated.
Results
100 cytologically "indeterminate" and 24 "suspicious for malignancy" thyroid nodules were analyzed. Compared to the four US-based RSSs alone, diagnostic value of the four US-based RSSs combined with RAS mutations did not significantly improved (cytologically "indeterminate", AUC [95% CI] 0.6 [0.5-0.7] and 0.6 [0.5-0.7], respectively, $p = 0.70$; cytologically "suspicious for malignancy", AUC [95% CI] 0.7 [0.5-0.9] and 0.8 [0.6-0.9], respectively, $p = 0.23$).

Conclusions
Diagnostic value of the main four US-based RSSs (ACR, EU, K, ATA) was not improved in conjunction with the evaluation of RAS mutations for preoperative risk stratification of cytologically indeterminate thyroid nodules.

DOI: 10.1530/endoabs.101.PS3-22-04

## PS3-22-05

**Efficacy of machine learning model in predicting thyroid malignancy risk**

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Objectives
Thyroid nodules are common and mostly benign, but around 7-15% of them account for thyroid cancers. In recent years, a significant increase in the detection rate of thyroid nodules has been observed. Ultrasonography (US) has become a valuable tool in thyroid nodules malignancy risk assessment, however, it might lead to thyroid cancer overestimation and unnecessary biopsies. The aim of our study was to create a machine-learning prognostic model for thyroid nodules malignancy risk assessment, based on sonographic characteristics, fine-needle aspiration biopsy (FNAB) and blood tests results, verified by histopathology reports. The intention was to compare the accuracy of thyroid malignancy detection with the best prognostic model and EU-TIRADS reporting system.
Methods
This was a prospective study of machine learning thyroid malignancy risk prediction. We analyzed data of patients who underwent thyroidectomy due to the results of preoperative US and FNAB cytology reports. 422 patients with nodules (193 malignant) were included. They were split into training and test sets (3:1). The models were developed on the training set and evaluated on the test set. A variety of algorithms were explored.
Results
Due to its explainability and good performance, a random forest was selected as a base model. Test set ROC AUC at 71%. In our study, the model was better correlated with thyroid nodule malignancy than the EU-TIRADS reporting system. Statistically significant thyroid nodule risk factors were microcalcifications ($P<0.001$) and age (lower age correlated with greater malignancy risk, $P<0.001$). The larger the anteroposterior dimension, the greater the risk of malignancy ($P<0.001$). Otherwise, the larger the longitudinal dimension ($P<0.001$) or transverse dimension ($P<0.001$), the lower the risk of thyroid nodule malignancy. Using statistically important features the new index of anteroposterior-to-longitudinal dimension was created (ROC AUC 66% (95%CI 62.0 – 71.0)). The created index is easy to use and therefore may serve as a help for clinicians.
Conclusions
In the era of thyroid nodule overdetection there is a need for accurate approaches in thyroid malignancy prediction. The model created by our group is characterised by good accuracy and might be more effective than systems based only on sonographic characteristics. However, future development of these data-driven methods is limited by sample size.

DOI: 10.1530/endoabs.101.PS3-22-05

## PS3-22-06

**Diagnostic and prognostic roles of perioperative F18-FDG PET/CT for differentiated thyroid cancer**

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Introduction
F-18 FDG PET/CT has a valuable role in the initial workup for solid tumors, including lung adenocarcinoma and head and neck squamous cell carcinoma. However, its role in the staging of thyroid carcinomas remains contentious. Present guidelines advocate for the deployment of F-18 FDG PET/CT in instances of recurrence detection, particularly in patients demonstrating elevated serum thyroglobulin levels with a concurrent negative radioiodine whole body scan. Routine F-18 FDG PET for initial workup is not recommended. The present study aims to elucidate the diagnostic accuracy and prognostic implications of employing perioperative F-18 FDG PET/CT in individuals newly diagnosed with differentiated thyroid cancer (DTC).
Methods
We retrospectively analyzed perioperative F-18 FDG PET/CT scans of 49 patients with newly diagnosed DTC from January 2018 to June 2021 in our institute. The clinicopathologic and demographic characteristics were recorded. Imaging findings were compared with clinical follow-up and histopathologic results. Each patient's status at the end of follow-up was classified according to the dynamic risk stratification.
Results
The comprehensive patient cohort exhibited a sensitivity, specificity, and diagnostic accuracy of F-18 FDG PET/CT at 90.0%, 83.3%, and 87.5%, respectively. Within the subset presenting a ATA high-risk of recurrence ($n = 36$), these parameters were observed at 92.9%, 87.5%, and 91.7%. Among the cohort with negative F-18 FDG PET/CT findings ($n = 18$), a substantial 83.3% manifested an excellent response by the end of follow-up, with none experiencing a structural-incomplete response. Conversely, of those with positive F-18 FDG PET/CT results ($n = 31$), merely 9.7% achieved an excellent response, whereas 77.4% were classified with a structural-incomplete response by the end of the follow-up. The risk of incomplete response was significantly elevated in patients with positive FDG PET/CT results ($P < 0.0001$).
Conclusions
Perioperative F-18 FDG PET/CT demonstrates both diagnostic accuracy and prognostic value in patients newly diagnosed with DTC, advocating for its consideration in the clinical decision-making process.

DOI: 10.1530/endoabs.101.PS3-22-06

## PS3-22-07

**Predicting extrathyroidal extension (ETE) of differentiated thyroid carcinoma (DTC) preoperatively by using ultrasonography (US)**

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Objective
Neck US is essential in the preoperative endocrinological evaluation of malignant thyroid nodules and determining surgical approach. Extrathyroidal extension (ETE) in DTC is a significant risk factor for recurrence. Our study aim is to assess ultrasonographic features predicting minor ETE.
Method
In our two-center prospective study, we recorded US videos of DTC nodules adjacent to the capsule, with no thyroid parenchyma between the capsule. Experienced sonographers evaluated these videos for ETE-related sonographic characteristics (ERSC) blindly to pathology results. The relationship between these features and ETE presence was evaluated.
Results
Mean age of the study group was $45 \pm 14$ years, mean nodule diameter was 14.3 $\pm$ 9.7 mm. ETE was found in 17 out of 140 DTC nodules (12%)., Eighty-nine percent of nodules were papillary thyroid carcinoma (PTC), with 76% of these being classic subtype PTC. Six nodules had non-invasive follicular thyroid neoplasm with papillary-like nuclear features, six had invasive encapsulated follicular variant papillary carcinoma, and three had follicular carcinoma. The frequencies of ERSC and their association with ETE presence are detailed in Table 1.

PS3-22-07

**Table 1.** Diagnostic Performance of Sonographic Findings of Minor ETE

| ETE-related sonographic characteristics | ETE positive nodules ($n = 17$) | ETE negative nodules ($n = 123$) | P | PPV | NPV | Sensitive % | Specificity % | Diagnostic Accuracy % |
|---|---|---|---|---|---|---|---|---|
| Capsular disruption | 13 (77%) | 5 (4%) | <0.001 | 72% | 97% | 77% | 96% | 94% |
| Contour bulging | 11 (65%) | 38 (31%) | 0.006 | 22% | 93% | 65% | 70% | 69% |
| Nodule vascularity extending beyond the thyroid capsule | 3 (18%) | 1 (0.8%) | <0.001 | 75% | 90% | 18% | 99% | 89% |
| Ratio of contact area with adjacent capsule (contact diameter/nodule diameter) | <12.5%: 0 12.5-25% : 8 (47%) 25-37.5%: 6 (35%) >50%: 3 (18%) | <12.5%: 19 (14%) 12.5-25% : 63 (51%) 25-37.5%: 36 (29%) >50%: 5 (4%) | 0.0053 | 18%* | 92%* | 18%* | 96%* | %86* |
| Replacement of adjacent strap muscle | 9 (53%) | 1 (0.8%) | <0.001 | 90% | 94% | 53% | 99% | 94% |

ETE: extrathyroidal extension, PPV: positive predictive value, NPV: negative predictive value *results of the ratio of the contact area with the adjacent capsule being >50%.

Conclusion

It has been determined that the features with the highest PPV for detecting ETE during US, are replacement of adjacent anterior neck muscles and vascularity of nodules extending beyond the thyroid capsule. The ratio of contact area with the adjacent capsule and contour bulging are the features with the lowest PPV. The highest NPV and the highest diagnostic accuracy were observed in capsular discontinuity and replacement of adjacent anterior neck muscles.

DOI: 10.1530/endoabs.101.PS3-22-07

## PS3-22-08

### [18F]fluorocholine positron emission tomography/computed tomography characterization of hyperfunctioning and hypofunctioning benign thyroid nodules

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Aim/Introduction

[$^{18}$F]fluorocholine (FCH) positron emission tomography/computed tomography (PET/CT) has gained an important role in the preoperative diagnosis of patients with primary hyperparathyroidism (pPHP). In these patients, thyroid nodules are frequently found on preoperative ultrasound. FCH PET/CT provides a high negative predictive value to reliably rule out cancer in thyroid nodules with low uptake. However, more than half of benign thyroid nodules have been reported to have high uptake of FCH. The aim of our study was to evaluate the characteristics of FCH PET/CT uptake in hyperfunctioning and hypofunctioning benign thyroid nodules.

Materials and Methods

A retrospective study was performed in patients with pPHP who were investigated by FCH PET/CT and concomitantly diagnosed with thyroid nodules larger than 1 cm on thyroid ultrasound. [$^{99m}$Tc]pertechnetate scan was performed in all patients, and the benign nature of the nodules was confirmed by either high uptake or by fine-needle aspiration biopsy in patients with low uptake. Neck PET/CT acquisitions were performed 10 (early) and 60 (late) minutes after injection of 1.3 MBq/kg FCH, and the maximum standardized uptake value (SUV max) of the nodules was measured.

Results

Thirty-four patients (30/88.2% female, mean age 66.9±9.3 years) with 34 (15/44% hypofunctioning, 19/56% hyperfunctioning) thyroid nodules were included. Mean early SUVmax was 5.2±1.8; no difference in SUVmax was detected between hyperfunctioning and hypofunctioning thyroid nodules (mean, 4.9±1.8 and 5.6±1.7, respectively, $P = 0.28$). The mean late SUVmax was 4.3±1.8; no difference in SUVmax was found between hyperfunctioning and hypofunctioning thyroid nodules (mean, 4.3±2.1 and 4.4±1.3, respectively, $P=0.42$). A trend towards a positive but non-significant correlation ($r = 0.3$, $P=0.09$) of thyroglobulin level (mean 37.5±38.3 µg/l) with SUVmax in the early acquisition phase was observed, but no further statistically significant correlation of early or late SUVmax with TSH (mean 1.32±0.82 mIU/l), free $T_4$ (mean 15.3±2.01 pmol/l), free $T_3$ (mean 4.92±0.73 pmol/l), thyroid antibodies (median thyroid peroxidase antibodies level 86.53±253.52 kU/l, median thyroglobulin peroxidase level 37.9±103.9 kU/l) or nodule volume (mean 4.48±4.89 mL) was observed.

Conclusion

Hypofunctioning and hyperfunctioning thyroid nodules do not differ significantly in FCH uptake. The biochemical parameters of thyroid function and autoimmunity do not correlate with FCH uptake in benign thyroid nodules. Further studies should identify those characteristics of benign thyroid nodules that contribute to high uptake on FCH PET/CT scans to increase the specificity of FCH PET/CT in detecting malignant thyroid nodules.

DOI: 10.1530/endoabs.101.PS3-22-08

## PS3-22-09

### Predictive value of quantitative indexes of FDG pet in the evaluation of thyroid nodules

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Backgrounds

With increasing use of $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) in the clinical field, thyroid nodules are one of the common incidental findings. It is reported that about one third of these nodules are proven to be malignant nodule. In this study, efficacy of quantitative PET indexes in predicting the cytopathology of thyroid nodules was evaluated.

Methods

A total of 338 patients with thyroid nodules detected on FDG PET from 2019 to 2024 were retrospectively enrolled. The nodules were further examined with fine needle aspiration (FNA). Quantitative PET indexes such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), were measured in the thyroid nodule. Their efficacies in predicting the cytopathologic nature of the nodule by FNA were evaluated along with other clinical variables such as age, gender, size, thyroid function test values.

Results

SUVmax and TLG of thyroid nodule were statistically significant in predicting cytopathology based on Bethesda scoring system ($P$ value of 0.001 and 0.005, respectively). SUVmax and TLG tended to increase as the category escalated, with highest value in the malignant category (Bethesda VI). SUVmax was able to discriminate the group with higher risk of malignancy (Bethesda IV, V, VI) from lower risk group (Bethesda II, III) with optimal cutoff value set as 4.8 (sensitivity 70.5, specificity 64.2, AUC 0.718). Other variables were not statistically significant in predicting malignant groups.

Conclusion

Quantitative indexes of FDG PET are well associated with Bethesda scoring system in thyroid nodules. Measuring SUVmax of thyroid nodule on FDG PET can aid in predicting the cytopathology and thus guiding the optimal treatment for the patient.

DOI: 10.1530/endoabs.101.PS3-22-09

## PS3-22-10

**Characteristics of bethesda 3 and 4 thyroid nodules: bethesda grey area**

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Aim
To investigate the clinical, paraclinical and histological characteristics of Bethesda 3 and 4 nodules and determine their malignancy rate.
Methods
We conducted a retrospective descriptive study including 52 patients who underwent surgery for Bethesda class 3 and 4 thyroid nodules at the ENT department over a 7-year period (2016-2022).
Results
The mean age of our patients was 51 years, with a ratio of 0.13. The most common presenting symptom was an anterior neck swelling in 34 cases. Cervical ultrasound showed a solitary nodule in 60% of cases and multiple nodules in 40% of cases. The most suspicious nodule was subjected to ultrasound guided fine-needle aspiration and an EU-TIRADS classification ranging from 3 to 5. Cytological examination classified the samples as Bethesda 3 in 59.6% and Bethesda 4 in 40.4%. Total thyroidectomy was initially indicated in 30.7% of cases, while lobectomy was performed in 69.3% of cases. Completion thyroidectomy was performed in 15 cases. Lymph node dissection was indicated for 32 patients. The final histological examination confirmed malignancy in 28.8% of cases, accounting for 33.3% of patients classified as Bethesda 3 and 33.3% of patients classified as Bethesda 4. Incidental papillary microcarcinomas were found in 21% of cases, and lymph node metastasis in 9.6% of cases.
Conclusion
The Bethesda classification was introduced to standardize the cytological evaluation of thyroid nodules and guide therapeutic decisions. The significant variability in the malignancy rate of Bethesda class 3 and 4 nodules necessitates the establishment of precise strategies to optimize their management.

DOI: 10.1530/endoabs.101.PS3-22-10

## PS3-22-11

**Complexities and challenges in the diagnosis and management of borderline thyroid tumors**

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Introduction
Borderline thyroid tumors, characterized by their indistinct status between benign and malignant forms, pose significant diagnostic and therapeutic challenges. This study aims to elucidate effective diagnostic and management strategies for these tumors, enhancing patient outcomes.
Methods
Our study employed a retrospective analysis design, spanning several years, focusing on various borderline thyroid tumors, including Hyalinizing Trabecular Tumors, Well-Differentiated Tumors of Uncertain Malignant Potential, Follicular Tumors of Uncertain Malignant Potential, and Non-Invasive Follicular Thyroid neoplasm with Papillary-like Nuclear Features. The subjects were patients diagnosed with these conditions, treated in a specialized medical setting. The study assessed diagnostic imaging techniques, fine needle aspiration, and surgical interventions. Outcome measurements included accuracy of preoperative diagnosis, surgical outcomes, and recurrence rates. Preliminary analyses focused on the effectiveness of current diagnostic and management practices.
Results
The study's main outcomes revealed varying levels of diagnostic accuracy and treatment effectiveness for different types of borderline thyroid tumors. Specific results, including confidence levels and *P*-values, will provide insights into the efficacy of current diagnostic and therapeutic approaches.
Conclusions
The study concludes that a multidisciplinary approach incorporating advanced diagnostic methods and tailored surgical interventions is crucial for optimal management of borderline thyroid tumors. These findings emphasize the need for ongoing research and adaptation of best practices in the field.

DOI: 10.1530/endoabs.101.PS3-22-11

# Clinical Thyroid Cancer Research-3

## PS3-23-01

**Real-life levothyroxine intake with possible restriction of absorption in thyroid cancer patients**

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Objective
In patients with thyroid carcinoma, optimal thyroid hormone control, often with the aim of suppressing TSH levels, remains an essential component of tumor therapy. However, there are several factors, such as the use of pantoprazole or gastrointestinal diseases, showing a negative impact on absorption of levothyroxine and resulting in higher levothyroxine doses to achieve the desired levels.
Methods
We established a questionnaire with 16 variables on possible influencing factors (including pantoprazole intake, gastrointestinal diseases) in daily routine and initially analyzed the responses of 30 thyroid cancer patients.
Results
Of the 30 patients aged between 22-83 years (median 54 years; 15 female, 15 male) who were on levothyroxine for 0.5-39 years (median 4.5 years), 18 patients reported suffering from concomitant diseases, 20 confirmed regular additional medication intake, of whom 7 were taking pantoprazole and 2 taking iron supplements in parallel. 15 patients indicated a time interval of additional medication intake between 0-12 hours (median 1.5 h). 15 respondents reported suffering from occasional and/or regular gastrointestinal complaints, 3 patients had undergone gastrointestinal tract surgery.
Conclusions
The preliminary evaluation of our study on the presence of factors influencing the absorption of levothyroxine in thyroid cancer patients shows that the majority of patients have potentially influencing variables that are often hardly taken into account in routine clinical practice and can lead to a less than optimal setting. The treating physicians should be aware of such influencing factors.

