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Oral Presentations

Oral Session 1: Highlights in Thyroidology: in Memory of Jacques Dumont

OP-01-01

Patient-Derived medullary thyroid cancer organoids; a model for patient-tailored drug and tracer screening

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Background
Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor derived from the parafollicular C-cells of the thyroid gland. Mutations in the gene encoding the Rearranged during Transfection (RET) tyrosine kinase, play a vital role in the development of MTCs. In patients with distant metastases, only targeted therapy can prolong survival. Tyrosine kinase inhibitors (TKIs) block tyrosine kinases such as RET and thereby inhibit tumor proliferation. However, it is difficult to determine the best treatment option for each individual patient. This study therefore aims to set up an MTC organoid model to study its potential for patient-tailored drug and PET tracer screening.
Methods
Cells were isolated from surgically obtained MTC biopsies, suspended in Matrigel, and plated in tissue culture plates with defined growth medium. For self-renewal potential assessment of putative MTC stem cells, the MTC-organoids (MTOs) were dissociated and replated every three weeks (passaging). To check origin, MTC-specific proteins were characterized by immunofluorescent (IF) staining. To determine the functionality of the MTOs, hormone concentrations were measured in the medium. Moreover, response to various TKIs was investigated by measuring hormone concentrations in the medium. Lastly, we evaluated whether the MTOs could bind various PET tracers (^{18}F-FDG, ^{18}F-DOPA and ^{18}F-PSMA), to validate their potential for PET tracer screening and development.
Results
Nine MTC biopsies were cultured to MTOs. We found a maximum organoid forming efficiency of 6.3% in passage 1 (p1), 5.9% in p2, and 9.4% in p3 indicating self-renewal potential of MTC cells. IF staining showed expression of four MTC-specific markers: Calcitonin Related Polypeptide Alpha (CALCA), Carcinoembryonic Antigen-related Cell Adhesion Molecule (CEACAM), Thyroid Transcription Factor 1 (TTF1), and Somatostatin (SST), in both tissue and MTOs. Secretory hormones, calcitonin and CEA, were observed in the medium indicating functionality of the MTOs. MTOs from four patients - two with Cys634Arg, one with Met918Thr and one without RET mutation - were exposed to TKIs (vandetanib, cabozantinib, selpercatinib or pralsetinib) during 72 hours. Concentrations of calcitonin and CEA after TKI exposure were only reduced in patients with the Cys634Arg mutation. Exposure to PET tracers showed cell-specific binding to ^{18}F-FDG and ^{18}F-DOPA but not ^{18}F-PSMA, indicating increased glucose metabolism and a neuroendocrine origin, but no PSMA target receptor, respectively and thus MTC-specific uptake.
Conclusion
MTC organoids can be successfully cultured, maintained and expanded, and show MTC-specific functionality. Moreover, the variable response to TKIs and specific binding of clinically used PET tracers may indicate the potential use of MTOs in prediction models. This however warrants further studies.

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OP-01-02

Long-Term outcomes of active surveillance for low-risk papillary thyroid carcinoma: is lifelong follow-up necessary?

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Objective
As a measure to reduce overtreatment, active surveillance (AS) for low-risk papillary thyroid carcinoma (PTC) has spread from Japan and gradually become accepted around the world. Older age is known to be a favorable factor for progression under AS; however, long-term evidence is still limited and lifelong monitoring is considered inevitable. The present study reviewed the results of AS from the 1990s and explored the possibility of completing follow-up.
Methods
Patients with low-risk PTC (all T1a, occasional T1b, N0M0) were provided information regarding AS and immediate surgery, and autonomously selected their preferred management option. For patients who chose AS, ultrasound was conducted every 6 or 12 months. Calcification patterns of the tumor were classified into weak (none or micro) and strong (macro or rim). Progression was defined as either tumor enlargement ($\geq$3 mm from the initiation) or development of clinically apparent lymph node metastasis (LNM).
Results
AS was conducted for 650 patients. Mean age at presentation was 53.4 $\pm$ 12.8 years and the median duration of follow-up was 8 (range, 1-29) years. During AS, tumor enlargement occurred in 71 (10.9%) patients and 9 (1.4%) patients developed LNM. Overall, 80 (12.3%) patients showed progression. Cumulative rates of progression at 10 and 20 years were 11.5% and 25.3%, respectively. Eventually, 62 (9.5%) patients underwent conversion surgery (31 due to tumor enlargement; 9 due to LNM; 22 due to other reasons), but no patient experienced postoperative recurrence. Multivariate analysis revealed that older age (hazard ratio [HR], 0.98; $P = 0.012$), male sex (HR, 0.22; $P = 0.037$), and strong calcification (HR, 0.50; $P = 0.045$) were significant predictive factors for non-progression. Degree of calcification correlated with patient age and duration of follow-up. Eighty-eight patients who developed rim calcification did not show subsequent progression. Median age and duration of follow-up at the time progression was identified were 55 (range, 24-84) years and 4 (range, 1-20) years, respectively. Only 2 patients showed progression after 15 years of follow-up and 5 patients showed progression after reaching the age of 80 years. The 40 patients who needed conversion surgery due to progression had a median age of 53 (range, 27-81) years, and only 1 patient was over the age of 80 years.
Conclusions
Progression under AS was extremely rare in tumors with rim calcification or old patients ($>$80 years) with long-term follow-up ($>$15 years). Intensive monitoring for low-risk PTC might not be necessary for these patients.

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OP-01-03

Circulating MIR-146A and MIR-21 predict glucocorticoid response in thyroid eye disease

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Introduction
Thyroid eye disease (TED) is an immune-mediated disorder of the eye. Intravenous glucocorticoid (GC) is the first-line treatment for active moderate to severe TED patients. However, the rate of response is between 50 and 80%. Reliable and easily accessible markers of responsiveness to GC therapy are still lacking.
Aim of the study
We aimed to explore the possible role of miR-146a and miR-21 as a predictor of responsiveness to GC treatment in TED.
Materials and Methods
We performed a prospective longitudinal study on 30 consecutive adult patients with active moderate to severe TED and eligible for GC therapy. Clinical, ophthalmological and blood samples were collected for each patient before and after treatment. All patients received the standard GC treatment with methylprednisolone iv (cumulative dose of 4.5g). In case of severe diplopia and ocular motility disruption patients underwent also orbital radiotherapy (50%). The response to GC treatment was defined as a decrease of the clinical activity score (CAS) of 2 or more points or disease inactivation (CAS $<$ 3) at 24 weeks.
Results
Twenty-three (77%) patients were considered as responders to GC. Ten patients (33%) experienced at least one side effect related to GC therapy. The baseline circulating miR-146a and miR-21 expression levels were positive correlated

($P < 0.0001$). Moreover, both miR-146a and miR-21 showed a positive correlation with CAS (respectively $P < 0.0001$ and $P = 0.0076$). At univariate analysis thyroid surgery, higher CAS, greater proptosis and higher pre-treatment circulating levels of miR-146a ($P = 0.01$) and miR-21 ($P = 0.03$) emerged as predictive factor of responsiveness to GC. A receiver operating characteristic curve analysis (ROC) revealed that both miR-146a (cut-off above 0.45) and miR-21 (cut-off above 0.95) could predict the responsiveness to GC with a PPV of 100%.

Conclusion

This is the first study investigating the role of pre-treatment circulating miR-21 and miR-146a to predict responsiveness to GC therapy in active moderate to severe TED patients. Serum pre-treatment miR-21 and miR-146a emerged as new simple, objective and reliable markers of GC sensitivity. Using a cut-off we could avoid unnecessary GC treatment and direct the therapeutic strategy ab initio towards a second-line therapy especially in the era of precision medicine.

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OP-01-04

Should hypothyroxinaemia during early gestation be regarded as a condition of oxidative stress?

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Background

Normal pregnancy is a state of physiological oxidative stress (OS) with oxidants facilitating the implantation of the embryo and optimal decidualisation but counterbalanced by antioxidants. Pro-oxidant processes exceeding the anti-oxidants capacity result in imbalanced OS, which has been associated with the ''big four'' obstetric complications: pre-term birth, intra-uterine growth retardation, pre-eclampsia and diabetes gravidarum. Important OS balance modulators are TH, hCG, CRP, the cytokine IL-6 and the iron status, often reflected by the serum ferritin level.

Rationale of the study

Early gestational hypothyroxinaemia has also repeatedly been associated with poor obstetric outcome and with impaired offspring neurodevelopment. Non-thyroidal illness has been conceptualized as a model of impaired balance of OS due to inflammation.

Aim of the study

In an area with sufficient iodine intake, to evaluate the possible association between 1st trimester hypothyroxinemia and the different parameters involved in OS including ferritin, IL-6, CRP, and hCG, adjusting for age and parity.

Methods

Between June 2018 and December 2022, the Brabant Study (BrSt) recruited 2835 pregnant women. We defined hypothyroxinaemia as FT4 $< 5^{th}$ percentile with TSH between 2.5-97.5th percentiles and a reference group with adequate FT4 levels, i.e., between 10 - 90th percentiles and normal TSH levels.

Results

68 women on T4 replacement therapy were excluded and 12 women had incomplete data. Data-analysis refers to 2762 women. Of these, 122 had hypothyroxinaemia and 2114 belonged to the reference group. There were 147 women with low ferritin ($< 5^{th}$ percentile: < 17 µg/l), 129 women with high CRP ($> 95^{th}$ percentile: > 14.58 mg/l) and 136 women with a high Il-6 level ($> 95^{th}$ percentile: > 3.71 µg/l). Significantly more women with low ferritin, high CRP and high IL-6 status belonged to the hypothyroxinemic group compared to the control group (χ^2 (1): 12.9, 11.1 and 10.9, all $P < 0.001$). Moreover, hypothyroxinemic women had significantly lower hCG levels (MW-U: $Z = 4.6$, $P < 0.001$) than the control group. Multiple logistic regression showed that hypothyroxinemia was independently associated with low iron status (OR: 3.6, 95%CI: 2.1-6.4), high CRP (OR: 2.1, 95%CI: 1.1-4.2), high IL-6 (OR: 2.3, 95%CI: 1.2-4.5), lower log hCG levels (OR: 6.6, 95%CI: 2.6-16.6), and higher age (OR: 1.08, 095%CI: 1.03-1.14).

Conclusion

Different modulators of OS – which are all separately associated with poor obstetric outcome – seem to be associated with hypothyroxinaemia during early gestation calling into question whether hypothyroxinaemia should be thought of as an example of OS, as reported in non-thyroidal illness.

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OP-01-05

RNA guanine-quadruplexes as novel regulators of translation and alternative splicing of tr alpha isoforms

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Objectives

The thyroid hormone receptor α (TRα) is crucial for organ development, regulation of growth, heart rate and energy homeostasis. In humans, *THRA* encodes for the two major TRα isoforms, TRα1 and TRα2. TRα2 is generated by alternative splicing and is unable to bind T3 and thus antagonizes TRα1 signaling. Therefore, the physiological effects of TRα require strictly controlled spatiotemporal expression of TRα isoforms. However, the mechanisms that regulate expression and cellular abundance of TRα isoforms are largely unknown. To fill this gap of knowledge we looked beyond classical concepts of post-transcriptional regulation and focused on RNA guanine-quadruplexes (RNA-G4s). RNA-G4s can act as *cis*-regulatory elements on translation and alternative splicing and RNA-G4s are present in *THRA*. Thus, we hypothesize that RNA-G4s play a role in the regulation of translation and alternative splicing of TRα isoforms.

Methods and Results

We used *in silico* predictions tools (QGRS-Mapper) and analysis of genome wide G4-sequencing data to identify G4-forming sequences in the 5'-UTR of TRα 58 bp upstream to the translational start site and two G4-forming sequences in intron 9, 148 bp downstream to the alternative splice site in exon 9. All three RNA-G4s are highly conserved among mammals. Circular dichroism spectroscopy and FRET-melting analysis confirmed formation of stable parallel RNA-G4s, as well as structural destabilization by specific point mutations. To determine the effect of the RNA-G4 in the 5'-UTR on translation we established a dual-luciferase reporter assay. Destabilization of the RNA-G4 by point mutations increased translation efficiency more than 3-fold. Remarkably, qRT-PCR confirmed that transcription was unaffected, demonstrating that the wild-type RNA-G4 sequence indeed represses translation of TRα1 and TRα2. We used the RG6-splicing reporter system to show that the two G4 sequences in intron 9 affect alternative splicing by increasing exon inclusion up to $25 \pm 3\%$ compared to $5 \pm 1\%$ using a vector with G4-disrupting mutations. Co-transfection with the splicing factor ASF/SF2 further increased exon inclusion up to $39 \pm 3\%$, but only in cells with functional RNA-G4s, demonstrating that the G4s serve as *cis*-regulatory factors controlling alternative splicing of TRα.

Conclusions and Outlook

These data provide novel mechanistical evidence that RNA-G4s regulate translation and alternative splicing of TRα isoforms. Currently, we test G4 ligands to modify TRα expression pharmacologically and unravel the physiological and cell-specific relevance of these G4s by using a CRISPR/Cas9 approach. Identification of tissue-specific G4-interacting factors is the next step as this might explain the spatiotemporal differences in TRα isoform expression.

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OP-01-06

Phenotypic differences in resistance to thyroid hormone alpha: differential recruitment of cofactors by thyroid hormone receptor alpha 1 mutants

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Background
Resistance to thyroid hormone alpha (RTHα), caused by mutations in the T3-receptor alpha 1 (TRα1) isoform, includes growth retardation, intellectual disability, and abnormal thyroid function tests. The current paradigm entails that disease features arise from decreased T3 action in TRα1-expressing tissues. However, also for patients that carry mutations that completely abolish T3-stimulated activity, neurological features vary strongly, ranging from mild motor impairments to severe intellectual disability and absence of speech. This implies that other mechanisms besides impaired T3-binding affect the neurocognitive phenotype, such as altered recruitment of regulatory cofactors. Our aim was to elucidate the molecular mechanisms underlying the large differences in neurocognitive features among RTHα patients.
Methods
Human SHSY5Y neuroblastoma cells were stably transduced with FLAG-HA-tagged (FH) wild type (WT), C380fsx387-TRα1 (severe phenotype) or F397fsx406-TRα1 (mild phenotype), or empty vector as control. Cells were stimulated for 4 hrs with vehicle or 10 nM T3 and transcriptomes were analyzed by RNAseq. To characterize the TRα1-interactome, WT FHTRα1 was tandem-affinity purified from nuclear extract from and co-purifying proteins identified by LC-MS/MS. Selected cofactors were further tested for co-immunoprecipitation with WT and mutant FHTRα1 in SHSY5Y cells, or FLAGTRα1 in transiently transfected HepG2 cells. Direct interactions between receptors and the co-repressor NCoR1 were further tested using a mammalian two-hybrid system.
Results
In contrast to WT, cells expressing the frameshift mutants C380fsx387-FHTRα1 and F397fsx406-FHTRα1 lacked any T3-stimulated gene expression. Unstimulated gene expression also differed for the mutants, particularly for the more severe C380fsx387-TRα1 mutant, with many dysregulated genes involved in neuronal development and migration. Compared to WT and F397fsx406-TRα1, C380fsx387-TRα1 showed a reduced interaction with the corepressor NCoR1 in co-immunoprecipitation and in the 2-hybrid assays, and an increased association with CHD4, ADNP and HP1γ, three proteins that form a repressive complex (ChAHP) that is important for neuronal lineage specification. The nonsense-mutant C380X-TRα1 also displayed decreased NCoR1 and increased ChAHP recruitment, indicating that the location of the mutation, rather than the altered amino acid sequence caused by the frameshift causes the changes in cofactor recruitment.
Conclusion
C380fsx387-TRα1 and F397fsx406-TRα1 both lack T3-binding but show differential effects on gene expression in human neuronal cells, which likely causes the neurological phenotypic differences in RTHα. C380fsx387-TRα1 has increased recruitment of the repressive ChAHP complex, which likely contributes to the severe clinical phenotype in patients with this mutation. Major rearrangement in cofactor recruitment is a disease mechanism for nuclear receptors that has not been previously described.

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Oral Session 2: Thyroid hormone action in the brain

OP-02-01

Impact of thyroid hormone transport on hippocampal gabaergic and glutamatergic systems in the mouse CNS

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Inactivating mutations in highly specific thyroid hormone (TH) transporter MCT8 result in a severe form of psychomotor retardation characterized by neurological impairments and frequent epileptic seizures of unknown etiology. These symptoms are thought to be a consequence of impaired central TH uptake across brain barriers and/or into neural cells. Mct8/Organic anion transporting polypeptide 1c1 double knockout (M/O-dKO) mice replicate characteristics of human MCT8 deficiency. Here, we aim to investigate the mechanisms underlying the seizure susceptibility in MCT8 deficient patients by studying the hippocampus of M/O-dKO mice in more detail, a brain area involved in many forms of epilepsy. We first performed a detailed characterization of inhibitory GABAergic interneurons by immunofluorescence during early postnatal development at P12 and in adulthood (P120). At P12, we detected a reduction in the general GABAergic marker glutamate decarboxylase 67 in M/O-dKO mice, a decrease in parvalbumin, and an increase in somatostatin positive cells that both label different subtypes of inhibitory interneurons. While these differences were no longer present at P120, a pronounced increase in calretinin positive mossy cell numbers, the major excitatory neuronal subtype in the hilus of the dentate gyrus, was observed in adult M/O-dKO mice only. Moreover, qPCR analysis of whole hippocampus homogenates revealed alterations in the expression of excitatory glutamatergic receptor subunits in M/O-dKO at both time points. To further investigate whether the differences can be attributed to a cell-autonomous function of Mct8/Oatp1c1 in distinct neurons, conditional mouse lines with a specific deletion of both TH transporters either in all GABAergic inhibitory interneurons (using Gad2-cre) or in all excitatory glutamatergic neurons (using Vglut2-cre) were generated and are currently analyzed. So far, no alterations in calretinin positive mossy cells were seen in both conditional knockout models indicating that mossy cell development is compromised by the TH deficient state in M/O-dKO mice. Altogether, our results point to an abnormal neuronal development in the hippocampus in the absence of Mct8 and Oatp1c1 that can disrupt the proper excitation/inhibition balance and thus impact seizure susceptibility.

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OP-02-02

Development of an image-based method for spatial registration of T3-induced changes in cell types and gene expression in human cerebral organoids

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Thyroid hormone (TH) signaling is essential for nervous system development. The clinical relevance of this simple statement is underscored by the severe neurological phenotypes resulting from global TH deficiency or perturbed local TH signaling during fetal development. A major aim of our research is to better understand the local action of TH during early human cortex development using cerebral organoids derived from human induced pluripotent stem cells (hiPSC) as a model system. We show that these organoids recapitulate major cytoarchitectural and transcriptional aspects of early cortex morphogenesis. Using single cell RNA-seq, we characterized TH-responsive gene expression programs with temporal and cell type-specific resolution and identified TH-induced changes in the relative abundance of neuronal cell types. Exploiting the laminar organization of progenitor and neuronal cell types in organoids, we next aimed to register TH-dependent gene expression programs in a spatial dimension. We use single molecule fluorescent *in situ* hybridization (smFISH) in combination with informative cell layer markers to characterize spatial expression profiles. Cryosections of organoids cultured in presence of a range of T3 media levels (0 to 20 nM T3) were stained by immunofluorescence or smFISH and high-resolution images were acquired by confocal microscopy. We next developed a quantitative image analysis pipeline based on tools implemented in ImageJ and QuPath software permitting (I) detection of changes in the relative abundance of neuronal cells types in specific cell layers and (II) quantification of spatial gene expression levels. One of the most critical steps in quantitative image analysis is a precise cell segmentation. Here, densely packed neuronal progenitor populations proved a formidable challenge that was successfully overcome by application of deep learning approaches. We will report results from a first series of proof-of-concept experiments where we document changes in neuronal subtype abundance in response to different T3 media levels. In addition, we devised an analytic pipeline to quantify changes in regional gene expression for T3-responsive genes (i.e. *DIO3, SEMA3C, EPHA4*) in developing organoids. Registering the spatial patterns of T3-induced gene expression will complement the analysis of cell type-specific gene expression changes in order to reveal the potential role of layer-

specific niche characteristics in shaping coordinated responses of cortical tissue to varying TH levels.

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OP-02-03

Effects of maternal administration of TH-Analog sobetirome and its CNS-Selective prodrug SOB-AM2 in murine MCT8-deficient fetuses

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Inactivating mutations in the thyroid hormones (TH) transporter monocarboxylate transporter 8 (MCT8) lead to the X-linked rare disease named MCT8 deficiency or Allan-Herndon-Dudley Syndrome (AHDS). AHDS pathophysiology is characterized by peripheral hyperthyroidism and cerebral hypothyroidism, which results in severe neurological impairments. Although AHDS leads to a spectrum of severe endocrine and neurological alterations, treatment options for MCT8-deficient patients are limited, and none have been able to prevent or effectively ameliorate the neurological impairments. Other than the complex symptomatology exhibited by patients, additional problems in the search for therapies for AHDS stem from the early onset of its alterations. In humans, CNS histopathological features have been found as early as in the fetal stages. In this context, treatment in postnatal stages, even if it was able to recover TH status and impede further alterations from happening, may not be enough to recover alterations happening from fetal stages. Thus, the aim of this work was to find and evaluate an effective therapeutic option from the earliest possible stage. This study explored the effects of the TH-analog sobetirome and its CNS-selective amide prodrug, Sob-AM2, in the treatment of pregnant dams carrying fetuses lacking Mct8 and deiodinase type 2 (Mct8/Dio2 KO), as a murine model for MCT8 deficiency. Pregnant dams carrying Mct8/Dio2 KO fetuses were treated with sobetirome or Sob-AM2 for 7 days, starting at embryonic day 12.5 (E12.5). Dams' body weight over pregnancy and TH levels were measured. Then, the effect of treatments on the expression of TH-dependent genes was measured in the placenta, fetal liver, and fetal cerebral cortex. Maternal sobetirome treatment led to spontaneous abortions and fetal malformations. Sob-AM2 treatment, however, revealed no apparent harmful effects. Moreover, gene expression analysis revealed that Sob-AM2 crossed effectively the placental as well as the brain barriers and was found to exert thyromimetic effects in Mct8/Dio2 KO fetal tissues. Sob-AM2 treatment mediated thyromimetic effects in the fetal liver by increasing the expression of deiodinases, while in the brain it was able to increase the expression of several T3-dependent genes in Mct8/Dio2 KO fetuses. Our data demonstrate that maternal administration of Sob-AM2 can cross the placental barrier and access the brain and other fetal tissues, in MCT8-deficiency to exert thyromimetic actions by modulating TH-target gene expression. These observations thus indicate that Sob-AM2 has the potential to prevent neurodevelopmental alterations in the MCT8-deficient fetal brain by addressing cerebral hypothyroidism, hence representing a promising option for AHDS patients.

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OP-02-04

Unravelling the effects of the effect of mutant thrß in cortical neuron differentiation

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Patients with resistance to thyroid hormone β (RTHβ) often display a neurocognitive phenotype, but the underlying biological defects have not been characterized. The predominant receptor isoform expressed in brain tissue is TRα1 leading to the assumption that this receptor accounts for most of the T3 effects. Nevertheless, TRα and TRβ are both expressed in brain therefore our study aims to understand the impact of a mutant THRβ on TH action in the brain. The peripheral blood mononuclear cells (PBMCs) were expanded and reprogrammed into induced pluripotent stem cells (iPSCs) from one RTHβ patient, harbouring p.M442V variant and affected with anxiety and severe short memory impairment, and one healthy control. The generated iPSCs were then differentiated into cortical neurons, using previously validated protocol. By qRT-PCR analysis we observed that both THRβ1 and THRβ2 are expressed in the differentiated cortical progenitors and neurons in the ratio of 1:2 respect to THRα, thus confirming the possible implication of THRβ in the neurological derangements of the RTHβ patient. We found a higher expression of MCT8 and a lower expression of in the patient cortical neurons compared to control at all different developmental days (rosette, neurons at 79 and 110 days of maturation). Surprisingly, a significant reduction was detected in the expression of the vesicular glutamate transporters (VGLUT1 and VGLUT2) in the RTHβ patient, while the vesicular GABA transporter (VGAT) and GABA decarboxylase 1 (GAD1) expression remained unchanged, in keeping with the known role of THRα during the GABAergic neuron development. Interestingly, in animal models VGLUT1 deficiency causes impaired visual attention, anxiety and depression, and VGLUT1/2 expression correlates with learning and memory. In conclusion, we report the unprecedented generation of cortical neurons from one RTHβ patient. Interestingly, the THRβ is expressed and appears involved in cortical neuron development. This model will be useful to understand the molecular basis underlying the neurological manifestations of RTHβ patients.

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OP-02-05

MCT8 expression changes under pathophysiological conditions in the adult human brain

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Adequate thyroid hormone levels are crucial for cell homeostasis in the adult human brain. To supply neuronal and glial cells, thyroid hormone (TH) transporters such as the monocarboxylate transporter 8 (MCT8) are required. While implications in TH levels in the human brain seem to play a role in neurodegenerative diseases such as Alzheimer's disease (AD), altered expression of TH transporters has not been described yet. Our study therefore aimed to evaluate MCT8 expression levels in different brain regions and cell types in adult human *post mortem* brain samples without pathological alterations and such affected by AD. Following our evaluations, we demonstrated proteomic and transcriptomic MCT8 expression in astrocytes, various neuronal subgroups and endothelial cells in 8 different brain regions (inter alia hippocampus, occipital, motor, prefrontal and temporal cortex). Performing colocalization studies using both in situ hybridization and immunohistochemistry, we showed that cells containing RNA of the SLC16A2 gene (MCT8 coding) also express the proteomic correlate. By using different MCT8 antibodies, we detected distinct staining patterns in MCT8-positive neurons which we investigated using stimulated emission depletion (STED) super-resolved microscopy. Most cells showed signals located at the cellular membrane while others showed perinuclear signals. To examine whether the progression of AD is associated with up- or down-regulation of MCT8 expression levels, we performed Braak staging of neurofibrillary degeneration on all our brain samples and divided them in a Braak-high and a Braak-low group. We found no evident qualitative differences in MCT8 staining patterns and strength between these groups. To further investigate MCT8 expression dependency, we are currently developing a data analysis pipeline for publicly available single cell/single nucleus RNA sequencing (sc/snRNAseq) data of previous studies on human brain tissue. Our findings suggest that MCT8 is of relevance even in the adult and elderly human brain as the TH transporter is expressed in most endothelial cells and a high number of glial and neuronal cells in different brain regions. While we found no qualitative differences in MCT8 staining patterns between the samples affected and not affected by AD, local changes in TH availability cannot be omitted. We expect that by analysing various sc/snRNAseq datasets we aim to clarify whether TH-related genes are dysregulated in neuronal and glial cells of AD patients.