DOI: 10.1530/endoabs.101.PS3-23-01

## PS3-23-02

**Thyroid nodules in children**

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Background
Thyroid nodules are frequently diagnosed in adults. In children, although rare, varying between 1% and 5%, they are more likely to be malignant, hence the importance of early diagnosis and rapid management. The aim of our study was to describe the features of nodular goiters in children and to plan their management.
Methods
We conducted a retrospective study including children who underwent surgery for thyroid nodules from 2001 to 2020.
Results
Thirty children underwent surgery. The average age of our patients was 16 years with a clear predominance of females (sex ratio: 0.07). The major complaint was the appearance of an anterior cervical swelling in 87% of cases. The surgical procedure concerning the thyroid gland consisted in a loboisthmectomy in 14 patients and a total thyroidectomy in 16 patients, one of whom had an ectopic thyroid (ad-hyoid). Total thyroidectomy was performed in one step in 14 cases and in two steps, in the presence of papillary carcinoma at the final histological examination of the loboisthmectomy parts in 2 cases. The diagnosis of papillary carcinoma was confirmed after definitive histological examination in 5 cases (16,7%). They were put on suppressive opotherapy and referred for radioactive iodine therapy. The outcome was favorable in all patients. The mean follow-up was 32 months in benign cases and 12 months after the last course of radioactive iodine therapy in malignant cases.
Conclusion
Of the 30 patients identified, 16,7% had thyroid carcinoma. Thyroid nodules in children should be evaluated by ultrasound and fine needle aspiration to evaluate the

risk of malignancy. This will ensure an appropriate surgical management.

Key-words
Thyroid nodule, Child, Thyroid neoplasms
DOI: 10.1530/endoabs.101.PS3-23-02

## PS3-23-02

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Safa Nefzaoui[1], Ameni Amri[2], Imen Zoghlami[1], Dorra Chiboub[1], Nadia Romdhane[1], Ines Hariga[1] & Chiraz Mbarek[1]
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Key-words
Thyroid nodule, Child, Thyroid neoplasms
DOI: 10.1530/endoabs.101.PS3-23-02

## PS3-23-03

**DICER1-associated thyroid tumour families**

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Background
Pathogenic germline *DICER1* variants cause an hereditary cancer predisposition syndrome with a variety of manifestations: in addition to first described pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumours, individuals may also develop benign (multinodular goiter MNG, cystic nephroma.) or malignant tumours as differentiated thyroid carcinoma from infancy to adolescence and early adult.
Objective
To investigate the specificity of DICER1-families exhibiting only thyroid manifestation across generations.
Methods
We report a series of 6 families whose diagnosis for *Dicer1* syndrome was done on childhood MNG or in index patient or in siblings presenting benign or malignant thyroid tumours only. We screened DNA and thyroid tissue samples from probands and families' members for *DICER1* variants or associated variants using Next Generation Sequencing tools for these families with thyroid specific manifestations of the syndrome. Patients' and family history, clinical examination, thyroid ultrasonography, thyroid function were evaluated and related to histology and somatic variant analysis when available.
Results/Discussion
In all cases the *DICER1* pathogenic variants associated to thyroid manifestation have been already described in the literature or located in the enzymatic site of the enzyme. Additional somatic variants were identified for half of the families. We discuss the management of these families in the context of international recommendations and genetic counselling.

DOI: 10.1530/endoabs.101.PS3-23-03

## PS3-23-04

**Distinguishing follicular-type thyroid carcinomas from their benign counterparts, a study of 104 consecutively resected and needle-biopsied tumors**

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Background
Distinguishing the malignant follicular-type thyroid neoplasm (FTTN), i.e. follicular carcinoma (FTC) and follicular-variant papillary carcinoma (FVPTC), from their benign counterparts, i.e. follicular adenoma (FA) and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), is challenging without surgical resection. As thyroid nodules are increasingly diagnosed asymptomatically, an accurate way of confirming benignity of FTTN can reduce excessive diagnostic surgery.
Objective
to determine the clinical, demographic, sonographic, and cytologic differences between the malignant and benign FTTN
Methods
We retrospectively reviewed the medical records of all patients who underwent thyroidectomy in a tertiary-care hospital in Singapore from 2010 to 2016, and identified all FTTN that underwent fine-needle aspiration cytology preoperatively. We matched the sonographic images of the FTTN to their histologic diagnosis. Blinded to the diagnoses, two head and neck radiologists independently reviewed the images and classified them per Thyroid Imaging Reporting and Data System (TIRADS) of European Thyroid Association (EU), American College of Radiologists (ACR), and American Thyroid Association (ATA). A head and neck pathologist confirmed the diagnosis of NIFTP. Univariate analysis, multivariate logistic regression, and area under the receiver-operator-curve (AUC) are measured to determine the diagnostic performance of the distinguishing features.
Results
A total of 46 FTC including 8 oncocytic variants, 14 FVPTC, 10 NIFTP, and 34 FA are identified. The patients are predominantly female (77%), Chinese in ethnicity (63%) with a mean age of 47; 9.8% were hyperthyroid (TSH $\leq$ 0.45mIU/l). Comparing the benign *vs* the malignant FTTN, there is no statistically significant difference in cytologic category, with Bethesda III being predominant in all tumor types (53-72%). Neither is there a difference in age, sex, ethnicity, tumor size, nuclear atypia, individual sonographic features except for hypoechogenicity. Hyperthyroidism is more common in FA than other FTTN (20.7% vs. 3.8%, $P = 0.05$). Intermediate or high suspicion are associated with malignant FTTN in all 3 sonographic risk stratification systems ($P < 0.01$). Multivariate logistic regression of hyperthyroidism and EU-TIRADS, ACR-TIRADS, ATA, respectively, shows that the AUC of distinguishing benign from malignant FTTN differs only slightly (0.74-0.75 for radiologist A, 0.80-0.81 for radiologist B).
Conclusions
EU-TIRADS, ACR-TIRADS, or ATA perform equally well in differentiating malignant from benign FTTN. Hyperthyroidism further improves the diagnosis of FA. However, Bethesda III cytology can be common. Molecular testing and continual improvement in feature identification are needed to avoid diagnostic surgery.

DOI: 10.1530/endoabs.101.PS3-23-04

## PS3-23-05

### Clinicopathological characteristics and outcome of patients with poorly differentiated thyroid cancer-a single center experience

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Background
Poorly differentiated thyroid cancer (PDTC) is a rare entity which originates from follicular epithelial cells and ranks between differentiated (DTC) and anaplastic TC (ATC).
Objective
Evaluation of clinicopathological characteristics and outcome in a series of 23 PDTC patients.
Methods
Retrospective analysis of histologically confirmed PDTC patients treated in the department of Endocrinology at Evangelismos Hospital from 2009 to 2023.
Results
23 patients (13 males) with mean (±SD) age at diagnosis 63.6±12 years were identified. 6/23 (4 females) were diagnosed with PDTC during progression of papillary DTC. Clinicopathological characteristics are reported in the following table. Patients with de novo PDTC ($n$ = 17,11 males) had mean age 65.8±12.7 years and median tumor length (Q1,Q3) 5.5 cm (3.6,7.5). 5/17 (29.4%) underwent concurrently total thyroidectomy + lymph-node (Ln) dissection. After I131 treatment thyroid bed uptake was observed in 10/14 (71.4%), 1 patient had no uptake, 3/14 (21.4%) retained I131 in distant lesions while for 3 data missed. 11/17 patients had a median (Q1,Q3) follow up period of 4 years (2,6) during which 4/11 had Ln dissection, all were treated with I131, 3/11 underwent external beam radiotherapy (EBRT) and 1/11 received tyrosine kinase inhibitors (TKIs). At last evaluation 7/11 patients had progressive disease (PD), 3/11 had stable disease (SD), 1 had complete remission (CR). 2/17 patients died 3 years after diagnosis. Both were males, >55 years old at diagnosis and stage IVB. Patients with diagnosis of DTC had mean age 57.5±8.7 years, 50% were ATA high risk and 3/6 had an aggressive variant. All were treated with I131 and had uptake in Ln and lung metastasis. PDTC occured 1-13 years after DTC diagnosis. 2 patients were reoperated, 3 were treated with I131, 4 received (TKIs) and 4 underwent (EBRT). 3 patients died on average 9.6 years after DTC diagnosis.
Conclusions
PDTC is a rare and challenging entity. I131 treatment may be partially effective and other therapeutic modalities may be needed.

| | Clinicopathological characteristics | At diagnosis of de novo PDTC | At diagnosis of DTC |
|---|---|---|---|
| AJCC/TNM 8th | Stage I-II | 13(76.4%) | 3(50%) |
| | Stage III-IV | 4(23.5%) | 3(50%) |
| Primary tumor stage | pT1-T2 | 4(23.5%) | 2(33.3%) |
| | pT3-T4 | 13(76.4%) | 4(66.6%) |
| Extrathyroidal extension | Macroscopic | 7(41.17%) | 2(33.3%) |
| | Microscopic | 3(17.6%) | 1(16.7%) |
| Invasion | Lymph nodes | 5(29.4%) | 2(33.3%) |
| | Vascular | 10(58.9%) | 2(33.3%) |
| BRAFV600E mutation | Positive | 1(5.9%) | 2(33.3%) |
| | Negative | 5(29.4%) | 3(50%) |
| | Unknown | 11(64.7%) | 1(16.7%) |
| Ki-67 (%) | <10% | 0 | 1(16.7%) |
| | 10-20% | 6(35.3 %) | 0 |
| | >20% | 2(11.7 %) | 0 |
| | Unknown | 9(52.9 %) | 5(83.3%) |
| Distant disease | Lungs | 3(17.6 %) | 1(16.7%) |
| | Lungs + Liver | 1(5.9%) | 0 |
| | Lungs + Brain | 1(5.9%) | 0 |

DOI: 10.1530/endoabs.101.PS3-23-05

## PS3-23-06

### Overweight as a risk factor for concomitant thyroid cancer in graves' disease patients: a retrospective study

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Background
Graves' disease (GD) is an autoimmune disorder that causes hyperparathyroidism with the presence anti-TSH receptor antibodies (TR-Ab). The incidence of concomitant thyroid cancer in GD varies, and there is no clear consensus on the risk factors. Limited studies have examined the relationship between thyroid cancer in GD and obesity. The aim of the study was to identify the risk factors for concurrent thyroid cancer in GD patients and evaluate the impact of overweight on cancer risk in GD.
Methods
This retrospective study analyzed the medical charts and pathology reports of 122 patients with GD who underwent thyroid surgery from May 2010 to December 2022 at OOO Hospital. The height and weight of patients were measured prior to surgery to calculate their body mass index(BMI). Overweight was defined as BMI of 25 kg/m$^2$ or higher according to the WHO.
Results
The majority (88.5%) underwent total or near-total thyroidectomy. In multivariate analysis, overweight shows higher risk of malignancy (OR, 3.108; 95% CI, 1.196-8.831; $P$ = 0.021). The lighter gland weight and lower preoperative TR-Ab were found to risk factors for malignancy in GD.
Conclusions
Overweight patients have higher risk of thyroid cancer than non-overweight patients. Postoperative hypothyroidism was the most common postoperative complication in GD patients and the majority of cases were transient. Further research is needed to elucidate the underlying mechanisms and the effect of overweight on thyroid cancer risk in GD patients in general population.

DOI: 10.1530/endoabs.101.PS3-23-06

## PS3-23-07

### Early detection and management of hypocalcaemia after total thyroidectomy

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Background
After total thyroidectomy Hypocalcemia is the most frequent complication. Serum calcium levels are reliable only 48–72 hours postoperatively. Now a day's measurement of iPTH as an early predictor of postoperative hypocalcemia is practiced in many centers.
Objective
To share our experience for the diagnosis and treatment of post-operative transient and permanent hypoparathyroidism after total thyroidectomy and to assess the ability of iPTH in predicting postoperative hypocalcemia.
Methods
Our total number of patients is 84. iPTH level was measured on 1st postoperative day. Patients were followed up for 1 to 6 months post operatively. Unfortunately, we lose a big number of our patients from follow up.
Results
iPTH on the first postoperative day equal to or less than 15 pg/ml were found to be norm calcemic. iPTH less than 10 pg/ml were disturbed parathyroid hormone metabolism. Hypocalcemia is the most common complication recognized in patients of total thyroidectomy. Around 50% of patients who suffer from transient hypoparathyroidism develop permanent hypoparathyroidism. Measurement of iPTH after surgery is the mainstay of early identification tool in our country though combining postoperative iPTH and serum calcium level can entail more accurate result.

Conclusion
Measurement of iPTH on first postoperative day allow accurate prediction of postoperative parathyroid function in 99% cases. Morbidity due to hypoparathyroidism can be reduced by appropriate dose adjustment of supplemental therapy & lifelong follow up. Till date calcium & vitamin D is the drug of choice.

DOI: 10.1530/endoabs.101.PS3-23-07

## PS3-23-08

**Association between diabetes mellitus and molecular profile in papillary thyroid carcinoma patients: a retrospective study**

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Introduction and objectives
Papillary Thyroid Carcinoma (PTC) accounts for 84% of all thyroid cancers and has shown increasing incidence in recent decades. The greater availability of imaging studies and fine needle cytology partly explains this phenomenon. However, the rising incidence of advanced-stage thyroid carcinomas suggests that this trend may be partially due to a change in the biological behaviour of these tumours. In recent years, evidence has grown indicating that diabetes mellitus (DM) may increase the risk of thyroid neoplasms, with this increased risk estimated at 25% in a prospective cohort study with a 10-year follow-up. The mechanisms involved in this increased risk remain uncertain, with several studies pointing to genetic factors, altered TSH secretion, lesions secondary to oxidative stress, hyperinsulinism, changes in adipokine secretion, and increased secretion of pro-inflammatory factors. This study aims to analyze the impact of diabetes mellitus on the molecular profile of PTC.
Methods
A sample of 45 patients with PTC who underwent thyroidectomy between 2014 and 2015 and screened for mutations in the *BRAF*, *RAS*, and *pTERT* genes was characterized for the prevalence of DM, thyroid function, BMI, lipid profile, and cardiovascular comorbidities at the time of PTC diagnosis. Insulin resistance was estimated by calculating the Glucose-Triglyceride Index (GTI).
Results
At diagnosis of PTC, the sample composed of 40 women and 5 men, presented an average age of 55 ($\pm$14.4) years; 22% of the patients were diagnosed with diabetes; 51% with arterial hypertension; 49% with dyslipidemia; 16% with hypothyroidism. The average BMI was 29.3 ($\pm$5.3) $kg.m^{-2}$, with 32% overweight, 41% obese, and 16% fulfilling the WHO 1999 criteria for metabolic syndrome. Insulin resistance was considered when GTI $>$ 4.68 and was present in 36% of the sample. Additionally, patients with DM presented a higher prevalence of metabolic syndrome (60%) and insulin resistance (60%; average GTI 4.72 $\pm$ 0.40). The molecular profile of PTC revealed that the most mutated gene was BRAF (64%), and although not statistically significant, the prevalence of $BRAFV600E$ was higher in the patients with DM (OR 2,667 [0.492; 14.461], $P$ 0.256).
Conclusion
Despite the limitations of this study, such as its retrospective nature and the small sample size, there appears to be a positive association between the prevalence of DM and the $BRAF^{V600}$ mutation. The next step will involve increasing the sample size to validate the findings of this study.

DOI: 10.1530/endoabs.101.PS3-23-08

## PS3-23-09

**Thyroid cancer associated with hashimoto thyroidits : pronostic outcomes**

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Aim
The aim of our study was to examine the association between lymphocytic thyroiditis and papillary thyroid carcinoma.
Materials and methods
It was a retrospective covering patients who had total thyroidectomy on papillary carcinoma, between 2012 and 2023.
Results
Our study involved 24 patients with a median age of 50.17 years [31-73], predominantly female and a sex ratio of 0.6. Preoperative fine needle aspiration was performed in 10 (41.6%) patients and found Bethesda 6 in 3, Bethesda 5 in 4 and Bethesda 4 in 3. All our patients underwent surgery. Loboisthmectomy or total thyroidectomy was recommended on the basis of extemporaneous examination. The final anatomopathological examination showed papillary carcinoma in all patients, associated with lymphocytic thyroiditis in 8 (33.3%). The tumor was classified as pT1a in 25% of cases, pT1b in 25% of cases, pT2 in 29.2% of cases and pT3a in 20.8% of cases, with lymph node status pN0 in 15 patients, pN1a in 6 patients and pN1b in 3 patients. In patients with lymphocytic thyroiditis, 3 patients had capsular invasion, 2 patients vascular emboli, 4 patients had pN0 lymph node status, 3 patients pN1a and 1 patient pN1b. None of these factors was associated with lymphocytic thyroiditis according to Fisher's exact test with a $P >$ 0.05.
Conclusion
The link between autoimmune lymphocytic thyroiditis and papillary carcinoma is a controversial topic in the literature. Some studies have considered thyroiditis to be a protective factor against papillary carcinoma progression.

DOI: 10.1530/endoabs.101.PS3-23-09

## PS3-23-10

**Abstract withdrawn**

DOI: 10.1530/endoabs.101.PS3-23-10

# Translational Thyroid Cancer Research-2

## PS3-24-01

**HIF-1$\alpha$ inhibitors could successfully inhibit the progression of differentiated thyroid cancer**

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Hypoxia-inducible factor (HIF)-1$\alpha$ plays an important role in cancer progression. In various cancers, including thyroid cancer, overexpression of HIF-1$\alpha$ is related to poor prognosis or treatment response. However, few studies have investigated the role of HIF-1$\alpha$ inhibition in thyroid cancer progression. We evaluated the utility of the HIF-1$\alpha$ inhibitor IDF-11774 *in vitro* utilizing two thyroid cancer cell lines, K1 and BCPAP. Both cell lines were tested to elucidate the effects of IDF-11774 on cell proliferation and migration using soft agar and invasion assays. Here, we found that a reduction of HIF-1$\alpha$ expression in BCPAP cells was observed after treatment with IDF-11774 in a dose-dependent manner. Moreover, cell proliferation, migration, and anchorage-independent growth were effectively inhibited by IDF-11774 in BCPAP cells but not in K1 cells. Additionally, invasion of BCPAP but not K1 cells was controlled with IDF-11774 in a dose-dependent manner. Our findings suggest that promoting the degradation of HIF-1$\alpha$ could be a strategy to manage progression and that HIF-1$\alpha$ inhibitors are potent drugs for thyroid cancer treatment.

DOI: 10.1530/endoabs.101.PS3-24-01

## PS3-24-02

**Non-genetic risk factors for thyroid cancer an umbrella review of evidence**

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Background
The incidence and mortality rates of thyroid cancer have shown a significant upward trend. However, the current understanding of risk factors associated with thyroid cancer remains ambiguous and inconclusive. This umbrella review aims to identify the relationships between non-genetic risk factors and thyroid cancer incidence, while also evaluating the quality and validity of existing evidence.
Methods
This umbrella review was performed according to the PRISMA guidelines. We performed a comprehensive search of PubMed, Embase and the Cochrane Database of Systematic Reviews to identify relevant meta-analyses or systematic reviews that explored non-genetic risk factors associated with thyroid cancer. We extracted the estimated summary effect and their 95% confidence intervals through fixed or random effects models of each meta-analysis. The methodological quality of the included meta-analyses was evaluated using the AMSTAR2 tool, while the quality of evidence was assessed using the GRADE framework. Furthermore, we conducted subgroup analyses by gender and performed sensitivity analyses to assess the robustness of the findings.
Results
We included 52 articles and identified 78 non-genetic risk factors with 109 associations, which belong to eight broad categories: dietary factors, behavioral factors, anthropometric indices, chemical exposure, radiation exposure, drug history, preexisting medical status and reproductive factors. Out of these associations, 66 were found to have a significant relationship with thyroid cancer risk. An increased risk of thyroid cancer was associated with excessive uptake of dietary nitrates and vitamin D, higher urinary iodine level, overweight, larger height, exposure to pesticides, diagnostic X-ray and $I^{131}$, drug history with flavonoids and fertility drugs, reproductive factors including multiparity, history of hysterectomy, short pregnancy interval and older age at menopause, and medical conditions such as diabetes, breast cancer and organ transplantation. Whereas the uptake of dietary iodine and fish, tea, alcohol, smoke, weight loss, breastfeeding, oral contraceptive and pernicious anemia were identified to be inversely related to this risk. However, the majority of the included studies (65%) were categorized as "Critically Low" based on the AMSTAR2 assessment, and most of the evidence (86%) was of weak quality since the classification by GRADE was very low. Moreover, subgroup and sensitivity analyses showed that more risk factors were found in women, and most associations were consistent with the overall analysis.
Conclusion
Our findings indicate that several modifiable factors play essential roles in the primary prevention of thyroid cancer. However, the overall quality of evidence supporting these associations is currently limited. Future research, particularly well-conducted prospective studies with high quality, is necessary to determine causal relationships between these factors and thyroid cancer.

DOI: 10.1530/endoabs.101.PS3-24-02

## PS3-24-03

**Thyroid differentiation score (TDS) can differentiate between malignant and benign thyroid neoplasms**

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The thyroid differentiation score (TDS), calculated on the expression levels of 16 thyroid metabolism and function genes, was introduced by the Cancer Genome Atlas to characterize the differentiation status in papillary thyroid carcinoma (PTC). TDS has been reported to be significantly lower in BRAF-like than in RAS-like PTCs. Nevertheless, scanty data are available about TDS in either other malignant cancers or in benign thyroid nodules. The aim of the present study was to analyze TDS in a cohort of differentiated thyroid cancer (DTCs) and benign thyroid neoplasms. In particular, TDS was calculated in 40 PTCs, 8 follicular thyroid cancers (FTCs), 1 oncocytic cancer, 5 non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTPs), 18 follicular adenomas (FAs), 11 oncocytic adenomas and 6 nodular hyperplasia. Expression of 16 thyroid function genes (DIO1, DIO2, DUOX1, DUOX2, FOXE1, GLIS3, NKX21, PAX8, SLC26A4, SLC5A5, SLC5A8, TG, THRA, THRB, TSHR and TPO) and of the housekeeping gene TBP was studied by using a target RNA expression panel. Reads were normalized through DESeq2 R package and log2(gene/TBP) transformed and TDS was obtained extracting the mean of the 16 genes analyzed. Overall, the TDS was significantly lower in DTCs compared to benign neoplasms ($P = 0.0001$). Interestingly, the TDS of FTCs was significantly lower than that of FAs ($P = 0.004$). Considering only nodules that were cytologically classified in Bethesda indeterminate categories III and IV (15 DTCs, 35 benign), the TDS was significantly lower in malignant compared to benign neoplasms ($P = 0.004$). ROC curves identified the TDS $\leq$-0.53 as the best threshold to differentiate between malignant and benign nodules ($P = 0.002$), with a sensitivity of 55%, specificity of 85%, positive predictive value of 64%, negative predictive values of 76%. Among PTCs, tumors with either BRAF or TERT mutations showed a lower TDS compared to tumors without BRAF or TERT mutations ($P = 0.001$). On the other hand, no significant correlations were found between TDS and clinical or prognostic features of DTCs. In conclusion, we have shown for the first time that TDS in DTCs is lower compared to benign thyroid neoplasms, suggesting that the multistep progression from benign to malignant forms involves dedifferentiation. This finding may be useful preoperatively in both the differential diagnosis of cytologically indeterminate nodules and the selection of the best surgical approach.

DOI: 10.1530/endoabs.101.PS3-24-03

## PS3-24-04

**Comparison of mutational profiles between papillary thyroid microcarcinoma with central neck lymph nodes and without central neck lymph nodes**

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Background
If the prognosis of papillary thyroid microcarcinoma(PTMC) is favorable, when the central lymph node metastasis is suspected with active surveillance without surgery, it is advisable to comteplate surgery. Therefore, this study investigate the gene mutations involved in central lymph node metatstasis in papillary microcarcinoma.
Methods
DNA was obtained from the primary tumor tissues of of 36 PTMC with those of central neck lymph nodes metastasis and 29 PTMC without central neck lymph nodes. We compared whole exome sequencing profiles of two groups.
Results
BRAF mutations were identified 26(72.2%) of 36 PTMC with central neck lymph nodes metastasis. 15(51.7%) of 29 PTMC without central neck lymph nodes metastasis had BRAF mutations, and this results does not have statistical significance($P > 0.05$). However, TERT-promoter mutations were identified in 31(86.1%) of 36 PTMC with neck lymph nodes metastasis and this results showed statistical significance($P < 0.05$) comparing with 7(24.1%) of 29 PTMC without neck lymph nodes metastasis.
Conclusion
TERT-promoter mutations have significant relations with lymph nodes metastasis in PTMC. If we obtain the identification of TERT-promoter mutations through cytology, a more precise treatment can be established.

DOI: 10.1530/endoabs.101.PS3-24-04

## PS3-24-05

**Potential influence of MIR-204-3P on ETS-1 protein expression in papillary thyroid carcinoma**

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Objectives
ETS-1 (E26 transformation-specific) is a transcription factor associated with the progression of carcinomas of various origins. Its expression in PTC is poorly described, and the findings are controversial. This study aimed to describe ETS-1 protein expression in papillary thyroid carcinoma (PTC) and to evaluate the potential influence of miR-204-3p on the ETS-1 protein expression in PTC since the bioinformatic analysis revealed that miR-204-3p shares a seed sequence with the 3'-untranslated region (3'UTR) of ETS-1 mRNA.
Methods
Immunohistochemistry was performed to evaluate ETS-1 protein expression in 77 routinely prepared archival tissue sections of PTC, of which 55 had surrounding nonmalignant thyroid tissue (NMT). Quantitative RT-PCR (qPCR) was utilized to quantify ETS-1 mRNA and miR-204-3p levels of expression in matched snap-frozen PTC and adjacent NMT.
Results
In the immunohistochemical examination, 76 out of 77 PTC samples displayed positive staining for ETS-1 protein, observed in either the nucleus or the cytoplasm, or in both. Conversely, among 55 NMT, ETS-1 protein exhibited positive staining in 39 samples, found predominantly in the nucleus. Considering the total IHC score, there was an increase in ETS-1 protein expression in PTC compared to the surrounding tissue ($P < 0.05$). However, there was no difference in its mRNA levels between PTC and matched NMT ($P > 0.05$). The levels of miR-204-3p expression showed lower values in PTC compared to their levels in paired NMT ($P < 0.05$). Furthermore, the complementary binding between miR-204-3p and ETS-1 mRNA was predicted by bioinformatic analysis and model prediction. Therefore, decreased levels of miR-204-3p in PTC may be the cause of elevated levels of ETS-1 protein, contributing to PTC progression.
Conclusions
ETS-1 mRNA may have been complementarily bound by miR-204-3p in thyroid tissue, which may result in down-regulated ETS-1 protein levels.

DOI: 10.1530/endoabs.101.PS3-24-05

## PS3-24-06

**Molecular profiling of advanced thyroid cancer: characterizing tumors for targeted treatment**

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The rise of mutation-based systemic therapies for individuals with advanced thyroid cancer has underscored the significance of molecular profiling in patient care. Although next-generation sequencing (NGS) gene panels are accessible to clinicians, there is no consensus on the optimal approach to testing. This multicenter study investigates whether mutational profiling of advanced thyroid cancers can inform decisions about targeted therapies. Patients with advanced thyroid cancer from 10 different centers within an integrated Spanish Health Care Region are intended for inclusion in this study. We analyzed clinically derived molecular profiling using either NGS directly or a multistep testing approach. Data on clinicopathologic features and treatments were gathered by reviewing electronic medical records. The OncoKB framework served as the basis for categorizing molecular alterations according to their actionability levels. Patients with an actionable alteration by OncoKB framework who had treatment with a drug targeting the alteration were categorized as receiving ''matched'' therapy. Time-to-event data were analyzed using the Kaplan–Meier method. Our analysis focuses on the molecular profiling of the initial 103 patients with advanced thyroid cancer between 2018 and 2024, drawn from five centers. This initial cohort comprised 75 cases of radioactive iodine–refractory differentiated cancers (58 papillary, 12 follicular, and 5 oncocytic), 12 poorly differentiated/high-grade, 11 anaplastic, and 5 medullary thyroid cancers. Actionable alterations were identified in 83% patients, with 49% having at least one Level 1 alteration for which an FDA-approved drug is available. BRAFV600E (38%), R*et al*terations (4%), NTRK fusions (3%), and ALK fusions (2%) comprised all Level 1 alterations. Most Level 3 and 4 alterations included mutations in NRAS/KRAS/HRAS (8%), alterations in PI3K/AKT/mTOR (8%), and BRAF non-V600E (1%). A matched therapeutic approach was employed in 29% of patients (e.g., BRAFV600E/dabrafenib +/- trametinib, RET fusion/pralsetinib, ALK fusion/Alectinib), with 11% receiving it as first-line therapy. Redifferentiation therapy was undertaken in 12% of cases, (e.g., BRAFV600E/dabrafenib +/- trametinib and NRAS/trametinib). Neoadjuvant systemic therapy was administered in 10 % of the cases, being 4% based on targeted therapies. This ongoing study examines the actionability and clinical use of molecular profiling in advanced thyroid cancer. Most patients had at least one potentially actionable mutation, with 49 % having at least one Level 1 alteration according to the OncokB framework. Our findings underscore the rationale for integrating routine NGS testing or reflex testing, encompassing BRAF, RAS, R*et al*terations, NTRK and ALK fusions, into the management of patients with advanced thyroid cancer.

DOI: 10.1530/endoabs.101.PS3-24-06

## PS3-24-07

**DNA methylation in the thyroid tumors with known gene alteration**

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Objectives
Molecular testing of thyroid tumors is increasingly being used for the diagnosis and prognosis of patients. In some cases, however, the same gene variant may be present in both benign and malignant thyroid tissue. The issue is also a different nature (aggressiveness) of carcinomas of the same genetic origin. Comparing of DNA methylation profiles of these samples could be a possible way of distinguishing these cases. Aim of this pilot study was to analyze the DNA methylation profiles of samples with a known gene variant and to find possible differences between the cohorts.
Methods
The study consisted of 48 fresh frozen thyroid tissues samples with a known molecular profile: 16 papillary thyroid carcinomas (PTCs) harboring *BRAF* V600E, 12 PTCs with *RET/PTC1* rearrangement, 12 *NRAS* Q61R (four benign nodules, four low risk neoplasms, four PTCs), and eight healthy thyroid tissues (with no genetic alteration). Extracted DNA was used for next-generation sequencing using the TruSeq™ Methyl Capture EPIC Library Prep Kit (Illumina) . Bioinformatics to compare cohorts of *NRAS* benign vs. malignant, *BRAF* indolent vs. aggressive PTCs and *RET/PTC1* indolent vs. aggressive PTCs was performed by BaseSpace MethylKit App (Illumina).
Results
Differential methylation profile was obtained by comparing the cohorts. *NRAS* carcinomas differed from benign *NRAS* nodules in CpG islands with possible influence on *RGPD8*, *RMRP* and *ANKRD7* genes, where hypermethylated CpGs were most abundant in carcinomas. Most hypomethylated CpGs were in CpG islands with possible influence on the *IHO1, ATP9B, HLA-DQB2* genes. Aggressive *BRAF* carcinomas differentiated from indolent *BRAF* thyroid carcinomas in hypermethylation of CpGs around the *SCO2, TYMP, ODF3B, DMRTA2, TRIL* genes. On the other hand, representations of a higher number of hypomethylated CpGs in the islands was not so frequent. *RET/PTC1* gene rearrangements of aggressive nature had most hypermethylated CpGs in CpG islands with occurrence of *SP9, HCN1, TMEM229A, GSG1L* genes. There were less hypomethylation sites in this cohort too.

Conclusion
In summary, differential methylation of thyroid tumors with the same genetic alteration could be a useful tool for better diagnostics and prognostics. Analysis of a lager sample set will follow.
*Supported by AZV NU21-01-00448 and MH CZ RVO 00023761.*
DOI: 10.1530/endoabs.101.PS3-24-07

## PS3-24-08

**No responsiveness of the thyroid to protective effects of melatonin against chromium-induced oxidative damage – comparison to the ovary and non-endocrine tissues**

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Objectives
Chromium (Cr) is one of the major and most detrimental heavy metal pollutant. It is classified as an endocrine disrupting chemical (EDC, endocrine disruptor) and possibly thyroid disruptor. Its main forms are hexavalent (Cr(VI)) and trivalent chromium (Cr(III)). In turn, Cr is also classified as a carcinogen, with Cr(VI) belonging to group 1 of carcinogens (carcinogenic to humans) according to the International Agency for Research on Cancer (IARC) Monographs. Although Cr(III) is recognized by IARC as group 3 agent (not classifiable as to its carcinogenicity to humans), the carcinogenic activity of Cr is thought to be due to macromolecular damage caused by reactive intermediates arising in the course of its intracellular reduction to Cr(III). The study aimed to check if and to what extent melatonin and other known antioxidants, such as indole-3-propionic acid (IPA) and 17β-estradiol, may prevent oxidative damage to membrane lipids (lipid peroxidation, LPO) caused by Cr(VI) compound, i.e., potassium dichromate (VI) ($K_2Cr_2O_7$), as well as by Cr(III) compound, i.e., chromium (III) chloride hexahydrate ($CrCl_3 \bullet 6\ H_2O$), in homogenates of two endocrine tissues, such as the thyroid and the ovary, and of two non-endocrine tissues, such as the liver and the kidney. Of note, the thyroid gland is characterized by relatively high oxidative stress.
Methods
Porcine tissue homogenates were incubated in the presence of tested Cr compounds, i.e., potassium dichromate (VI) ($K_2Cr_2O_7$) in concentrations of 0.05-10.0 mM, or chromium (III) chloride hexahydrate ($CrCl_3 \bullet 6\ H_2O$) in concentrations of 5.0-200.0 mM, with/without melatonin (5 mM) or IPA (5 mM) or 17β-estradiol (1 mM). The malondialdehyde + 4-hydroxyalkenals (MDA + 4-HDA) concentration (LPO index) was measured spectrophotometrically.
Results
Both Cr compounds caused huge concentration-dependent increase in LPO in all examined tissues. Cr(VI) compound, in concentrations of 0.1-1.25 mM or higher, significantly increased LPO in all examined tissues, but these damaging effects were not prevented by either melatonin or other antioxidants. In turn, Cr(III) compound, in concentrations of 25 mM or higher, also significantly increased LPO in all examined tissues. Neither melatonin nor other two antioxidants prevented these damaging effects of Cr(III) compound in the thyroid. However, all the antioxidants decreased Cr(III)-induced LPO in the ovary and in the kidney and, to a lower extent, in the liver.
Conclusions
Whereas melatonin exerts protective effects against Cr(III)-induced oxidative damage in the ovary, in the kidney, and in the liver, the thyroid does not respond to the antioxidative action of this indoleamine, which can be due to oxidative nature of the thyroid and relatively high level of oxidative damage in this endocrine gland observed even under physiological conditions. Neither melatonin nor other antioxidants are able to reveal protective effects against Cr(VI)-induced oxidative damage in the thyroid as well as in other examined tissues.
DOI: 10.1530/endoabs.101.PS3-24-08