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Oral Session 3: Signalling in Thyroid cancer

OP-03-01

Patient-Derived in vitro models for unraveling medullary thyroid cancer microenvironment and therapy resistance

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from parafollicular C-cells. Nowadays different targeted therapies are available, directed mostly against the main genetic driver of MTC, RET, and against the common pro-oncogenic pathways of VEGF, EGFR and c-MYC. Despite this, an escape phenomenon has been observed with sudden disease progression during treatment, leaving surgery as the only curative treatment. The evaluation of pre and post treatment genetic landscape of RET-mutated cancers recently demonstrated that Selpercatinib resistance is acquired either by appearance of secondary RET solvent front mutations or by the positive selection of a minor RET-wild type tumor subpopulation. So far, practically no attempts have been made to explain the intrinsic biological mechanisms responsible for medical therapy failure in MTC, mainly because of the lack of *in vitro* models closely representing cancer complexity. We hypothesized that, similarly than in other cancers, therapy resistance may be the result of a shift in between different cellular subpopulations and of biological changes induced in cancer cells by specific microenvironmental factors. The main aim of this study was the establishment of patient-derived MTC primary cell lines that can be grown in tridimensional models and conserve the ability to shift toward a more mesenchymal stem-like phenotype. We successfully established primary cell lines from 4 patients. We characterized their phenotype and response to targeted therapies through Western Blot, Confocal Microscopy, ELISAs, ELDAs, RT-qPCR and proliferation assays. Our data demonstrated that these cells secrete high levels of the MTC markers calcitonin and CEA when grown in differentiation media. When cultivated in a tridimensional setting they all show a significant increase in the stem and neuroendocrine precursor markers such as SOX2, OCT4, EPAS1, TUJI and FOXA1. Anyway, among the cell lines we observed significant differences in the markers expression, which correlate with sphere forming abilities, probably reflecting the differences in the composition of the original tumors. Our studies show that these cells are generally more resistant to TKIs treatment than the widely used immortalized MTC cell line (TT), as observed in the MTC patients *in vivo*. Moreover, changes of the growth conditions, observed during 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 currently used for MTC treatment.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 the future study of therapy resistance mechanisms evolution.

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OP-03-02

Determination of the role of map kinase and PI3K/AKT signaling pathways in the regulation of multidrug resistance proteins in thyroid cancer

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Thyroid cancer (TC) has one of the fastest increasing incidences worldwide and primarily involves papillary thyroid cancer (PTC). Cancer cells have numerous mechanisms that govern drug resistance, among which activation of multidrug resistance (MDR) genes encoding ABC efflux pumps plays an important role. Acquisition of drug resistance by TC cells is becoming a significant obstacle to effective therapy, leading to insensitivity to classical chemotherapeutics, but also to specific kinase inhibitors. Nevertheless, this process is poorly understood. We aimed to elucidate the role of P-gp (*ABCB1*) and BCRP (*ABCG2*), key representatives of ABC transporters, in the biology of PTC. We focused on the crosstalk between the expression of *ABCB1* and *ABCG2* genes, and activity of MAPK and PI3K/AKT signaling pathways. We used PTC-derived TPC1 (*RET/PTC1*) and BCPAP (*BRAF*V600E) cell lines, siRNA-mediated MDR-encoding gene silencing, clinical inhibitors of MAPK (trametinib and dabrafenib) and PI3K/AKT pathways (AKT inhibitor VIII), as well as RT-qPCR, Western blot, protein fractionation, confocal microscopy and RNA sequencing techniques, among others. We observed a strong relation between the expression of MDR genes and the mutational status of PTC cells. Silencing of *ABCB1* and *ABCG2* resulted in a change in the activity of MAPK and PI3K/AKT pathways. Similarly, inhibitor-driven suppression of signaling cascades changed levels and intracellular localization of P-gp and BCRP proteins. Interestingly, the decreased expression of P-gp, resulting from kinase inhibitor or siRNA treatments, is compensated by increased expression of BCRP, and vice versa. Large-scale transcriptome analysis confirmed the relationship between *ABCB1* and *ABCG2* expression, and the activity of the MAPK and PI3K/AKT pathways in PTC. Silencing of the MDR genes contributed to alterations in various common cellular processes, such as regulation of gene expression and signaling (including through the MAPK and PI3K/AKT pathways), cell cycle and proliferation. Trametinib and dabrafenib-induced inhibition of the MAPK pathway led to changes in numerous related biological processes, including regulation of proliferation, differentiation, cell cycle, migration and apoptosis. Similarly, PI3K/AKT pathway suppression led to disruption of key biological processes, including apoptosis, angiogenesis and migration. Changes in the various biological processes found in the transcriptome analysis (caused by silencing of the *ABCB1* and *ABCG2* genes) revealed that the role of drug efflux pumps in PTC is complex and goes beyond the typical function of xenobiotic transporters. Also, regulation of the expression of these genes depends on many factors, which is consistent with the results of studies on other types of cancer. These studies will assist in greater understanding of the drug resistance phenomenon in TC. This research was supported by the National Science Centre (No. 2018/29/B/NZ3/02642).

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OP-03-03

Involvement of mapk-scaffold proteins iqgap in thyroid cancer

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Undifferentiated thyroid carcinomas are extremely aggressive and currently lack effective treatment. Aberrant RAS-ERK signaling, triggered mainly by BRAF and RAS mutations, is responsible for the occurrence and progression of most thyroid carcinomas, which led to the clinical use of small kinase inhibitors targeting kinases of the pathway. The results were disappointing, because of the emergence of resistance and high-associated toxicity. A more specific approach, targeting signaling regulators, could circumvent those problems. IQGAPs are

scaffold proteins considered hubs of signaling, that have been associated with other human carcinomas and could represent excellent therapeutic targets. In this work, we are interested in defining IQGAPs involvement in thyroid carcinomas, taking into account the main oncogenic drivers, BRAF and RAS. We interrogated public databases to examine IQGAPs expression and their association with clinicopathological features in human thyroid carcinomas. IQGAPs loss- and gain-of-function clones were generated, using cell lines derived from human anaplastic thyroid carcinomas, to analyze IQGAPs involvement in signaling, transcriptional regulation by RNA sequencing and tumor-related processes using different functional assays. A chick-embryo model was employed to explore the participation of IQGAPs in thyroid tumorigenesis *in vivo*. The results show that IQGAP1 expression is high in human thyroid tumors, especially in those with BRAF mutations, and is associated with aggressive tumor features. The opposite occurs with IQGAP2, suggesting a tumor suppressor role. IQGAP1 silencing and IQGAP2 overexpression affected tumor-related cellular processes, and the outcome depends on the driver mutation. The underlying mechanism is not straightforward, as several signaling pathways were disturbed. Importantly, IQGAP1 silencing and IQGAP2 overexpression, while not prevented ERK phosphorylation, blocked the phosphorylation of Ribosomal S6 Kinase (RSK), a key cytoplasmic ERK effector. RNAseq analysis suggested the acquisition of partial mesenchymal phenotypes, and extracellular matrix regulation, upon IQGAP1 and 2 silencing. *In vivo* experiments indicate that IQGAP1 is not involved in the growth of the primary tumor, but it is required for intravasation and metastatic dissemination. Our data suggest that IQGAPs pro- or anti-tumorigenic abilities depend on the oncogenic driver, and that modulate tumor cellular processes, at least in part through RSK, leading to a reduction of metastatic dissemination.

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OP-03-04

Exploring the potential of siglec15 as novel immunotherapeutic target in (thyroid) cancer: focus on innate immune cells

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Objectives
The mortality in thyroid cancer (TC) is unacceptably high and novel immune based strategies are necessary, especially for cancers that are resistant to existing therapies. Recently, the receptor SIGLEC15 has been proposed as potential novel target in different cancers, but little is known about its exact function and regulation. Given its high expression in tumor associated macrophages and the high density of these cell in thyroid cancer makes this anti-inflammatory receptor an attractive target to study. Novel insights in the regulation and function of SIGLEC15 will allow us to develop tailored therapies incorporating SIGLEC15 as mechanistic target which will subsequently benefit the growing group of TC patients. Finally, general concepts obtained during this study may be applicable to other cancers as well.
Methods
Using different thyroid cancer cell lines we investigated the effect of cancer conditioned media on the phenotype of primary monocytes and macrophages as well as different monocytic cell lines. Additionally, we performed targeted proteomic analyses to pinpoint mediators in the media that influence SIGLEC15 expression on the immune cells. Subsequently we extended these experiments to co-cultures and trans-well experiments using cancer and (innate) immune cells. Finally, we generated different thyroid cancer and monocytic cell lines with stable SIGLEC15 overexpression to mimic the high expression of SIGLEC15 in the tumor microenvironment.
Results
Comparing the different thyroid cancer conditioned media in their ability to influence SIGLEC15 expression on either primary immune cell or innate immune cell lines we identified several interesting hits that will be validated in future experiments. As engagement of SIGLEC15 with its ligand leads to an anti-inflammatory cascade and induction of pro tumoral mediators we expected to measure an increase in anti-inflammatory cytokines. Surprisingly, when challenging the immune cells with LPS after they were differentiated in tumor conditioned medium, we measured higher levels of different pro-inflammatory cytokines such as TNF-a, IL-6 and lower levels of the anti-inflammatory cytokine IL-10. When culturing immune and thyroid cancer in either trans-well or direct co-cultures we obtained comparable results. Interestingly when culturing immune cells with a stable over expression of SIGLEC15 together with different thyroid cancer cells we observed a strong increase of IL-8.
Conclusion
Our results strengthen the hypothesis that SIGLEC15 plays an important role in the development and progression of thyroid cancer. Targeting this receptor in the context of infiltrating immune cells such as (tumor associated) macrophages might lead to a more pro-inflammatory and anti-tumoral phenotype.

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OP-03-05

From nucleus to mitochondria: insights into the role of tert in aggressive papillary thyroid carcinomas

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TERT is the protein component of the telomerase enzyme and is overexpressed in many cancer types. The most well-known role for TERT is the regeneration of telomeres allowing the avoidance of senescence and the continued proliferation of stem and cancer cells. Recent studies have identified other roles for TERT in compartments outside the nucleus, in particular in mitochondria, with a protective role against endogenous and therapy-induced oxidative stress (OS). A small subset of papillary thyroid cancers (PTCs) may dedifferentiate and become resistant to radio-iodine therapy, a trait often found in TERT promoter mutated cases, significantly reducing overall survival rates. We aimed to study the role of TERT extra-nuclear localization in the progression of PTC. For this purpose, we studied TERT nuclear export by confocal immunofluorescence, resistance to OS with specific fluorescent probes and proliferative properties with WST-8 in the K1 papillary thyroid cancer immortalized cell line transfected with wild-type TERT and specific TERT constructs that limit its localization to the nucleus (TERT-nuc) or to the mitochondria (TERT-mito). Moreover, we investigated the effect of SRC kinase inhibitor PP2, which reduces TERT nuclear exit, on K1 cell proliferation. We found that TERT shuttled into the cytoplasm and partly to the mitochondria in response to OS increase either from H2O2 or the BRAF inhibitor PLX4720. Moreover, we proved that mitochondrial TERT is able to reduce mitochondrial OS under H2O2 challenge and to induce mitochondrial fragmentation. Finally, we demonstrated that K1 cells transfected with the TERT-nuc or treated with PP2 had a reduced proliferative advantage compared to those transfected with wild-type TERT and untreated cells, respectively. In conclusion, we provide insights into the involvement of mitochondrial TERT in OS response and, for the first time, in BRAF inhibitor therapy-induced stress resistance. These data, which will be extended to other thyroid cancer subtypes, suggest that disrupting TERT mitochondrial localization by inhibition of SRC kinase, involved in TERT nuclear export, may represent an effective solution to therapeutic resistant PTCs.

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Oral Session 04: Young Investigators Session / Clinical + Translational

OP-04-01

Interaction between DIO2 polymorphisms and LT4 treatment on psychological well-being outcomes and cardiovascular risk factors: a population-based cross-sectional study in uk biobank

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Objectives
Some evidence suggests gene-treatment interactions might cause persistent symptoms in individuals receiving levothyroxine (LT4) treatment. We investigated, as previously hypothesized, if single nucleotide polymorphisms (SNPs) in rs225014 (Thr92Ala), rs225015, or rs12885300 (ORFa-Gly3Asp) in the Deiodinase 2 gene (DIO2), or rs17606253 in the Monocarboxylate Transporter 10

gene (MCT10) were associated with outcomes indicative of local tissue hypothyroidism in LT4-treated patients and controls.
Methods
We included 18,761 LT4-treated patients and 360,534 controls in a population-based cross-sectional study in UK Biobank. LT4 treatment was defined as a diagnosis of hypothyroidism and self-reported use of LT4 without use of T3. Outcomes were psychological well-being, cognitive function, and cardiac risk factors. Associations were evaluated by linear, logistic, or ordinal logistic multiple regression. Adjustments included sex, age, sex-age interaction, and genetic principal components 1-10.
Results
Compared to controls, LT4 treatment was adversely associated with almost all outcomes, most noteworthy: Increased frequency of tiredness ($P < 0.001$), decreased well-being factor score ($P < 0.001$), increased reaction-time ($P < 0.001$), and increased BMI ($P < 0.001$). Except for a significant association between the minor rs225015 A allele and financial dissatisfaction, there was no association of rs225014, rs225015, rs12885300, or rs17606253 with any outcomes in LT4-treated patients. For all outcomes, carrying the risk allele at these four SNPs did not amplify symptoms associated with LT4 treatment compared to controls.
Conclusions
rs225014, rs225015, rs12885300, and rs17606253 could not explain changed psychological well-being, cognitive function, or cardiac risk factors in LT4-treated patients. Our findings do not support a gene-treatment interaction between these SNPs and LT4 treatment.

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OP-04-02

Teprotumumab-Related adverse events in thyroid eye disease: a multi-center real world study

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Objectives
The insulin-like growth factor I receptor (IGF-1R) plays a significant role in the pathology of thyroid eye disease (TED), an autoimmune disorder characterized by orbital inflammation. Teprotumumab, a human monoclonal antibody targeting IGF-1R, has demonstrated efficacy in treating moderate-to-severe TED. A significant proportion of patients experienced adverse events (AEs), with 74% and 85% reporting an AE and 12% and 5% reporting serious AEs in Phase 2 and 3 trials, respectively. However, clinical trials had limited inclusion criteria. This study assessed the real-world duration, incidence, and severity of AEs in TED patients treated with teprotumumab.
Methods
This was a multi-center retrospective observational cohort study of patients with TED of all stages and activity levels treated with at least four infusions of teprotumumab. Patients were seen at six tertiary centers in the United States. AE metrics, relation to teprotumumab infusions, and related interventions were assessed throughout patient follow-up. Smoking history, thyroid status, previous thyroid and TED treatments, medications, and medical history were collected on chart review.
Results
The study included 131 patients with a mean CAS reduction of 3.1. Proptosis improved by an average of 3.0 ± 2.1 mm in 76% (100/131) of patients and GDS improved by at least one point for 36.3% (33/91) patients. AEs occurred in 81.7% (107/131) of patients. Patients had a median of 4 AEs. Most AEs were mild (74.0%, 97/131), 28.2% (37/131) were moderate, and 8.4% (11/131) were severe. Mean interval AE onset was 7.9 weeks after the first teprotumumab infusion. Resolved AEs had a mean duration of 18.4 weeks. Patients had a mean follow-up of 70.2 ± 38.5 weeks after the first infusion. Forty-six percent (60/131) of patients had at least 1 persistent AE at last follow-up. The most common type of AEs were musculoskeletal (58.0%, 76/131), followed by gastrointestinal (38.2%, 50/131), skin (38.2%, 50/131), ear and labyrinth (30.5%, 40/131), nervous system (20.6%, 27/131), metabolic (15.3%, 20/131), and reproductive system (12.2%, 16/131). The incidence of each type of teprotumumab-related AE was higher in all categories than previously reported (**Table 1**). Ten patients (7.6%) discontinued therapy due to AEs, including hearing loss (n = 4), multiple AEs (n = 3), inflammatory bowel disease flare (n = 2), and hyperglycemia (n = 1).
Conclusions
AEs were commonly reported with teprotumumab treatment. Most were mild and reversible; however, serious AEs occurred that warranted treatment cessation. Treating physicians should inform patients about AE risk, properly screen patients prior to treatment, monitor patients closely, and have a low threshold for treating AEs should they develop.

Table 1: A comparison of the incidence of AEs in the clinical trails with AEs in this study.

	Our Data		Clinical Trial Data: Teprotumumab-Related	
Adverse Event	Affected Patients	Percent	Affected Patients	Percent
Any AE	107	82%	47	56%
Muscle Spasm	76	58%	16	19%
Fatigue	36	27%	3	4%
Diarrhea	36	27%	7	8%
Alopecia	35	27%	8	10%
Hearing Change	40	31%	4	5%
Dysguesia	11	8%	4	5%
Hyperglcemia	14	11%	7	8%

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OP-04-03

Long-Term outcome of the thyroid function in graves' disease: a nationwide danish register study

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Background
Little is known about the long-term outcome of the thyroid function in Graves' disease in a large epidemiological setting.
Objective
The aim was to evaluate the long-term outcome of the thyroid function in patients diagnosed with Graves' disease in Denmark in the period 1995-2018. Our research objectives were to investigate the incidence of disease, use of antithyroid drugs, radioactive iodine, thyroidectomy and levothyroxine during follow-up, and thyroid related drug usage at end of follow-up.
Methods
This was a nationwide register-based cohort study. Data from the Danish National Patient Register and the Danish National Prescription Register were retrieved. Patients $\geq$18 years of age with an ICD-10 diagnosis code for Graves' disease or thyroid associated ophthalmopathy were included. The patients were followed until end of study, migration, or death.
Results
43,579 individuals were included and followed for median 9.7 years [4.2-15.2]. The annual incidence of Graves' disease declined from 29.5/100,000 in 1995 to 8.3/100,000 in 2018. Drug prescription data were available in 33,096 patients, of whom 5.4% underwent thyroidectomy. Antithyroid drugs were used by 10.6% among individuals followed for $\geq$20 years. At end of follow-up, 43.6% of patients were without any thyroid related drugs. Spontaneous conversion into hypothyroidism occurred in 8.1%.
Conclusions
Large differences in the long-term outcome of the thyroid function in Danish patients with Graves' disease were shown. A minority of patients underwent ablative treatment. Nearly half of the patients achieved disease remission at end of follow-up, while approximately 8% converted into hypothyroidism spontaneously during the study period.

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OP-04-04

The association between maternal thyroid function and language acquisition in offspring aged 12 to 37 months: an odense child cohort study

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Introduction
Maternal thyroid function in early pregnancy is crucial for fetal neural development. Early offspring language acquisition is an important indicator of fetal neural development and a predictor of future cognitive development. We aimed to investigate how the mother's thyroid function and the presence of thyroid autoimmunity in early pregnancy are associated with offspring's language acquisition at the age of 12-37 months.
Methods
This study was embedded in the prospective Odense Child Cohort (OCC). Mothers were excluded in case of known thyroid disease. A blood sample was drawn at median 12th gestational week (range: 8-20) and analyzed for free thyroxine (FT4), thyrotropin, and anti-peroxidase antibodies (TPOAb). The Danish adaption of the MacArthur-Bates Communicative Development Inventories (MB-CDI) parent reports was assessed every third month when the child was 12-37 months and was used to evaluate the offspring's vocabulary. Data from all completed MB-CDI reports (productive vocabulary) for each child was included in the analysis. Associations between maternal FT4, thyrotropin, and TPOAb, respectively, and scores in the MB-CDI were evaluated by conditional growth models, with thyroid variables as predictors, estimating inter-individual variability in intra-individual patterns of change (in MB-CDI-scores) over time (offspring age) and main effects of covariates.
Results
The study included 735 mother-child pairs (383 boys and 352 girls). The probability of producing words within the MB-CDI at the age of 12 to 37 months correlated negatively with maternal FT4 in both girls and boys ($P < 0.001$). Likewise, language acquisition was better in both girls and boys when maternal FT4 was below the 20th percentile compared to children exposed to a maternal FT4 above the 80th percentile ($P < 0.001$, $P = 0.002$, respectively). Language acquisition was better for girls with maternal thyrotropin >2.5 mIU/L than for those with maternal thyrotropin ≤ 2.5 mIU/L ($P < 0.001$). The same trend was evident for boys after the age of 27 months ($P < 0.001$). Language acquisition at age 12-37 months for both girls and boys was inversely correlated with TPOAb levels, as TPOAb >11 kIU/L decreased the probability of producing words compared to those with maternal TPOAb levels <11 kIU/L ($P < 0.001$).
Conclusion
Language acquisition in offspring at age 12-37 months correlated inversely with maternal FT4 and serological markers of thyroid autoimmunity in early pregnancy. Thus, thyroid autoimmunity *per se* may have a negative impact on fetal neural development. However, the finding that maternal thyroid function in the lower-normal range may be favorable for language acquisition contrasts with the current perception.

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OP-04-05

Active surveillance: a feasible option for indeterminate thyroid nodules

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Introduction
The surgical approach is the first line treatment for patients with an indeterminate nodule, both without and with nuclear atypia (TIR3A and TIR3B, respectively, as defined by Italian Consensus for thyroid cytology). However, there are no prospective studies about the feasibility of active surveillance in patients with indeterminate thyroid nodules.
Methods
Eighty-six consecutive patients who decided to undergo active surveillance for at least one indeterminate nodule, diagnosed with fine needle aspiration cytology, were enrolled in this prospective study, and were consequently submitted to neck ultrasound every 6-12 months. Disease progression was defined as detection of nodule enlargement in two consecutive evaluations (at least 3 mm in all diameters) and/or of a metastatic lymph-node. In such cases, patients were submitted to surgery. Molecular analysis was performed in a subgroup of samples.
Results
The median age at enrollment was 43 years (9-77 years, IQR 24). 78/86 patients exhibited a single indeterminate nodule: 20/78 (25.6%) TIR3A and 58/78 (74.4%) TIR3B. The remaining 8/86 patients had two indeterminate nodules. At baseline, median biggest diameter was 13 mm (5-58 mm, IQR 8). After a median follow-up of 24.5 months only 3/86 patients (3.5%) showed an increase in dimensions after 20, 36 and 37 months, respectively: two of them were submitted to surgery and their final diagnosis was minimally invasive follicular carcinoma; they were both cured during a follow-up of 29 and 4 months. The third patient is waiting for surgery. 8/86 (9.3%) patients were recently submitted to surgery due to their choice, without any evidence of disease progression: 2/8 (25%) presented a papillary thyroid carcinoma while the other 6 had a benign final diagnosis. The molecular analysis of 25/94 (26.0%) nodules showed that 12/25 (48%) were negative, 12/25 (48%) had one of the *RAS* gene family mutations (5/25 *NRAS*, *HRAS* 4/25 and *KRAS* 3/25) and 1/25 (4%) a $BRAF^{K601E}$. Despite the small number of analyzed cases, no correlation was observed between the presence of a gene alteration and the disease progression.
Conclusions
This study suggests that active surveillance is feasible for patients with indeterminate nodules. In our group, only 3.5% of patients demonstrated disease progression during a median follow-up of 24 months and their outcome was optimal despite the delayed surgery. Moreover, our data confirm the higher prevalence of RAS gene mutation (*HRAS, NRAS* and *KRAS*) and the absence of $BRAF^{V600E}$ mutation in indeterminate nodules without any correlation with the progression of the nodule.

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OP-04-06

Cardiac function during early treatment for differentiated thyroid carcinoma

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Background
Differentiated thyroid carcinoma (DTC) survivors have an increased risk of cardiovascular mortality but, the pathophysiological mechanism remains largely unknown. Early treatment for high-risk DTC entails thyroid surgery, radioiodine therapy with thyroid hormone (TH)-withdrawal, and thyroxine suppression therapy (THST). During treatment, patients cycle from severe hypothyroidism to exogenous subclinical hyperthyroidism. TH changes in early DTC treatment might affect cardiac workload and cause structural cardiac changes. Cardiac Magnetic Resonance imaging (CMR) enables accurate imaging of ventricular volumes and is considered the gold standard to investigate cardiac structure and systolic function.
Aim
To investigate cardiac function and morphology during changes in TH-levels in early DTC treatment by means of CMR.
Methods
In 18 patients with DTC (female: 89%; median age 47 [IQR 35-59] years), CMR was performed in 2 consecutive study visits, during short-term hypothyroidism and after 20 weeks of THST (TSH targeted <0.1 mU/l). In 5 patients an extra CMR was performed before treatment, during euthyroidism. The paired t-tests or Wilcoxon Singed Rank test were performed as appropriate. CMR data was indexed for body surface area (m^2) and data is presented as median [interquartile range].
Results
During THST, cardiac function was increased compared to values during TH-withdrawal (Table 1). In patients included during euthyroidism heart rate, left and right ventricular ejection fraction, stroke volume-index and cardiac-index decreased during

TH-withdrawal, but were not completely restored during THST to euthyroid values in 3 out of 5 patients.

Conclusion

These results suggest that cardiac work, particularly in the left ventricle, is associated with changes in TH-levels during early DTC treatment. This is most importantly demonstrated by increases in left ventricular ejection fraction, stroke volume index and cardiac index during THST. However, results from the small subgroup analysed during euthyroidism possibly suggest that cardiac function does not recover in all patients during THST.

Table 1. Cardiac parameters during changes in TH-levels ($n=18$).

		TH-withdrawal	THST	P
Heart rate	*(bpm)*	61.5 (57.5-64.3)	72.5 (63.8-79.8)	0.01
Left ventricle				
ED Volume-index	*(mL/m²)*	64.1 (50.0-68.2)	69.7 (66.4-73.6)	<0.01
ES Volume-index	*(mL/m²)*	26.1 (23.4-30.3)	25.2 (21.6-30.4)	0.96
Stroke volume-index	*(mL/m²)*	35.5 (27.0-41.9)	43.7 (38.6-48.5)	<0.01
Ejection fraction	*(%)*	55.9 (49.7-61.4)	63.6 (59.0-66.6)	0.03
Cardiac-index	*L/(m²·min)*	1.9 (1.6-2.5)	3.1 (2.8-3.4)	<0.01
Right ventricle				
ED Volume-index	*(mL/m²)*	69.6 (58.3-75.0)	70.4 (65.4-80.4)	0.06
ES Volume-index	*(mL/m²)*	38.8 (33.9-42.8)	38.6 (34.0-45.6)	0.67
Stroke volume-index	*(mL/m²)*	32.6 (26.3-36.0)	31.4 (27.8-40.5)	0.41
Ejection fraction	*(%)*	46.7 (43.5-50.8)	44.2 (41.6-50.2)	0.73
Cardiac-index	*L/(m²·min)*	1.8 (1.4-2.2)	2.4 (1.9-2.9)	0.04

Abbreviations: ES = End Systolic, ED = End Diastolic.