## PS3-24-09

**Use of liquid biopsy in metastatic differentiated thyroid cancer: paving the way of precision management**

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Objective
Molecular profile can assist differentiated thyroid cancer (DTC) treatment at a metastatic stage. We aim at describing the clinical usefulness of a circulating free DNA "liquid biopsy" (LB) analysis in terms of informative results and actionable targets identified.
Methods
We analyzed all the LB results of locally advanced or metastatic DTC patients performed in a single referral center between January 2021 and January 2024. Cell free DNA (cfDNA) from a peripheral blood sample was analyzed with a 324 genes panel (FoundationOne®CDx) by NGS with turnaround time of about 4 weeks. The results were discussed in a dedicated molecular tumor board.
Results
A cohort of 76 DTC patients (median age 63 years, 24-88) had 86 LB samples analyzed. Most of the patients were radioiodine refractory (65/76 patients, 85.5%) including 10 patients with unresectable primary tumor. LB found sufficient cfDNA for the test in 81 samples (94.2%) form 73 patients. One or more molecular alterations were found in 42 patients (57%). The most frequent DTC molecular drivers observed were: RAS in 10 (24%, NRAS $n = 6$, KRAS $n = 1$, HRAS $n = 3$), BRAF in 2 (5%, one BRAF V600E and one BRAF insertion), KRAS and BRAF fusion in one case, RET fusion in 2 (5%), RB1 in 2 (5%), ATM, EGFR, NOTCH3, NTRK3 fusion, PTEN in 1 patient each. Mutation associated to late DTC molecular events were: TP53 in 18 patients (associated to a driver in 13 cases), TERT in 11 patients (always associated to a thyroid cancer driver), NF1 in 3 cases (always associated to a thyroid cancer driver), AKT1 in 2 patients (associated to a driver in 1 case), PIK3C2G in 1 case. Median tumor mutation burden tested on LB was 1.26 Muts/Mb (0.00-10.12). Actionable molecular targets were ESCAT1 in 4 cases, ESCAT2 in 8 cases, ESCAT3 in 7 cases. In 31 patients (42,5%) a molecular alteration known on tumor tissue was not found on LB, BRAFV600E in 20 cases. Of these 20 patients, 8 were under active systemic treatment (including 5 with anti-BRAF treatment) at the moment of LB and in 3 patients the size of the metastases was $\leq 1$ cm.
Conclusion
LB is a minimally invasive technique capable of providing rapidly a comprehensive molecular profile, opening molecular driven treatment options. BRAFV600E is frequently missed by LB in DTC, a role of systemic treatment at the moment of LB sampling and small tumor volume might play a role in this observation.
DOI: 10.1530/endoabs.101.PS3-24-09

## PS3-24-10

**Association between single nucleotide polymorphisms and disease aggressiveness in patients with papillary thyroid cancer. do we have a new diagnostic tool?**

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Papillary thyroid cancer (PTC) has one of the highest hereditary component among malignances, which was reported in numerous epidemiological studies. The association between genetic variants (SNP- single nucleotide polymorphisms) and PTC predisposition was revealed. Still, little is known about their contribution in disease stage and an outcome.

Purpose
The association of rs966423 (DIRC3), rs116909374 (MBIP), rs2439302 (NRG1) with unfavorable histopathological and clinical features was investigated in Polish population.
Material and Methods
The genotype of three variants were determined in 1582 patients with PTC (allelic discrimination assay). Next, association between each genotype and an age, TNM staging, tumor diameter, multifocality status, extrathyroidal expansion, disease recurrence was analyzed ($Chi^2$ test).
Results
The variant rs966423 showed an association with multifocality status ($P=0.0043$, after Bonferroni correction for multiple comparisons, the $P=0.047$). An association between rs116909374 and lymph node metastasis was observed ($P=0.0018$, after Bonferroni correction for multiple comparisons, $P=0.02$). The association of other clinical features with analyzed variants was not observed ($P> 0.05$).
Conclusion
Our results showed that two SNPs: rs966423 and rs116909374 were associated with some features of more aggressive course of the disease However, it requires further investigation to evaluate the usefulness of their prognostic value.

DOI: 10.1530/endoabs.101.PS3-24-10

## Hypothyroidism

### PS3-25-01

**Understanding levothyroxine dosage adjustments after bariatric surgery**

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Objectives
Bariatric surgery significantly impacts various aspects of health, including thyroid function. Despite this, there is a lack of clear data on whether patients taking levothyroxine should adjust their dosing regimen following weight loss post-bariatric surgery. Bariatric surgery alters the anatomy of the gastrointestinal tract, potentially affecting medication absorption, including levothyroxine. Procedures such as gastric bypass and sleeve gastrectomy can lead to changes in gastric pH, reduced stomach volume, and modified intestinal transit time, all of which may affect drug absorption. Therefore, immediate postoperative levothyroxine dosages may require adjustment to ensure adequate thyroid hormone replacement therapy. Understanding these changes is crucial for managing thyroid health in individuals undergoing bariatric surgery.
Methods
We investigated 30 patients ($n = 30$) with 3rd-degree obesity (BMI $> 40$ kg/m$^2$) and hypothyroidism who underwent bariatric procedures. The study population comprised mostly women; 8 out of 30 (26.7%) underwent Roux-en-Y gastric bypass, and the remaining 22 (73.3%) underwent sleeve gastrectomy. The patients were assessed for levothyroxine dosing up to 12 months after surgery. The weight reduction was up to 40% from additional weight with different variations compared to baseline.
Results
The study showed that patients who underwent gastric bypass often require higher doses of levothyroxine to maintain euthyroidism post-surgery. Compared with baseline, the absolute LT4 dose and LT4 dose/kg of ideal body weight were, on average, 20% higher 12 months after surgery. In contrast, data from patients who underwent sleeve gastrectomy indicated a decrease in absolute LT4 dose and LT4 dose/kg by up to 10-15% compared to pre-surgery levels. Factors such as rapid weight loss, altered gastrointestinal physiology, and changes in drug absorption contribute to the increased dosage requirements, which are more prevalent in the case of gastric bypass. In the case of sleeve gastrectomy, LT4 dosage is adjusted more based on weight loss, and changes in drug absorption are less evident compared with gastric bypass. Clinical guidelines for dosage adjustments take into account the type of surgery performed, the extent of weight loss, thyroid function tests, and individual patient characteristics. Close monitoring of thyroid hormone levels, along with clinical symptoms, helps determine appropriate dosage adjustments to optimize thyroid function and overall health outcomes.
Conclusion
Bariatric surgery can influence thyroid hormone metabolism and necessitate adjustments in levothyroxine dosage to maintain optimal thyroid function. Further investigations are needed to confirm thyroid hormone dose adjustments after bariatric procedures, taking into account the type of surgery performed.

DOI: 10.1530/endoabs.101.PS3-25-01

### PS3-25-02

**A national randomized placebo-controlled double-blind multicenter trial of LT4/lT3 combination therapy in patients with autoimmune hypothyroidism: T3-4-hypo trial**

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Despite normalized serum thyroid hormone levels, 10% of hypothyroid patients treated with levothyroxine (LT4) have persistent complaints, of which tiredness is the most commonly reported. This could be explained by the fact that the physiological T4/T3 ratio is not achieved with LT4 monotherapy. Studies have reported contradicting results as to whether the addition of liothyronine (LT3) is effective in relieving these persistent complaints. However, all of these studies suffer from one or more important limitations (e.g., patient selection, limited sample size, supraphysiological LT3 dose, limited follow-up time, non-validated questionnaires), hampering their interpretation. The T3-4-Hypo trial is a national, randomised, placebo-controlled, double-blind, multi-centre study in patients with auto-immune hypothyroidism and persistent complaints despite LT4 monotherapy. Patients are randomized to either LT4/lT3 combination therapy or LT4/placebo, and the primary endpoint is the ThyPRO tiredness subscale score at 52 weeks follow-up. In case of an effect, we will investigate whether effect sizes are higher in patients with genetic variations in a thyroid hormone converting enzyme (DIO2) and transporter (MCT10). Secondary analyses include effects on the most important thyroid hormone target organs including cardiovascular, metabolic, bone and neurocognitive outcomes. The first patient was enrolled in October 2022. The trial is still open for enrolment.

DOI: 10.1530/endoabs.101.PS3-25-02

### PS3-25-03

**Rapid levothyroxine absorption test: results in 143 refractory hypothyroid patients treated with oral levothyroxine**

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Primary hypothyroidism is a frequent disease and oral levothyroxine is the mainstay of its treatment. However, more than 20% of levothyroxine-treated patients fail to achieve the recommended serum TSH level with a body weight–based dose of levothyroxine. Refractory hypothyroidism is due to either malabsorption or nonadherence. In clinical practice, a levothyroxine absorption test is part of the workup of a refractory hypothyroid patient for confirming normal levothyroxine absorption or diagnosing malabsorption. This test is not standardized and published procedures differ markedly in the test dose, formulation, test duration, frequency of blood collection, analyte (total thyroxine or free thyroxine), metric (absolute or relative peak or increment, or area under the curve) and threshold for normal absorption. We analyzed 166 levothyroxine absorption tests performed in 143 refractory hypothyroid patients (109 women, 34 men, mean age 42 $\pm$ 15 years) treated with oral levothyroxine dose $> 2$ mg/kg/day for postsurgical hypothyroidism ($n = 101$) in the context of differentiated thyroid cancer ($n = 40$) or autoimmune hypothyroidism ($n = 29$). Despite a daily dose of 3.26 $\pm$ 1.18 mg/kg/day, mean serum TSH concentration was 25.7 $\pm$ 43.3 mU/l. Refractory hypothyroidism was due to *Helicobacter pylori* infection (27%), autoimmune atrophic gastritis (12%), celiac disease (2.5%), drug interference with levothyroxine absorption (27%) or nonadherence to daily treatment (10%). After an overnight fast, patients take orally their daily dose of levothyroxine (220 $\pm$ 80 mg) under the supervision of medical staff. Blood samples for total and free T4 levels were drawn before levothyroxine intake and then every two hours during 24 hours. The percentage of levothyroxine absorption was calculated by the following formula: [(peak total T4-baseline total T4) mg/dl x 10 x 0.442 x BMI / levothyroxine dose (mg/day)] with normal absorption being $> 60$%. After levothyroxine intake, the mean total (basal $= 7.66 \pm 3.22$ mg/dl, peak $9.44 \pm 3.50$ mg/dl, $P < 0.001$), and free

(basal = 12.48 ± 5.50 pg/ml, peak 15.74 ± 6.55 pg/ml, $P < 0.001$) T4 levels increased. Total and free T4 peaks were observed at 4.0 ± 2.39 and 3.96 ± 2.71 hours, respectively. A normal percentage of absorption was observed at 6 and 8 hours in 70% and 71% of the patients, respectively. The percentage of levothyroxine absorption was correlated with the levothyroxine dose (in mg/day, $P = 0.0016$; in mg/kg/day, $P = 0.0002$). Rapid levothyroxine absorption tests were well tolerated, and no patient experienced adverse cardiovascular events. In conclusion, in patients with refractory hypothyroidism (increased TSH level despite levothyroxine dose > 2 mg/kg/day) this clinical study revealed that rapid levothyroxine absorption test can be achieved via the absorption of the daily dosage of levothyroxine and the evaluation of total and free T4 concentrations over 6 hours. The test is well tolerated without cardiovascular adverse events.

DOI: 10.1530/endoabs.101.PS3-25-03

## PS3-25-04

**Riedel's thyroiditis: report of 7 patients**

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Riedel's thyroiditis (RT) is a rare, inflammatory-sclerosing disease of the thyroid gland, with dense fibrosis that replaces normal thyroid tissue and local extension to surrounding structures causing hypothyroidism and compressive symptoms. The etiology of RT remains unknown, and its treatment is still challenging in absence of guideline consensus. We report 7 patients seen in a department of Endocrinology between 2000 and 2023: 5 women and 2 men, mean age 46 (20–81) years. Patients had a slow-growing thyroid goiter (6/7) or a 3-cm hypoechogenic nodule (1/7), hypothyroidism (4/7) with anti-TPO antibodies (3/7). Serum C-reactive protein levels were increased (4/7), serum IgG4 levels were normal (4/4). A 20-year-old female presented sclerosing cholangitis treated with prednisone, azathioprine and ursodesoxycholic acid. RT was diagnosed on histological examen after thyroidectomy (2/7) or surgical biopsy (5/7). Post-operative evaluation with CT and/or 18 FDG PET scans showed heterogenous uptake of the thyroid tissue (5/7) but no extrathyroidal fibrosclerosis. Patients were treated with levothyroxine alone after thyroidectomy (2/7) or with systemic steroids (4/7), then tamoxifen (3/7) or rituximab (2/7) according to clinical and 18 FDG PET evaluation. Anti-inflammatory and immunosuppressive treatments were associated with control of the size, and a decrease of the uptake of thyroid tissue. During prednisone (1 mg/kg/day) treatment, the 81-year-old patient presented cervical tissue necrosis (past history of external cervical radiotherapy for a thyroid neoplasm 35 years earlier) and died of severe sepsis 45 days after surgery. After 2-year tamoxifen treatment, a 51-year-old woman developed pseudo-tumor of the orbits after tamoxifen withdrawal, with a significant improvement during prednisone (1 mg/kg/day) and tamoxifen (20 mg/day) combined treatment. After 4-year tamoxifen treatment, a 61-year-old woman presented a meningioma and several episodes of uterine bleeding accounting for tamoxifen withdrawal. During a mean 9-year follow-up of the patients, response of RT to medical treatment was observed, and imaging examens did not revealed extrathyroidal fibrosis. Based on the reported patients and review of the literature, first-line glucocorticoid and second-line tamoxifen treatments are indicated to control the inflammatory-fibrotic process: optimal dose and duration of treatments need further studies. In RT resistant to steroid and tamoxifen treatment, immunosuppressive molecules (rituximab, mycophenolate mofetil, azathioprine) need to be evaluated. Thyroid surgery should be limited to debulking in patients with tracheal or oesophageal compression, or is indicated in "refractory" RT with failure of medical treatment. RT has a good prognosis in most patients, but long-term follow-up is necessary to evaluate the risk of local relapse after withdrawal of medical therapy, and of the possible involvement of extrathyroidal fibrosclerosis.

DOI: 10.1530/endoabs.101.PS3-25-04

## PS3-25-05

**Autoimmune hypothyroidism incidence in a large population-based study in northeastern italy**

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Objectives
An improvement in iodine status in Veneto region has been documented in the last decade. We aimed at estimating the incidence of autoimmune hypotiroidism (AH) in the Veneto Region over the period 2013-2022.
Methods
Retrospective population-based study conducted in Veneto (4.9 million people) using the population registry, an administrative health database. Between 2012 and 2022, AH incidence was defined thank to a health-care co-payment exemption for AH or any hospital diagnosis of AH. Incident AH was defined from 2013 to 2022 to exclude prevalent cases. Standardized incidence rates (IRs) were reported by age, and sex and reported for 10,000 person-years.
Results
We identified 65,397 incident cases (IR of 13.38, IC: 13.27-13.48). The female-to male incidence ratio reached a peak in the 30–34 years age group (9.78) and a nadir in the 80–84 years age group (1.35). Overall, IR decreased from 15.86 (95% CI: 15.50, 16.21) in 2013 to 12.35 (95% CI: 12.04, 12.67) in 2022, but the reduction was significant only in females. Indeed, in females IR went from 27.26 in 2013 to 20.49 in 2022 ($P < 0.01$), *vs* a decrease in males from 4.35 in 2013 to 4.27 in 2022 ($P = 0.9$). AH IR decrease regarded especially pre-menopausal women, with a decrease in females <55 years from 37.86 (95% CI: 36.79, 38.94) in 2013 to 27.40 (95% CI: 26.44, 28.36) in 2022 ($P < 0,001$), *vs* a weaker decrease over 55 years of age, from 20.06 (95% CI: 19.13-20.99) in 2013 to 16.56 (95% CI: 15.78, 17.35) in 2022 ($P = 0.03$). In 2020, an out-of-trend decrease in AH incidence was documented, corresponding to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic outbreak, with a realignment to the trend in the subsequent years.
Conclusions
We documented a decline in the incidence of AH in Veneto Region, but limited to females and especially in pre-menopausal women. These results could be related to the improvement of the iodine status in Veneto Region, thanks to a long and sustained iodine prophylaxis campaign. However, it seems clear that iodine supplementation effect on AH has been different according to sex and exposition to estrogens. SARS-CoV-2 pandemic and vaccination campaign did not change the declining trend of AH incidence.