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Oral Session 05: Young Investigators Session / Basic

OP-05-01

Development and successful treatment of a novel mouse model for anaplastic thyroid cancer

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Anaplastic thyroid cancer (ATC) is the most aggressive thyroid cancer with a median survival of about 6 months. So far, no therapies offering a survival benefit are established. Thus, new therapeutic approaches are urgently needed. In general, genetic alterations leading to ATC increase PI3K and MAPK/ERK signaling and include mutations in receptor tyrosine kinases and tumor suppressor genes. They often occur together with the loss of P53, the most prevalent mutation in human ATC. Among such mutations are mutations and rearrangements of the *anaplastic lymphoma kinase* (ALK) gene. To study ATC and potential treatment options, we generated a mouse model with inducible thyrocyte-specific expression of constitutively active mutant ALK^{F1174L} and homozygous deletion of TP53 due to a Cre recombinase under control of the thyroglobulin promoter (*$TgCreER^{T2+/0}$; ALK^{F1174L};$Trp53^{-/-}$* mice, here referred to as $TP53^{KO}/ALK^{F1174L}$ mice). Fifty days after birth, thyrocyte-specific ALK^{F1174L} expression and TP53 knockout was induced by i.p. injection of tamoxifen. Median survival of $TP53^{KO}/ALK^{F1174L}$ mice was severely reduced (105 d) and the mice showed massively enlarged thyroids. Histopathology confirmed development of ATC. To investigate the effects of pharmacologic inhibition with ALK inhibitor TAE-684 *in vitro*, we established a primary cell line from an advanced $TP53^{KO}/ALK^{F1174L}$ mouse thyroid cancer. These cells were injected s.c. into wildtype mice and the resulting tumor was again an ATC, confirming the ATC origin of the cell line. Treatment of these ATC cells with the ALK inhibitor TAE-684 decreased AKT and ERK phosphorylation and induced cytotoxicity in a dose-dependent manner, demonstrating a therapeutic effect. We therefore treated $TP53^{KO}/ALK^{F1174L}$ mice with TAE-684 for 30 days, which significantly extended median survival of the treatment group compared to the solvent group (66 days vs. 18 days, $P<0.0001$). From these data we conclude that patients with ALK-positive ATCs would benefit from ALK inhibitor treatment, e.g. with crizotinib. However, as treatment efficacy ultimately is limited, second-line treatments need to be investigated. The $TP53^{KO}/ALK^{F1174L}$ mouse model and the derived cell lines will serve as tools to explore the molecular characteristics of ATCs, especially signaling pathway activation and tumor microenvironment, and to test novel therapeutics for the treatment of advanced thyroid cancers *in vitro* and *in vivo*.

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OP-05-02

Thyroid tumor microenvironment: deconvolution of tumor composition using DNA methylation data

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Introduction

Most thyroid cancer (TC) patients have a good prognosis, but some of them show aggressive behavior and are resistant to treatment. Still no effective biomarkers are available to predict which patients will progress. Epigenetic alterations are a hallmark of cancer, and profiling DNA methylation has allowed a better understanding of the epigenetic landscape of TC and its influence in TC progression. However, bulk DNA methylomes include information not only from tumoral cells but also from other cell populations that compose tumor microenvironment (TME) and influence tumor progression, aggressiveness and treatment response.

Objective

Our objective is to characterize the TME of TC to better understand its role and clinical application.

Methods

We applied a deconvolution approach to bulk DNA methylation array data using PRmeth, an R-based method that allows deconvolution of partially available DNA methylation data. We profiled the methylome of a large cohort of thyroid samples ($n=114$), including normal tissue (NT), low-risk papillary and follicular TC (PTC and FTC, respectively), metastatic PTC and FTC (both radioiodine avid (RAI-A) and refractory (RAI-R)), and paired metastases, using EPIC arrays, and analyzed data from external sources which in addition to NT, PTC and FTC, included PDTC and ATC ($n=1000$). We also used publicly available data of 13 cell types known to be part of the TME as well as some TC cell lines as references.

Results

In total 19 cell populations were identified, including 1 for fibroblasts, 1 for endothelial cells, 11 for immune cells, and 1 for TC highly undifferentiated cells. We also identified 5 unknown groups present in all samples that would correspond to normal follicular cells and different cancer cells. Results showed different cell-type proportions according to histology. Interestingly, we found almost no immune infiltration in FTC (low-risk and metastatic), while infiltration was higher in PTC and increased along PTC progression. PDTC and ATC showed the highest levels of infiltration with more than half of ATC cells being immune cells. The comparison between RAI-A and RAI-R PTC, or RAI-A and RAI-R FTC, did not show differences in the immune infiltration but in the proportion of the different cancer cell populations.

Conclusion

We conclude that the TME of a TC is key for tumor progression, being more important in some histological subtypes than in others. The high immune infiltration in highly aggressive tumors makes them good candidates for immunotherapy.

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OP-05-03

The role of thyroid hormone transporters in macrophage function

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Innate immune cells, including macrophages, are functionally affected by thyroid hormone (TH). Macrophages can undergo phenotypical alterations, shifting between pro-inflammatory (M1) and anti-inflammatory (M2) profiles. Previous studies have established that increased TH concentrations shift macrophages into a more pro-inflammatory phenotype. Cellular TH concentrations are, in part, determined by TH transporters, cellular gateways facilitating bidirectional TH transport. An important TH transporter family is the monocarboxylate transporters (MCT) family including Mct8 and Mct10. To investigate the contribution of Mct8 and Mct10 in macrophage function, we used bone marrow derived macrophages (BMDM) from mice lacking Mct8 (Mct8ko), Mct10 (Mct10ko), or both (Mct8/10dko). Isolated BMDM from wild type (WT) and knockout mice were then polarized into M1 or M2 cells using LPS + interferon gamma or IL-4 respectively. To determine the intracellular TH availability in BMDM, mRNA expression of TH responsive genes was measured in the cells of wild type (WT) and knockout mice. Macrophage phenotype was assessed by measuring cell surface marker expression using flow cytometry, and secretion and expression of pro-inflammatory (TNFα and IL-1β) and immunomodulatory (IL-10) cytokines. T3 responsive gene expression was unchanged in unpolarised Mct8KO and Mct10KO BMDM vs WT BMDM. In Mct8/10dKO cells T3 responsive gene expression was decreased, suggesting that only when both transporters are absent intracellular T3 availability decreases. After polarization into M1 macrophages, Mct8ko macrophages showed increased secretion of TNFα, and increased IL-1β gene expression compared to WT M1 cells, suggesting an increased pro-inflammatory profile. Mct10KO M1 cells were unchanged compared to WT M1 cells. In Mct8/10dko M1 macrophages, CD86 (an M1 surface marker) was increased compared to WT M1 cells, while TNFα secretion was increased as well. After polarization into M2 macrophages, both Mct10ko and Mct8/10dKO macrophages demonstrated increased IL-10 expression while M2-surfacemarkers were unaltered compared to WT M2 cells. In conclusion, only the absence of both Mct8 and Mct10 reduces intracellular TH availability. Pro-inflammatory macrophage phenotype is enhanced in both Mct8KO and Mct8/10dKO M1 macrophages compared to WT, whereas both Mct10 and Mct8/10dKO M2 BMDM show increased anti-inflammatory cytokine secretion compared to M2 WT cells. This suggests that these effects may be at least partially due to other functions of the Mct8 and Mct10 transporters and not solely a T3 effect. These results provide new insights in the complicated interplay between TH and the immune system. It also emphasizes the importance of future research, as clinical implications are unknown and remain to be elucidated.

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OP-05-04

Multi-Trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications

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Introduction
In the last decade, it has become clear that not only overt but also subclinical hypo- and hyperthyroidism are associated with several adverse clinical outcomes, including atrial fibrillation, coronary heart disease, stroke and mortality. More recently, various studies have suggested that even small differences in thyroid function within the reference range are associated with clinical consequences. Genetic factors are responsible for up to 58-71% of the variation in thyrotropin (TSH) and free thyroxine (FT4) levels. However, to date only a fraction of the genetic footprint of TSH and FT4 has been clarified. Furthermore, the genetic background of triiodothyronine (T3) has been understudied, emphasizing the need for agnostic approaches such as genome-wide association studies (GWAS) to further unravel the additional underlying genetic contributors.
Methods
We conducted large GWAS meta-analyses of thyroid function in up to 271,040 individuals of European ancestry from the ThyroidOmics Consortium, including reference range TSH, FT4, free and total T3, and proxies for metabolism (T3/FT4 ratio). Secondary analyses included colocalization with mRNA levels using GTEx, functional enrichment and pathway analyses as well as polygenic risk score and Mendelian randomization analyses on a wide range of clinical endpoints.
Results
We revealed 198 loci associated with TSH (84 novel), 84 loci associated with FT4 (45 novel), and 29 novel loci for the T3 related traits. The loci explained 14.1%, 6.0%, 9.5% and 1.1% of the variation in TSH, FT4, total and free T3 concentrations, respectively. For FT4, the tissue enrichment and colocalization analyses revealed genes expressed in various peripheral tissues, whereas TSH-associated genes were predominantly expressed in the thyroid including multiple genes with a known role in the TSH signaling cascade and thyroid hormone synthesis, such as *PDE8B, PDE10A* and *TPO*. Genetically determined variations in reference range thyroid function were associated with a wide range of clinical outcomes including lipids, blood pressure, coronary artery disease, cardiac dysrhythmias, autoimmune diseases, and cancer.
Conclusion
This is the currently largest and most complete genetic analysis of thyroid function. These results leverage impact on understanding thyroid hormone physiology, reveal causal effects of reference range thyroid function on various diseases, and highlight multiple genes involved in thyroid function and metabolism. Furthermore, this study fosters possibilities applying genetics in diagnostics and identifying candidates for therapeutic targets to personalize treatment of thyroid diseases.

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OP-05-05

Distinguishing beneficial local from adverse systemic thyroid hormone action in alcoholic liver disease

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Thyroid hormones (TH) reduce liver steatosis. As steatosis is the initial step of alcoholic liver disease (ALD), we hypothesized that TH treatment could ameliorate ALD. Wildtype (WT) mice were treated with either ethanol (EtOH) or liquid control diet for 10 days followed by a single EtOH or maltose binge on day 11. In both groups, diet was supplemented with either T3 or solvent. Serum triglycerides (TG) were

increased by EtOH and, surprisingly, further elevated by T3. Liver weight and hepatic lipid content were increased by T3 in the EtOH group. T3 treatment did not protect from ALD and rather aggravated EtOH-induced liver steatosis. White adipose tissue (WAT) weight was reduced by EtOH and T3 treatment. Furthermore, WAT expression of thermogenic genes (*Ucp1*, *Pgc1a, Dio2*) and lipases (ATGL, HSl) was upregulated by T3, indicating that T3 action in WAT led to lipolysis and subsequently fatty acid accumulation in the liver, explaining the more severe ALD phenotype. To distinguish hepatic from such extrahepatic T3 effects, we performed the same experiment in hepatocyte-specific TH receptor beta knockout (hepTRβKO) mice. Absence of TRβ in hepatocytes aggravated the phenotype of T3 and EtOH treated mice even further with increased liver weight and hepatic lipid content. RNA-Sequencing and pathway analysis showed that T3 and TRβ induced beta oxidation and oxidative phosphorylation and repressed lipid synthesis. CYP2E1 is induced by EtOH and metabolizes EtOH, which generates reactive oxygen species (ROS) and liver damage in ALD. CYP2E1 induction by EtOH was completely prevented by T3 treatment (RNA and protein expression). The comparison of WT with hepTRβKO mice demonstrates beneficial local hepatic effects of TH on lipid metabolism and CYP2E1 expression, which partially compensate the adverse effect of WAT lipolysis. Therefore, employing exclusively beneficial local TH action, avoiding extrahepatic adverse effects, is highly desirable. We next repeated the experiment in WT mice replacing T3 by MGL-3196 (Resmetirom), a hepatocyte-specific and TRβ-selective TH analog. Pituitary *Tshb* expression, heart weight/tibia length ratio and serum TH concentrations were not altered by MGL-3196. Compared to T3, MGL-3196 treatment led to reduced serum TG concentration and liver weight on control and EtOH diet. We conclude that systemic T3 effects (increased lipolysis) are adverse in ALD and override beneficial local hepatic T3 effects (increased beta oxidation, reduced lipid synthesis and ROS production), precluding T3 treatment in ALD. Yet, hepatocyte-specific TRβ agonists, such as MGL-3196, can harness the beneficial hepatic effects while avoiding extrahepatic effects, allowing therapeutic use of TH action.

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A minimally invasive human biomarker system for the estimation of tissue thyroid hormone status and its application in amiodarone treated patients

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Objective
Serum TSH and thyroid hormone (TH) levels are routinely used as main measures of thyroid function. While these are highly valuable markers, it is becoming more evident that under specific conditions, their predictive power for tissue TH status is limited due to the highly complex nature of tissue-specific TH signaling. This led to a high demand for human tissue TH action markers that could allow the characterization of tissue TH economy. Therefore, our goal was to develop a biomarker system for minimally invasive assessment of TH status using human hair follicles. The biomarker-based prediction model was used to assess the correlation of tissue TH status and blood TH levels in amiodarone treated ($\geq$1-month, AMIO) patients.
Methods
To identify thyroid hormone regulated genes in the human hair follicles (HF), Next Generation Sequencing (NGS) followed by qPCR validation was performed on HF of hypo, eu- and hyperthyroid patients. Only patients without thyroid disease were included in the euthyroid group. Hair follicles were also collected from AMIO patients (treatment longer than 1-month) diagnosed as hypo, eu or hyperthyroid.
Results
Seventeen differentially expressed TH-responsive genes were selected with NGS as potential biomarkers followed by validation with Taqman qPCR on at least 52 independent samples. Four genes showing at least 3-fold change in expression were used to build a classification model with multinomial logistic regression (sensitivity for hypo-, eu-, hyperthyroid classification 0.79; 0.82; 0.81 respectively) to predict TSH-based status of samples (39 hypo-; 55 eu-; 42 hyperthyroid patients; 62.5% female). This model was deployed to determine if measured serum TSH and tissue marker expressions of AMIO patients (41% female, 20 hypo-; 44 eu-; 15 hyperthyroid) correlate similarly to calibrator samples. We found that AMIO patients with TSH in the hypo- or euthyroid range had hypo- or euthyroid marker gene expression patterns, respectively. However, the prediction model indicated that 73% of AMIO patients with hyperthyroid TSH (Me = 0.001 IQR: 0.001-0.013) and fT4 (Me = 56.3 IQR: 29-66.8) levels did not have tissue hyperthyroidism. This discrepancy could be due to the inhibitory action of AMIO on several steps of TH transport, metabolism and signaling.
Conclusions
To assess human tissue TH economy, we developed a minimally invasive qPCR-based biomarker system using hair follicles and built a prediction model. Our model indicates that most AMIO patients diagnosed as hyperthyroid are not hyperthyroid at the tissue level. This corresponds to the lack of unambiguous hyperthyroid symptoms in this patient group.

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Oral Session 6: Pregnancy

OP-06-01

Antithyroid drug exposure during 1,191,904 pregnancies in denmark: a 20-year longitudinal study before and after implementation of iodine fortification

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Objectives
Hyperthyroidism in pregnant women is a clinical concern, and it is important to surveil any change in the occurrence of hyperthyroidism within the pregnant population specifically, especially when a mandatory iodine fortification (IF) program is implemented as it was in Denmark in the year 2000. This longitudinal study aimed to investigate any change in the use of antithyroid drugs (ATD) for the treatment of hyperthyroidism in Danish pregnant women during a 20-year period before and after the implementation of IF.
Methods
We performed a nationwide register-based study of all singleton liveborn pregnancies in Denmark from 1997-2016 (n = 1,191,904). Before the implementation of mandatory IF, regional differences in iodine status were seen with moderate iodine deficiency in west and mild iodine deficiency in east Denmark (divided by the Great Belt). Information on maternal use of ATD in pregnancy was obtained from registrations of redeemed prescriptions of drugs and linked to information in the Medical Birth Register. Longitudinal changes regarding ATD use in pregnancy were evaluated as the frequency per 1,000 pregnancies and using logistic regression (adjusted odds ratio (aOR) with 95% confidence interval (CI)) adjusting for potential confounders (e.g. maternal age and smoking).
Results
Before the year 2000, and thereby before the implementation of mandatory IF, the use of ATD in pregnancy was lower in west than in east Denmark (Table). After the year 2000, and thereby after the implementation of mandatory IF, the use of ATD in pregnancy increased overall and in east and west Denmark specifically (Table). The

	Year of pregnancy	ATD use per 1,000 pregnancies (95%CI)	aOR (95% CI)
Full nationwide cohort	1997-1999	1.74 (1.55-1.95)	Reference
	2001-2005	2.76 (2.56-2.98)	1.53 (1.33-1.77)
	2012-2016	2.23 (2.04-2.43)	1.26 (1.08-1.46)
East Denmark cohort (prior mild iodine deficiency)	1997-1999	2.02 (1.72-2.37)	Reference
	2001-2005	2.81 (2.51-3.13)	1.32 (1.08-1.61)
	2012-2016	2.13 (1.86-2.43)	0.97 (0.78-1.21)
West Denmark cohort (prior moderate iodine deficiency)	1997-1999	1.54 (1.30-1.81)	Reference
	2001-2005	2.72 (2.44-3.02)	1.72 (1.40-2.10)
	2012-2016	2.26 (1.99-2.55)	1.54 (1.24-1.91)

increase reached a similar plateau in both regions and was followed by a decrease towards the end of the 20-year period, which was most pronounced in east Denmark (Table).
Conclusions
The use of ATD for the treatment of hyperthyroidism in pregnancy in Denmark increased in the years following the implementation of mandatory IF and then levelled out. However, baseline values and the observed changes during follow-up differed according to prior population iodine status in each of the regions.

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OP-06-02

Optimizing the dutch newborn screening for congenital hyothyroidism by using amino acids and acylcarnitines via a machine learning based approach

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Objectives
Congenital hypothyroidism (CH) is an inborn thyroid hormone (TH) deficiency mostly caused by disturbances at the thyroid level (thyroidal CH, CH-T). Less frequently, but equally important, CH can be the result of hypothalamic/pituitary dysfunction (central CH, CH-C). Most CH newborn screening (NBS) programs are based on the measurement of thyroid-stimulating hormone (TSH), thereby only detecting CH-T. The Dutch NBS detects CH by measuring total T4 concentrations in newborns as a first tier followed by TSH in the 20% lowest daily T4 concentrations. Thyroxine binding globulin (TBG) is measured in the 5% lowest T4 concentrations to exclude false-positive referrals due to (partial) TBG deficiency. The T4/TBG ratio is calculated as an indirect measure of free T4. The Dutch T4-TSH-TBG algorithm effectively detects both CH-T and CH-C, however, at the cost of a low positive predictive value (PPV) of 21% in the period 2007-2017. A slightly higher PPV of 26% was yielded when using a machine-based learning model on the adjusted dataset described below (methods) based on the original parameters of the Dutch CH NBS. Recent studies describe an association between THs and amino acids (AAs) and acylcarnitines (ACs) of which several are measured during NBS for other diseases. Therefore, we aimed to investigate whether AAs and ACs contribute to discriminate newborns with and without CH using a machine-based learning model which leads to reduction of false-positive referrals.
Methods
Dutch NBS data between 2007-2017 (sex, gestational age and weight, age at NBS, T4, TSH, TBG, T4/TBG ratio, AAs, ACs) from 1079 false-positive referrals and newborns with CH-T (431) and CH-C (84), as well as data from 1842 newborns with a normal CH screening (from 2019) were used. A Random Forest model including all these data was developed and the PPV and area under the ROC curve (AUROC) of this model to predict CH were calculated.
Results
The Random Forest model yielded an artificial sensitivity of 100%, while obtaining a PPV of 48% and AUROC of 0.99. Besides TSH and T4, tyrosine and succinylacetone were the main parameters contributing to the model's performance. A second model emphasizing parameters contributing to predict CH-C showed that T4/TBG ratio contributed most, TSH did not contribute but gestational age, C16:1, phenylalanine, and C2 were important parameters.
Conclusions
Adding several AAs and ACs to this machine-based learning model led to a significant improvement of the PPV (26% to 48%) suggesting AAs and ACs benefit the current algorithm.

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OP-06-03

Thyroid function in childhood is associated with sex, age, bmi, maternal thyroid function, pax8 gene methylation

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Objectives
To assess antenatal and individual-level predictors of thyroid function across two longitudinal cohorts of children.
Methods
Data were taken from two cohorts i) CATSII: 5-10 year-old children enrolled in the CATS (Controlled Antenatal Thyroid Screening) study II from the UK ii) 'PAX8': Children from the ENID (Early Nutrition and Immune Development) trial, a pregnancy and infant supplementation trial in The Gambia (Africa) recruited to the PAX8 study aged 5-8 years based on PAX8 gene region methylation at age 2. CATSII children were classified as 'Normal' if their mothers had normal thyroid function during pregnancy, 'Untreated' in case of maternal suboptimal gestational thyroid function (SGTF) and 'Treated' in case of maternal SGTF treated with levothyroxine during pregnancy. PAX8 participants were recruited into "high" and "low" groups i.e. from the top and bottom methylation quantiles. Children with positive TPO antibodies or with abnormal thyroid function were excluded from analysis.
Results
Data were available for 80 CATS children (excluded: $n = 3$ positive TPO antibodies, $n = 1$ high TSH) and 118 from PAX8 study (none positive for TPO antibodies). For both cohorts: In unadjusted comparisons, girls had higher FT4 compared to boys (CATS: 15.1 pmol/L vs. 14.37 pmol/L, $P < 0.05$. PAX8: 14.0 pmol/L vs. 13.3 pmol/L, $P < 0.05$) and girls had higher FT3 compared to boys in CATSII cohort (5.9 pmol/L vs. 5.4 pmol/L, $P < 0.01$). There were no significant associations with TSH. For the CATSII cohort: In multiple linear regression models, adjusted for age and BMI, Sex (Male $\beta = -0.47$, $P = 0.16$) was not significantly associated with FT4. However, 'Normal' group children had significantly lower FT4 ($\beta = -0.93$, $P < 0.05$) compared to 'Untreated' group. In multiple linear regression models, FT3 was significantly associated with Sex (Male $\beta = -0.39$, $P < 0.01$), Age ($\beta = -0.13$, $P < 0.05$) and BMI ($\beta = 0.05$, $P < 0.05$) but not in the Treated group. For the PAX8 cohort: In multiple linear regression models, adjusted for age and BMI, Sex (Male $\beta = -0.78$, $P < 0.01$) and PAX8 methylation group (Low PAX8 $\beta = 0.80$, $P < 0.01$) were significantly associated with FT4. In multiple linear regression models, FT3 was significantly associated with Age ($\beta = -0.18$, $P < 0.01$) but not Sex, BMI or PAX8 methylation group.
Conclusions
Untreated SGTF was associated with higher FT4 in offspring compared to those whose mothers had normal gestational thyroid function and points to an early programming effect on children's FT4. Lower PAX8 methylation was associated with higher FT4. Children's Sex, Age, BMI were associated with a range of thyroid measures with some consistencies across disparate cohorts.

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OP-06-04

Changes in TSH suppression during pregnancy reveals novel mechanism for increased thyroid hormone production: comparison between euthyroid and thyroidectomized pregnant women

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Objective
Clarify mechanisms determining thyroid homeostasis during pregnancy at hypothalamic-pituitary level.
Methods
Retrospective analysis of 251 pregnant women. 220/251 euthyroid without thyroxine therapy (Group 1), 31/251 thyroidectomized under thyroxine replacement therapy (Group 2). Patients under thyroxine replacement therapy with a TSH between 0.4 and 4.0 were included in the study. Patients with combined T3/T4 therapy were excluded.
Results
The median TSH, FT3, FT4 and FT3/FT4 in Group 1 vs Group 2 were: TSH 1.6 (0.9,2.3) vs 0.5 (0.3,1.7) $P = <0.01$, FT3 4.5 (4.0-4.8) vs (3.9-4.7) $P = 0.23$, FT4 14.2 (12.1-15.5) vs 16.5 (14.8-20.1) $P = <0.001$, FT3/FT4 0.3 (0.3-0.4) vs 0.2 (0.2-0.3) $P = <0.001$. We examined the correlation between FT3/TSH and FT4/TSH in the two groups. Group 1 FT4/TSH correlation: before pregnancy $>r=-0.09$ $P = 0.38$, first trimester $r=0.08$ $P = 0.55$, second trimester $r=0.10$ $P = 0.34$, third trimester $r=-0.38$ $P = 0.02$, after pregnancy $r=0.04$ $P = 0.71$. Group 1 FT3/TSH correlation: before pregnancy $r=-0.01$ $P = 0.90$, first trimester $r=-0.11$ $P = 0.39$, second trimester $r=0.16$ $P = 0.12$, third trimester $r=-0.12$ $P = 0.49$, after pregnancy $r=-0.05$ $P = 0.65$. Group 2 FT4/TSH correlation: before pregnancy $r=-0.54$ $P = 0.008$, first trimester $r=-0.41$ $P = 0.14$, second trimester $r=-0.50$ $P = 0.009$, third trimester $r=-0.40$ $P = 0.09$, after pregnancy $r=-0.12$ $P = 0.71$. Group 2 FT3/TSH correlation: Before pregnancy $r=-0.21$ $P = 0.34$, first trimester $r=-0.16$ $P = 0.57$, second trimester $r=-0.39$ $P = 0.04$, third trimester $r=0.18$ $P = 0.45$, after pregnancy $r=-0.13$ $P = 0.70$. **Discussion.** Taken together these results indicate that in euthyroid pregnant women T4 is less effective in suppressing TSH in the first trimester, this phenomenon is extended to T3 in the second trimester, while TSH suppression by T4 and T3 is recovered in the third trimester. In contrast, in thyroidectomized women T4 suppression of TSH is lower but was maintained in all trimesters, as well as T3 suppression that is lost only in the second trimester. These data suggest that during pregnancy the increased secretion of thyroid hormones is due not only to an increased thyroid stimulation by hCG, but also to reduced negative feedback of thyroid hormones at hypothalamus/pituitary level. The reduced variation in TSH suppression in thyroidectomized pregnant women suggest that this phenomenon may be determined by a change in deiodinase activity in euthyroid pregnant women. Since this mechanism is inhibited by T4 replacement therapy, it is reasonable to suppose that is based upon the modulation of Type 2 Deiodinase activity.

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OP-06-05

The association of gestational thyroid function with gestational diabetes mellitus: an individual participant meta-analysis

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Objective
Gestational thyroid dysfunction and gestational diabetes mellitus (GDM) are common complications during pregnancy and often co-occur. Since thyroid hormones increase glucose uptake and insulin sensitivity, it has been hypothesized that hypothyroidism might increase the risk of GDM. Our aim was to study if maternal thyroid function test abnormalities are risk factors for GDM.
Methods
A systematic search of Ovid MEDLINE, EMBASE and Web of Science was performed by two reviewers independently from inception to October 12, 2022 for prospective cohort studies with data on maternal thyroid function and GDM. We issued open invitations to authors to participate in the current study. We excluded participants who used assisted reproductive technology, had pre-existing thyroid disease, multiple pregnancies or were taking medications that affect thyroid function. The primary outcome was GDM. Individual-participant data were analyzed using logistic mixed-effects regression models adjusting for maternal age, BMI, smoking, parity, ethnicity, and gestational age at blood sampling. The study protocol was registered with PROSPERO CRD42022371927. Since screening methods (universal or selective) differed considerably between cohorts, sensitivity analyses including only cohorts which performed universal screening were done.
Results
From 468 published articles, 36 cohorts were invited and 21 cohorts were included after agreeing to participate. After exclusions, 64370 participants were included in the analyses. Of participants with complete data, 239 (0.4%) had overt hypothyroidism, 1896 (3.3%) had subclinical hypothyroidism, 1299 (2.3%) had isolated hypothyroxinemia, 850 (1.5%) had subclinical hyperthyroidism and 533 (0.9%) had overt hyperthyroidism. There were 1789 (2.8%, range 0.5-12.9%) cases of GDM in all cohorts. In the subset with universal screening, including 8 cohorts with 15702 participants, 1020 women had GDM (6.5%, range 1.6-12.9%). Isolated hypothyroxinemia was associated with a higher risk of GDM as compared to euthyroid women [absolute risk 3.2% vs 2.3%, respectively; Odds Ratio (OR), 1.56; CI, 1.21-2.01; $P = 0.001$]. In the continuous analyses, each 1 SD decrease of free thyroxine (FT4) was associated with an increased risk of GDM [OR, 1.14; 95% CI, 1.08-1.18; $P < 0.001$]. In the universal screening only analysis similar results were found [OR, 1.14; 95% CI, 1.05-1.22; $P = 0.001$]. For thyroid stimulating hormone and other disease entities no significant association was found.
Conclusions
Among pregnant women, both isolated hypothyroxinemia and relatively low FT4 concentrations were significantly associated with a higher risk of GDM. These findings add to the existing evidence on the risk of adverse events in women with gestational thyroid dysfunction and could inform the decision on targeted screening programs for GDM.

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Oral Session 7: Thyroid hormone receptors

OP-07-01

Monocyte and macrophage function is impaired in patients with resistance to thyroid hormone due to a mutation in thyroid hormone receptor ALPHA

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Resistance to thyroid hormone due to a mutation in thyroid hormone receptor alpha (RTHα) is a syndrome whose features include delayed growth and neurocognitive development. Macrophages, which derive from circulating monocytes and have recently been recognized as important thyroid hormone target cells, are innate immune cells that are capable of adopting a wide range of phenotypes. Assuming the right phenotype in the right setting is crucial as macrophage dysfunction has been linked to a broad spectrum of diseases including cancer and diabetes. Knockdown of thyroid hormone receptor alpha (TRα) results in impaired macrophage function in murine and in vitro models, suggesting that T3 signalling via the TRα is a key regulator of macrophage function. The aim of this study is to assess monocyte and macrophage in patients with a severe form of RTHα. Monocytes were isolated from peripheral blood mononuclear cells (PBMCs) derived from 7 RTHα patients and 7 healthy controls. Monocytes were phenotyped using cell surface marker expression and differentiated into macrophages *in vitro*. Monocyte-derived macrophages were treated with lipopolysaccharide (LPS) to induce a pro-inflammatory phenotype, IL-4 to induce an immunomodulatory phenotype or solvent control. Macrophage phenotype was measured using cell surface marker expression and cytokine secretion. Finally, fresh whole blood from RTHα patients and healthy controls was treated with LPS, after which cytokine secretion was quantified as a measure for whole blood pro-inflammatory response. RTHα patients show changes in circulating monocyte subtypes, with a lower percentage of classical monocytes and increased intermediate and non-classical monocytes compared to healthy controls. Increased intermediate monocytes are associated with cardiovascular and autoimmune disease. Monocyte-derived macrophages from RTHα patients exhibit an impaired response to pro-inflammatory stimuli characterized by reduced expression of CD80 and reduced secretion of TNFα after LPS compared to healthy control macrophages. RTHα macrophages polarized into an immunomodulatory phenotype demonstrate decreased secretion of the immunomodulatory cytokines TGF-β and IL-17a compared to cells from healthy controls, suggesting an impaired ability to generate a pro-inflammatory Th17 adaptive immune response. Interestingly, LPS-treated whole blood from RTHα

patients also showed a significantly lower concentration of IL-17a than in healthy controls. In conclusion, monocytes and macrophages derived from RTHα patients exhibit changes in phenotype and response to inflammatory and anti-inflammatory stimuli. This novel human data demonstrates an important role for T3 signaling via the TRα in both the pro-inflammatory response of the innate immune system and the shaping of the subsequent adaptive immune response.

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OP-07-02

Tanycytic thyroid hormone signalling in the regulation of hypothalamic functions and hormone uptake

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Thyroid hormones (TH) play an important role in brain development, central nervous system functions and energy metabolism. In order to mediate these effects in the brain, TH are actively transported through the blood-brain barrier from the periphery to the brain. Tanycytes are specialized ependymal cells that line the wall and the base of the third ventricle in the mediobasal hypothalamus. The cell bodies are in contact with the cerebrospinal fluid and send their processes to hypothalamic nuclei (α-tanycytes) and the fenestrated vessels (β-tanycytes) in the median eminence (ME). Tanycytes projecting to the ME act as gatekeepers for the entry of peripheral substances (eg: leptin and ghrelin) and control hormonal release of hypophysiotropic hormones (eg: GnRH and TRH). They express the repertoire to transport and activate TH and respond to TH themselves. Our previous data suggested that TH modulates tanycytic functions and morphology, which in turn plays a role in the TH transport to the hypothalamus. However, the precise mechanism of how TH and their receptors modulate tanycytic functions is unclear. In this project we use specific genetic tools to manipulate the tanycytic TH transport as well as the tanycytic TH signalling pathway, to investigate the physiological relevance of the interaction between TH and tanycytes. We inhibit or activate TH receptor functions by either overexpressing a dominant negative mutant ($TR\alpha1^{DN}$) or a dominant positive mutant ($TR\alpha1^{VP16}$) of Thyroid hormone receptor α1 in tanycytes. We use qPCR, RNAscope and calcium imaging as tools to investigate the changes in the hormonal axes and gene expression on inhibiting or activating THRα specifically in tanycytes. We further probe into the possible metabolic changes in the mice by using indirect calorimetry. It has previously been shown that addition of the TRH analog taltirelin led to an increase in the size of the endfeet of tanycytes. To further understand the morphological changes of tanycytes due to TH, we performed scratch assays to track the migration patterns of primary tanycytes. Overall, we hypothesize that the modulation of the gatekeeper functions of tanycytes by inhibition or activation of TRα1 specifically in tanycytes and regulation of tanycytic endfeet morphology has an important impact on the central regulation of physiological functions and diseases. A better understanding of how local TH actions modulate tanycytic functions could provide the basis for an improved treatment opportunity of patients with central TH resistance.

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OP-07-03

Rapid screening of thra variants pathogenicity in the zebrafish model

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Mutations in *THRA*, a ligand-inducible transcription factor, cause Resistance to Thyroid Hormone α (RTHα). RTHα manifests with features of hypothyroidism (skeletal dysplasia and growth retardation, neurocognitive impairment, low metabolic rate, reduced intestinal transit) reflecting hormone resistance in TRα-expressing tissues, but associated paradoxically with near-normal circulating TH levels. The lack of clear-cut, abnormal thyroid function tests together with variable phenotype in RTHα, makes diagnoses of this disorder by linking relatively nonspecific clinical features (e.g., growth retardation and neurocognitive abnormalities) with *THRA* variants with unknown significance (VUS) identified by WES and NGS immensely challenging. In this work, we analyzed 20 different *THRA* VUS identified by whole exome sequencing belonging the 100K project, using zebrafish as a model system. The *THRA* mutant-injected zygotes exhibited, at vary degrees, several developmental defects, consisting of abnormal morphology index (AMI) or skeletal malformation (SMI). Head size, pericardial edema, body length, curved tail, and jaw malformations were used to calculate the AMI (0 = unaffected, 1-3 = moderate, 3-5 = severe). The A263S were only mildly affected, as most of the embryos were comparable with the WT injected zygotes. The R228C, T275M, T273A, R384C, V282L, P224L, I299T, M256T, L287P, R266L, G278R, and D268N exhibited moderate phenotype, whereas the remaining variants (H381Q, G291S, P399S, E403K, L400Tfs*7 and del268-273) severely affected embryo morphology. Interestingly, the exposure of high T3 concentration was able to significantly rescue the AMI in zygotes injected in most of the THRA mutant mRNAs, except for the G291S, E403K, L400Tfs*7 and del268-273 transcripts. Skeletal abnormalities were then investigated visualizing cranial cartilage development and bone mineralization in WT or THRA mutant larvae at 120 hpf. Malformations of ceratohyal, ceratobranchial arches and pectoral fins cartilages, and the absent mineralization of hyomandibular, operculum, and cleithrum were quantified to compute SMI (0 = normal, 1-4 = moderate, 4-6 = severe). Consistently with AMI, A263S was similar of those of WT larvae, whereas R228C, T275M, T273A, R384C, V282L, P224L, I299T, M256T, L287P, R266L, G278R, D268N, H381Q and P399S moderately affected skeletal development and benefited from the exposure to high T3 dosage. Lastly, zygotes injected with G291S, E403K, L400Tfs*7 and del268-273 mRNAs were those who showed the most severe SMI at 120 hpf, which were also insensitive to T3 treatment. All these findings correlate with the variable clinical spectrum reported in the patients or the biochemical in vitro data and structural model. We propose zebrafish as a rapid and reliable *in vivo* model for VUS screening, representing a strong tool to stratify THRA variants pathogenicity.

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OP-07-04

Characterizing cell-type specific activities of tralpha2 in the modulation of thyroid hormone action

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Objectives
The canonical function of thyroid hormone receptors (TRs) as mediators of thyroid hormone action on target gene expression is well known. However, the physiological function of the thyroid hormone receptor α splice variant TRα2, that does not bind thyroid hormones, remains elusive. Initial studies addressing the function of TRα2 indicated that it might act as a TRα1 antagonist, but the mechanisms underlying the dominant-negative activity of TRα2 are poorly understood. Further functional studies to characterize TRα2 have been impaired by the lack of reliable isoform-specific antibodies.
Methods and Results
In order to allow specific detection of TRα2, we added different fusion tags to the C-termini of TRα1 and TRα2. To gain first insights into isoform-specific actions, we initially used ectopically expressed TRα isoforms in HEK293 cells for Co-immunoprecipitation (Co-IP) followed by mass spectrometry to obtain isoform-specific protein interactions. By this, we could identify several binding partners interacting with both isoforms. Moreover, in subsequent Co-IP experiments we gained insights into homo- and heterodimerization properties of TRα2 and identified the C-terminal part of TRα2 as the main protein-binding domain by using different TRα1 and 2 protein fragments. Currently, we are investigating whether the interaction of TRα2 with selected binding partners exert T3-independent transcriptional activities and if these functional protein complexes explain the dominant-negative activity described for TRα2.
Conclusions and Outlook
Our preliminary data suggest that TRα2 shares several binding partners with TRα1, and, in contrast to TRα1, thyroid hormones do not affect complex formation of TRα2 with other proteins. We will next further dissect the effect of TRα2 and its binding partners on TRα1 action and expand our analyses to other e.g. cardiac and neuronal cell types. Moreover, we are currently finalizing the generation of induced pluripotent stem cells expressing endogenously tagged TRα isoforms generated by a CRISPR/Cas9-

based approach. IPSCs will be differentiated into selected cell types for further analyses to obtain isoform-specific protein interactions and genome-wide DNA binding profiles of the endogenous receptors. Combining these data sets will give us new insights into tissue-specific activities of TRα2 and its role in thyroid hormone action.

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OP-07-05

Thyroid hormone action in chronic ischemic heart disease

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Background
Ischemic heart disease (IHD) is one of the leading causes of death worldwide. Thus, there is the necessity to find new therapeutic approaches. Thyroid hormones (TH) have a major impact on cardiac function and even appear to improve the outcome after acute ischemia/reperfusion and in chronic heart failure. Still, TH signaling within the heart is not yet completely understood.
Aim
This project aims to investigate the influence of TH receptor alpha (TRα) on IHD using specific mouse models that allow to evaluate the contribution of canonical and non-canonical TH signaling (DNA-binding and regulation of gene expression vs. signaling pathway activation, respectively).
Methods
8-10-week-old C57BL/6J mice underwent permanent ligation of the left descending coronary artery (LAD) and were treated p.o. with 250, 500 or 750 ng/ml T3 for 8 weeks directly after surgery to evaluate the optimal T3 dosing. To evaluate the impact of the different TH signaling pathways, we used wild type (WT), TRα knockout (TRαKO) and knock-in mice with a mutation that abrogates DNA-binding of TRα and canonical TRα signaling (TRαGS). Cardiac function was assessed by echocardiography, remodeling was assessed by histological staining (H&E and SR). TH levels in serum were analyzed by ELISA. Further, sarcomere contraction parameters as well as cardiomyocyte hypertrophy were analyzed using isolated adult cardiomyocytes (CM) from WT, TRαKO and TRαGS mice or neonatal mouse CM (NMCM), respectively. Cardiac vascularization was determined by ani-CD31 immunohistochemistry.
Results
Eight weeks after LAD ligation, heart weight and histologically determined CM size were increased in T3 (500 ng/ml) treated WT mice compared to solvent treated controls. Echocardiography and histological analyses revealed a significantly improved ejection fraction, reduced fibrosis within the remote area and a reduced infarct size in response to T3. Interestingly, the total cardiac vessel number increased with T3 dose and proportional to heart weight, indicating T3-induced neoangiogenesis. Comparison of untreated WT, TRαKO and TRαGS hearts suggests that this effect originates from noncanonical TRα signaling as TRαGS mice had the highest total cardiac vessel length among the genotypes. *In vitro* analyses using CM isolated from WT, TRαKO and TRαGS hearts suggest significant differences in contractility shown by reduced maximal sarcomere shortening of TRαKO and TRαGS compared to WT. Similarly, as observed *in vivo*, we could successfully induce hypertrophic growth of NMCM by 48 h T3 treatment.
Conclusion/Outlook
Our experiments show that T3 is indeed cardioprotective in IHD with improved cardiac function and vascularization eight weeks after myocardial infarction. Current experiments will reveal further how canonical and noncanonical TRα signaling is involved in these T3 mediated cardioprotective effects.

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Oral Session 8: Hypothyrodism/Nodules

OP-08-01

Evaluation of learning methods similar to deep learning and device using deep learning for the diagnosis of thyroid nodules

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Evaluation of learning methods similar to deep learning and device using deep learning for the diagnosis of thyroid nodules.
Background
We recently developed a deep convolutional neural network algorithm (SEveRance Artificial intelligence program, SERA) using 13,560 ultrasonography images of thyroid nodules labeled benign and malignant and this algorithm showed comparable diagnostic performance with experienced radiologists. We wondered whether this self-learning method of SERA could be adapted for human learning as an ancillary approach to man-to-man training.
Methods
Twenty-one internal medicine residents studied the "learning set" in three replicates which was composed of 3,000 images of selected from 13,560 thyroid nodules and their diagnostic performances were evaluated before study and after every learning session using the "test set" which was composed of 120 thyroid nodule images. The diagnostic performances of eight radiology residents were evaluated before and after man-to-man training using the same "test set". After final test, all readers once again evaluated the "test set" with the assistance of SERA.
Results
Before study, the mean area under the receiver operating characteristic (AUROC) of internal medicine residents were considerably lower than that of radiology residents (0.578 and 0.701, respectively). Diagnostic performance of internal medicine residents, although not as much as radiology residents who received man-to-man training (AUROC = 0.735), increased over the course of the learning program (AUROC = 0.665, 0.689, and 0.709, respectively). All diagnostic performances of internal medicine residents and radiology residents were better with the assistance of SERA (AUROC 0.755 and 0.768, respectively).
Conclusion
A novel iterative learning method using selected ultrasound images from big data sets can help beginners learn to differentiate between benign and malignant thyroid nodules. With the assistance of SERA, the diagnostic performances of readers with various experiences in thyroid imaging could be further improved.

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OP-08-02

Individuals on levothyroxine have higher hads anxiety and depression scores than the general population and this is exacerbated by the THR92ALA substitution in DIO2, particularly at higher doses

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Context
Approximately 15% of people with hypothyroidism remain symptomatic despite treatment. The Thr92Ala substitution in *DIO2*, may influence T3 tissue levels.
Methods
We assessed HADS anxiety and depression scores in HUNT2 in 50,901 individuals (6,687 homozygous for Thr92Ala) of whom 1,480 had a history of levothyroxine use (180 homozygous for Thr92Ala). Anxiety and depression caseness (score > = 8) by levothyroxine and Thr92Ala status was assessed using logistic regression, adjusting for age, sex and educational attainment.
Results
The Thr92Ala substitution was present in 13% of the population and was not associated with increased HADS scores in individuals not on levothyroxine. Compared to individuals not on levothyroxine, HADS total score was 0.71 points higher (0.39-1.02, $P < 0.001$) in subjects on levothyroxine overall, and 1.83 points higher (0.93-2.73 $P < 0.001$) in individuals on levothyroxine who were also homozygous for Thr92Ala. Thr92Ala non-homozygous individuals on levothyroxine were 22% more likely than those not on levothyroxine to reach the threshold for HADS anxiety caseness, whilst homozygous individuals were 208% more likely. In GENTHYR individuals on higher doses of levothyroxine (≥100mg) with Thr92Ala had higher HADS caseness OR = 1.86 (95%CI 1.10-3.14) $P = 0.02$, but this was not seen in individuals on lower doses.

Conclusion
Individuals homozygous for Thr92Ala in *DIO2* on levothyroxine have significantly reduced quality of life compared to those non-homozygous, in a dose-dependent manner but there is no effect in the absence of LT4. Since individuals are not aware of their genotype, this provides strong objective evidence for a biological basis to persistence of symptoms in some individuals on LT4.

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OP-08-03

Diagnostic performance of ultrasound-based risk stratification systems for thyroid nodules: a systematic review and meta-analysis

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Objectives
The aim of this study was to evaluate the diagnostic performance of biopsy criteria in four society ultrasonography (US)-based risk stratification systems (RSSs) or thyroid imaging reporting and data system (TIRADS) including the 2021 Korean (K)-TIRADS for thyroid nodules.
Methods
Ovid-Medline, EMBASE, Cochrane, and KoreaMed databases were searched and other eligible articles by manual search were included to identify original articles investigating diagnostic performance of biopsy criteria for thyroid nodules ($\geq$ 1 cm) in widely used society RSSs including American College of Radiology (ACR)-TIRADS, American Thyroid Association (ATA) system, European (EU)-TIRADS, and 2016/2021 K-TIRADS.
Results
Eleven articles were included. The pooled sensitivity and specificity of US-based RSSs were 82% (95% CI: 74-87%) and 60% (95% CI: 52-67%) for ACR-TIRADS, 89% (95% CI: 85-93%) and 34% (95% CI: 26-42%) for ATA system, 88% (95% CI: 81-92%) and 42% (95% CI: 22-67%) for EU-TIRADS, and 96% (95% CI: 94-97%) and 21% (95% CI: 17-25%) for 2016 K-TIRADS. The sensitivity and specificity were 76% (95% CI: 74−79%) and 50% (95% CI: 49−52%) for the 2021 K-TIRADS$_{1.5}$ (1.5 cm cut-off for intermediate suspicion nodule) and 91% (95% CI: 89-93%) and 40% (95% CI: 38−41%) for the 2021 K-TIRADS$_{1.0}$ (1.0 cm cut-off for intermediate suspicion nodule) in a multicenter study. The pooled unnecessary biopsy rates of ACR-TIRADS, ATA system, EU-TIRADS, and 2016 K-TIRADS were 41% (95% CI: 32-49%), 65% (95% CI: 56-74%), 68% (95% CI: 60-75%), and 79% (95% CI: 74-83%), respectively. The unnecessary biopsy rate was 50% (95% CI: 47-53%) for the 2021 K-TIRADS$_{1.5}$ and 60% (95% CI: 59-62%) for the 2021 K-TIRADS$_{1.0}$.
Conclusions
The unnecessary biopsy rate of the 2021 K-TIRADS$_{1.5}$ was substantially lower compared with that of 2016 K-TIRADS and comparable to that of ACR-TIRADS. The 2021 K-TIRADS may help reduce the potential harm due to unnecessary biopsy.

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OP-08-04

Testing for a causal role of thyroid hormone measurements within the normal range: a systematic mendelian randomization study

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Background
Numerous observational studies suggested that variation in thyroid function parameters even within the normal range associates with adverse, in particular non-thyroidal, health outcomes, but causality for most remains to be established.
Methods
We combined individual level and summary level genetic prediction methods, i.e., polygenic scores and Mendelian randomization (MR), to systematically test for an association between liability to variations in thyrotropin (TSH) and free thyroxine (FT4) within the normal range and more than 6,000 molecular traits (metabolites and proteins) and 1,500 diseases across three large population-based cohorts. We replicated and expanded findings in a phenome-wide MR study in the OpenGWAS data base.
Results
We observed little evidence that genetic predisposition explaining variation in TSH and FT4 within the normal range to be associated with non-thyroidal traits across all data sets. Notable exceptions included associations between TSH and atrial fibrillation (odds ratio = 0.92, adjusted p-value = 3.61×10^{-2}) as well as cardiometabolic biomarkers such as sex hormone binding globulin (β = -0.060, adjusted p-value = 9.37×10^{-36}) or total cholesterol (β = 0.030, adjusted p-value = 4.06×10^{-8}), highlighting known pathways of thyroid hormone action.
Conclusion
Contrary to what has been shown in observational studies, we find little evidence of an association between genetically determined thyroid function within the normal range and non-thyroidal phenotypes, suggesting that previous findings suffered from confounding and that screening for thyroid function parameters in otherwise healthy adults is unlikely to have relevant public health impact.

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OP-08-05

Thyroid hormone profiles in individuals on non standard thyroid hormone replacement

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Context
Up to 15% of people with hypothyroidism remain symptomatic despite treatment with levothyroxine. A proportion of these utilise combination thyroid hormone replacement, T3 monotherapy and desiccated thyroid extract (DTE). We sought to explore thyroid hormone profiles in these patients.
Methods
We performed hourly blood tests (8.30am-4.30pm) to assess TSH, T3 and T4 levels in 49 individuals (n = 14 combination thyroid hormone replacement, n = 14 on T3 monotherapy and n = 21 on DTE). Area under the curve (AUC) analysis was performed and odds of having a very low TSH) (<0.05mU/l) and completely suppressed TSH (<0.02mU/l) at 08:30 were undertaken with adjustment for age.
Results
T3 monotherapy and DTE had higher AUCT3 levels and lower AUCT4 levels than combination thyroid hormone replacement. Highest T3 levels were seen with T3 monotherapy. Combined T3 and T4 dose, T3 dose and T4 dose were **not** associated with increased odds of a very low or a completely suppressed TSH. AUCT3 was associated with increased odds of very low TSH OR = 2.95 (95%CI 1.45, 6.03) P = 0.003 and a completely suppressed TSH OR = 2.21 (95%CI 1.12, 4.38) P = 0.02. Maximum T3 was associated with increased odds of very low TSH OR = 2.51 (95%CI 1.24, 5.05) P = 0.01 and completely suppressed TSH OR = 2.31 (95%CI 1.13, 4.70) P = 0.02. No association was seen with AUCT4 or maximum T4 level. Any T3 level above 7.0pmol/l was associated with increased odds of a very low TSH OR = 11.7 (95%CI 1.23, 111) P = 0.03.
Discussion
T3 levels have a greater negative impact on TSH levels than T4 levels. This impedes maintenance of normal TSH levels in individuals on non standard thyroid hormone replacement. Notably the peak T3 levels observed during the day have a substantial impact and appear to be more important in influencing TSH levels than total T3 dose. Taken together this suggests that strategies to reduce peak T3, such as slow release T3, should be investigated as a path to enabling moderate T3 doses without substantially suppressing TSH.

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Oral Session 9: Thyroid Eye Disease

OP-09-01

VRDN-001, a full antagonist antibody to IGF-1 receptor: *in vitro* pharmacology and phase 1/2 results in patients with thyroid eye disease (TED)

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Objectives
Antagonism of the IGF-1 receptor (IGF-1R) has been shown to reduce TED-related inflammation and proptosis. VRDN-001, a high-affinity antagonist antibody to IGF-1R, has distinct pharmacological properties that may enable differentiated dosing and better efficacy than observed with other antibodies. We assessed VRDN-001 in *vitro* pharmacology compared with teprotumumab and clinical proof of concept in a phase 1/2 randomized controlled trial (NCT05176639).
Methods
Inhibition of biotinylated IGF-1 binding to IGF-1R expressing FreeStyle™ 293-F cells was assessed by flow cytometry; inhibition of IGF-1 mediated signaling (phosphorylation of IGF-1R and AKT) was assessed in primary human ocular choroidal fibroblasts. In the phase 1/2 trial, adults with active moderate-to-severe TED and clinical activity score (CAS) $\geq$4 were randomized to 2 infusions 3 weeks apart of either 3, 10, or 20 mg/kg VRDN-001 or placebo. Safety and efficacy through 6 weeks were assessed.
Results
In the *in vitro* studies, VRDN-001 provided near-complete inhibition of IGF-1 binding and IGF-1 mediated signaling at concentrations $\geq$50 nM; in contrast, teprotumumab provided only partial inhibition of IGF-1 binding and IGF-1R signaling. In the phase 1/2 trial of VRDN-001 (n =21) vs placebo (n =6), baseline characteristics were similar between groups. All 3 doses of VRDN-001 showed similar reduction in proptosis and clinical activity at 6 weeks. Across all doses, the overall responder rate (% of patients with $\geq$2-mm reduction in proptosis and $\geq$2-point reduction in CAS) was 67% (14/21; VRDN-001) vs 20% (1/5; placebo). Mean reduction in CAS was 4.1 (VRDN-001) vs 1.8 (placebo), and CAS decreased to 0 or 1 for 62% (13/21; VRDN-001) vs 20% (1/5; placebo). Complete resolution of diplopia occurred for 54% (7/13; VRDN-001) vs 0% (0/3; placebo). AEs were mostly mild, with no severe or serious AEs reported.
Conclusions
VRDN-001 provides near-complete inhibition of IGF-1 binding and IGF-1R signaling, which may explain the rapid, marked reductions in proptosis and clinical activity in patients with TED enrolled in the phase 1/2 trial. The potential clinical efficacy and safety of VRDN-001 in TED will be further assessed in the THRIVE phase 3 randomized controlled trial.

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OP-09-02

Preclinical pharmacokinetics and clinical exposure prediction for VRDN-003, a next-generation half-life extended antibody to the IGF-1 receptor for thyroid eye disease

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Objective
Evidence shows that IGF-1 receptor (IGF-1R) antagonism reduces the inflammation and proptosis that occur in thyroid eye disease (TED). VRDN-001 is a full antagonist to IGF-1R, and VRDN-003 is a next-generation, half-life extended version of VRDN-001 designed to enable subcutaneous (SC) administration. We compared the *in vivo* pharmacokinetic (PK) parameters of VRDN-001 and VRDN-003 and used a PK model to simulate potential VRDN-003 SC dosing regimens.
Methods
PK parameters were assessed in cynomolgus monkeys, with a single 7.5-mg/kg dose administered via intravenous (IV) infusion or SC injection. PK samples were collected at 12 time points (VRDN-001 group) or 15 time points (VRDN-003 group); non-compartmental PK parameter estimates were calculated using Phoenix WinNonlin v8.3 PK software. A 2-compartment PK model based on VRDN-001 clinical data, with adjusted clearance to reflect the half-life extension of VRDN-003, was developed and potential clinical dose regimens were simulated.
Results
In cynomolgus monkeys, bioavailability was similar for VRDN-001 (70%) and VRDN-003 (71%). For both IV and SC administration, half-life was approximately 2 times as long for VRDN-003 vs VRDN-001, AUC_{inf} approximately 65% greater, and clearance approximately 40% slower (Table 1). Average serum concentration of VRDN-001 administered IV Q3W was 106 µg/mL for 10 mg/kg and 32 µg/mL for 3 mg/kg. The PK model predictions for average serum concentration of VRDN-003 administered SC (300 mg in 2 mL with a 600-mg loading dose) were 104 µg/mL if given Q2W and 56 µg/mL if given Q4W.
Conclusions
VRDN-003 half-life in cynomolgus monkeys is approximately twice as long as it is for first-generation anti-IGF-1R antibodies. Based on human PK modeling, SC dosing of VRDN-003 either once or twice monthly will produce drug concentrations in the range of those achieved with Q3W IV administration of 3 mg/kg VRDN-001 and 10 mg/kg VRDN-001. These results suggest the potential for VRDN-003 efficacy via self-administered SC injection.