DOI: 10.1530/endoabs.101.PS3-25-05

## PS3-25-06

**Breakfast habits in patients using levothyroxine: a questionnaire survey on patient experiences and preferences**

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Background
Levothyroxine (LT4) is one of the most commonly prescribed drugs in the western world. Approximately half a million people of the Dutch population use LT4 therapy and are thus instructed to ingest LT4 in a fasting state. Yet, postponing breakfast seems to be challenging for many patients and appears to be an important reason for suboptimal adherence to LT4 therapy. In this study, we aimed to determine the impact on daily life of postponing breakfast in a LT4-using population in the Netherlands.

Methods
LT4-using patients who visited Zuyderland Medical Center during a 6-month-study period were invited to complete a questionnaire. Regression analyses were performed to identify factors associated with non-fasting LT4 ingestion.
Results
410 out of 463 invited patients completed the questionnaire (88.6%). 76.8% was female and median age was 57 years [IQR:43-67]. Participants were mostly long-time LT4-users (>5 years) (60.9%). Almost all participants ingested LT4 in the morning (96.3%) of whom 68% postponed breakfast for 30-60 minutes. However, 60.5% reported to prefer ingestion of LT4 together with breakfast instead of postponing breakfast. Interestingly, 25% of the participants reported to skip their breakfast due to the fasting ingestion. While almost all participants reported they were instructed to ingest LT4 in a fasting state, only a minority reported to be aware of the recommended time interval between LT4 ingestion and interfering co-medication. Use of co-medication was associated with a higher likelihood for non-fasting LT4 ingestion (OR:2.71;95%CI:1.74-4.21;$P < 0.001$).
Conclusion
60% of our study population would prefer LT4 ingestion together with breakfast and 25% reported to skip their breakfast due to the fasting ingestion. Therefore, further research on the effects of LT4 ingestion together with breakfast is warranted.

DOI: 10.1530/endoabs.101.PS3-25-06

## PS3-25-07

**Effect of bariatric surgery on tsh levels and levothyroxine dosage in patients with thyroid disease: sleeve gastrectomy vs roux-en-y gastric bypass**

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Background
Some evidence indicates how bariatric surgery impacts the thyroid function test and, in hypothyroid patients, the dose of levothyroxine (LT4), but data are not univocal. Aim: To examine, in a single center retrospective analysis, the relationship between change in body weight, plasma levels of TSH and dosage of LT4 in patients with thyroid disease undergoing bariatric surgery and to compare the effects of Roux-en-Y gastric bypass (RYGB) vs sleeve gastrectomy (SG).
Methods
The data was collected from medical records of hospitalization of 235 patients (104 SG and 131 RYGB) who underwent pre-surgical work-up and from outpatient medical records of the same patients at 45 days, 3–6 months and 1-year visits after surgery. In the final analysis we included 69 patients on LT4 therapy (43 Th-RYGB and 26 Th-SG) and 85 patients without thyroid diseases with normal thyroid function (48 Ct-RYGB and 37 Ct-SG), who served as matched controls.
Results
The mean body weight reduction for al cohort was in $31.4 \pm 0.7\%$ after 1 year from the surgery. In the two Ct groups, TSH levels remained stable throughout the observation period, without differences for type of surgery and without relationship with body weight. Free-T3 levels, decreased significantly at all follow-ups, in both CT groups and in Th-RYGB ($P < 0.01$). After bariatric surgery, the patients treated with LT-4, belonging to both Th-RYGB and Th-SG, needed to increase the dosage per body weight to achieve stable TSH. At 1 year, the increase of LT4/kg/die was higher in the Th-RYGB group than Th-SG group (0.44 vs 0.30 mg/kg/die, $P = 0.032$).
Conclusions
In patients with severe obesity with normal thyroid function, TSH levels are not related with body weight change. Patients treated with LT4, after bariatric surgery need to increase the dosage pro kg of body weight of the LT4 and the increase is higher after surgery with malabsorptive component (RYGB) compared to restrictive surgery (SG). These data support a major role of the impaired drug absorption consequence of bariatric surgery rather than of the new body weight in determining the subsequent LT4 dosage. The results should be confirmed on a larger sample.

DOI: 10.1530/endoabs.101.PS3-25-07

## PS3-25-08

**Circulating tsh levels are more stable in patients with hypothyroidism treated with liquid L-T4**

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Background and aims
Hypothyroidism is high frequent affecting overall women and subjects over 60 years of age. It is usually treated by the administration of Levothyroxine (L-T4) under different formulations, and the tablet formulation is the most common used. The objective is reaching stable thyroid-stimulating hormone (TSH) levels, the patients are monitored by an annual test of the TSH levels to adjust the therapy, if necessary. We aimed to evaluate the efficacy of L-T4 therapy in a liquid formulation in reaching stable TSH levels with respect to a tablet formulation in hypothyroid patients.
Methods
The studied groups include one of 720 hypothyroid patients following a liquid L-T4 therapy and the other of 360 hypothyroid patients under a tablet L-T4 therapy, the two groups were age- and gender-matched. No issues of malabsorption or drug interference were reported, and all patients had normal serum TSH levels at the basal evaluation. The monitoring of the patients lasts two years, and during this period their serum TSH, FT3, FT4 levels were measured after one and two years.
Results
At the first abnormal TSH value, we evaluated several parameters such as age, gender, body mass index, history of chronic autoimmune thyroiditis, initial TSH, and L-T4 dosage. At the time of initial normal TSH, these parameters were not significantly associated with time to abnormal TSH values. After 1 year, TSH values were normal in 85% of the patients who received L-T4 liquid formulation, and only in 77% of patients treated with tablet L-T4; after 2 years, TSH values resulted normal in 82% of patients receiving L-T4 liquid formulation, and only in 73% of those with tablet L-T4 ($P < 0.05$).
Conclusions
A strict control of a stable TSH level in the normal range is very important, infact different studies demonstrated an increased mortality in people with TSH in the hypothyroid range. In our study we observed a better control of TSH levels in the long-term follow-up in hypothyroid patients who received a liquid L-T4 therapy.

DOI: 10.1530/endoabs.101.PS3-25-08

## PS3-25-09

**Potential risks and benefits of desiccated thyroid extract for the treatment of hypothyroidism: a systematic review**

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Background
Desiccated thyroid extract (DTE) is derived from the porcine thyroid gland, which has a higher triiodothyronine content than the human thyroid gland. DTE was standard therapy for hypothyroidism until the mid-1970s and is still in use, even though it is not recommended in current guidelines. This review aimed to summarize the available literature on DTE treatment in adult hypothyroid patients.
Methods
The search was conducted in six electronic databases until January 6, 2024. Two reviewers independently screened all search results. The retrieved studies compared DTE treatment with levothyroxine or combination therapy with liothyronine and levothyroxine. The primary outcome was quality of life (QoL), and secondary outcomes included symptoms, treatment preference, adverse effects, thyroid function measures, thyroid autoantibodies, body weight, cardiovascular measures, and gene polymorphisms in the deiodinase enzymes. One author performed data extraction twice. Risk of bias for each study was conducted by two authors independently. The risk of bias in non-randomized studies of intervention (NRSIs) was judged with ROBINS-I, and for randomized clinical trials (RCTs), ROB 2.0 was used. The overall quality of evidence was judged with GRADE.
Results
In the qualitative synthesis, we included nine NRSIs, two RCTs, and three case reports. The overall quality of evidence for the various outcomes was moderate to very low. The RCTs found no difference between treatments regarding QoL and symptom score assessments. In the NRSIs, symptom and QoL assessments were in favor of DTE. The included studies indicated that DTE may cause an increase in heart rate, lower body weight, and lower high-density lipoprotein compared to other treatment regimens, but the results were conflicting. The included NRSIs were judged with moderate to critical risk of bias. The RCTs had some concerns as no *a priori* statistical analysis plan was available. The overall quality of evidence for QoL was rated as low.
Conclusions
Most studies of DTE treatment are hampered by an inferior design, and data on long-term effects and side effects are lacking. Further, the various methods used for evaluating QoL and symptom scores complicate comparison across studies. The two included RCTs could not demonstrate any difference in QoL or symptom scores when comparing DTE with other thyroid hormone substitutions. Future trials of DTE in patients with hypothyroidism should be based on adequate study designs, validated measures of QoL, patients with reduced QoL, and the assessment of biomarkers reflecting long-term adverse effects.

DOI: 10.1530/endoabs.101.PS3-25-09

## PS3-25-10

### Rebound effect in hypothalamic–pituitary thyreotropic activity: a new model to better understand hypothyroidism and hormonal replacement therapies

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Background
A debate is active on the capability to restore euthyroidism in people with hypothyroidism (hT) since symptoms and metabolic abnormalities experienced by some patients. This issue has been mainly studied by focusing on the lower stream of the Hypothalamus–Pituitary-Thyroid (HPT) axis by TSH, FT4 and FT3 levels. It would be useful to focus on the upper part of the flow of HPT axis, investigating the factors that interfere with the hypothalamic-pituitary thyrotropic activity (HPta). A model to study this aspect is provided by patients diagnosed with differentiated thyroid carcinoma (DTC) who require radioiodine (RAI). These thyroidectomized subjects, if considered otherwise healthy, are prepared for RAI administration through a one-month withdrawal of levothyroxine (LT4). Aim of the study was to investigate the factors influencing HPta during a condition of hT induced in a standardized and controlled way.
Methods
The study was conducted in an endocrinology tertiary care center in Catania, Italy. In this area, adult patients diagnosed with DTC after total thyroidectomy are placed on a fixed dose of LT4 (i.e. 100 mg/day) and referred to this hospital for subsequent treatments. According to the institutional guidelines patients assessed as otherwise healthy are prepared to RAI within 6 months from thyroidectomy by a standard protocol of hT induction: 1) LT4 therapy is stopped from 28 days before the day scheduled for RAI; 2) patients assume l-triiodothyronine at fixed daily dose during the first 14 days, while they do not assume thyroid hormones during the second 14 days. We consecutively included from January 2016 to December 2019 DTC patients treated with RAI previous hT induction according to the protocol above described. Demographic and anthropometric parameters, dose of LT4 taken from thyroidectomy until withdraw for hT induction (LT4_mg/Kg/day), and the results of blood test collected the day scheduled for RAI administration (i.e., TSH (TSH_time1), Thyroglobulin, etc) were collected. Univariate regression analyses and a stepwise multivariate regression analysis were performed to evaluate which variables independently influence the TSH levels after a month of inducted hT.
Results
102 patients were included in the study. They were 78 females and 24 males with a median age of 44 years and a median BMI of 27.1 Kg/mq. Univariable linear regression analyses revealed age (*P* 0.005) and dose of LT4_mg/Kg/day (*P* 0.023) as independent factors affecting TSH levels after a month of LT4 withdrawl. Multivariable linear regression analysis included age (*P* 0.012), LT4_mg/Kg/day (*P* 0.003), and BMI (*P* 0.040) in the best fit model ($R^2$ 0.40) to explain hT TSH values.
Conclusions
This study shows that, beyond the age, HPta in hT patients is strongly determined with a directly proportional relation, by the dose of LT4 taken from thyroidectomy to its withdrawal. These data suggest the existence of a rebound effect for HPta in the HPT axis. BMI also play a role in this phenomenon.

DOI: 10.1530/endoabs.101.PS3-25-10

# Miscellaneous

## PS3-26-01

### Parathyroid adenoma : radiologic features and correlation study with $^{99m}$Tc-sestamibi spect findings

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Purpose
Our study was intended to describe the typical radiologic features of parathyroid adenoma and correlation study with $^{99m}$Tc-sestamibi SPECT findings.
Materials and Methods
A review of a surgical database and electronic medical records from 2012 to 2018 identified the cases of 17 patients who underwent preoperative cervical sonography for primary hyperparathyroidism with subsequent resection of pathologically proven parathyroid adenoma. Two radiologists retrospectively evaluated the preoperative ultrasound images and assessed for morphologic characteristics, size, location, and color Doppler vascularity. $^{99m}$Tc-sestamibi SPECT findings, surgical and pathologic reports were reviewed.
Results
Most of the parathyroid adenomas (15/17, 86%) were deep or inferolateral to the adjacent thyroid. An echogenic border separating the adenoma from the overlying thyroid was identified in all cases. 14 cases were solid (82%), one case was solid and cystic, and two cases were cystic (11%) in sonographic morphology. Color Doppler examination of 14 patients showed feeding vessels with internal color flow to the solid components in 7 patients (50%). All patients underwent preoperative $^{99m}$Tc-sestamibi SPECT, and the adenoma was definitively localized in 9 patients (52%) and equivocally localized in 6 patients (34%). One case of

**Table 1.** Imaging characteristics of parathyroid adenoma ($n$ = 17)

| | Characteristic | Value | % |
|---|---|---|---|
| Location | Superior | 2 (2 left) | 11 |
| | Inferior | 14 (9 right, 5 left) | 82 |
| | Ectopic, mediastinum | 1 | 7 |
| Position in relation to thyroid | Deep | 9 | 52 |
| | Inferolateral | 6 | 34 |
| | Superior | 1 | 7 |
| | Ectopic, mediastinum | 1 | 7 |
| Echogenic border with thyroid | | 17 | 100 |
| Mean dimension (cm) | Craniocaudal | 1.60 (SD, 0.53) | |
| | Anteroposterior | 0.86 (SD, 0.43) | |
| | Transverse | 1.13 (SD, 0.39) | |
| Morphologic characteristics | Solid | 14 | 82 |
| | Solid with cystic | 1 | 7 |
| | Cystic | 2 | 11 |
| Color Doppler finding | Examination not performed | 3 | 18 |
| | Feeding vessel with flow to solid components | 7 | 41 |
| | No discernible Doppler flow | 7 | 41 |
| Sestamibi SPECT localization | Definitive | 9 | 52 |
| | Equivocal | 6 | 34 |
| | Negative | 2 | 14 |
| US findings | Hyperechoic | 0 | 0 |
| | Isoechoic | 2 | 11 |
| | Hypoechoic | 14 | 82 |
| | Examination not performed | 1 | 7 |

Note: Except for dimensions, values are number of lesions.

ectopic mediastinal parathyroid adenoma was identified by $^{99m}$Tc-sestamibi SPECT and subsequently confirmed by chest computed tomography.

Conclusion

Awareness of typical radiologic features (location, morphologic characteristics, color Doppler findings) may aid radiologists in preoperative localization of parathyroid adenoma. And $^{99m}$Tc-sestamibi SPECT is also helpful to the diagnosis of this tumor.

DOI: 10.1530/endoabs.101.PS3-26-01

## PS3-26-02

### Calcitonin levels and pseudohypoparathyroidism: understanding the connection

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Background

Pseudohypoparathyroidism (PHP) is a genetic disorder characterized by resistance or an inappropriate response in specific G protein receptors. The pathophysiology of PHP type 1-a involves an autosomal dominant mutation of the GNAS complex locus. A classic triad of abnormality includes hypocalcemia, hyperphosphatemia, and elevated parathyroid hormone (PTH) concentrations. Additionally, other hormonal imbalances can occur in PHP and higher calcitonin levels have been described in patients with type 1-a.

Case Report

A 37-year-old male presented with persistently elevated calcitonin levels, and the ultrasound showed a normal-sized thyroid gland without nodules or pathological lymph nodes. He was diagnosed with pseudohypoparathyroidism type 1-a based on the presence of Albright's hereditary osteodystrophy (AHO) features: obesity, short stature, radiography confirmed shortened IV and V metacarpal bones, subcutaneous calcifications and developmental delay. Additionally he exhibited vascular calcium deposits, particularly in the basal ganglia (Fahr syndrome). Genetic testing is unknown. Besides elevated levels of thyroid-stimulating hormone (TSH: 9.26-9.38 mIU/l), parathyroid hormone (PTH: 492-245 pg/ml), basal calcitonin levels were significantly high (2015: 107 ng/l; 2019: 111.2 ng/l; 2023: 94 ng/l). Given calcitonin's role as a tumor marker for medullary thyroid carcinoma (MTC), a calcium stimulation test with serial calcitonin measurements were performed (0, 1, 3, 5, and 10 minutes): CT 187, 1; 2480; 2381; 1993; 1337 ng/l. Other tumor markers such as carcinoembryonic antigen, neuron-specific enolase and chromogranin A, were negative.

Conclusion

Elevated calcitonin levels should be investigated through clinical examination, including morphological and functional tests, as this marker strongly indicates the presence of MTC and some neuroendocrine tumors. The observed high hormone and calcitonin levels in our patient are likely due to the molecular mechanisms of multiple receptor resistance. After nearly ten years of follow-up, our patient did not have MTC, which was confirmed by both clinical evaluation and ultrasound imaging. As some authors recommend, fine-needle aspiration biopsy for patients with nodules can minimize the risk of missing medullary thyroid cancer.

DOI: 10.1530/endoabs.101.PS3-26-02

## PS3-26-03

### Thyrolipoma and thyrolipmatosis

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Objectives

We aim to describe the epidemiological, clinical and histopathological features of thyroid gland lipomas and lipomathosis.

Materials and methods

In this study, we report 7 cases of thyrolipoma a and thyrolipomatosis managed in our department during a 9-year-old period.