Table 1 V and SC PK Parameters of VRDN-001 and VRDN-003

Drug	ROA	V_z[a] (mL/kg)	CL[a] (mL/day/kg)	$t_{1/2}$ (days)	AUC_{inf} (µg*day/mL)	%F
VRDN-001	IV	78 ± 6	8.5 ± 2.1	6.6 ± 1.3	915 ± 191	70
	SC	112 ± 23	13.1 ± 5.6	6.3 ± 1.4	636 ± 222	
VRDN-003	IV	86 ± 17	5.2 ± 0.8	11.9 ± 3.4	1480 ± 223	71
	SC	132 ± 2	7.2 ± 1.2	12.8 ± 2.0	1050 ± 182	

[a]V_z and CL are V_z/F and CL/F for SC routes of administration. ROA, route of administration; V_z, apparent volume of distribution of the terminal phase; CL, total clearance rate; $t_{1/2}$, half-life; AUC_{inf}, area under curve extrapolated to infinity; %F, bioavailability.

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OP-09-03

Linsitinib, AN IGF-1R inhibitor, attenuates disease development and progression in a model of thyroid eye disease

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Study objective
We investigated the effect of linsitinib, a dual small-molecule kinase inhibitor of the insulin-like growth factor 1 receptor (IGF-1R) and the Insulin receptor (IR),

on Graves' Disease and thyroid eye disease. Graves' disease (GD), also known as 'Basedow's disease', is the most common cause for hyperthyroidism, typically presenting in patients between 40-60 years. GD is an autoimmune condition of the thyroid which is caused by autoantibodies against the thyroid stimulating hormone receptor (TSHR), leading to overstimulation of the thyroid gland. Thyroid eye disease (TED) is the most common extra thyroidal manifestation of GD and occurs in about 50% of the clinical cases.
Methods
To induce Graves' Disease in mice we immunized mice 3-times with a plasmid encoding for the A-subunit of the TSHR. During an *early* and *late* stage, resembling the active and chronic state of the autoimmune disease, linsitinib was administered orally for four weeks. Typical clinical features in thyroid eye disease and inflammation were determined by histology and MRI.
Results
As seen in the histology, linsitinib prevented autoimmune hyperthyroidism, morphological changes, formation of brown adipose tissue in the orbita and orbital immune cell infiltration into the orbit in the active state as well as the chronic phase. To evaluate the effect of linsitinib during the course of therapy, living mice were examined via MRI. A distinctive migration of immune cells in the orbit, visualized by F19 imaging, with consecutive inflammation can be seen in the TSHR-immunized group, which is completely blocked by treatment with linsitinib. In addition, the orbital inflammation was partnered with the onset of muscle edema and formation of brown adipose tissue in TSHR-immunized mice, effects that were abrogated upon application of linsitinib.
Conclusion
In summary, we demonstrate the development of GD and TED in a mouse model upon immunization against the TSHR. The IGF-1R antagonist linsitinib blocks the development of the local pathologies of GD and TED in an *early* and *late* phase of the autoimmune disorder and also prevents development of the autoimmune response. We show that treatment of immunized mice with linsitinib after disease onset significantly limited the severity of the disease, indicating the clinical significance of the findings and providing a path to therapeutic intervention of Graves' Disease. Our data support the use of linsitinib as a novel first line treatment of thyroid eye disease.

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OP-09-04

Novel, rapid, sensitive bioassay for thyrotropin receptor stimulatory antibodies- a multicenter, single blind study

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Background
Autoantibody mimicry of hormone action at the thyrotropin receptor (TSH-R) and aberrant signaling of TSH-R by autoantibodies (TSH-R-Ab) causes autoimmune thyroid disease (AITD), hyperthyroidism and hypothyroidism, both of which affect millions of patients worldwide. In this multicenter, single blind study, the specificity, sensitivity and performance of a novel bioassay for stimulatory TSH-R-Ab were tested.
Methods
TSH-R-Ab were measured in a blinded manner with a TSH-R binding immunoassay (Cobas e411, Roche), and both stimulatory (TSAb) and blocking (TBAb) bioassays with luciferase release as readout (Thyretain®, Quidelortho) according to manufacturer's instructions. TSH-R-Ab was also measured using the new TSAb bioassay (TurboTM). TurboTM utilizes a cAMP biosensor that is an engineered form of firefly luciferase in which the cAMP-binding domain of protein kinase A is fused between the N- and C-termini such that the luciferase is inactive until cAMP binds to the cAMP binding site. Using this biosensor, luciferase activity is proportional to intracellular cAMP levels. TurboTM detects TSAb in serum at room temperature, in a real-time homogeneous format, which delivers results in 60 minutes. It does not require cell culture, sample dilution, washing or cell lysis steps.
Results
Eight-hundred forty-four samples of unselected, consecutive patients with AITD and control subjects, devoid of autoimmune endocrine and thyroid disorders, were included. Mean age (SD) was 49 (14.7) years, range 1-89 years. Female: male sex ratio was 3.7:1. The four TSH-R-Ab assays were negative in all 174 controls. In contrast, the Turbo TSAb, Thyretain® TSAb and the binding assays detected TSAb in 557 of 670 (83%), 526/670 (78%) and 430/637 (67%) AITD samples, respectively (TurboTM bioassay vs binding immunoassay, chi-square test $P < 0.001$). The results of the Turbo bioassay highly correlated with both thyroid function in Graves' hyperthyroidism as well as with the clinical activity and severity of Graves' orbitopathy ($P < 0.001$). Inter- (two users) and intra- (two lots) assay comparison for the Turbo bioassay showed coefficient of variations of only 4%, 3%, and 2%, respectively. The two TSAb bioassays, TurboTM and Thyretain®, correlated (Spearman's $r = 0.7$, $P < 0.001$). Furthermore, the magnitude of serum levels in both TSAb bioassays correlated with TSH-R-Ab binding (both $P < 0.001$). Finally, seventeen AITD samples showed dual TSH-R-Ab positivity in the TBAb and TSAb bioassays.
Conclusions
The novel, rapid, easy-to-perform, sensitive and specific TurboTM bioassay performs better than the established TSH-R-Ab binding immunoassay and the Thyretain® bioassay. It provides clinically useful information for the accurate diagnosis and management of AITD patients.

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OP-09-05

Clinical and visual outcomes of dysthyroid optic neuropathy after surgical orbital decompression

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Objectives
Dysthyroid Optic Neuropathy (DON) is a severe complication of Graves' Orbitopathy (GO), requiring prompt treatment. First line treatment is high dose intravenous steroids, then surgery is considered mandatory. We studied the clinical outcomes of surgery for DON, with and without previous therapy with steroids.
Methods
88 orbits of 56 patients with DON were treated with surgical orbital decompression. 33 orbits (37.5 %) underwent surgery as first line treatment, while 55 (62.5%) after unresponsiveness to high dose steroids. We studied, before and after surgery (1 week, 1, 3, 6, 12 months), pinhole best corrected visual acuity (p-BCVA), colour sensitivity, automated visual field, pupil reflexes, optic disc and fundus appearance, exophtalmometry and ocular motility. Clinical activity score (CAS) was used to grade GO activity. Exclusion criteria were previous orbital surgery, concurrent neurological or ophthalmologic diseases, incomplete follow-up. Surgery was considered successful if no other intervention was needed to preserve visual function.
Results
Surgery was successful in 77 orbits (87.5%). The remaining 11 orbits (12.5%) needed further intervention. Overall, all parameters of visual function (except for diplopia) improved significantly at follow-up ($P < 0.05$) and GO inactivated (CAS < 3) within one month. At three months (primary endpoint), all 77 responding orbits had p-BCVA > 0.63 and the 11 unresponsive orbits had p-BCVA ≤ 0.63. At follow-up, visual field parameters and colour sensitivity showed no correlation with responsiveness. At primary endpoint, the ROC curve analysis applied to p-BCVA (decimal notation) resulted in an AUC of 0.993 (95% CI 0.978–1.000; $P < 0.0001$) with a cut off of > 0.63 (100 % sensitivity and 88.9 % specificity). Therapy with high dose steroids before surgery was associated to a better response rate (96% vs.73%; $P < 0.005$) and to a higher final p-BCVA (0.89 ± 0.11 vs. 0.82 ± 0.20, $P < 0.05$). Balanced wall decompression resulted in a better response compared to only medial wall decompression (96% vs. 80%;

$P < 0.05$). Significant inverse correlation was found between final BCVA and patient's age (r = -0.42; $P < 0.0005$). Unresponsive orbits had worse p-BCVA ($P < 0.001$) and higher proptosis ($P < 0.005$) at baseline.
Conclusions
Surgical decompression is an excellent treatment for DON. After surgery, all but one parameter (diplopia) improved. P-BCVA > 0.63 at three months was highly associated to a successful response. We also observed that steroids administered before surgery seem to maximize its efficacy. The time between 1 and 3 months after surgery appears to be very important to identify those orbits that need additional surgery to treat DON.

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Oral Session 10: Novel diagnostics in Thyroid cancer

OP-10-01

Identification of clinical and histopathological risk factors for radioactive iodine refractory disease in patients with follicular and hurthle cell thyroid carcinoma

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Introduction
Historically, treatment of follicular thyroid carcinoma (FTC) and oncocytic thyroid carcinoma (OTC) is based on thyroidectomy followed by radioiodine (RAI) therapy. Both tumor types have a good prognosis (10-year survival 80-94%), but this changes significantly once RAI-refractory disease occurs (median 3.5 years), which limits further treatment possibilities. The main risk factors for developing RAI-refractory disease in FTC and OTC are unknown. Our aim was to identify clinicopathological risk factors for developing RAI-refractory disease in FTC and OTC patients, facilitated by an extensive histopathological revision.
Methods
All adult FTC and OTC patients treated at the Erasmus MC between 2000 and 2016 were retrospectively included ($n = 142$). The 2015 ATA Guidelines were used to define RAI-refractory disease. An extensive histopathological revision was performed independently by two pathologists, applying the 2022 WHO Guidelines. Risk factors were identified using logistic regression, and a sensitivity analysis on histological subtype was performed to distinguish between FTC and OTC.
Results
Of the 142 included patients, 36 became RAI-refractory (25.4%; $n = 16$ FTC) over a median follow-up time of 8.5 years [IQR: 5.0-11.4]. Patients developed RAI-refractory disease after a median of 2 years [IQR: 0.9-4.4] and 2 therapies [IQR: 2-3] after initial diagnosis. RAI-refractory disease was mostly diagnosed based on the criterion of disease progression despite sufficient RAI dosage (38.9%). Patients with refractory disease had a significantly worse 10-year survival than the RAI-sensitive group (62.4% vs 95.9%; $P < 0.001$). Clinical risk factors were higher age at diagnosis (OR 1.05; 95%CI 1.02-1.08) and presentation with distant metastasis (OR 4.99; 95%CI 2.03-12.3). Histopathological risk factors were $\geq$4 foci of vascular invasion (OR 8.13; 95%CI 2.58-25.6), no encapsulation (OR 6.83; 95%CI 2.76-16.9), extra-thyroidal extension (OR 5.43; 95%CI 2.12-13.9) and oncocytic cell metaplasia (OR 3.98; 95%CI 1.80-8.79). Results remained unchanged after correction. Compared to FTC, presentation with distant metastasis was the strongest risk factor in OTC patients for RAI-refractory disease, rather than classical histopathological features.
Conclusion
To our knowledge, this is the first study that extensively revises histopathology in a large cohort of FTC and OTC patients, and that correlates clinical and histopathological risk factors with development of RAI-refractory disease. Age at diagnosis, distant metastasis at presentation and tumors showing no encapsulation, extensive vascular invasion or oncocytic cell metaplasia are risk factors for RAI-refractory disease. Our data can aid clinical decision making, particularly in those who have a high probability to develop RAI-refractory diseases, such as patients with OTC presenting with distant metastasis.

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OP-10-02

Role of the telomere abnormalities and chromosome fragility on the risk of second malignant tumor in papillary thyroid cancer patients

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Objectives
Genomic instability play a role in cancer development through different mechanisms including chromosome fragility and in particular the altered telomere length (TL). Previous studies showed that the presence of short telomeres in the blood was associated with development of sporadic head and neck, bladder, lung, renal and breast cancer. In thyroid cancer, has been demonstrated that familial form of papillary thyroid cancer (FPTC) has shorter telomeres in blood leukocytes compared to the sporadic form of PTC (NFPTC). Moreover, higher rate of second malignant tumor (SMT) in FPTC has been recently reported, suggesting the impact of genetic background in the cumulative risk of developing SMT in thyroid cancer patients. The aim of this study was to evaluate the association between the presence of shorter telomeres in blood leukocytes and the risk of SMT in PTC patients.
Methods
We retrospectively evaluated 119 PTC patients (43 FPTC and 76 NFPTC) characterized for TL by Telomerase Fluorescence *in situ* hybridization (FISH) assay on lymphocyte metaphase chromosomes using a fluorescein-conjugated telomere PNA probe.
Results
In our analysis we observed a significantly shorter TL in PTC patients with SMT when compared to PTC patients without SMT ($P = 0.0207$). We performed the ROC curve analysis to find a cut-off of TL able to predict the risk to develop SMT beyond PTC. Our analysis showed that a TL <0.715 (AUC: 0.6853; AUC CI: 0.5307-0.8398) was significantly associated with the risk to develop SMT in PTC patients. Moreover, we observed that the shorter TL was more frequent in FPTC compared to NFPTC patients ($P < 0.0001$) and the patients with familial form of PTC developed SMT more frequently than NFPTC patients (20.9% vs 7.9%, $P = 0.03$).
Conclusions
The chromosome fragility might play an important role in cancer development in thyroid cancer patients. Our study demonstrates that PTC patients with chromosome instability, characterized by shorter telomeres, are more likely to develop SMT beyond thyroid cancer.

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OP-10-03

KI67 proliferative index, but not mitotic count and necrosis, is a prognostic factor in patients with medullary thyroid cancer: a single-center retrospective analysis according to the 2022 who pathological classification

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Background
The 2022 WHO Classification of Endocrine and Neuroendocrine Tumors has introduced, as other neuroendocrine neoplasms, new pathological features to classify medullary thyroid carcinoma (MTC) in low/high grade. However, whether it can be reliable in clinical practice should be confirm by further studies.
Aim
To verify the predictive value of the 2022 WHO grading system in patients with MTC.
Materials and Methods
Tumor tissue from 45 patients with MTC were reviewed to assess mitotic count, Ki67 proliferative index and necrosis and classified in high grade in presence of at least one of the following features: mitotic count $\geq$5 per 2 mm^2, Ki67 $\geq$5% or tumor necrosis. Uni- and multivariate analyses were performed to identify clinicopathological factor associated with persistent/recurrent disease.
Results
Data of 45 patients with MTC (14 M, 31 F). Necrosis was present in 24 (53.3%) of tissue specimens: 21 had focal and 3 had diffuse necrosis. No patient had mitotic count

≥ 5 per 2 mm^2, indeed median mitotic count was 1 (range 0-3). Median Ki67 was 2% (range 1-15) and 6 patients had Ki67 $\geq 5\%$. Therefore, 27 (60%) patients were classified as high grade, whereas 18 (40%) were low grade MTC. During a median follow-up of 89.8 months (IQR 51-106 months), 13 (28.9%) patients had persistent/recurrent disease with a median time to progression (TTP) of 8.6 months (IQR 3.2-48.7). Factors associated with event of disease during the follow-up were: tumor size (HR = 1.09, 95%CI = 1.05-1.15; $P < 0.001$), lymph node metastases (HR = 4.37, 95%CI = 1.37-13.97; $P = 0.01$) and ki67 (HR = 1.24, 95%CI = 1.07-1.45; $P = 0.005$). No different risk of progressive disease was observed between low and high grade because both features necrosis and mitosis count didn't lead to worse outcome. At multivariate analysis, tumor size and ki67 were independently associated with persistent/recurrent disease. Progressive disease was more likely in patients with Ki67 ≥ 2 (HR = 3.15, 95%CI = 1.05-9.45; $P = 0.04$) and survival analysis demonstrated a trend across patients with ki67 ≤ 2, $2 <$ ki67 < 5 and ki67 ≥ 5: median TTP was 6.4 months for the latter (log-rank p value for trend = 0.01).

Discussion

We didn't observe a prognostic role for mitotic count and necrosis, contrary to ki67 in patients with MTC. Although we analyzed only 45 patients, we speculate that a two-tiered grading (low/high) may be not totally accurate. Indeed, we observed a slight increased risk of progressive disease also in patients with $2 <$ ki67 < 5. Therefore, a third category of intermediate grade may be suitable if other studies confirm our findings.

Conclusions

Ki67 index is a reliable prognostic factor and further studies are needed to better investigate its role in patients with MTC.

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OP-10-04

Improvement in neck ultrasound report quality following implementation of ETA guidelines for postoperative cervical ultrasound for thyroid cancer follow-up, a prospective population study

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Objective

We prospectively evaluated the quality of postoperative neck ultrasound (POU) for thyroid cancer patients in our healthcare region after the implementation of European Thyroid Association (ETA) guideline-based POU assessment with one radiology group in 2018.

Methods

Our analysis involved 672 differentiated thyroid cancer (DTC) patients treated at our center between April 1, 2017, and March 1, 2023. POU report quality was compared between radiology group 1, which implemented ETA guideline-based assessment, and other radiology groups. Differences in POU quality were evaluated before and after implementation of guideline-based assessment. Additionally, we evaluated the ability of undetectable (< 0.2 ng/mL) or low-detectable (0.21 to 0.99 ng/mL) serum thyroglobulin (Tg) measurements at 1-year follow-up (FU) to predict the absence of persistent disease or relapse at 3-year FU based on American Thyroid Association (ATA) treatment de-escalation guidelines.

Results

Radiology group 1 had significantly higher mean utility scores (UtS) for POU reports of abnormal thyroid bed nodules compared to other radiology groups (4.84 vs. 3.62 for indeterminate nodules, 5.24 vs. 3.95 for suspicious nodules; $P < 0.001$). All radiology groups had a significant increase in mean UtS for POU reports after the implementation of guideline-based assessment by radiology group 1 compared to reports done between December 2013 and January 2018 (4.98 vs. 3.88 for radiology group 1, 3.81 vs. 2.96 for other radiology groups; $P < 0.05$). Radiology group 1 continued to have significantly higher mean UtS for POU reports than other groups after implementation (4.98 vs. 3.81, $P < 0.0001$). Assessing POU reports according to the ETA guideline-based abnormal lesion classification rules revealed that 94% of POU reports describing suspicious thyroid bed nodules and 85% of reports describing suspicious LNs by radiology group 1 were considered sufficient, compared to only 45% and 68% of those reported by other radiology groups. For 242 patients with normal US lesion status (US-N) and Tg < 0.2 ng/mL (Tg-N) at 1-year FU, 233 had US-N at 3-year FU, and the negative predictive value (NPV) for US-N and Tg-N was 96%. For patients with US-N and Tg 0.2–0.99 ng/mL (Tg-I) at 1-year FU, the NPV for US-N and Tg-I was also 96%.

Conclusions

Implementation of 2013 ETA POU reporting guidelines allows provision of high-quality POU reports to clinicians, which can lead to increased accuracy in estimating risk of recurrence of thyroid cancer and reduce unnecessary repeat POU.

Table Mean UtS for indeterminate/suspicious thyroid bed nodules: pre-ETA and post-ETA.

Mean UtS	Radiology group 1	Other Radiology groups	P value
Pre-ETA	3.88	2.96	<0.05
Post-ETA	4.98	3.81	<0.0001
P value	<0.05	<0.05	

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OP-10-05

Hypothyroidism and the risk of cancer: a danish register-based long-term follow-up study

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Objective

Globally, cancer is one of the leading causes of death. Therefore, identification of risk factors is of paramount interest. Whether thyroid dysfunction is a cancer risk factor is currently being debated. The aim of this study was to evaluate the risk of cancer in patients diagnosed with hypothyroidism.

Methods

This is a register-based nationwide cohort study of individuals diagnosed with hypothyroidism referred to Danish hospitals (followed from 1995-2017). Each hypothyroid individual was matched to four reference individuals from the general population according to age and sex. Using Fine & Gray competing risk regression models, we studied the association of hypothyroidism and all-cause cancer, adjusted for pre-existing morbidity. Sub-analyses were stratified for cancer site, (breast, prostate, lung, and colorectal respectively) and age when first diagnosed with hypothyroidism.

Results

The cohort consisted of 96,825 patients diagnosed with hypothyroidism (followed for a median of 11.4 years (range: 6.1-17.9)), 16,482 of whom received a cancer diagnosis. The reference population consisted of 387,300 individuals (followed for a median of 10.9 years (range: 5.7-17.5)), 56,737 of whom received a cancer diagnosis. Receiving a hypothyroidism diagnosis was associated with an increased risk of all-cause cancer (sub-distribution hazard ratio (SHR): 1.10; 95% confidence interval (CI): 1.08-1.12), as well as an increased risk of colorectal- (SHR: 1.13; 95% CI: 1.08-1.18) and breast cancer (SHR: 1.12; 95% CI 1.08-1.16). The risk of lung- (SHR: 0.81; 95% CI 0.77-0.85) and prostate cancer (SHR: 0.86; 95% CI 0.79-0.95) was lower in hypothyroid patients compared to the reference population. Sub-analyses stratified by age when first diagnosed with hypothyroidism yielded similar results.

Conclusion

In this register-based study, hypothyroid patients referred to Danish hospitals had an increased risk of all-cause cancer, as well as breast- and colorectal cancer, but a decreased risk of lung- and prostate cancer compared to the general population. Whether a causal link exists remains to be proven.

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Oral Session 11: Autoimmunity/Hyperthyroidism

OP-11-01

Effect of gluten-free diet on autoimmune thyroiditis progression in patients with no histological confirm of celiac disease: a meta-analisys

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Background
Hashimoto's thyroiditis (HT) is the most common autoimmune disease worldwide. Prevalence of celiac disease (CD) is higher in HT patients and HT is the most prevalent coexisting disease in CD patients. In the last years, interest about gluten free diet (GFD) has increased for its supposed extraintestinal anti-inflammatory effect, so many patients with HT initiate GFD on their own.
Objectives
Aim of this meta-analysis is to examine all quantitative literature available data about the effect of a GFD period on TgAb, TPOAb, TSH, FT4 and FT3 levels in patients with HT and no histological confirm of CD.
Methods
The study was conducted according to MOOSE. The search was performed on databases Medline and Scopus. No language restriction was used. The last search was performed on November 16th, 2022. Quality assessment was performed. Data collection included patients with HT and no gastrointestinal disease or presenting any gastrointestinal disease with negative histology for CD. Meta-analyses were performed using random-effect model. Statistical analyses were performed using StataSE 17.
Results
The online search retrieved 371 articles and 4 studies with total 87 patients were included for quantitative analysis. The risk of bias was generally low. We observed an overall reduction trend of antibody levels with effect size of -0.39 (CI: -0.81, 0.02; $P = 0.06$; $I^2 = 46.98\%$) for TgAb and of -0.68 (CI: -1.30, -0.05; $P = 0.03$; $I^2 = 74.73\%$) for TPOAb, after 6 months of GFD. These heterogeneities were solved with sub-analyses between patients with only HT and patients with HT and non-celiac gluten sensitivity (NCGS) (HT-NCGS) (TgAb $P = 0.02$) (TPOAb $P = 0.01$). TSH levels showed a significant reduction with effect size -0.35 (CI: -0.64, -0.05; $P = 0.02$; $I^2 = 0\%$) and FT4 levels showed a significant elevation with effect size 0.35 (CI: 0.06, 0.64; $P = 0.02$; $I^2 = 0\%$), after the same period of GFD (6 months). FT3 levels, instead, did not display a significative variation compared to the pre-diet levels (overall effect size 0.05; CI: -0.38, 0.48; $P = 0.82$; $I^2 = 51.24\%$). However, this heterogeneity was solved with a sub-analysis between HT patients and HT-NCGS patients (FT3 $P = 0.04$). The performed sub-analyses evidenced statistically significant changes for HT-NCGS patients in TgAb (Overall effect size -0.75; CI: -1.16, -0.34; $P < 0.001$; $I^2 = 0.00\%$) and TPOAb (Overall effect size -1.15; CI: -1.58, -0.72; $P < 0.001$; $I^2 = 0.00\%$) levels.
Conclusions
This is the first meta-analysis investigating the effect of GFD on HT. Our results seem to indicate a positive effect of the gluten-deprivation on thyroid function and its inflammation, in particular in patients with HT and NCGS. However, current evidences are not yet sufficient to recommend this dietary approach to all patients with diagnosis of HT.

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OP-11-02

Systematic assessment of polyautoimmunity in patients with established lymphocytic thyroiditis

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Background
The association of autoimmune thyroiditis (AIT) with nonendocrine autoimmune disorders has been reputed for long time as a variant of type 2 polyglandular autoimmune syndrome (PAS2). Nowadays, it is framed in the picture of polyautoimmunity and its relevance is owed to its prevalence, far higher than PAS 2, and its expanding galaxy. Systematic studies on this field are rather scanty and mostly based only on the presence of circulating antibodies. Our study has been designed, over the last ten years, to diagnose all the autoimmune disorders sequentially diagnosed in patients with already known lymphocytic thyroiditis.
Methods
In a cohort of 9,415 consecutive outpatients, AIT was diagnosed in 2884 (30.6%). If suspected on clinical and/or immunological ground, the presence of further autoimmune disorders was ascertained on the basis of Consensus or Guidelines specific for each disease. Histological confirmation was obtained in all gastrointestinal disorders.
Results
The presence of AIT in a frame of poly-autoimmunity has been observed in 358 patients (12.8%)(315W/43M; median age = 39 years). Of these, 34 patients (10.5%) had more than one autoimmune disorder associated with AIT. The most frequent associated disease was chronic atrophic gastritis (CAG) (30.4%), followed by non-segmental *vitiligo* (19.9%), celiac disease (11,8%), and multiple sclerosis (7.2%). The juvenile form (<30 yrs) accounted for 14.5% of the whole sample and was characterized by a higher frequency of celiac disease (44.2%) associated with thyroiditis, followed by *vitiligo* (13.4%), while CAG was less observed (7.7%). These poly-autoimmune patients showed peculiar clinical features. In fact, thyroxine malabsorption was higher than in patients with isolated thyroid diseases (34.6 vs 8.1%; $P < 0.0001$;OR = 5.953). Unexplained anemia was also significantly higher in euthyroid patients with polyautoimmunity (23.2 vs 6.8%; $P < 0.0001$ OR = 4.105) than in euthyroid patients with isolated AIT. Also, recurrent pregnancy loss was also clearly increased (6.9% vs 1.7%; $P < 0.0001$; OR = 4.06) in poly-autoimmune patients as compared with isolated AIT.
Conclusions
Additional autoimmune disorders were diagnosed in 1/8 patients with AIT and 1/10 of them was younger than 30 years. Atrophic gastritis, *vitiligo* and celiac diseases were the most frequent autoimmune disorders associated with AIT, with a clear age-related prevalence. The presence of thyroxine malabsorption, chronic unexplained anemia and recurrent pregnancy loss in patients with AIT are clinical features of poly-autoimmunity and should prompt further diagnostic workup for associated autoimmune disorders.