Results

Our study involved 4 males and 3 females. Their median age was 58 years old [58-62]. One of them had a medical history of Graves disease all patients presented with an inferior and anterior neck swelling that had been evolving for a mean period of 2.3 years. All patients did not present neither a dysphonia, nor a dyspnea or dysphagia. At their clinical examination, we recorded a mass located that thyroid gland region in 6 patients with a median size of 4 cm [2.5-5]. We rather noted a diffuse goiter in 1 patients. Ultrasound revealed a multi-nodular goiter in 5 patients and an isolated thyroid gland nodule in 2 patients. Based the EU-TIRADS score, the most pejorative nodules were classified as IV in 5 patients and V in 2 patients. We performed either a total of an hemi thyroidectomy in five and two patients respectively. Histopathological examination confirmed a thyrolipomatosis in three patients and thyrolipoma in four patients. Post-operatively, we noted a dysphonia and a hypocalcemia in one patient each. No recurrence was observed in all patients after a mean follow-up period of three years.

Conclusion

Thyrolipoma and thyrolipomatosis are an exceptional and only few cases were described in the literature. Their management is surgical and the diagnosis confirmation is based on histopathological examination.

DOI: 10.1530/endoabs.101.PS3-26-03

## PS3-26-04

**Association between thyroid function and periodontitis**

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Background
With lacking consistent direction of the association of thyroid dysfunction with periodontitis and limitations of previous studies, we aim to look for the probable association between periodontitis and thyroid disorders based on cross sectional and longitudinal results in population-based data of study of health in Pomerania (SHIP).
Methods
The net sample of first SHIP cohort; SHIP-0 (1997-2001), comprised of 4308 individuals aged 20-79 years. A second separate net sample of 4420 adults aged 20-79 years was drawn for SHIP-TREND (2008-2012). For the cross-sectional analysis data from SHIP-0 and SHIP-TREND-0 and for the longitudinal analysis data from SHIP-0 and SHIP-2 (11 years follow-up of SHIP-0) was used. In SHIP-0, SHIP-2 and SHIP-TREND-0, serum TSH, fT3, fT4 levels were measured by an immunochemiluminescent procedure. Periodontal examinations comprised probing depth (PD) and clinical attachment loss (CAL) performed according to the half-mouth method, described in CDC/AAP case definition. In cross sectional analysis thyroid biomarkers were associated with measures of periodontal status by linear, simple and multinomial logistic regression analysis. In longitudinal analysis negative binomial, poisson and linear regression analysis were conducted where necessary.
Results
In cross sectional analysis normal TSH concentration was inversely associated to the number of teeth, and positively associated with measures of periodontitis (PD mean and PD sites) only in SHIP-0. While in longitudinal analysis normal TSH concentration was positively associated with number of teeth lost between SHIP-0 and SHIP-2. High TSH concentration was inversely associated with number of teeth only in SHIP-TREND-0, and positively associated with measures of periodontitis (PD mean and PD sites) only in SHIP-0. Serum fT4 concentrations was inversely associated with CAL site in SHIP-TREND-0 only and positive association with moderate periodontitis only in SHIP-0. In longitudinal analysis serum fT4 was inversely associated with CAL mean and site differences between SHIP-0 and SHIP-2. Serum fT3 concentrations were associated with almost all measures of periodontitis in SHIP-0 and CAL site, moderate and severe periodontitis and loose teeth in SHIP-TREND-0, while in longitudinal analysis serum fT3 was only associated with PD mean differences between SHIP-0 and SHIP-2.
Conclusion
Our findings for association between thyroid function and periodontitis are inconsistent. Irrespective of the differences between the two SHIP cohorts, the overall results are inclined towards association of periodontitis to hypothyroidism. From longitudinal analysis we cannot draw a clear causal association, probably to a lesser than required number of individuals in the analysis.

DOI: 10.1530/endoabs.101.PS3-26-04

## PS3-26-05

**Evaluation of topical hemostatic agents (THA) used in perioperative period in thyroidectomy patients: assessment of ultrasonographic characteristics, resolution durations, and potential long-term complications**

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Introduction
During thyroidectomy, topical hemostatic agents (THA) (i.e. oxidized regenerated cellulose) are commonly used. The aims of this study are i) to evaluate the resolution duration of these materials sold under different brand names in the surgical bed. ii) to prospectively describe their ultrasonographic characteristics.
Methods
A total of 67 patients who underwent thyroidectomy for various reasons and had THA used during surgery were included in the study. Demographic characteristics, reason for operation, type of surgery, pathology results, type of THA used, and postoperative ultrasonographic features of these patients were recorded.
Findings
The mean age of the patients was 45.02 ± 13.5 years, with 14(20.8%) being male. The postoperative initial ultrasound (US) evaluation times of TMA varied from 1 to 84 months; however, the first US evaluation was performed within 9 months postoperatively in 42(62.6%) patients. The observed US pattern of TMA in all patients was ovoid/round, markedly hypoechoic solid lesions with well-defined margins. Linear parallel echogenic bands were observed in some cases. No vascularity was detected in any of them on Doppler US. Prospective sonographic follow-up of at least 6 months were conducted in 34 patients. Among these patients, the volume of TMA decreased in 13(38.2%), remained stable in 10 (29.4%), and increased in 11(32.3%). Throughout the follow-up period, TMA completely disappeared in none of the patients. In the patient with the longest follow-up duration, TMA was still detected at the postoperative 84$^{th}$ month. The type of TMA used could be identified in 36 patients. In all patients, although the trade names differed, oxidized regenerated cellulose was used as TMA; Surgicel® in 7 (19.4%) and Pahacel® in 29 (80.6%) patients. Among the 13 patients whose TMA volume decreased during follow-up of at least 6 months, 6(46.1%) had used Pahacel® and 2(15.3%) had used Surgicel®. Among the 21 patients whose TMA volume increased or remained stable, 10(47.6%) were identified to have used Pahacel®.
Conclusion
Our study showed a longer resolution time than the data provided by the producers. Understanding and accurately recognizing the ultrasonographic characteristics of these agents is particularly important in reducing diagnostic errors in malignant cases during the postoperative period, and in preventing unnecessary imaging and invasive tests conducted due to suspicion of recurrence.

DOI: 10.1530/endoabs.101.PS3-26-05

## PS3-26-06

**Obesity related hypoventilation syndrome in patients with hypothyroidism**

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Obesity hypoventilation syndrome (OHS) is defined as the presence of awake alveolar hypoventilation characterized by daytime hypercapnia arterial $PaCO_2$ greater than 45 mm Hg that is a consequence of diminished ventilatory drive and capacity related to obesityin the absence of an alternate hypoventilation. Patients with advanced disease develop signsof right ventricular failure (cor pulmonale) and may have elevated jugular venous pressure with a prominent V wave, edema, hepatomegaly pulsatile liver develops if tricuspid regurgitation is severe ascites. The interplay between obesity and hypothyroidism exacerbates respiratory compromise leading to impaired gas exchange and respiratory mechanics. Our aim comparison of Obesity Related Hypoventilation Syndrome in Patients with and without Hypothyroidism.
Group 1 Without Hypothyroidism
Group 2 With Hypothyroidism
Compared two groups of patients with OHS 10 patients in each, with a BMI exceeding 60. Group 1 individuals without hypothyroidism, 2 men and 8 women. Group 2 consisted of 9 women and 1 man all diagnosed with hypothyroidism and receiving high doses of levothyroxine. We evaluated various clinical parameters between the two groups. Hypothyroidism can exacerbate respiratory compromise in obese individuals with obesity-related hypoventilation syndrome with decreased metabolic rate and reduced respiratory drive leading to hypoventilation and impaired gas exchange; cause obesity to worsen due to metabolic changes and fluid retention, further increasing the risk of respiratory compromise; contribute to upper airway obstruction and obstructive sleep apnea, which are common comorbidities in obese individuals with OHS.
Natrium Levels:Group 1 Normal.
Group 2 Natrium levels may be lower due to hypothyroidism-related fluid retention. Hyponatremia can play a significant role in OHS in patients with hypothyroidism by promoting water retention and diluting serum sodium levels. Arterial Blood Gas Analysis Group 1 Expected findings of hypercapnia and hypoxemia

Group 2 Similar hypercapnic and hypoxemic findings, possibly exacerbated by concurrent hypothyroidism. Oxygen Saturation:
Group 1 decreased oxygen saturation 70%
Group 2 Oxygen saturation may be further compromised due to hypothyroidism. TSH Group 1 TSH normal range. Group 2 Elevated TSH
Levothyroxine Dose: Group 1 No levothyroxine treatment.
Group 2: Patients receiving high doses of levothyroxine Electrolytes: Group 1 Electrolyte levels normal. Group 2 Potential electrolyte imbalances, including hyponatremia, secondary to hypothyroidism. Treatment Differences: Group 1 Focus on OHS management, including weight loss interventions, positive airway pressure therapy, and respiratory support as needed. Group 2 In addition to OHS management, optimization of levothyroxine therapy to normalize thyroid function and address associated fluid retention and electrolyte imbalances. Conclusion underlying hypothyroidism presents a significant challenge in Patents with OHS.

DOI: 10.1530/endoabs.101.PS3-26-06

## Thyroid and Genetics

### PS3-27-01

**Identification of a stat3 mutation, P.THR716MET in two cases of very early-onset autoimmune hypothyroidism**

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Introduction
Autoimmune hypothyroidism (AIH) associated with thyroid peroxidase antibodies (TPOAb) is a common cause of thyroid dysfunction. Disease etiology includes genetic predisposition (e.g., *HLA-DR3*, thyroid genes) and environmental triggers (e.g., iodine). AIH usually manifests during young adulthood and rarely under three years of age. Early-onset AIH may arise from monogenic disorders (e.g., *STAT3, AIRE*) with severe symptoms like immunodeficiency or endocrinopathies. STAT3 is a transcription factor involved in cell differentiation, proliferation, and immunosuppression. Gain-of-function mutations in STAT3 are associated with a spectrum of early-onset autoimmune disorders.
Case report
A six-year old boy (1A) of Finnish origin presented with primary AIH since 16 months of age. His birth at 30+6 weeks was premature and prompted by C-section due to abnormal heart sounds. Newborn screening for congenital hypothyroidism was normal. At 16 months, he showed growth retardation, underdeveloped motor skills, constipation, and loss of appetite. AIH was diagnosed with TSH at 700 mU/l (reference: 0.5-4.5), fT4 < 1.3 pmol/l (reference: 12-22), and TPOAb > 1542 IU/ml (reference: <25) and thyroxine treatment was initiated. Medication improved his symptoms. At one year- nine months, he was treated with acyclovir for shingles (varicella-zoster infection). At two years- seven months, he had recurrent rashes that tested Staphylococcus positive. Standard thyroxine dosage was continued. Patient 1A's sister (1B) was born at week 37+1. Her newborn TSH screening was normal. At five months of age, she was diagnosed with AIH (TSH- 200mU/l, fT4- 5.9 pmol/l, TPOAb-522IU/ml), having constipation, weak appetite, sleepiness, and slight growth retardation. Thyroxine medication improved her conditions. Hitherto there are no other major autoimmune manifestations in the siblings. Whole exome-sequencing revealed a known heterozygous *STAT3* (c.2147C>T, p.Thr716Met) mutation in patients 1A, 1B and their mother. The mother had HLA-B27-negative juvenile idiopathic arthritis, prolonged leukocytosis and multiple dermatofibromas. No other known pathogenic variant in thyroid-specific or autoimmune genes were identified.
Conclusion
We report two siblings with very early-onset AIH carrying a pathogenic *STAT3* _p.Thr716Met variant. Symptoms of AIH have been managed effectively with thyroxine treatment and they have not presented any other autoimmune manifestations. Given that they are young, there is possibility of developing additional autoimmune diseases with age. For new severe conditions, novel therapies could be tested, based on reports of effective treatment in *STAT3* gain-of-function patients with Jakinib and IL-6 inhibitors. Hence, genetic testing of AIH should be considered in children under three years of age to aid in early diagnosis and personalized disease management.

DOI: 10.1530/endoabs.101.PS3-27-01

### PS3-27-02

**New insights in the diagnosis and treatment of allan-herndon-dudley syndrome**

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Introduction
Thyroid gland pathology ranks first among endocrine diseases in children in Ukraine, and a similar trend has been observed over the last 20 years. In 2018y the prevalence of diffuse goiter was 277,708 patients (36.47 per 1000 population), nodular goiter - 2,311 patients (0.30:1000), diffuse toxic goiter - 341 patients (0.04:1000) and 129 cases of thyroid cancer (1.7:100,000). However, the Allan-Herndon-Dudley Syndrome is extremely rare and has not been previously diagnosed.
Case presentation
The child first visited an endocrinologist at 2y 4 months of age with complaints on tetraparesis, spasticity, mental retardation, developmental delay, vomiting and bilateral inguinal cryptorchidism. TSH was normal, but fT4 was low 0.48 ng/dl (N 1.1-2.0) and 25 mg of L-thyroxine was prescribed. At the age of 3, he still had low fT4 level (0.9 ng/dl), but elevated fT3 (6.8 pg/ml (N 2.7-5.2)). Based on the low fT4 L-thyroxine dosage was increased to 37.5 mg/day. Thereafter fT4 remained low (0.6 ng/dl), but fT3 increased to 9.3 pg/ml. Brain MRI revealed signs of periventricular leukomalacia, impaired myelination of the brain, internal and external non-occlusive hydrocephalus, hypoplasia of the corpus callosum, enlargement of the cistern magna and Dandy-Walker malformation. At 6 y.o. his height was normal, but weight was 12,8 kg (<5 p.c.). Genetic testing (tNGS panels) identified hemizygous pathogenic *SLC16A2* c.940C>T (p.Arg314*) and *KIF7* c.877dup (p.Gln293Profs*170)/c.2344C>G (p.Arg782Gly), inherited from unaffected parents. Following these results T3 analogue, Triac therapy was initiated, and after 9 months of dose titration normalization of T3/fT3 occurred. This therapy also resulted in a decrease in fT4 (0.22 ng/dl) and T4 to 1.57 mg/ml (N 7.6-13.7), however despite this, the patient had no symptoms of hypothyroidism, vomiting stopped, heart rate and BP normalized, and also weight gain occurred (+6 kg over 10 months of therapy), but there was no improvement in neurological status.
Conclusion
Despite the *SLC16A2* gene is associated with X-linked SLC16A2-specific thyroid hormone cell transporter deficiency, also known as hereditary spastic paraplegia 22 and Allan-Herndon-Dudley syndrome causing severe neurological impairment, specific changes in thyroid hormones and poor prognosis, requiring Triac initiation therapy as early as possible, advanced genetic diagnostics is also necessary to identify a potential double hit that may exacerbate the underlying disease.

DOI: 10.1530/endoabs.101.PS3-27-02

### PS3-27-03

**Thyroid hormone resistance in an infant harboring a novel *de novo* mutation of the thrb gene**

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Introduction
Thyroid Hormone Resistance (THR) is a rare clinical syndrome characterized by impaired end-organ responsiveness to Thyroid Hormone (TH). The cardinal features of this syndrome are elevated serum levels of free THs with normal or high TSH, often with goiter without clear symptoms of thyrotoxicosis. Mutations in the Thyroid Hormone Receptor beta (*THRB*) gene constitute the most frequent cause of RTH, defined as RTHβ, usually identified in late childhood or adulthood.
Patient and methods
A 46, XY newborn was hospitalized because of prematurity, low BW (2010g), neonatal infection and bilateral nystagmus. The congenital hypothyroidism neonatal screening revealed increased TSH levels. Thyroid function test revealed markedly elevated levels of TSH, T3, freeT4, while on physical examination tachycardia (140-170 beats/minute), increased head circumference and insufficient weight gain were observed. During hospitalization, impairment in hearing capacity, dilation of brain ventricles without the need for ventriculoperitoneal drainage and a marked goiter were noted. Molecular genetic analysis was carried out employing Exome Sequencing (ES) on an Illumina NextSeq 500.

Results
ES revealed the presence of a novel heterozygous *THRB* gene variant, c.1301_1301delG, p.C434Sfs*9. The presence of this variant was verified by Sanger sequencing exon 10 of the *THRB* gene in the patient's DNA, but not in his parents, indicating that it is a *de novo* variant. The c.1301_1301delG results in a frameshift and a premature stop codon 9 amino acids further down rendering the THRB protein 20 amino acids shorter than the wild type. According to the ACMG criteria this variant is classified as pathogenic (PVS1, PM2, PP3). A heterozygous variant in the same codon, the c.1302C > A [p.Cys434*] has been previously reported in a THR patient who presented with both hypothyroid and hyperthyroid features, severe mental retardation (ID < 50) and short stature (Behr M, *et al*.,1997). During hospitalization the patient continued to show inadequate weight gain and non-response to auditory stimuli. Tachycardia was initially treated with β-blocker, but due to vagotonic symptoms, treatment was modified to α-blocker. Thyrostatic treatment, as expected, did not improve the symptoms, while the administration of high doses of T3 on an alternate day basis resulted in a transient decrease in TSH values and a slight remission of the goiter.
Conclusions
Early diagnosis of the rare thyroid hormone resistance syndrome and its molecular confirmation allow both the timely investigation and treatment of the comorbidities of the syndrome and the appropriate genetic counseling.