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OP-11-03

Effects of acute triiodothyronine treatment in patients with anterior myocardial infarction undergoing primary angioplasty: does infarct size matter?

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Objectives
Triiodothyronine (LT3) administration for 48hours in patients undergone primary angioplasty showed favourable effects on cardiac function and remodelling early after myocardial infarction (Thy-Repair, EudraCT 2016-000631-40, Thyroid 2022 Jun;32(6):714-724). The present study investigated whether this beneficial effect was dependent on the severity of infarct size. The extent of infarct size is one of the main determinants of morbidity and mortality after myocardial infarction.
Methods
This is a post hoc analysis which included data from 41 patients participating in the Thy-Repair ($n = 20$ placebo and $n = 21$ LT3). LT3 treatment started after stenting as an intravenous (i.v.) bolus injection of 0.8μg/kg of LT3 followed by a constant infusion of 0.113μg/kg/h i.v. for 48 hours. All patients had CMR at hospital discharge and end-points were left ventricular (LV) ejection fraction (LVEF), LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), Left Ventricular Mass Index (LVMI) and Infarct Volume (IV). Patients were divided in two groups based on the median value of the infarct size; small infarct size with IV ≤ 20% of the LV and large infarct size with IV > 20% of the LV.

Results
In patients with small infarct size, LVEF, LVEDVi, LVESVi and IV at discharge were similar in both placebo and T3 treated group. In patients with large infarct size, despite similar IV, LVEDVi and LVESVi were significantly reduced while LVEF was significantly increased in T3 treated group vs placebo.
Conclusion
These data indicate that the favourable effects of acute LT3 treatment on cardiac function and remodelling early after myocardial infarction is mainly observed in patients with large infarct size. This is of therapeutic relevance since postinfarcted cardiac remodelling frequently occurs in this group of patients.

Table CMR measurements at discharge expressed as mean ± SD

	Small Infarct Size		Large Infarct Size	
	Placebo (n = 11)	LT3 (n = 8)	Placebo (n = 10)	LT3 (n = 13)
LVMI, g/m^2	59.7 ± 16.1	56.3 ± 9.4	66.6 ± 16.0	58.3 ± 6.1
LVEDVi, ml/m^2	90.9 ± 19.8	92.8 ± 14.5	112 ± 23.8	91.8 ± 18.6*
LVESVi, ml/m^2	40.8 ± 18.2	44.9 ± 14.1	68.3 ± 21.5	49.0 ± 14.0*
LVEF, %	56.8 ± 10.2	52.2 ± 10.5	39.9 ± 8.7	47.3 ± 6.5*
Infarct Volume, ml	14.0 ± 11.8	16.8 ± 3.8	39 ± 10.7	35 ± 8.0

Normal distribution of variables was estimated with Shapiro-Wilk test of normality. Normally distributed data were compared using an independent t-test.
* $P < 0.05$ vs placebo with large infarct size

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OP-11-04

Comparison of long-term mortality and cardiometabolic effects of treatment for hyperthyroidism: egret study

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Objectives
Hyperthyroidism has been linked to long-term cardiovascular and metabolic morbidity and increased mortality. Current evidence indicates differential cardiometabolic effects from antithyroid drugs (ATD) and definitive treatment options (radioiodine or thyroidectomy). We aimed to assess differences in mortality and cardiometabolic outcomes depending on treatment modality to better inform patient-clinician decision-making.
Methods
We identified 55,318 patients with newly diagnosed hyperthyroidism, treated with ATD, radioiodine or thyroidectomy from CPRD, a UK population-based electronic health record database (>2,000 contributing primary care practices, >16M patients). Health records were linked with Office for National Statistics (ONS) mortality data, Hospital Episode Statistics (HES), and Health Survey for England for background BMI comparison. All-cause mortality, major cardiovascular events (MACE: cardiovascular death, heart failure or stroke) and post-treatment BMI and obesity were studied. A 'target trial' approach was used to allow to elucidate causal effects from observational data. Confounding was controlled for using inverse-probability weights (IPW). Mortality was assessed as time-to-event (Cox PH model); other outcomes were modelled as binary (logistic regression). Missing data at baseline was imputed with MACE algorithm. Funded by NIHR RfPB, NIHR200772.
Results
Patients treated with ATD comprised 77.6% of the cohort; 14.6% were treated with radioiodine, and 7.8% with thyroidectomy. The average follow-up was 12.1 years (SD 5.2). Compared to the ATD treated, mortality was significantly decreased in patients treated with radioiodine (HR 0.87 [0.83-0.92]) or with thyroidectomy (HR 0.80 [0.73-0.90]). The estimated risk of MACE if the population were treated with ATD was 10.2% (9.9-10.5), which significantly increased by an additional 1.3% (0.5-2.1; P = 0.001) with radioiodine but not with thyroidectomy (0.1% [-1.1, 1.3], P = 0.08). Compared with background population, thyroidectomy was associated with an increased likelihood of obesity in both men (OR = 1.57 [1.29-1.91], $P < 0.0001$), and women (1.27 [1.16-1.39], $P < 0.0001$), while radioiodine was in women (1.13 [1.06-1.20], P = 0.0002) but not in men (1.04 [0.93-1.16], P = 0.5).
Conclusion
EGRET is the first large study using population-based linked community and hospital data to elucidate the long-term consequences of treatment modalities for hyperthyroidism. We confirmed a decreased mortality in patients undergoing definitive treatment whereas a slightly increased risk of obesity was found in patients treated with radioiodine and surgery. Compared to medical treatment, a small increase in cardiovascular events was noted with radioiodine.

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OP-11-05

Association between thyroid function and osteoarthritis: a population-based cohort study

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Background
Previous genetic and animal studies implied a potential association between thyroid hormone and osteoarthritis (OA), but this has not been confirmed in the general population. We aim to investigate whether thyroid function is associated with hand, hip or knee OA.
Methods
We included 9,054 participants from Rotterdam Study with baseline measurement of thyroid-stimulating hormone (TSH), free thyroxine (FT4) and radiographs. Joint radiographs were scored using the Kellgren and Lawrence (KL) score system, with OA defined as KL ≥2. Overall progression of knee and hip OA was defined as any increase of KL score during follow-up except the increase from 0 to 1. Severity of OA was determined by the sum of KL scores. We used multivariable regression models to investigate the association of thyroid function with prevalence, severity, incidence and progression of OA. The associations were adjusted for age, sex and additionally adjusted for body mass index (BMI) and physical activity. We conducted stratified analyses by sex, age and weight and post-hoc analyses stratified by weight-bearing physical activity.
Results
Higher levels of FT4 were associated with an increased risk of prevalent knee OA (age- and sex-adjusted odds ratio [OR] 1.02, 95% CI 1.00-1.04). The effect estimate became stronger with further adjustment of BMI and physical activity (OR 1.04, 95% CI 1.01-1.06), corresponding to an OR of 1.62 (95% CI 1.21-2.18) across the reference range of FT4. We identified a consistent positive association of FT4 with severity of knee OA. In longitudinal analyses, there was a borderline significant association between FT4 and progression of knee OA (age- and sex-adjusted OR 1.02, 95% CI 0.99-1.05). The association became stronger after adjusting for BMI and physical activity (OR 1.03, 95% CI 1.00-1.07), and restricting to euthyroid participants (OR 1.05, 95% CI 1.02-1.08). However, we did not identify any significant association of TSH and FT4 with prevalence, severity, incidence or progression of hand and hip OA. Stratified analysis indicated that the association of FT4 with prevalent knee OA was more pronounced among individuals aged ≥65 years, and those with BMI ≥30 kg/m^2. In post-hoc analyses, participants with high levels of weight-bearing physical activity showed a significant association between FT4 and prevalent knee OA (OR 1.05, 95% CI 1.01-1.10).
Conclusion
Our study indicated that higher FT4 levels may increase the risk of knee OA, particularly in individuals with extra joint-loading, such as obesity and weight-bearing physical activity. Future studies are warranted to validate our findings.

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Oral Session 12: Emerging Insights into Thyroid Cancer Genetics

OP-12-01

Prospective evaluation of thyrospec molecular testing of indeterminate thyroid nodule cytologies following diagnostic pathway optimization

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Objectives
Molecular diagnostic tests for indeterminate thyroid nodules (ITNs) are marketed based on negative predictive value (NPV) and benign call rate. Arguments that unnecessary surgeries are avoided based on NPV/BCR incorrectly assume that all ITNs would undergo diagnostic surgery in the absence of molecular testing. In our practice with centralized triage and cytopathology the resection and malignancy rate, respectively, were 21% and 26% for AUS/FLUS and 56% and 43% for FN/SFN, prior to molecular testing implementation. If each positive molecular test result triggered surgery, implementation of molecular testing would substantially increase overtreatment. Therefore, following optimization of ultrasound malignancy risk assessment (Wu *et al* ETJ 2022) and evaluation of local malignancy rates (Ghaznavi *et al* Acta Cytologica 2022) in each Bethesda cytologic category for our diagnostic pathway, we locally developed and validated ThyroSPEC, a low-cost (€650) molecular diagnostic test that detects 117 point mutations and 23 gene fusions in residual routine FNA material.
Methods
We followed 615 consecutive patients with ITN from July 2020 to July 2022 with reflex ThyroSPEC testing in the context of a centralized, optimized thyroid nodule diagnostic pathway to determine the strengths and gaps of this integrated diagnostic pathway.
Results
The resection rate for ITNs was 217/615 (35%) with molecular testing at a 59/143 (41%) prevalence of malignancy in AUS/FLUS and 21/41 (51%) prevalence of malignancy in FN/SFN, a relative increase of 13% ($P = 0.0913$) in the resection rate and 15% ($P = 0.2438$) in the malignancy rate since implementation of ThyroSPEC.
Conclusions
This ongoing study involved first optimizing the local ultrasound and cytology practices as major factors in decision-making, then implementing a custom molecular test into a low resection rate thyroid nodule diagnostic pathway. This resulted in improved decision-making and higher diagnostic yield particularly for diagnostically difficult ultrasound intermediate suspicion nodules.

Table 1: ThyroSPEC performance stratified by ultrasound malignancy risk categories. Ranges are from resected nodules only ($n = 52,71,32$) to all resected nodules plus unresected nodules with more than 1 year follow up ($n = 88,161,78$).

Cytology	n	Sensitivity	Specificity	NPV	PPV
ATA Low Suspicion, TR3	52-88	72%	56-83%	79-92%	46-52%
ATA Intermediate Suspicion, TR4	71-161	80%	69-79%	78-93%	52-72%
ATA High Suspicion, TR5	32-78	46%	83-84%	70-89%	35-67%

The primary reason for surgery in ThyroSPEC positive and negative ITNs was mutation status 78/103 (76%) and ultrasound or cytology risk categories 38/106 (36%), respectively. RAS mutations had a 22% prevalence and 58% malignancy rate, therefore resecting all RAS positives would induce overtreatment.

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OP-12-02

Comparative analysis of somatic copy number alterations (SCNA) between hürthle cell tumors (HCT) and oncocytic variant of follicular cell derived thyroid tumors (OV-FCDTT)

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Objectives
Somatic copy number alterations (SCNAs) have been the most common genetic alterations identified in cancer, that frequently related with extensive genomic instability and to an aggressive behavior. Hürthle cell carcinoma is known to be aggressive, having the highest incidence of recurrences, distant metastasis and RAI therapy resistance among all differentiated follicular cell derived thyroid carcinomas. Due to these differences and recent molecular discoveries, Hurtle cell tumors (HCTs) have been defined and characterized as a separate histological subtype among follicular cell derived thyroid carcinomas in the 4th WHO endocrine blue book edition. Until this last classification, HCTs were considered as subtypes of follicular thyroid tumors. For that reason, most of the previous studies on SCNAs include both the HCTs and other thyroid tumors presenting some level of oncocytic morphology, the oncocytic variant of other follicular cell derived thyroid tumours AKA mitochondrion-rich non-Hürthle thyroid tumours (OV-FCDTTs). Hence, to better understand the genomic instability affecting HCTs, we conducted a SCNA analysis comparing HCTs vs OV-FCDTTs separately.
Methods
DNA extracted from 12 HCTs and 6 OV-FCDTTs was submitted to shallow whole-genome sequencing (sWGS). Sequencing reads were aligned to the reference human genome (GRCh37) using the Burrows-Wheeler Aligner (BWA v0.7.15). Copy number alterations (meaning, copy number gains and losses, gene amplifications and homozygous deletions) were determined using QDNAseq by deriving the Log2 ratio values across all genomic regions of the tumor samples from the Log2 values taken from a normal reference.
Results
HCTs had more SCNAs than OV-FCDTTs, including copy number losses of chromosomes 9q and 22q ($n = 5/12$, 42% for both), and gains of chromosomes 19 ($n = 7/12$, 58%) and 20q, ($n = 6/12$, 50%). In addition, we identified 42 genes that were found to present amplification ($n = 36$) or deletion ($n = 6$) in HCTs. From the 36 amplified genes, 7 were found to be recurrently affected (*UBR3, SLC9A9, SEC63, GRIA2, FER, FRS2* and *NELL2*), and from the 6 deleted genes, 2 of them were seen to be recurrently affected in HCTs (*SLC25A46, ACSS3*). In OV-FCDTTs, only 5 genes were found to be amplified ($n = 3$) or deleted ($n = 2$) with only 2 genes being recurrently amplified (*SOX14* and *TIPARP*).
Conclusions
We found that HCTs have a higher genomic instability, when compared to OV-FCDTTs, has verified by the frequent occurrence of SCNA. Additional studies are warranted to better elucidate if the genetic instability detected in HTC's is associated with the prognosis features of those tumours.

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OP-12-03

Different histological variants in multifocal PTC analyzed by NGS show an independent molecular origin

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Objective
Currently, data about the molecular profile of multifocal papillary thyroid cancer (PTC) are still controversial. The aim of this study was to fully characterize by NGS the molecular profile of different histological variants in patients affected by multifocal PTCs.
Methods
for this purpose, 12 multifocal PTC patients have been studied based to the following inclusion criteria: 1) a minimum of two tumors foci per patient with at least two different histological variants. In total, we retrospectively analyzed 47 foci with a mean number of foci per patient of 4. In all these cases, DNA and RNA were obtained from tumoral tissue obtained from all variants and studied by NGS-targeted sequencing using 2 custom panels designed to analyze mutations and gene fusions involved in thyroid carcinogenesis. TERT promoter mutations (C228T, C250T) have been investigated as well by droplet digital PCR (ddPCR).
Results
Of the 12 patients analyzed, only 2/12 (16.7%) cases showed concordant molecular profiling between the different lesions while the other 10/12 (83.3%) showed a discordant molecular profile that was specific for the variant analyzed. In these latter cases, 5/10 (50%) cases showed a somatic driver mutation in all lesions analyzed with the BRAF-V600E as the most frequent in the classical variant PTC; on the other side, RAS mutation were mainly found in follicular and solid variants. Other 4/10 showed both positive and negative lesions while in 1/10 showed the AGK-BRAF fusion in only one of the lesions studied while the others resulted to be negative. In one of the concordant cases showing six lesions harboring a BRAF-V600E mutation, a TERT C228T mutation was detected in only 1 tall-cell variant lesion: interestingly the only lymph-node metastasis studied in this patient harbored the same TERT mutation in addition to BRAF.
Conclusions
From the data obtained, we mostly observed a different molecular driver associated to different histological variants in the multifocal tumor of the same patient. The independent molecular origin of these lesions has an important clinical impact and suggests that a more thorough analysis should be dedicated to multifocal PTC cases especially in decision of the right target therapy.

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OP-12-04

Genetics of familial non-medullary thyroid carcinoma - investigation of two families'

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Introduction
By Next Generation Sequencing (NGS) our team identified in two families presenting a phenotype compatible with familial non-medullary thyroid carcinoma (Family C and Family R), two new potentially pathogenic germline mutations. Family C presented p.Gly106Arg mutation in the KCNB2 gene, that codifies a voltage-gated potassium channel (vgKCN). Since potassium efflux by the cell is a necessary condition for cellular homeostasis, vgKCN disruption can impact the function of other ion channels. Mice studies showed that KCNE2 disruption indirectly impairs sodium-iodide symporter (NIS) function, and therefore iodide uptake by the cell, resulting in hypothyroidism or goiter. Family R presented p.Gly486Arg mutation in the ubiquitin-specific protease (USP) USP42, known for regulating p53, cell cycle arrest and apoptosis. Evidence shows that deregulation of USPs may be involved in carcinogenesis.
Hypothesis
In family C, by indirect effect on NIS function, vgKCN mutations may increase predisposition to thyroid cancer and help explain why some patients do not respond to radioiodine (RAI) therapy. In family R, by deregulation of the deubiquitinating processes, USP42 may be involved in thyroid carcinoma development.
Methodology
In silico studies using two NGS databases (18 and 513 sporadic thyroid cancer patients, respectively) were conducted. Alterations in 59 genes were searched for copy-number variation, point mutations and other alterations. *In vitro* assays using Nthy-ori 3-1 and FRTL-5 cell lines are ongoing. siRNAs are being used to silence USP42 gene. CRISPR-RNP will be used to knockout USP42 gene and to knock-in clones that harbor the specific mutations of KCNB2 and USP42 found in both families. Morphologic and functional assays will be performed in the transformed cell clones. Finally, *in vivo* assays will be conducted in zebrafish to replicate *in vitro* results.
Results
In silico results showed that KCNA3, KCNH7, KCNS3 and USP39 genes were underexpressed while KCNC1, KCNC3, KCNG2, KCNH2, USP42, BRAF and KRAS were overexpressed. BRAF, RAS, TERT and USP mutations were also identified, as well as vgKCN alterations. No significant association was found between vgKCN and USP alterations regarding patient clinical-pathological characteristics. By siRNAs we successfully downregulated USP42 in human thyroid Nthy-ori 3-1 cell line, as verified by RT-PCR. Protein expression is currently being analysed by Western blot and cellular functional assays are being conducted.
Conclusions
If our hypotheses are verified, vgKCN and USPs mutations could represent new markers, and possibly pharmacological targets, both in familial and in sporadic thyroid cancer.

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OP-12-05

Braf fusion genes in a large cohort of thyroid carcinomas

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Objectives
Effective patient management is about finding a balance between overtreatment and undertreatment. Finding the border is very difficult due to the hardly predictable development of carcinoma. Molecular markers and their testing could help distinguish between low-grade and high- grade carcinomas. One of these

molecular markers is a *BRAF* fusion gene. The aim of this study was to identify *BRAF* fusion genes in thyroid carcinomas, to correlate them with clinical and histopathological features and to determine the prognostic significance of *BRAF* fusion genes based on long-term follow-up of patients with carcinoma harboring this mutation.
Methods
The cohort consisted of 1161 fresh frozen thyroid carcinomas including 993 papillary thyroid carcinomas (PTCs). Based on the detected mutation, samples were triaged. Samples positive for the *BRAF*, *HRAS*, *KRAS*, *NRAS, RET* or *NTRK* fusion gene mutations were excluded from further *BRAF* fusion gene analyses. Samples were analyzed for the presence of *BRAF* fusion genes using the FusionPlex Comprehensive Thyroid and Lung panel (Invitae) by next-generation sequencing (MiSeq, Illumina).
Results
BRAF fusion genes were detected in 33/993 (3.3%) PTCs, of which 3/124 (2.4%) were from pediatric and adolescent patients (2-20 years old) and 30/869 (3.5%) from adult patients with PTC. The mean age of diagnosis was 46.2 $\pm$ 17.8 years and the female to male ratio was 3.7:1. A total of 23 types of *BRAF* fusions were found, including the following partner genes: *ABCC1, AGK, AVEN, BRWD1, C16orf74, CCNY, CHCHD3, CLIP2, CTNNAL1, CUL1, DLG1, GNAI3, MKRN1, NPAT, OPTN, PARP12, RNF150, RRM1, SLC9A8, SND1, SNX1, TNS1, TPD52*. In four cases, PTC harbored not only the *BRAF* fusion but also the *TERT* mutation. Lymph node metastases were found in 11 (33.3%) patients. Distant metastases were identified in 4 (12.1%) patients. Four adult patients (12.1%) died of the disease, in three cases carcinomas were also positive for the *TERT* mutation.
Conclusion
In summary, there are many types of *BRAF* fusion genes, only a few of which were recurrent. *BRAF* fusions occurred with similar frequency in pediatric and adult patients, and were even slightly more frequent in adult patients. Coexistence of the *TERT* mutation was associated with a worse prognosis. Genetic molecular testing of *BRAF* fusions is important for patient's diagnosis and prognosis and also for possible targeted therapy.
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Oral Session 13: Pathophysiological actions of thyroid hormones

OP-13-01

Deiodinase type 3 depletion in fibroadipogenic progenitors improves regeneration of dystrophic muscle
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Fibro-adipogenic progenitors (FAPs), a muscle-resident stem cell population, have recently emerged as important actors of muscle regeneration by interacting with myogenic progenitors (MPs) to promote the formation of new muscle fibers. However, in pathological condition, as muscle dystrophies, this coordinated response is lost and then an accumulation of FAPs is observed. In particular, in a mouse model of Duchenne muscle dystrophy (mdx), the accumulation of a specific subpopulation of FAPs, named Vcam1 has been demonstrated. The reduction of Vcam1+ FAPs is associated with an improvement of muscle phenotype. We observed that thyroid hormone (TH) signaling is active in FAPs, that deiodinase type 3 is expressed specifically by Vcam1+ FAPs. We hypothesized that an intracellular hypothyroid state, assured by D3 expression, is a condition determining the Vicam1+ FAPs features. We found that D2, D3, thyroid hormone transporters and receptors, were expressed in FAPs thus suggesting that TH signal is active in this cell context. To verify if the D3 expression and the consequent hypothyroid status of Vicam1+ FAPs cells is a condition important for their expansion in a context of muscle dystrophy, we investigated the effects of Dio3 selective depletion in FAPs in Mdx mice. In mdx muscle from Dio3 depleted FAPs mice (D3KO-FAP), the number of Vicam1+ FAPs cells was lower than what observed in control mice (D3WT-FAP, 288333 vs 131667 $P = 0.028$). Furthermore, the depletion of D3 in FAPs cells improved muscle phenotype. Cross sectional area of muscle fibers from D3KO-FAP mice were bigger than those from D3WT-FAP mice (2036 μm^2 vs 1780 μm^2 $P = 0.022$), whereas the extension of necrotic areas was smaller. The mRNA Pax7, MyoD, Myogenin and NeoMHC expression were higher in D3KO-FAP muscle than D3WT-FAP muscle, indicating that the D3 FAPs cells depletion enhances muscle regeneration. Interestingly, the mRNA expression of Myh2 and the number of MHCII positive fibers (a positive target gen of TH), were higher in D3KO-FAP than in D3WT-FAP (6,8% vs 10% $P = 0.05$). Taken together, these data show that TH signaling is active in FAPs and that D3 expression is required for the amplification of Vicam1+ FAPs cells. The reduction in Vicam1+ FAPs cells, induced by D3 depletion, improved muscle dystrophic phenotype. Our work could have numerous applications in muscle research for muscle dystrophies diseases, by providing a better understanding of the mechanisms underlying TH availability in the control of FAPs functions.
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OP-13-02

Induced types 2 and 3 deiodinase in the muscle of critically ill patients correlates with endoplasmic reticulum and mitochondria alterations: Implications to nonthyroidal illness syndrome pathophysiology
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Dysregulation of types 2 and 3 deiodinases (D2 and D3) alters the metabolism of thyroid hormones in the patients with nonthyroidal illness syndrome (NTIS). Previous studies have demonstrated that deiodinase expression varies in the muscle in different disease models. Nevertheless, the location of D2 and D3 and the effect of oxidative stress on reticulum endoplasmic (ER) and mitochondrial function are not described in human muscle with different types of acute disease and NTIS.
Objective
Evaluate the location of D2 and D3 mRNA and determine its correlation with ER stress and mitochondrial function in the muscle of NTIS patients.
Methods
A cohort study with 96 critically ill patients was evaluated. Muscle tissue was biopsied on admission to ICU and seven days after. Blood was collected. Ultrasonography (US) of the quadriceps was performed at admission and on day seven. The total carbonyl content and GSH levels were used as a parameter of intracellular redox imbalance. ER stress and mitochondria crosstalk were determined through Grp75, Grp78, PGC1A and COX4. D2 and D3 expressions were localized with *in situ* hybridization RNAscope.
Results
Patients had a medium age of 59 $\pm$ 15 years, majority males, SAPS 64.5 $\pm$ 10 and T3 levels of 47 $\pm$ 11.2 ng/dL. The formation of carbonyls, a marker of oxidated proteins, was increased ($P < 0.001$). GSH levels were diminished ($P < 0.001$). ER and mitochondria studies demonstrated high stress, augmented crosstalk, and apoptosis of these organelles in muscle. Muscle DIO2 (augmented by 5-fold) and DIO3 (augmented by 3-fold) expressions were colocalized on PDGFA, PAX7, and MYOD positive cells and immune muscle cells (positive F4/80 macrophages) . Interestingly, US from quadriceps associated lower T3 levels with lower muscle thickness at admission. Moreover, on day seven, muscle US showed extensive fiber derangement when compared to day one.
Conclusion
Muscle alterations on ER and mitochondria were directly correlated with deiodinase expression and location, T3 levels and mortality, independently of the initial disease.
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OP-13-03

Thyroid hormone signalling regulates beta-cell pathological growth, dedifferentiation and transdifferentiation in diabetic pancreas
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Diabetes mellitus is one of the greatest health crises of our time. In response to diabetic stress, pancreatic beta-cells undergo a set of profound phenotypical alterations, including dedifferentiation, polyploidisation and hypertrophy, and apoptosis. Although we know that thyroid hormone (TH) signalling controls these phenomena in response to various injuries, little is known about its role in the pathobiology of diabetic pancreas. The aim of this study was to investigate the role of TH signalling in the pathogenesis of diabetes in Zucker diabetic fatty (ZDF) rats and in *in vitro* human model of glucose-induced injury. Results showed that diabetic stress induces beta-cell apoptosis, decrease in the expression of mature beta-cell markers (PDX1, NKX6.1, insulin) and simultaneous increase in glucagon expression and the number of bihormonal cells. Interestingly, treatment with T3 reversed these alterations by increasing the insulin secreting area and normalising the expression of PDX1 and NKX6.1. Moreover histological and imaging analysis showed that T3 treatment ameliorated the structure and organisation of pancreatic islets and prevents beta-cell polyploidization. To assess whether TH signalling plays a role in pathological changes in human pancreatic beta-cells, we exposed purified human beta-cells to high concentrations of glucose and evaluated phenotypic changes. Results from immunofluorescence analysis showed that high glucose injury concurrently induced an increase in glucagon-positive cells and a decrease in insulin-positive cell numbers, further confirming that the high concentration of glucose induces the transdifferentiation of beta- into alpha-cells. Importantly, we also observed a significant reduction in the number of cells after high glucose injury, compared to control cells and an increase in cell area. Remarkably, treatment with T3 significantly increased intracellular insulin content and decreased the number of transdifferentiating cells, restored cell numbers to the control level, and markedly reduced the pancreatic beta-cell area. Conversely, the inhibition of T3 binding to TRα1 with desbutyl-dronedarone – before adding T3 to glucose-stressed cells – completely abrogated the beneficial effects of T3, and largely enhanced further transdifferentiation of beta-cells into alpha-cells. This implies that the unliganded TRα1 may trigger opposite actions with respect to the liganded receptor in the diabetic pancreas. All together these data indicate that TH signalling plays a crucial role in diabetes-induced beta-cell pathological growth, dedifferentiation and transdifferentiation.

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OP-13-04

Vandetanib downregulates type 2 deiodinase in fibro/adipogenic progenitors

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Purpose
Treatment with tyrosine kinase inhibitors (TKI) has been associated with alterations in circulating thyroid hormone levels, possibly related to perturbations in peripheral thyroid hormone metabolism. In this study, we evaluated the effect of the multi-kinase inhibitor vandetanib on the expression of the three deiodinase selenoenzymes.
Materials and Methods
Cell models that endogenously express either D1 (HepG2 and HEK-293), D2 (HeLa and KMH-2) or D3 (K1 and Cal-62), respectively, were treated with vandetanib 2 uM in time-course experiments. Deiodinase expression levels were assessed by RT-PCR. PDGFRA-EGFP mice were administered with 50 mg/kg vandetanib daily and sacrificed after 14 or 28 days. Fibro/ adipogenic progenitors (FAPs) were isolated by FACS sorting after muscle digestion. D2 deiodination assay was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results
In vitro, vandetanib determined a strong cell-specific downregulation of Dio2 expression in KMH-2 cells, and no changes in deiodinase expression were found in other cell lines. The effect of vandetanib was then analyzed in mice in two tissues wherein D2 action is highly relevant, i.e. brown adipose tissue (BAT) and pituitary. 28 days after daily treatment with vandetanib, Dio2 mRNA levels in both BAT and pituitary were unchanged compared to controls. Therefore, we hypothesized that specific cell types dispersed in selected organs would play an important role in the vandetanib-mediated effects on TH metabolism. We found that FAPs (i.e. interstitial mesenchymal progenitors crucial for muscle regeneration process) from heart and skeletal muscle in mice express elevated levels of Dio2 and other genes relevant for TH metabolism. Strikingly, Dio2 expression in FAPs from both heart and skeletal muscle dramatically decreased after treatment for 14 days with vandetanib, and Dio2 inhibition persisted after 28 days of treatment. Importantly, liver expression of Dio1 and Dio3 in vandetanib-treated mice was unchanged compared to untreated controls, as well as markers of TH action such as Malic Enzyme and Spot14. We also measured D2 activity in skeletal muscle FAPs from vandetanib-treated mice compared to controls and found that the D2 activity in mice treated with vandetanib for 14 days was reduced of about 60% compared to controls.
Conclusion
Vandetanib determined a dramatic downregulation of D2 expression and activity in mesenchymal precursors from skeletal and heart muscle. Given the widespread diffusion of mesenchymal cells within the body, our results may explain at least partially the alterations in thyroid hormone levels that occur in TKI-treated patients.

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OP-13-05

Thyroid hormone action in acetaminophen-induced acute liver failure

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Objectives
Acute liver failure (ALF) is a rare but life-threatening condition with severe liver dysfunction. In ALF liver regeneration capacity is exceeded due to loss of hepatocyte function. A well-known trigger of ALF is paracetamol (acetaminophen, APAP) intoxication. Unfortunately, based on the poor prognosis and rapidly increasing mortality rate liver transplantation offers the so far only effective therapeutic strategy. Even if the underlying mechanisms of ALF are not yet fully understood, it is well known that triiodothyronine (T3) positively favors hepatocyte proliferation via thyroid hormone receptor β (TRβ) signaling and could therefore improve liver regeneration. Using the APAP mouse model, we asked whether hepatic T3 signaling influences ALF progression and regeneration.
Methods
ALF was induced via i.p. injection of 300 mg/kg body weight of APAP (or solvent control) in male C57BL/6J mice. T3 (100 µg/kg body weight or solvent control) was administered 6 h (progression) and 24 h (regeneration) post APAP intoxication via oral gavage. Twelve hours to 72 h post APAP intoxication, liver function test, liver histology, proliferation and hepatic T3- and APAP-responsive markers were evaluated.
Results
APAP increased serum transaminase activities. Liver histology revealed centrilobular hepatocyte necrosis and inflammation by APAP intoxication. Serum T3 concentration and hepatic T3-responsive markers showed successful T3 administration 12-24 h post oral gavage. T3 impacts hepatocyte proliferation and APAP-responsive markers evaluated by Pcna and Cyp2e1 staining suggesting improved hepatocyte regeneration and metabolism.
Conclusions and outlook
Our data indicate that T3 positively favors liver regeneration and metabolism after APAP-induced ALF in male C57BL/6J mice, which will be further studied in comparison to hepatocyte-specific TRβ knockout mice. We expect that results of this study provide new insight how hepatic thyroid hormone signaling improves the course of APAP-induced ALF, with the aim of optimizing the treatment and prognosis of patients.

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Poster Presentations

Poster Session 1: Cancer

PS1-01-01

Impact of the 3rd edition of bethesda system for reporting thyroid cytopathology on grey zone categories

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First TBSRTC editions have made advances in problems of thyroid management. However, the real grey zone 'AUS/FLUS' and 'FN/SFN'categories have been remained to be problematic with the wide range of ROMs documented in the literature alongside two editions. The ROMs of 'AUS/FLUS' and 'FN/SFN' categories were defined as 5-15% and 15-30% and the management was 'repeat FNA' and 'lobectomy' -respectively- in the first edition. Dual terminology, especially in 'AUS/FLUS' category referring different type of atypia: AUS -nuclear atypia- and FLUS -pattern atypia- together with the indication of 'either AUS or FLUS would be selected by a laboratory because they are synonymous' was enough to lead to a confusion and create a waste-basket category. 2 nd edition tailored to prevent the overuse of this category and patient management of AUS/FLUS category offered molecular testing beside the choice of repeat FNA. During these two editions the literature have been continued to represent higher ROMs than TBSRTC suggested and studies with the suggestion of subcategorization for those categories were increased. Following the perplexity of the indetermined categories, the 3 rd edition of TBSRTC finally offered a subcategorization to these categories and 'AUS/FLUS' category will be divided into 'AUS-nuclear atypia' and 'AUS, other' and 'FN/SFN' category will be divided into 'SFN (non-oncocytic)' and 'SFN-oncocytic'. This is a retrospective study of patients with surgery and FNA dates between 2009 and 2019, and whose nodules were cytologically diagnosed as AUS or SFN according to TBSRTC-2017. The following data was noted for each subject: Patients' age and sex, the type of surgery, the number of nodules evaluated for each patient, the nodule sizes, cytological and histological diagnoses of the nodules and ROMs for each cytological categories and subcategories. Statistical analysis is made on PASW Statistics 18.0.0. Chi-square was used to correlate 2nd and 3rd Bethesda categories/subcategories with surgical outcomes and ROMs. Histopathological examination was performed on total thyroidectomy 91 and on lobectomy 9%. 203 nodules had size information, and mean size was 28,2 (8-68) mm.Of these nodules,31%were diagnosed as AUS and 69% were diagnosed as SFN in their FNA. Surgery revealed 23CLT(chronic lymphocytic thyroiditis), 38 BFN (benign follicular nodule), 56 FA (follicular adenoma), 26 AO (oncocytic adenoma),2WDT-UMP(well differentiated tumor uncertain malignant potential), 4 NIFT-P, 97PTC(papillary thyroid carcinoma), 2 FTC(folicular thyroid carcinoma)and 4 OC(oncocytic carcinoma) cases. Both division based on oncocytic features and subdivision based on PTC nuclear features showed high significance ($P < 0{,}001$) for histological diagnoses of the nodules. Similarly in terms of ROMs, division based on oncocytic features showed high significance ($P = 0{,}015$) and subdivision based on PTC nuclear features showed even higher concordance ($P < 0{,}001$) ROMs of SFN category and its subcategories.

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PS1-01-02

Serum potassium in thyroid cancer patients undergoing thyroid hormone withdrawal prior to radioactive iodine treatment: a retrospective study at a single institution

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Background
Several case reports and a few studies reported that hypothyroid patients have elevated serum potassium (K+) levels. However, hypothyroidism has not been widely accepted as a cause of hyperkalemia. This study aims to determine the incidence of hyperkalemia and factors influencing serum K+ levels in thyroid cancer patients who have hypothyroidism due to thyroid hormone withdrawal before radioactive iodine (RAI) treatment.
Methods
We retrospectively reviewed the electronic medical records of 956 patients with thyroid cancer and post-thyroidectomy who underwent RAI in Ramathibodi hospital between January 2017 and June 2021. Demographic data, medication history, and laboratory parameters including serum K+ level and thyroid function tests in patients were collected in both euthyroid (<1 year prior to RAI) and hypothyroid states. The incidence of hyperkalemia and factors influencing serum K+ levels were evaluated.
Results
A total of 508 patients (mean age 52 years, female 79.3%) were included in the final analysis. The incidence of hyperkalemia (K+ $\geq$5.0 mEq/l) was 2.76%. No patients had developed severe hyperkalemia (K+ $\geq$6.5 mEq/l). The mean of serum K+ level in the hypothyroid state was significantly higher than in the euthyroid state (4.18 ± 0.38 mEq/l vs 4.13 ± 0.36 mEq/l, $P < 0.01$). The mean of change in serum K+ level between euthyroid and hypothyroid state was 0.05 ± 0.39 mEq/l. Several factors were associated with serum K+ level in the hypothyroid state (positive correlation: age, use of angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers, metformin, serum creatinine, serum K+ level during the euthyroid state; and negative correlation: use of thiazide). During the hypothyroid state, hyperkalemia had more developed in patients with serum K+ higher than 4.2 mEq/l (OR 8.83, $P < 0.01$) or serum FT4 higher than 1.38 ng/dL (OR 7.05, $P < 0.01$) in the euthyroid state.
Conclusion
The incidence of hyperkalemia was low in hypothyroid patients in our cohorts. However, physicians should raise awareness of hyperkalemia in patients who have baseline serum K+ = 4.2 mEq/l or serum FT4 $\geq$1.38 ng/dL.

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PS1-01-03

Efficacy and safety of radiofrequency ablation in active surveillance candidate for low-risk papillary thyroid microcarcinoma

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Purpose
Although some studies presented good outcome of Radiofrequency Ablation (RFA) for Papillary Thyroid microcarcinoma (PTMC), its benefit has not been fully elucidated. The purpose of our study was to report the results from a prospective study investigating efficacy and safety of RFA in active surveillance candidate for low-risk PTMC.
Materials and Methods
Since November 2018, RFA has been prospectively performed in active surveillance candidates for low-risk PTMC in a single center. Clinical ex¬amination including ultrasonography, thyroid function, and questionnaires for quality of life (QoL) were scheduled before and after RFA at every 6 months during the first 3 years.
Results
RFA was performed at 100 PTMC (mean, 6.2 mm; size range, 2.3 – 10.0 mm) of 100 patients (17:83 = M:F, mean age, 42.7 years; age range, 27 – 59). During 22.3 months (range 12 – 48 months) follow up period, serial volume reduction rates of ablation zone were -1036.3% at immediate post ablation state, -192.5% at 2 months, 47.3% at 6 months, 92.0% at 1 year, and 98.2% at final follow-up after RFA. Complete disappearance was depicted in 61.0% at 1 year and in 88.0% at final follow-up. No complication occurred except for transient hoarseness of 1 patient. Lymph node metastasis at lateral compartment in 1 patient at 2 year follow-up and metachronous PTMC in 2 patients developed at 1.5 year and 2 year follow-up. QoL score tends to increase as time goes on.
Conclusion
Single center prospective study presented that RFA in active surveillance candatate for low-risk PTMC resulted in good clinical outcome.

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PS1-01-04

Papillary thyroid carcinoma from a thyroglossal duct cyst: a rare association

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Introduction
Thyroglossal duct cysts (TDC) are a very frequent congenital neck mass and are mostly benign. Papillary thyroid carcinoma (PTC) originating from a TDC represents an infrequent finding. Usually, the diagnosis is only made post-operatively after cyst's excision.
Case report
A 38-years old female patient was referred to the Endocrinology department due to Graves' disease. She had been treated with antithyroid drugs for 18 months without remission. Thyroid ultrasonography (US) showed an enlarged gland, without nodules. Thyroid scintigraphy showed high homogenous uptake of pertechnetate, without extra-thyroidal uptake. TSH receptor antibody levels at that time were 19.10 UI/l (N $<$ 0.55). It was administered 15.5 mCi of radioactive iodine (RAI), with hypothyroidism 3 months later (TSH 77.6 uUI/mL, N 0.55-4.78, and FT4 0.54 ng/dL, N 0.89-1.76). She was started on levothyroxine and remained euthyroid with 150 mg daily (TSH 1.1 uUI/mL, FT4 1.58 ng/dL). 14 months after RAI treatment, she noticed an enlarged and painless nodule on the anterior neck. Thyroid and cervical US showed a small, heterogeneous and hypoechoic thyroid gland with no defined nodules and, at the submandibular region, a 25 mm hypoechoic nodule with hyperechogenic foci, suggestive of a complex TDC. No pathologic lymphadenopathies were described. Cervical magnetic resonance imaging confirmed the presence of a complex TDC. A fine needle aspiration cytology was performed with inconclusive results. She was submitted to Sistrunk procedure to remove the cyst. Histology revealed a 5 mm PTC, without lymphovascular and neural invasion and a tumour-free surgical margin (pT1aNxR0). Postoperatively, cervical US was negative for suspicions lesions, with thyroglobulin (Tg) level of 2.20 ng/mL, anti-Tg of $<$ 1.30 UI/mL and TSH of 0.138 uUI/mL. Since the likelihood of a synchronous multifocal thyroid carcinoma was low, total thyroidectomy (TT) was not proposed, remaining the patient in clinical, analytical and imagiological follow-up.
Conclusion
We report a case of a patient with Graves' disease successfully treated with RAI, with a submandibular mass noticed 14 months later that turned out to be a TDC harbouring a microPTC. TDC are extremely common and, in the majority of the cases, an expectant attitude is taken. Malignity is rare and cytological analysis is only performed when suspicious characteristics in the US are present or when the patient complains of compressive symptoms. Given its rarity, the decision to perform TT and RAI in this setting depends on initial risk stratification, as with intraglandular tumors.

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PS1-01-05

Radioiodine therapy for thyroid cancer and dyfunction of the salivary and lachrymal glands in the start study: results at 6 months follow-up

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Background
Understanding of changes in salivary and lachrymal gland functions after radioiodine therapy (131I-therapy) remains limited; and, to-date no studies have evaluated dose-response relationships between absorbed dose from 131I-therapy and dysfunctions of these glands. This study investigates salivary/lachrymal dysfunctions in differentiated thyroid cancer (DTC) patients six months after 131I-therapy, identifies 131I-therapy related risk factors for salivary/lachrymal dysfunctions, and assesses the relationships between 131I-therapy radiation dose and these dysfunctions.
Methods
A study was conducted involving 136 DTC patients treated by 131I-therapy of whom 44 and 92 patients received 1.1 and 3.7 GBq, respectively. Absorbed dose to the salivary glands was estimated using a dosimetric reconstruction method based on thermoluminescent dosimeters measurements. Salivary and lachrymal functions were assessed at baseline (T0, i.e., immediately prior to 131I-therapy), and 6 months later (T6) using validated questionnaires and salivary samplings, with and without stimulation of the salivary glands. Statistical analyses included descriptive analyses and random-effects multivariate logistic and linear regressions.
Results
There was no difference between T0 and T6 in the level of parotid gland pain, nor was there difference in the number of patients with hyposalivation, but there were significantly more patients with dry mouth sensation and dry eyes after therapy compared to baseline. Age, menopause, depression and anxiety symptoms, history of systemic disease, and not taking painkillers in the last 3 months were found to be significantly associated with salivary or lachrymal disorders. Significant associations were found between 131I-exposure and salivary disorders adjusted on the previous variables: e.g. per 1-Gy increase in mean dose to the salivary glands, OR = 1.43 (95%CI 1.02-2.04) for dry mouth sensation, ß = -0.08 (95%CI -0.12;-0.02) mL/min for stimulated saliva flow, and ß = 1.07 (95%CI 0.42;1.71) mmol/l for salivary potassium concentration.
Conclusions
This study brings new knowledge on the relationship between the absorbed dose to the salivary glands from 131I-therapy and salivary/lachrymal dysfunctions in DTC patients 6 months after 131I-therapy. Despite the findings of some dysfunctions, the results do not show any obvious clinical disorders after the 131I-therapy. Nevertheless, by identifying risk factors, this study encourages clinicians to adapt the therapy for patients at risk of salivary/lachrymal complications.

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PS1-01-06

Morphometric analysis of lateral cervical lymph node metastasis in papillary thyroid carcinoma using digital pathology

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Objective
Digital pathology is the process of scanning conventional slides and then digitally stitching consecutive images into digital slides that can be viewed, managed, and analyzed on a computer monitor. In this study, we evaluated the area of metastatic foci in cervical lymph node (LN) metastasis in application of digital pathology and prognostic implication for predicting structural recurrence in patients with papillary thyroid cancer (PTC).
Methods
This study included 316 patients with PTC with LN metastasis who underwent total thyroidectomy between 2010 and 2020 at the Asan Medical Center in Korea. Initially, we reviewed the tumor cells in metastatic LNs by measuring the longest diameter from the single screenshots of histological images captured through a microscope's optics. Then we measured the longest diameter and the largest area using the whole slide imaging (WSI) scanner. Progression-free survival (PFS) were evaluated based on the diameter or area of metastatic foci in LNs using cut-off values by the Contal and O'Quigley methods.
Results
The median age of the patients was 45.6 years and 90 of 316 (28.5%) were male. The median primary tumor size was 17.0 mm and the median longest diameter of LNs were 10.0 mm (IQR 6.0-15.3), 10.8 mm (IQR 7.0-16.6) in tradition and digital pathology, respectively. The medain largest area was 41.6 mm^2 (IQR 18.5-121.1). There was a significantly positive correlation with the longest diameter between traditional and digital pathology (R = 0.928, P $<$0.001). The optimal cut off values for predicting structural recurrent disease were 8.0 mm in both traditional pathology (P=0.009) and digital pathology (P=0.016). There were

significant differences in the PFS based on the optimal cut off values in traditional and digital pathology ($P=0.006$ and $P=0.002$, respectively). The results of correlation analysis showed a significant quadratic relationship between diameter and area, with R sqaure values of 0.891 ($P<0.001$) in digital pathology compared to 0.727 ($P<0.001$) in traditional pathology. The cut-off value of area was 35.6 mm^2 ($P=0.005$) and there was a significant difference in PFS by this cut-off value ($P=0.015$).
Conclusions
There was no discernible difference in measuring the longest diameter of metastatic LNs between traditional and digital pathology. Digital pathology has an advantage to easily measure the area of metastatic foci, however this measurement was not more effective than traditional method in predicting prognosis of patients with PTC.

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PS1-01-07

Type 2 diabetes and obesity are not likely to be risk factors for thyroid cancer

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Background
Patients with type 2 diabetes (T2DM) are generally known to have increased risk of various types of cancer. However, the studies addressing the association between T2DM and thyroid cancer are heterogeneous and inconclusive. The aim of our study was to evaluate the patients who have already undergone thyroid surgery with histologically confirmed results as the 'gold standard'.
Methods
A retrospective study in 102 patients (74 women and 28 men) was performed. Three cohorts were established according to histology; malignant (M), benign (B) and low-risk carcinoma (MB). Only patients which were known to have prediabetes/T2DM and/or were screened for DM following the standards of the American Diabetes Association and the European Association for the Study of Diabetes, in the same year as the thyroid surgery was performed, were included. History of the patients, biochemical testing, thyroid ultrasound and FNA with molecular testing were performed. DNA from FNA samples was used for next generation sequencing to identify mutations in genes: BRAF, HRAS, KRAS, NRAS and TERT. RNA was used for Real Time PCR to detect RET/PTC1, RET/PTC3 and ETV6/NTR3 rearrangements. Fisher's exact test and Kruskal-Wallis one-way ANOVA of ranks were used for statistical analysis.
Results
Histologically, 44 findings were malignant (43.2%); especially papillary thyroid carcinoma (68.2%); 52 were benign (50.9%) and 6 (5.9%) were low-risk carcinomas. T2DM and prediabetes were present in 28 patients. Autoimmune thyroid disease was present in 40.6% and multinodular thyroid gland in 46.3% of the patients. The mutations were detected in 29/102 (28.4%), the most common mutation was BRAFV600E in 17/29 (58.6%). Men had presented significantly with larger thyroid nodules ($P = 0.014$), thyroid gland ($P < 0.001$), minimal thyroid cancer (TC) invasion ($P = 0.048$), advanced TC staging ($P = 0.041$) and T2DM ($P = 0.028$) in comparison to women. In contrast, M, B and MB cohorts had comparable age ($P = 0.353$), BMI ($P = 0.430$), thyroid nodule size ($P = 0.164$), thyroid gland volume ($P = 0.391$), glycaemia ($P = 0.718$) and Hb1AC ($P = 0.654$). In a smaller number of the patients ($n = 31$) we were able to calculate Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) without any difference between the cohorts ($P = 0.221$).
Conclusion
Type 2 diabetes and obesity as the principal cause of T2DM pandemic are not likely to be risk factors for thyroid cancer. We propose that histological confirmation is crucial in these studies. In conclusion, we would like to turn the attention to male population, because they seem to come with more advanced thyroid diseases.

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PS1-01-08

Significance of bilaterality and multifocality in papillary thyroid cancer

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Purpose
Papillary thyroid cancer (PTC) has a strong propensity for lymph node metastasis, which is related with local recurrence, and disease-specific survival in the elderly. We evaluated the association between lymph node metastasis and disease multifocality, bilaterality, and other clinicopathological variables to identify risk factors and aid surgical decision-making. The relationship between the number of foci and metastasis to cervical lymph node was also evaluated.
Methods
Patients with PTC ($n = 819$) undergoing thyroidectomy at our institution were included. The study population was segregated into four groups based on PTC multifocality and bilaterality.
Results
Cervical lymph node metastasis, tumor size, and tumor extent were significantly different between the study groups. The frequency of central and lateral cervical lymph node metastasis was the highest in the bilateral multifocal disease group, followed by the bilateral solitary group, unilateral multifocal group, and the unilateral solitary group. One PTC focus per thyroid lobe was associated with increased metastasis (53.8%). Moreover, lymph node positivity doubled with 5–7 foci (71.4%), and tripled with >8 foci (100%). Bilateral solitary and bilateral multifocal PTC were identified as independent predictors of cervical lymph node metastasis.
Conclusions
Bilateral PTC was associated with lymph node positivity, which increased proportionally with the number of PTC foci. Bilateral solitary or multifocal PTC were associated with more aggressive features such as larger primary tumor size, more frequent extrathyroidal extensions, and regional lymph node metastasis. The presence of multiple bilateral foci or more than 3 foci are independent risk factors of lymph node metastases.

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PS1-01-09

Risk of renal adverse effects in patients with advanced thyroid cancer who are undergoing radiological monitoring, with a particular focus on patients receiving tyrosine kinase inhibitors

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Introduction
Systemic treatment of advanced progressing thyroid cancer (TC) is based on molecularly targeted therapy with tyrosine kinase inhibitors (TKIs), mainly inhibitors targeting vascular endothelial growth factor receptors (VEGFR). Such treatment is related to numerous side effects. However, the relationship between TKIs and renal adverse events (RAEs) is unclear. VEGFR inhibitors are

associated with proteinuria. In some patients, increased serum creatinine level and the development of chronic kidney failure is observed. However, so far, it has not been determined whether these events are directly caused by TKIs or are more closely linked to iodinated contrast media used in computed tomography (CT), a well-known factor of kidney damage, to follow treatment response.
Aim
The aim of the study is to compare kidney function between TC patients with advanced disease treated and not treated with TKIs. Patients in both groups are followed by repeated contrast-enhanced CT scans. This comparison will consider the number of CT scans performed with iodine contrast media and their impact on the development of chronic kidney disease in both groups.
Methods
A retrospective analysis involves 328 TC patients with advanced inoperable or metastatic disease, including 96 patients treated with TKIs. The remaining 234 patients did not receive any systematic treatment. All patients received at least one VEGFR inhibitor (sorafenib, lenvatinib, cabozantinib, or vandetanib). The maximum number of contrast-enhanced CT scans performed in the TKIs group was 34, while the maximum number in the non-treated group was 16. The data analysis uses the glomerular filtration rate (GFR) as an indicator of kidney function, as per the KDIGO 212 scale. GFR changes over time in patients who received and did not receive VEGFR-TKIs are analyzed.
Results
Among 234 patients who did not receive any systematic treatment, 66.2% did not show any change in kidney function, while 26% experienced worsening of kidney function or developed chronic kidney disease. On the contrary, in 46,8% among 96 patients receiving VEGFR-TKI inhibitors kidney function worsened. Only in 47,9% of them kidney function remained unchanged. The use of TKIs was related with 2,48-fold higher risk of kidney damage compared to non-treated patients. The difference between the groups was statistically significant ($P < 0{,}001$).
Conclusion
TKIs may be associated with a higher risk of renal damage and the development of chronic kidney failure in patients with advanced TC. It should be considered when planning the follow-up schedule and the frequency of contrast-enhanced CT scans.

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PS1-01-10

Role of gender on adverse events in a consecutive series of 28 patients with advanced differentiated thyroid cancer receiving lenvatinib

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Introduction
The treatment with tyrosine-kinase inhibitor drugs (1st line Lenvatinib) in patients with radioiodine-refractory differentiated thyroid cancer (I-131) and disease progression can be burdened by important side effects which often require suspension/reduction of the therapy and correct multidisciplinary management.
Patients and methods
Clinical/histopathological characteristics, outcome, adverse events and the role of gender have been evaluated in a consecutive series of 28 patients with Radioactive iodine-refractory differentiated thyroid cancer and progressive disease (RECIST criteria) treated with Lenvatinib.
Results
Clinical/histopathological characteristics, clinical outcome and adverse events are shown in Table 1. The male/female ratio (1.5/1) showed an higher frequency of aggressive tumors in males. Most patients fell into stage II and about 25% had loco-regional and distant metastases at diagnosis. Almost all patients (93%) were treated with I-131. Radioactive iodine-refractory from diagnosis were of 3.8 years. Approximately 90% of patients experienced adverse events, mostly gastrointestinal disorders and hypertension. Analyzing them by gender, the only statistically significant difference was on gastrointestinal symptoms (0.02). Moreover other not significant differences probably depend on the low sample number. At last visit, 75% of the patients showed stable disease and 25% progressive disease.
Conclusions
Most of the side effects occur in the first weeks of therapy, however, periodic and early reassessment of any side effects is necessary to minimize the reduction and/or suspension of therapy.