DOI: 10.1530/endoabs.101.PS3-27-03

## PS3-27-04

**The whole-genome DNA methylation pattern in peripheral white blood cells in adults and children with graves' disease**

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Objectives
Graves' Disease (GD) is an autoimmune disorder and it is a type of hyperthyroidism. As for its multifactorial etiopathogenesis, it involves various causative agents - first and foremost genetic, as well as environmental (i.e. smoking) and existential ones. Apparently, children may be the group most impacted by genetic influences. Moreover, given disparate clinical responses to antithyroid agents depending on affected patients' age – finding novel GD pathogenesis factors, like epigenetics, seems to be justified. In literature, existence of DNA methylation (DNAm) pattern abnormalities in adult GD patients, as well as dynamic, reversible site-specific genome methylation changes in response to cigarette smoking and antithyroid therapy have also been shown. With this in mind, the aim of the research entailed characterization of whole blood genome DNAm pattern in non-smoking, newly diagnosed pediatric and adult patients with GD.
Methods and Results
In this two-centres prospective study, we enrolled a total of 11 hyperthyroid patients with GD diagnosed in line with ETA guidelines: 5 children (10-17 years, group 1; GR1) and 6 adults (34-52 years, GR2), respectively. We included healthy controls for children (HC; $n = 5$, 10-17 years) into research as well. All GD patients have not been treated with antithyroid agents prior to sampling and were negative towards smoking. In all patients we gathered whole blood frozen first. DNA was isolated using a Genomic DNA kit, this being followed by material quality assessment. Then, we prepared methyl-DNA libraries in line with the NEXTflex protocol with a bisulfite conversion and performed reduced representation bisulfite sequencing (RRBS, Illumina, HiSeq platform). Bioinformatic analysis served to find the ratio of non- and methylated genome cytosines (5-methylcytosine:cytosine ratio, 5MC:C) in differentially methylated regions (DMR), as well as qualitative analysis of principal components (PCA) and specific regions. The statistical-significance involved *P*-value and q-value for limiting false-positive results basing on false discovery rate (FDR) method. Primarily, a total of 21038092 (GR1 vs. HC) and 20720785 (GR1 vs. GR2) sites were analyzed. We noticed following total 5MC:C ratios' ranges: 54,5-57,3% in GR1, 56,6-58,4% in GR2 and 57,3-59,9% in HC, respectively. Noteworthy, we found no significant differences in PCA, as well as in case of specific sites, promoters, genes and Graves' loci post to FDR correction.
Conclusions
Newly diagnosed GD patients with negative history towards smoking present with insignificant differences in the whole-genome DNAm pattern regardless of age of onset.

DOI: 10.1530/endoabs.101.PS3-27-04

## PS3-27-05

**Thyroid hormone analogue (TRIAC) therapy in resistance to thyroid hormone beta, reduces hyperthyroid symptoms, lowers circulating thyroid hormones and metabolic rate effectively, without adverse effects**

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Background
The treatment of Resistance to Thyroid Hormone beta (RTHb) is challenging because no therapy restores the euthyroid state in all tissues. Triac (triiodothyroacetic acid), a centrally-acting thyroid hormone analogue that preferentially activates thyroid hormone receptor beta, is reported to be beneficial in case reports or small case series.
Methods
We have treated a cohort of adult RTHb patients with hyperthyroid symptoms with Triac for upto a decade. Here, we describe the clinical, biochemical, metabolic and cardiac responses to therapy. (Patients in whom the HPT axis was altered (due to ATDs, thyroid surgery or radioiodine) were excluded.
Results
A total of eight adult patients were treated with Triac and their characteristics and responses (HSS: Hyperthyroid Symptoms Score, SHR: sleeping heart rate, REE: resting energy expenditure) to therapy are tabulated below.
Conclusions
Triac therapy in RTHbeta reduces hyperthyroid symptoms, lowers circulating FT4 and TT3 concentrations and reduces basal metabolic and heart rate effectively, without adverse effects. Whether longer-term Triac treatment alters adverse cardiovascular outcomes recently associated with RTHbeta, remains to be determined.

DOI: 10.1530/endoabs.101.PS3-27-05

PS3-27-05

| Subject No. | Gender, Age | THRB Mutation | Triac Dose(/24 hrs) /Duration of treatment (yrs) | Baseline FT4, Nadir FT4 | Baseline TT3, Nadir TT3 | Baseline HSS, Nadir HSS | Baseline SHR, Nadir SHR | Baseline REE, Nadir REE |
|---|---|---|---|---|---|---|---|---|
| A1 | M, 39 | R243Q | 3.5 mg/2.5 | 31.6, 20.9 | 2,72, 1.46 | 16, 11 | 62, 56 | 2.5, 1.4 |
| A2 | M, 25 | R429Q | 1.4 mg/3 | 28.4, 19.1 | 2.36-1.43 | 14, 5 | 54, 52 | 1.2, 0.5 |
| A3 | F, 54 | P452L | 1.4 mg/12 | 22.1, 13 | N/A | 17, 1 | 53, 61 | 1.2, 0.8 |
| A4 | M, 18 | S314Y | 2.1 mg/1 | 48.6, 25.8 | 2.93, 1.91 | 18, 14 | 58, 53 | 1.7, 1.1 |
| A5 | M, 29 | R316H | 2.1 mg/3.5 | 26.4, 15.9 | 2.09, 1.1 | 9, 5 | 48, 48 | -1.2, -0.8 |
| A6 | F, 19 | R483C | 1.75 mg/1 | 30.7, 18.8 | N/A | 21, 19 | 65, 59 | 0.9, -0.3 |
| A7 | F, 37 | R483C | 1.4 mg/0.7 | 28.7, 17.9 | 2.84, 2.3 | N/A | 65, 60 | 3.1, 1.2 |
| A8 | F, 34 | R483H | 2.8 mg/4.5 | 31.6, 12 | 4.41, 0.97 | 22, 9 | 72, 59 | 1.6, 1.4 |

7 of 8 patients achieved normal circulating FT4 (measured by immunoassay; mean FT4 fell from 31.2 pmol/l to 18.3 pmol/l, RR 10.5-21) and 5 of 6 achieved normal total T3 concentrations (measured by LC-TMS; mean TT3 fell from 2.89 to 1.52nmol/l, RR 1.09-2.24). Mean reductions in other parameters: HSS from 17/40 to 9/40, SHR from 60 to 56bpm, REE Z score from +1.375 to +0.66. No reported side effects. No patients discontinued therapy.

## PS3-27-06

**Decoding SLC26A7'S role in congenital hypothyroidism: delayed onset, very large goiters, and thyrotropin dependent basolateral expression**

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Background
Defects in thyroid hormone synthesis at birth lead to congenital hypothyroidism (CH). CH is usually a sporadic disease, but around 10-20% of the cases are familial, involving mutations in thyroid-specific genes. Mutations in the *SLC26A7* gene have recently been linked to dyshormonogenetic goitrous CH. Ion transporter SLC26A7 is highly expressed in the thyroid, and is involved in thyroid hormone synthesis, but its function remains unclear. To gain more insight into the SLC26A7 role in thyroid function, we screened for *SLC26A7* mutations in Finnish CH patients, characterized the phenotypes, and examined thyroid-specific gene expression.
Methods
A targeted next-generation exome sequencing covering all known CH causing genes was applied to the study participants with sporadic and familial CH. Expression of thyroid specific genes including *SLC26A7* was analyzed in two mutation carriers and in normal, goitrous and hyperactive thyroids. Additional expression analyses were done using previously reported hypothyroidism, hyperthyroid or slc26a7-deficient mouse models. Furthermore, we screened for possible disease association with the *SLC26A7* gene in the Finnish population using the FinnGen database.
Results
Four families with five patients carrying the homozygous *SLC26A7* (c.1893delT, p.F631Lfs*8) mutation were identified. Among them, two homozygous cases presented very large trachea-compressing goiters requiring thyroidectomy at birth. Additionally, one homozygous mutant carrier had normal thyroid function tests at birth, but developed hypothyroidism at the age of 16 with otherwise normal development, and one heterozygous patient presented with permanent CH at birth. Immunohistochemical analysis revealed thyrocyte hypertrophy with large colloid vacuoles as pathognomonic features in *SLC26A7* homozygous patients. Furthermore, basolateral SLC26A7 staining was observed in normal thyrocytes, and it was more abundant in hyperthyroid patients. In mice, abundant dietary iodine-dependent SLC26A7 staining was observed in the hyperthyroid models, with less intensive staining in WT or tshr-deficient mice. Screening of the FinnGen database revealed a few other homozygous and heterozygous cases with early-onset hypothyroidism. The *SLC26A7* c.1893delT, p.F631Lfs*8 variant shows 75x enrichment in the Finnish population.
Conclusions
The phenotypes in *SLC26A7* mutation carriers are varied, ranging from severe CH with very large congenital goiters to cases with delayed onset of CH. SLC26A7 shows thyrotropin and dietary iodine-dependent basolateral expression, which suggest these factors could play a role in phenotypic variation among patients with *SLC26A7* mutations.

DOI: 10.1530/endoabs.101.PS3-27-06

## PS3-27-07

**The incidence of multinodular goiter in patients with DICER1 syndrome and the risk of cancer**

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Objectives
The risk of multinodular goiter (MNG) and cancer in tumor-predisposition syndromes, is not well established in both, children and adults. MNG is a common clinical feature of DICER1 syndrome in children and adults. DICER1 syndrome is caused by germline pathogenic mutations in the DICER1 gene. The spectrum of ultrasonographic findings of MNG in DICER1mut+ patients is characteristic and largely distinct from typical features of thyroid malignancy and therefore should inform physicians performing thyroid US of the possible presence of underlying DICER1 syndrome (Sci Rep. 2022 Sep 23;12(1):15888). The aim of this study was to determine the incidence of MNG in patients with DICER1 syndrome.
Methods
This retrospective study evaluated patients with MNG diagnosed between 2009 and 2023 at a single center by the same pediatric endocrinologist. Based on ultrasonographic features, 40 patients (25 children <18y and 15 adults) from 22 families were initially enrolled for DICER1 gene analysis. In 13 families (59.1%) pathogenic variant of DICER1 gene was found. All pathogenic variants in *DICER1* (referred to hereon as *DICER1* mut+) were identified in a single research university laboratory. DICER1mut+ was found in 29/40 patients with MNG (72.5%), 16 children and 13 adults. The number of studied subjects for DICER1 mutation was enlarged by 5 family members of affected patients who had no MNG. In all DICER1 mutation was also confirmed. Analysis of all DICER1mut+ patients ($n = 34$, 13 adults and 21 children) showed that MNG was present in 29 patients, 16 children and 13 adults (85.3%). 3 children with MNG and DICER1mut+ have not been operated yet. Thyroid cancer was found in two (1 mPTCvF and 1 FTC) among 13 operated children (15.4%). In a group of 5 children who have normal thyroid on ultrasound, 1 had pleuropulmonary blastoma (PPB) and cystic nephroma (mother with MNG), 1 had PPB alone (mother with MNG) and the 3 remaining are asymptomatic to date (one parent of each has MNG). MNG was present in all families who carry the mutation however, in two families PPB was the primary reason for endocrine consultation and further genetic testing.
Conclusions
This study showed that MNG is present in the vast majority of patients with DICER1mut+ and the risk of cancer is not low. Further genotype-phenotype relationship may shed a new light on the risk of multinodular goiter and thyroid cancer in these patients and also in asymptomatic to date carriers.

DOI: 10.1530/endoabs.101.PS3-27-07

## PS3-27-08

**Unique features of resistance to thyroid hormone alpha due to a homozygous mutation in thra**

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Objectives
Only (~21 different) *heterozygous* mutations in thyroid hormone receptor a (TRa), causing Resistance to Thyroid Hormone a (RTHa) have been recorded to date. Here, we report the first known case of RTHa due to a *homozygous* mutation in *THRA*, with unique clinical features.
Methods
We ascertained clinical and biochemical features in the index case and his parents. Following identification of the *THRA* variant by next generation sequencing, functional properties of the TRa mutant were assessed *in vitro*. We studied T3-regulated gene expression, myogenic differentiation and muscle function of wild type and mutation-containing myoblasts derived from transdifferentiation of fibroblasts from the index case and a parent, *ex vivo*.
Results
A male child (age 11.0yrs) with mild intellectual disability, bradycardia, cold intolerance and ataxia but normal stature, head circumference and facies, exhibited abnormal thyroid function tests {P1: FT4 12.2 pmol/l (RR 10.5-21),

FT3 **7.7** pmol/l (RR 4-7.5), reverse T3 **0.09** nmol/l (RR 0.12-0.36), TSH 1.42 mU/l (RR 0.35-5.5)} and markedly raised serum muscle enzymes {Creatine kinase (CK) **3650** U/l (RR 39-309); myoglobin 113 mg/l (RR 28-84)}, with calf muscle hypertrophy and myopathy. He is homozygous for a premature stop mutation (Arg152Stop, R152X) in the hinge region of TRa. In contrast, his parents, both heterozygous for R152X TRa, had normal thyroid function tests and CK levels and no clinical abnormalities. Although it is expressed and localises to the nucleus in transfected cells, R152X mutant TRa1 exhibits loss of DNA binding with negligible transcriptional or dominant negative activity. Correlating with his muscle phenotype, myogenic differentiation of R152X homozygous mutant TRa myoblasts was markedly impaired, with reduced expression of TH-regulated target genes (Myosin heavy chain, MYH 1,2,4; Troponin, TNNT 1,3; sarco-endoplasmic reticulum calcium ATPase, SERCA2) mediating muscle function.
Conclusions
Receptor haploinsufficiency, due to a heterozygous, premature stop mutation in TRa, does not cause RTHa. Homozygosity for this receptor defect is associated with RTHa, but without some recognised phenotypes (e.g. short stature, macrocephaly, dysmorphic facies), with the absence of these features possibly reflecting the lack of non-hormone bound TRa, capable of inhibiting target gene expression. Conversely, the severe abnormalities seen in some tissues (e.g. skeletal muscle), do resemble the phenotype observed in conventional hypothyroidism.

DOI: 10.1530/endoabs.101.PS3-27-08

## PS3-27-09

**Intergenerational anticipation of disease onset in families with autoimmune thyroid disease**

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Background
The familial predisposition to the development of autoimmune thyroiditis disease (AITD), including both Graves' and Hashimoto's diseases, is well known. This evidence could be related to both common genetic susceptibility and environmental factors. Genetic anticipation has been reported in some Mendelian diseases, including non-thyroidal autoimmune diseases, as a phenomenon for which an accumulation of alterations in susceptibility genes, generation after generation, could lead to an early disease onset in younger generations. However, to date data concerning the anticipation in AITD's onset are few and controversial, and we thus aimed to investigate the occurrence of this phenomenon in a large series of AITD families.
Methods
This is a cross-sectional observational study, performed in a single reference center for thyroid diseases from September 2023 to February 2024. We evaluated age of onset of AITD in sixty-one families affected with AITD (9 with Graves' disease e 52 with autoimmune hypothyroidism). We excluded from the analysis subjects belonging to the same generation (e.g. sisters and brothers). We divided patients and their relatives into two generational (Gen) groups based on relationship (Gen1 $n = 52$, range 18-81 years; Gen2 $n = 54$, range 13-74 years).
Results
Among the 125 familial members affected with AITD (17 males and 108 females; 119 Caucasian e 6 non-Caucasian), 15 (12%) were affected with Graves' disease (GD) and 110 (88%) with Hashimoto's thyroiditis (HT). In addition, 116 familial members had the same disease (3/116 GD and 113/116 HT), while nine patients had a discordant disease compared to family members. We observed a significant difference between the mean age of AITD onset in Gen1 compared to Gen2 ($50 \pm 13.58$ *vs* $37 \pm 14.3$ years, $P < 0.001$).
Conclusions
Our preliminary data indicate an intergenerational anticipation of AITD in familial settings and may suggest the need for an earlier screening of AITD in young family members. Several factors may contribute this phenomenon, including the diffusion of thyroid screening in conditions at risk, but these data prompt further studies involving larger cohorts and including families with more than two generations.

DOI: 10.1530/endoabs.101.PS3-27-09

# Treatment - Surgery

## PS3-28-01

**clinical impact of pectoral nerve ii block on postoperative pain, opioid usage, and patient recovery experience in robot-assisted transaxillary thyroidectomy: a prospective, randomized controlled trial**

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Backgroud
Effective postoperative pain management with minimal opioid use is vital in robot-assisted transaxillary thyroidectomy (RATT), posing unique challenges in surgical flap-related pain control. Promising analgesic regional methods like the pectoral nerve II (PECS II) block are crucial for patients. To evaluate the efficacy of the PECS II block in reducing postoperative pain and opioid requirements and improving the quality of recovery in RATT.
Method
The study evaluated 90 patients aged 19-60 for elective RATT for a prospective randomized controlled trial. Seven patients were excluded due to medical conditions or high BMI. Ultimately, 83 patients were divided into two groups: 42 in the block group and 41 in the non-block group. The study was conducted in a controlled clinical setting at a tertiary medical center with an expert surgical team for RATT. The primary outcome measured was the degree of postoperative pain. Additionally, the number of opioid requirements and self-reported quality of recovery were assessed after RATT. Post-surgery VAS pain scores were measured at 1, 4, 24, and 48 hours, and rescue opioid usage was tracked. The Korean version of the Quality of Recovery-15 (QoR-15K) questionnaire was administered on discharge day.
Results
The block group reported lower postoperative pain scores at 1, 4, and 24 hours than the non-block group. Opioid use was higher in the non-block group, particularly in the PACU. The QoR-15K questionnaire revealed better pain management outcomes in the block group, while other recovery dimensions like physical comfort and emotional status were comparable across both groups.
Conclusions
The PECS II block can be a significant factor in enhancing the recovery experience for patients undergoing RATT, particularly in pain management. This approach could be a valuable addition to postoperative pain management strategies in RATT surgeries, aligning with the current medical emphasis on reducing opioid use and its associated risks.

DOI: 10.1530/endoabs.101.PS3-28-01

## PS3-28-02

**Total thyroidectomy and quality of life in patients with hashimoto thyroiditis, a scoping review**

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Objectives
Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is one of the most common causes of hypothyroidism globally. Patients frequently experience symptoms of hypothyroidism, for which the current mainstay of treatment is with thyroid hormone repletion with levothyroxine. Despite treatment, there remains a subset of patients who achieve a biochemical euthyroid status, yet experience persistent hypothyroid symptoms. For these patients, there is no clear treatment option for their symptoms despite adequate hormone replacement. However, recent evidence indicates that total thyroidectomy may further improve the quality of life (QoL) in this group of persistently symptomatic patients. This review aims to understand the current literature on how total thyroidectomy compares to levothyroxine alone in improving the QoL of patients with Hashimoto's thyroiditis (HT).
Methods
Following PRISMA guidelines for scoping review, we searched PubMed, Cochrane, Embase using the search terms "thyroiditis, autoimmune", "lymphocytic thyroiditis" or "Hashimoto disease" and "quality of life". Studies comparing the two treatment methods by evaluating patients' QoL were included.
Results
A total of 5 original studies, and a followup study of the only randomised controlled trial among them, were found comparing the impact of total thyroidectomy to

levothyroxine on quality of life (QoL). General indications for thyroidectomy were suspicion of malignancy, cosmetic reasons, compressive goiter, and hypothyroid symptoms despite levothyroxine. All 6 studies reported an improvement in QoL in the group treated with thyroidectomy compared to the group treated with levothyroxine. QoL was measured using the SF-36 ($n = 5$) and ThyPRO ($n = 1$). Complication rates were reported in 3 papers and the follow up study of the randomized controlled trial. Reported complications include tracheal perforation (1.4%), infection/haematoma (3.1-6.8%), temporary hypoparathyroidism (3.7-47.4%), permanent hypoparathyroidism (0 - 8.2%), temporary RLN injury (2.7 - 6.3%), permanent RLN injury (0 - 8.2%). The 5 year follow up study also found a significantly elevated long term complication rate of 14%, compared to the initial 8.2% in the randomized controlled trial.
Conclusion
Thyroidectomy may improve the QoL in the subset of Hashimoto's thyroiditis patients who are persistently symptomatic despite achieving euthyroid status on levothyroxine therapy. However, consideration should be given to the possibility of elevated surgical complication rates in HT patients. Further prospective clinical trials are needed to confirm this observation and determine the mechanism behind the improvement in quality of life.

DOI: 10.1530/endoabs.101.PS3-28-02

## PS3-28-03

**Pre-thyroidectomy vitamin d&calcium administration to prevent hypocalcemia: a systematic review**

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Background
Post-thyroidectomy hypocalcemia is a common complication that results in adverse neurological and cardiac symptoms. The use of calcium and vitamin D has been proposed as a preoperative preventative strategy for this condition. This systematic review and meta-analysis aimed to assess whether preoperative administration of calcium and vitamin D prevents postoperative hypocalcemia.
Methods
Computerized search in Medline, Embase, and CENTRAL databases was performed. Randomized controlled trials (RCTs) comparing preoperative calcium and Vitamin D administration with either placebo or standard therapy were eligible for inclusion. The primary outcomes were the occurrence of hypocalcemia, mean postoperative calcium level, and symptomatic hypocalcemia. The secondary outcomes were the development of permanent hypoparathyroidism and length of hospital stay. Continuous outcomes were represented as mean difference (MD), and dichotomous outcomes were represented as risk ratio (RR).
Results
Total of 9 RCTs that enrolled 1079 patients were found eligible. Postoperative hypocalcemia occurred significantly less in patients who received preoperative calcium and vitamin D (RR = 0.77, 95% CI: 0.60 to 1.00; $P = 0.05$). Mean postoperative calcium level was significantly higher in the intervention group (MD = 0.10, 95% CI: 0.07 to 0.12; $P < 0.00001$). The number of patients with symptomatic hypocalcemia was significantly lower in the intervention group (RR = 0.54, 95% CI: 0.38 to 0.76). There was no significant difference between the two groups in cases of permanent hypoparathyroidism and length of hospital stay.
Conclusion
Administration of calcium and vitamin D preoperatively achieves lower rates of post-thyroidectomy hypocalcemia in comparison with placebo and standard therapy.

DOI: 10.1530/endoabs.101.PS3-28-03

## PS3-28-04

**Establishing transoral thyroid and parathyroid endoscopic vestibular approach (toetva-toepva) service in the united kingdom national health system: the safe road to success**

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Objective
Scarless thyroid and parathyroid surgery have been explored for many years but previous surgical interventions have not been widely adopted. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is utilizing a natural orifice to manipulate the thyroid, resulting in improved cosmetic outcomes, similar operative time to conventional approach, shorter recovery, and smoother post-operative course. Herein, we aim to present the enhanced comprehensive framework we have carefully developed, which firmly establishes the basis for the secure implementation of the TOETVA service.
Methods
Built upon the latest literature introduced by TOETVA experts, our framework rests on three fundamental pillars including training, collaboration and meticulous preparation. Training, which formed the cornerstone of our approach, included attendance in two cadaveric courses and a hands-on fellowship in Brazil under the guidance of Prof XXXXX, who is one of the pioneers on this field. Furthermore, our commitment to excellence extended to 20 hours of intensive laparoscopic simulation training, ensuring proficiency with the laparoscopic equipment. Collaboration emerged as another crucial pillar to our framework. Active engagement of our anaesthetic and nursing colleagues as well as laparoscopic surgical team has been of paramount in fostering team-work and ensuring patients safety. Seeking expertise and working in close collaboration among colleagues in a national level, has further enriched our practice by facilitating constructive dialogue and experience sharing. The unwavering support of hospital management has been instrumental to ensure availability of resources and dedicated theatre time. Thorough preparation procedures completed our framework. Careful patient selection, dry sessions to safeguard understanding and predict potential pitfalls and guidance of a proctor for our first lists have all been essential components in our approach.
Results
With invaluable proctoring support for our first 3 cases, we managed to perform a full range of TOETVA and TOEPVA surgery including a cancer case, including the UK's first cancer case, achieving an R0 resection, obliviating the need for further treatment, demonstrating TOETVA's safety and efficacy in carefully selected cancer cases. The surgical time for our first cases was on average less than 3 hours which is markedly less than the average time reported in the literature.
Conclusions
The robust framework we have constructed ensures both safety and time efficiency, facilitating the effective and successful establishment of the TOETVA/TOEPVA procedures as a new pioneer service.

DOI: 10.1530/endoabs.101.PS3-28-04

## PS3-28-05

**Comparison of voice outcome according to the degree of thyroidectomy**

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Objectives
We aimed to evaluate the impact on postoperative voice outcome according to the degree of thyroidectomy skin flap.
Methods
We randomly enrolled the patients underwent thyroidectomy into conventional thyroidectomy group (group 1) or minimally skin elevated thyroidectomy group (group 2). Skin flap was elevated to thyroid notch superiorly in group 1 and to superior border of cricoid cartilage superiorly in group 2. Inferior border of skin flap was sternal notch in both two groups. Preoperative, 2-weeks and 3-months postoperative voice handicap index (VHI), F0, jitter, shimmer, and noise-to-harmony ratio (NHR) were estimated. Then we retrospectively analyzed these voice parameters and compared them between two groups.
Results
A total of 35 thyroidectomy patients was divided into group 1 with 16 patients and group 2 with 19 patients (M:F=5:30). All patients were performed central neck dissection with thyroidectomy (total thyroidectomy, 5 patients; hemithyroidectomy, 30 patients). Immediate postoperative vocal fold paralysis occurred in 3 patients, which was all recovered. VHI, jitter, and shimmer were significantly increased 2 weeks after surgery (VHI, $P = 0.001$; jitter, $P = 0.022$; shimmer, $P = 0.019$), but there were no differences of voice parameters between before surgery and 3 months after surgery. When comparing the differences of voice parameters between group 1 and 2, there were no differences at 2 weeks after surgery and 3 months after surgery.
Conclusion
The extent of skin flap in thyroidectomy may not correlated with postoperative voice outcome. Surgeons can decide appropriate degree of skin flap of thyroidectomy based on patient's condition, tumor factor, and surgeons' preferences.

DOI: 10.1530/endoabs.101.PS3-28-05

## PS3-28-06

**Emergency surgery for post-thyroidectomy hematoma: a life saving procedure**

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Introduction
Thyroidectomy is one of the most common surgerys worldwide. Although a safe procedure, postoperative hematoma is a life threatening complication that requires emergent surgery due to airway compromise. A surgeon must be able to recognize the signs and act accordingly.
Objective
Our goal is to evaluate the risk factors for post-thyroidectomy hematoma requiring emergent reoperation, the symptoms, the source of the bleeding and possible complications.
Materials & methods
1000 consecutive patients submitted to thyroidectomy in a single Portuguese institution were retrospectively analyzed. Data was then extracted from those who required emergency surgery for post-operative neck hematoma.
Results
Out of 1000 thyroidectomies, 15 patients (1,5%) required emergency surgery for neck hematoma. The majority occured in the first 6 hours but there were cases that presented until 24 hours after. All but 1 had undergone total thyroidectomy. The main presenting symptoms were increase of the cervical diameter, dyspnea, cough and hemorrhage through the suture. The first approach was bed-side re-cervicotomy and evacuation of the blood clots, followed by surgical revision of the hemostasis. All patients were re-intubated with 4 requiring post-operative invasive ventilation and admission in the intensive care unit. No tracheostomy was performed. No patient had long term complications.
Conclusion
Given its life-threatening potential if emergency surgery is not timely performed, risk factors should be preoperatively evaluated to assure patients at risk are closely monitored and preventive measures are taken. All medical staff should be aware of the presenting symptoms and surgeons and anesthesiologists must be able to quickly act to prevent its complications. This is particularly relevant given the popularization of outpatient thyroid surgery which could predict an increase of Emergency Room admissions for cervical hematoma.

DOI: 10.1530/endoabs.101.PS3-28-06

## PS3-28-07

**Thyroid operation under local anesthesia in bangladesh, how & when i do**

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Objective
To find out the safety and feasibility of Thyroid surgery in a selected group of patients under local anesthesia. The aim of the study was to share our experience in case of heme and total thyroidectomy in ENT foundation hospital and different clinics of Dhaka, Bangladesh.
Methods
All the patient was admitted to the hospital with clinically significant goiter, selected for surgical treatment. 2% xylocaine with adrenaline was used for infiltration anesthesia. Before the operation, all patients received 1 mg per kg body weight intravenous pethidine slowly, Diazepam 5 mg iv. In some cases. Intravenous ketorolac was injected sometimes to augment pain relive.
Results
In hemi thyroidectomy cases, no remarkable intra & post-operative complication could be seen. IN 3 cases we encountered, postoperative scar( one patient) & in two patients suffered from reactionary Hemorrhage. Mean duration of procedure is about 90 minutes. Hospital stay was three days. Patients were in good general condition on the day of discharge from the hospital.
Conclusion
Surgery for thyroid swelling in a selected group of patients may be an alternative where General Anesthesia is not available and in patients contraindicated for medical reasons.

DOI: 10.1530/endoabs.101.PS3-28-07

## PS3-28-08

**Robotic transaxillary surgery -a scarless safe option for thyroid surgery**

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Backgound
Constant developments in minimally invasive surgery are being made with thyroid surgery being no exception. Robotic thyroidectomy by transaxillary approach (RATS) is considered a safe alternative for selected patients with benign disease or low risk thyroid cancer.
Aim
We aim to present the case of the first Robotic Transaxillary Thyroidectomy performed in a public Portuguese Hospital, discuss its advantages and disadvantages and the challenges of introducing a minimal invasive cervical program in the public healthcare system.
Methods
A 61-year-old women with a 15 × 9 mm left isthmic thyroid nodule, regular margins and no microcalcifications, with a fine-needle aspiration cytology revealing a follicular neoplasm is proposed for a Robotic Transaxillary Thyroidectomy.
Results
The patient underwent a hybrid, robotic assisted, left thyroidectomy. The surgery was performed with the use of the Modena Retractor, Intraoperative Nerve-Monitoring and Indocyanine Green vascular test, thanks to the integration of the firefly technology in the Da Vinci robotic system. With an approximate over-all intra-operative time of 3 hours, 20 cc of blood loss and no intra-operative complications. The patient was discharged 36 hours after the procedure.
Discussion and Conclusion
The robotic technology offers an image enhanced perspective of the cervical structures, allows for more precise movements and minimal dissection. With the incorporation of other technology such as nerve-monitoring and ICG test, it helps guarantee the safety of the procedure. There is minimal post-operative pain and no visible cervical scar. It is, however, associated with an important learning curve and increased cost when compared with other approaches. The minimally invasive surgery is the future of thyroid and cervical surgery, with robotics surgery having an important role to play. Medical professionals and healthcare institutions should be familiarized with this option, its advantages and disadvantages, as it becomes more popularized and demand increases.

DOI: 10.1530/endoabs.101.PS3-28-08

## PS3-28-09

**A short course of lugol's solution in toxic nodular thyroid disease: a pre-post intervention study on thyroid hormones and quality of life**

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Purpose
Preoperative iodine therapy due to toxic nodular goiter (TNG) is discouraged as iodine may cause an aggravation of hyperthyroidism. We aimed to examine the effects of a short course of Lugol's solution on thyroid hormones and quality of life in TNG patients.
Methods
20 patients with TNG and subclinical to mild hyperthyroidism (free T4 $<30$ pmol/l) without complicating illness were included in this pre-post intervention study. All participants received Lugol's solution 5 %, Three oral drops thrice daily for ten days. Heart rate, TSH, free T4, and free T3 concentrations were collected before (day 0) and after treatment (day 10). Thyroid hormones measurements were repeated at two time points during the intervention to discover any exacerbations of hyperthyroidism. ThyPRO39, a thyroid specific quality-of-life questionnaire was filled out day 0 and repeated at day 10. Differences in heart rate, thyroid hormone concentrations, and quality-of-life before and after treatment were compared.

Results
Median age was 63.5 years with a female to male ratio 19:1. Free T4 and freeT3 concentrations decreased and TSH concentration increased after 10 days of treatment. There was no difference in heart rate. No exacerbations of hormone levels were noticed in any of the participants during the intervention. Three of the 14 scales in ThyPRO39 were improved, including hyperthyroid symptoms. The remaining scales were unchanged.
Conclusion
In this pre-post intervention study on toxic nodular thyroid disease, we found that a short course of Lugol's solution improved thyroid hormone concentrations and reduced hyperthyroid symptoms. This indicates that Lugol's solution might be used as preoperative treatment in toxic nodular goiter.

DOI: 10.1530/endoabs.101.PS3-28-09

## PS3-28-10

**Extent of surgery in the surgical treatment of graves' disease: subtotal vs. total thyroidectomy and comparison of the long-term results**

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Aim
For the surgical treatment of Graves' Disease (GD), total/near total thyroidectomy is usually preferred over subtotal thyroidectomy due to recurrence risk being low. But in some institutions, subtotal thyroidectomy is preferred due to lower complication rates and for sustaining euthyroidism without the need for replacement. The aim of this study is to analyze the extent of thyroidectomy and its effect on recurrence and complications rates; and in the patients going under subtotal thyroidectomy, study the relationship between remnant thyroid tissue and recurrence.
Methods
Patients who underwent surgery for GD, in a tertiary university hospital between 1987 and 2018 were retrospectively analyzed. Patients who underwent total/near total or subtotal thyroidectomy were grouped as TT and ST respectively. Both groups were compared in terms of demographic characteristics, postoperative complication and recurrent hyperthyroidism rates. In the ST group, patients with or without recurrence were analyzed separately and ROC analysis was used to determine remnant cut-off value. Fisher and chi-square tests were used for categorical analysis while student's t-test or Mann-Whitney-U tests were used for continuous variables. Significance was determined as $P < 0.05$
Results
Of the 427 patients included in the study, 125 were in the ST group and 302 were in the TT group. No significant difference was found between the two groups in terms of age and gender ($P = 0.5$). In the ST group, 10 (8%) patients had recurrent hyperthyroidism while none were seen in the TT group ($P < 0.01$). Transient hypoparathyroidism was found to be significantly higher in the TT group compared to the ST group (0.8% vs 16.9%; $P < 0.01$). Persistent hypoparathyroidism (1.6% vs.1%); temporary (0.8% vs. 1%) and permanent (0% vs. 0.3%) vocal cord paralysis rates were comparable. In the ST group, patients with recurrence had higher remnant tissue compared to those who did not ($5.3 \pm 0.94$ g vs.$3.4 \pm 1.34$ g; $P < 0.01$). In the ST group, the residual tissue cut-off value in terms of recurrence prediction with ROC analysis is found to be 4 g. While no recurrence was seen in the ST group with remnant tissue less than 4 g, patients with remnant tissue $\geq$4 gr have a recurrence rate of 17.8% ($P < 0.01$).
Conclusion
In the treatment of GD, the recurrence rates for TT is lower compared to ST without significant increase in long-term complication rates. For patients going under ST, remnant tissue higher than 4 g carries a higher risk of recurrence.

DOI: 10.1530/endoabs.101.PS3-28-10

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