Table 1 Clinical, histopathological characteristics and clinical outcome of 28 patients with advanced differentiated thyroid cancer receiving Lenvatinib

	n.	(%)	
Patients (n.)	28		
Follow-up median (IQR) (months)*	12.6 (6.2-14.9)		
Age at diagnosis median (IQR) (years)	60.6 (50.6-65.9)		
Gender M/F (ratio)	17/11 (1.5/1)		
Histotype			
Papillary	10	35.7	
Follicular	10	35.7	
Poor differentiated	8	28.6	
Stage			
I	9	32.1	
II	12	42.9	
IVB	7	25	
I-131	26/28		
median, IQR	298 (100-300)	92.9	
Radioactive iodine-refractory from diagnosis, years (Median, IQR)	3.8 (1.3-8.2)		
Metastasis			
Lung	Aug-28	28.6	
Bone	Feb-28	7.1	
Lung + bone	Jun-28	21.4	
Multiple (>2 sites)	Dec-28	42.9	
Lenvatinib first dose (mg, median, IQR)	22 (14-24)		
Time to therapy reduction, months (median, IQR)	1.7 (0.69-3.38)		
Best response to therapy	4.0 (3.33-9.57)		
Alive at last visit	23/28	82.1	
Status			
progression	Jul-28	25	
stable	21/28	75	
Total adverse events	25/28	89.3	
Hypertension	14/28	50	
Asthenia	Sep-28	32.1	
Gastrointestinal symptoms (nausea, epigastric pain, Weight loss, vomiting)	16/28	57.1	
others	May-28	17.9	
Adverse events according to the gender	Male n. (%)	Female n. (%)	
Total	16/17 (94.1)	9/11 (81.8)	0.54
Hypertension	7/17 (41.2)	7/11 (63.6)	0.11
Asthenia	5/17 (29.4)	4/11 (36.4)	1.0
Gastrointestinal symptoms (nausea, epigastric pain, Weight loss, vomiting)	13/17 (76.5)	3/11 (27.3)	0.02
Others	2/17 (11.8)	3/11 (27.3)	0.65

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Graves' Disease

PS1-02-01

Preoperative management of graves' disease: should all patients be euthyroid?

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Context
Prior to thyroidectomy for Graves' disease, thyroid function should be adequately controlled to avoid complications such as thyroid storm. However, preoperative thyroid function control is sometimes difficult.
Objective
This study assessed the postoperative risks are increased or not if biochemically hyperthyroid patients undergoing total thyroidectomy in comparison to euthyroid patients.
Methods
A retrospective, cohort study was conducted. A total of 1,884 patients undergoing total thyroidectomy for Graves' disease from January 2010 to December 2020 were evaluated. Preoperative thyroid function, vital sign (heart rate and body temperature), thyroid storm, hypocalcemia, paralysis of the vocal cord, and postoperative bleeding were evaluated.

Results
The patients' mean age was 38 years, and 1,394 patients (75.6%) were female. A total of 1,644 patients (89.1%) were treated with anti-thyroid drugs, 213 patients (11.5%) with beta-blockers, 396 patients (21.5%) with potassium iodide, and 92 (4.9%) with glucocorticoids. At the time of surgery, 64.9% remained hyperthyroid as defined by the TSH level. On the other hand, serum free T4 and free T3 were in the normal range in 55.9% and 76.9% of cases, respectively. There was a significant difference in postoperative heart rate and the rate of transient hypocalcemia between the patients with a higher free T3 level more than normal range and those with normal free T3 level, but not in the other postoperative complications. No patient developed thyroid storm.
Conclusion
Preoperative thyroid function control was based mainly on control of serum free T3 levels in exceptional circumstances. Of the patients who were biochemical hyperthyroid status at the time of surgery, none developed sever complication.

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PS1-02-02

Predetermined vs calculated 131I activity for the treatment of patients with graves' disease: which is the best?

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Background
Graves' disease (GD) is an autoimmune disorder of thyroid gland and is the first cause of hyperthyroidism. Radioactive iodine (RAI) therapy is the most used second- line treatment after failure of anti-thyroid drugs. The optimal RAI's activity to be administered may be predetermined or calculated. Whether the latter is better is still a matter of debate.
Aim
To compare the risk of persistent hyperthyroidism in GD patients treated with predetermined vs calculated dose of RAI.
Materials and Methods
Retrospective analysis of 176 patients affected by GD (F: 126, M: 50), divided in: Group A, consisted of 141 patients treated by predetermined (10 or 15 mCi) RAI activity and Group B, consisted of 35 patients treated by calculated dose of RAI (Traino's formula). Uni- and multivariate logistic regression analysis was used to estimate factors associated with persistent hyperthyroidism after 40 days, 3 and 6 months from the RAI therapy.
Results
The baseline features of the two groups were not different except for the pretreatment thyroid volume (23.1 vs 16.6 ml in Group A and B, respectively; $P = 0.002$) and TRAb positivity (62.5% vs 85.3% in Group A and B, respectively; $P = 0.001$). At the multivariate analysis we found that no different risk of persistent hyperthyroidism was observed between predetermined and calculated RAI activity at 40 days (OR= 3.5, 95%CI= 1.0-12.5; $P = 0.06$), 3 months (OR= 1.3, 95%CI= 0.4-4.0; $P = 0.66$) and 6 months (OR= 0.55, 95%CI= 0.2-1.8; $P = 0.32$) after the treatment. At 6 months RAI therapy induced hypothyroidism or euthyroidism in 73.8% of Group A and 68.4% of Group B ($P = 0.62$) and the only factors independently associated with persistent hyperthyroidism were the pretreatment thyroid volume (5% increasing risk for each ml of increasing thyroid volume) and positivity of TRAb (5-fold increased risk with respect to patients with negative TRAb).
Discussion
According to American and European Thyroid Associations, a single administration of RAI should be administered to achieve hypothyroidism in patients with GD, whereas European Association of Nuclear Medicine considers hypothyroidism a side effect of the treatment. RAI activity calculated through dosimetry method should avoid hypothyroidism and unnecessary ionizing radiation exposure. In this study we found that the risk of persistent hyperthyroidism after 6 months from the RAI therapy was not different between the two methods and the most important parameters influencing the failure of RAI therapy were both pre-therapy thyroid volume and TRAb positivity.
Conclusions
The present study provided no convincing evidence for the superiority between predetermined and dosimetry methods to calculate RAI activity in patients with GD.

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PS1-02-03

Analysis of cost and treatment effects in the care given for graves disease - a swedish cost-utility analysis

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Background
Guidelines in healthcare shall be evidence-based, satisfy patients' needs and improve patients' outcomes. We aimed to estimate incremental costs after the introduction of a national guideline for Graves' disease in Sweden adding the Graves' Recurrent Events After Therapy (GREAT) score with genetic determinants to predict recurrence, a thyroid nurse, calcium-D-vitamin treatment preoperatively, and thyroid stimulating immunoglobulins.
Methods
To do a cost-utility analysis using quality of life (QoL) data from two Swedish studies, one in 1996 and one in 2012, to calculate QALYs.
Findings
Antithyroid drugs (ATD) was less costly, achieved 0.88 QALYs during 8 years, and dominated over radioactive iodine (RAI) treatment. The relevant ICER was ATD vs thyroid surgery. Surgery was more costly than ATD, but was also more effective, and the ICER was equal to 39 631 Euro (43 561 USD, 412 960 SEK) per QALY gained. In recurrent Graves' disease, the QALY weight for surgery after ATD was 0.76 compared to 0.79 when surgery was the initial treatment. If individuals requiring surgery could be identified at start of first treatment, QALYs would be higher (6.32) and the cost lower (13 947 Euro (15 351 USD, 145 330 SEK)). The net cost after the new guideline was +17.6%, which was an effect by more time with the patient for the thyroid nurse and genetic analyses 816 Euro (8500 SEK). If the GREAT score was also applied, the total net cost was +14.8% if 24% of the tested patients changed treatment to surgery.
Interpretation
Thyroid surgery was more cost-effective than RAI when ablative treatments is advocated. Prediction scores for recurrence directing patients to earlier thyroid surgery is cost-effective and facilitates introduction of a thyroid nurse. The price for genetic analyses is based on historical costs, but could it be lower the gain would be even larger. Also, the effect lasts probably much longer than the eight years we could observe in our study. If we assume a life-long effect, i.e. further 30 years, the cost per QALY drops significantly to around 2 498 Euro (2 747 USD, 26 000 SEK). This means that our calculations certainly overestimate the cost per won QALY. The threshold value for cost-effectiveness in Sweden is 48 000 Euro (53 000 USD, 500 000 SEK) per QALY gained and is approximately at the same level as other countries in Northwest Europe. Health economic evaluations shall accompany future guidelines.

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PS1-02-04

The relationship between mental fatigue, anxiety and depression in graves disease

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Background
Mental fatigue, depression and anxiety are common in Graves' disease (GD). Our aims were to assess the relationship between these variables among GD patients both in the hyperthyroid phase and after treatment. The pathogenic mechanisms involved in these symptoms are unknown and so is if previous psychiatric disease influences these symptoms.
Methods
This was a longitudinal case control study in Göteborg, Sweden, on 65 women with newly diagnosed GD and 65 matched controls. Consecutive patients were asked for participation and those included were examined in hyperthyroidism and after 15 months of treatment. Examinations included blood sampling,

clinical evaluation, and psychiatric testing with the Comprehensive Psychopathological Rating Scale for Affective Syndromes (CPRS) and the Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I). Mental fatigue was assessed with the Mental Fatigue Scale (MFS). The study also included a registry search for previous psychiatric diagnoses and previous prescriptions of psychoactive drugs in patients whom we asked for participation and in all Swedish women given a diagnosis of thyrotoxicosis during 2013–2018 compared to controls.
Results
There were no signs of an increased psychiatric comorbidity in the GD patients prior to the diagnosis when compared to matched thyroid healthy controls according to the SCID interview. In the registry search there was no difference in the prevalence of a psychiatric diagnosis or a prescription of psychoactive drugs between GD patients compared to matched controls. During the hyperthyroid phase, mental fatigue, depression and anxiety were significantly increased for GD patients compared to controls (all $P < 0.001$). At 15 months, significant improvements for GD patients were found for the items mental fatigue, depression and anxiety (all $P < 0.001$). The controls remained on a lower level. GD patients (38%) reported residual mental fatigue, 23.5% without depression and 15% combined with depression.
Conclusion
Graves' hyperthyroidism greatly affects the patients mood regardless of whether the patient previously had a psychiatric diagnosis or not. Having had a previous psychiatric condition aggravated the psychiatric symptoms but was not the cause of them. Mental fatigue (MF) and emotional distress are common in the hyperthyroid phase. These improve with treatment but are still more common in GD patients after 15 months of therapy than in controls. The residual MF was detected in this study as an isolated phenomenon distinct from depression. This indicates the importance of assessing MF in GD patients and underlines the need for rehabilitation and healthcare support as MF will have consequences for work ability.

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PS1-02-05

Association between radioactive iodine treatment and cancer risk in graves' disease: a nationwide cohort study

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Objectives
Radioactive iodine (RAI) therapy has potential therapeutic effects in treating Graves' disease (GD). However, whether RAI therapy for GD can increase cancer risk remains a controversial issue in medicine and public health.
Methods
Using the Korean National Health Insurance Service-National Health Information Database (NHIS-NHID, 2002–2020), we investigated hazard ratios (HRs) of overall and site-specific cancer associated with RAI in GD. Subsequent cancer was only defined as a primary malignancy treated at least 1 year after RAI therapy.
Results
A total of 10,737 GD patients who received RAI therapy (7,193 women, 67.0%; mean age, 43.7 $\pm$ 13.4 years) were matched to 53,003 GD patients without RAI therapy (35,471 women, 66.9%; mean age 43.8 $\pm$ 13.2 years) in a 1:4~5 ratio by age, sex, and health check-up data. The median follow-up duration was 8.7 years (interquartile range [IQR]: 5.2–12.1), and the median cumulative RAI dose was 15.0 mCi (IQR 10.0–17.1) in the RAI therapy group. During 2004-2020, the overall subsequent cancer rates were 5.66 and 5.84 per 1,000 person-years in the RAI and non-RAI groups, respectively, with an unadjusted HR of 0.97 (95% CI, 0.88–1.06); this remained at 0.92 (95% CI, 0.81–1.04) after adjustment for multiple clinical confounding factors. For leukemia, incidence rates were 0.12 and 0.05 per 1,000 person-years in the RAI and non-RAI groups, respectively, with an unadjusted HR of 2.39 (95% CI, 0.17–4.91): however, HR was insignificant of 2.03 (95% CI, 0.73–5.60) after adjustment for confounding factors.
Conclusions
This study identified that the overall cancer risk in GD patients with RAI therapy compared to those without was not significant in Korea. Further long-term studies are needed on the risks and advantages of RAI therapy in patients with GD.

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PS1-02-06

The role of selenium supplement in graves disease - a case report

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Introduction
Selenium is a mineral that plays a key role in the intracellular reactions of the thyroid. Some selenium-based proteins have a protective antioxidant function in thyrocytes. Likewise, Selenium is incorporated into deiodinases, helping in the synthesis of thyroid hormones. Through its antioxidant and anti inflammatory properties, selenium affects the development of autoimmune thyroid diseases, such as Graves Disease. Supplementation with selenium is often prescribed as an adjuvant therapy for autoimmune thyroid disease. Most studies focus on its impact on the level of thyroid peroxidase and thyroglobulin antibodies. We report a case of the effect of selenium supplementation on thyroid stimulating immunoglobulin (TSI) and Graves' hyperthyroidism. Key words: Selenium, Tsh, TSi, Graves Desease, Long time
Case Report
The patient, female of 19 years of age, came to an endocrinology clinic with complains of fatigue, insomnia, increased sweating, tachycardia and hand tremors. She has been treated with Selenium for thyroid problems (she referred she had before a value below the normal level of TSH but she had not a medical document to prove it at the time of the visit.) We retook the blood tests and performed a thyroid ultrasound (US). The US resulted normal. Blood tests were compatible with hyperthyroidism. TSI 1.26 IU/l ($<$1.22). Because of the increased level of thyroid hormones, the patient was started Methimazole 5 mg/day. She was not interrupted Selenium from 2 years. Within 6 weeks of treatment she was euthyroid and TSI were within the normal range. These results persisted even after three months.
Conclusion
Selenium plays an important role in thyroid autoimmune processes. Intervention with supplements of this micronutrient can significantly affect the restoration of euthyroid status and immunological stabilization in Graves Disease.

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PS1-02-07

Agranulocitosis caused by methimazole in a patient with graves' disease and multiple myeloma

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Introduction
Multiple myeloma (MM) is a lethal hematological malignancy with an incidence of 6.1/100 000 per year. The association of thyroid autoimmune diseases and MM is rare and has not been fully investigated. Also, it is well known that agranulocytosis is a potential lethal adverse reaction of antithyroid treatment.
Case report
We present the case of a 59-year-old female patient that presented with symptoms of hyperthyroidism. Objectively: Mild bilateral proptosis and a slightly enlarged thyroid gland. She had a partial left lobectomy in 2006 (euthyroid, before and after the intervention without any thyroid medication) and was diagnosed with MM and osteoporosis in 2016. Without significant family history. The laboratory tests revealed low TSH level, high (FT4, FT3 and TSH-R Antibodies) level. The thyroid ultrasound: Increased volume and vascularization. The Technetium 99 scintigraphy: Increased uptake throughout the thyroid. Her CBC test was normal (WBC were at the low level of the norm). The myelogram: Complete remission of MM. The diagnosis of hyperthyroidism due to Graves' disease in a patient with MM was concluded. The patient started treatment with a low dose of methimazole but the first days, in the afternoon, she had temperature of 38°C. We repeated everyday CBC, which had no changes from the previous lab tests. She continued the methimazole and in the next few days, her temperature was within normal range and CBC was also normal. After 9 days of admission, the patient got

discharged under treatment with low dose of methimazole. It was planned to be treated with radioactive iodine 131 as a definitive treatment, after she achieved euthyroidism. A week after discharge, the patient came back with severe sore throat, tiredness, and temperature of 39°C. Methimazole was discontinued immediately and the lab tests revealed agranulocytosis. After several days, her state improved with supportive therapy and got discharged from the hospital. Two weeks later she was treated with radioactive iodine 131, under treatment with Prednisone before and after taking iodine. Two months later, she was euthyroide and in a good general condition.
Conclusion
Based on available literature, patients with MM appear to be at increased risk for thyroid autoimmune conditions, our case, confirms that. By the other hand, maybe the condition of MM increases the risk of the agranulocitosis caused by antithyroid drugs. Every physician must be careful in using them, in patient with Graves' disease and MM, even if it is in complete remission of multiple myeloma.

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PS1-02-08

Evaluation of paraoxonase (PON-1) activity and advanced glycation end-products (AGES) as reliable markers of oxidative stress in graves' disease patients

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Objective
Oxidative stress has been implicated in the pathogenesis of hyperthyroidism, and its complications. Advanced glycation end products (AGEs), compounds derived from non-enzymatic transformation of macromolecules, are able to increase oxidative stress and promote inflammation and are increased in several oxidative stress-related disorders, including autoimmune thyroiditis. In the same diseases, the activity of paraoxonase-1 (PON-1), an anti-oxidant enzyme protecting against the oxidation of LDL and cell membranes, is decreased and it often negatively correlates with AGEs serum levels. No data are available on such oxidative stress parameters (AGEs and PON-1 activity) in Graves' Disease (GD).
Materials and Methods
We enrolled 35 GD patients (30 females, aged 33-58 years) and 38 age-, sex- and BMI-matched healthy controls. All GD patients were hyperthyroid without any medical therapy at recruitment, while HCs were euthyroid. Exclusion criteria: autoimmune, inflammatory and infection comorbidities, diabetes, renal failure. Serum levels of AGEs and PON-1 activity were simultaneously assayed in sera from each subject. For AGE determination, fluorescence intensity of diluted serum was recorded at emission maximum (~440 nm) upon excitation at 350 nm; results were expressed in arbitrary units per gram of protein (AU/g protein). Serum PON-1 activity was quantified by UV spectrophotometry. The method is based on the conversion of the substrate paraoxon to p-nitrophenol by the serum PON-1. The increase in absorbance of the resulting p-nitrophenol was measured spectrophotometrically at a wavelength of 412 nm, PON1 activity was expressed in U/l; 1 unit is equivalent to 1 mmol/min of p-nitrophenol.
Results
Serum AGEs were significantly higher in GD patients than controls (mean value 389 ± 47 AU/g protein; median 406 vs 295 ± 60 AU/g protein; median 290 AU/g protein; $P < 0.001$), while PON-1 activity was significantly lower in GD subjects than in controls (mean value 90 ± 54 U/l; median 67 U/l vs 256 ± 131 U/l, median 192 U/l; $P < 0.001$). The two parameters were inversely correlated ($P < 0.01$), clearly indicating an imbalance between endogenous production of oxidants and antioxidants in hyperthyroid GD patients. Also, PON-1 activity was inversely related to free-T4 and free-T3 levels ($P < 0.05$), suggesting that hyperthyroidism negatively affects the anti-oxidant PON-1 activity.
Conclusion
Increased formation and accumulation of AGEs contribute to enhanced oxidative stress, along with a decrease in PON-1 activity in autoimmune hyperthyroidism. The two parameters may serve as useful markers for monitoring the levels of oxidative stress in this disorder.

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PS1-02-09

Patientѐ experience of being affected by gravesѐdisease-the initial 3 month-phase

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Background
Graves' disease (GD) is the most common form of hyperthyroidism in Sweden. About 2000 patients are affected by GD annually (incidence 21/100 000) and a majority are women in working age. GD can be overwhelming for the affected patient. Health care professionals do their best to meet the patients' needs, but can we do more? The aim of this study was to explore patients' experiences of being affected by GD to improve healthcare.
Method
The patients were recruited at Sahlgrenska university hospital in Gothenburg, Sweden. Semi-structured face-to-face interviews were conducted with 3 men and 12 women affected by GD. A strategic sample was applied in order to get a wide distribution in the group of patients who were interviewed. The narratives were recorded and transcribed verbatim. The interviews were analyzed using qualitative content analysis.
Findings
Frequently expressed problems by the interviewees were overwhelming amount of information, change in their own personality, fatigue, and lack of energy. These factors had a negative impact on their daily life, physical and psychosocial functioning, and well-being. The informants highlighted the need of being listened to, tailored information, continuous contact, and a good treatment plan.
Conclusion
These findings indicate that patients often feel alienated from themselves in the early phase of their disease and are in a need of improved support from healthcare. By carefully listening to the patients' experiences and taking into account their resources and needs, healthcare professionals can improve health outcomes and optimize recovery based on each patient's situation.

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Miscellaneous 1

PS1-03-01

Goiter in history, literature, and art

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The documentation of goiter as a swollen neck is well known in the history before its medical description. Artists depicted what they saw in humans, the swollen human neck was the norm in many areas with endemic goiter in old Egypt, Greece, South America, and mountainous areas in central Italy and Switzerland. Sculptures from the ancient civilizations clearly demonstrated endemic goiters and cretinism in areas of environmental iodine deficiency. The engraved stones in old Egypt, and Andes monuments as well as Greek coins and sculptures were some great examples of showing goiter in the human body. This trend continued when painting became Europe's major source of artistic expression. There are many famous examples in art over many centuries such as the painting " The Madonna with Child" by Cranach, " Judith and Her Maidservant" by Gentileschi, as well as artwork by van der Weyden, Raphael, Botticelli, del Sarto, da Vinci, and di Pepo. This depiction of a large neck became more common during the Renaissance and Baroque periods due to the movement of realistic drawings of humans and continued through the 18th and 19th centuries. People with 'Swollen throats' were described by

historians and explorers of some Italian and Swiss Alpes. Water and air were often blamed for this. In literature, Shakespeare wrote a very good description of severe endemic goiter, referring to it both anatomically (portrayal of the throat) and epidemiologically (frequency of the disorder in mountainous regions) in The Tempest: 'When we were boys Who would believe that there were mountaineers Dew-lapp'd like bulls, whose throats had hanging at 'em Wallets of flesh? or that there were such men Whose heads stood in their breasts?' The severe endemic disease that caused humans to have swollen necks, cognitive impairment, mental retardation, and short stature in mountainous areas was described historically in Roman civilization and then was coined as " Cretinism" in Swiss-French literature before it was described medically due to endemic iodine deficiency.

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PS1-03-02

Safety and efficacy of prophylactic treatment for hyperthyroidism induced by iodinated contrast media in a high-risk population

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Introduction
The use of iodinated contrast media (ICM) can lead to thyrotoxicosis, especially in patients with risk factors, such as Graves' disease, multinodular goiter, older age, and iodine deficiency. Although hyperthyroidism may have clinically relevant effects, whether high-risk patients should receive prophylactic treatment before they are administered ICM is still debated.
Aim of the study
We aimed to demonstrate the safety and efficacy of prophylactic treatment with sodium perchlorate and/or methimazole to prevent ICM-induced hyperthyroidism (ICMIH) in a population of high-risk cardiac patients. We ran a cost analysis to ascertain the most cost-effective prophylactic treatment protocol. We also aimed to identify possible risk factors for the onset of ICMIH.
Materials and Methods
We performed a longitudinal retrospective study on 61 patients admitted to a tertiary-level cardiology unit for diagnostic and/or therapeutic ICM-procedures. We included patients with available records of thyroid function tests performed before and after ICM were administered, who were at high risk of developing ICMIH. Patients were given one of two different prophylactic treatments (methimazole alone or both methimazole and sodium perchlorate) or no prophylactic treatment. The difference between their thyroid function at the baseline and 11-30 days after the ICM-related procedure was considered.
Results
Twenty-three (38%) of the 61 patients were given a prophylactic treatment. Thyroid function deteriorated after the administration of ICM in 9/61 patients (15%). These cases were associated with higher plasma creatinine levels at admission, higher baseline TSH levels, lower baseline FT4 levels, and no use of prophylactic treatment. The type of prophylaxis provided did not influence any onset of ICMIH. A cost-benefit analysis showed that prophylactic treatment with methimazole alone was less costly per person than the combination protocol. On multivariate analysis, only the use of a prophylactic treatment was independently associated with a reduction in the risk of ICMIH. Patients not given any prophylactic treatment had a nearly five-fold higher relative risk of developing ICMIH.
Conclusion
Prophylactic treatment can prevent the onset of ICMIH in high-risk populations administered ICM. Prophylaxis is safe and effective in this setting, especially in cardiopathic patients. Prophylaxis with methimazole alone seems to be the most cost-effective option.

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PS1-03-03

Treatment of obesity with thyroid hormones: data from the thesis* collaboration. *treatment of hypothyroidism in europe by specialists, an international survey

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Objectives
The use of thyroid hormones (TH) to treat obesity is not supported by evidence based on efficacy and safety, and this is reflected in recommendations of major international guidelines on hypothyroidism and obesity. We aimed to explore views about this practice among European thyroid specialists and their associations with respondent characteristics.
Methods
Thyroid specialists from 28 countries were invited to participate in a questionnaire survey via national thyroid/endocrine professional organisations. The question about obesity was whether *'thyroid hormones may be indicated in biochemically euthyroid patients with obesity resistant to life-style interventions'*. Geographic regions were defined according to the UN Statistics Division. Gross national income (GNI) information stems from https://data.worldbank.org/.
Results
Out of 17,247 invitations 5,695 (65% women) valid responses were received (response rate 33.0%). Of these, 290 (5.1%) stated that TH were indicated as a treatment for obesity. This view was more common among non-endocrinologists (8.7% vs. 4.7%, $P < 0.01$), respondents working in private practice (6.5% vs. 4.5%, $P < 0.01$) and varied geographically (Eastern Europe, 7.3%; Southern Europe, 4.8%; Western Europe, 2.7%; and Northern Europe, 2.5%). Respondents from Northern and Western Europe were less likely to regard obesity as an indication for TH use than those from Eastern Europe ($P < 0.01$). GNI correlated inversely with the view that obesity was an indication for TH use (OR 0.969, CI: 0.961-0.977; $P < 0.001$, per 1000 US$). Of the 28 countries 21 have national guidelines for obesity, and 14 have for hypothyroidism too. The obesity guidelines did not influence the use of LT4 for obesity treatment in either univariate or multivariate models. The presence of thyroid guidelines was associated with less prescribing LT4 for obesity (univariate OR 0.68, 95%CI 0.53-0.88, multivariate OR 0.712, 95%CI 0.55-0.91).
Conclusions
Despite the lack of evidence and contrary to recommendations from guidelines (both national and international), about 5% of respondents to the THESIS survey stated that TH use is indicated as a treatment for obesity in euthyroid patients resistant to life-style interventions. This opinion was associated with working in the private sector, Eastern Europe, and countries with a low GNI. Our findings question the underlying motives and raise concerns about the ethical and safe use of TH by some European thyroid specialists if the attitudes expressed in the THESIS questionnaire represent actual practice.

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PS1-03-04

Association between immune-related thyroid dysfunction and the efficacy of immune checkpoint inhibitors

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Introduction
Immune checkpoint inhibitors (ICIs) are an effective treatment for advanced cancer, but they are not free from immune-related adverse events (irAEs). A common irAES is thyroid dysfunction (TD-irAEs) and, as such, may influence patient survival and response to ICIs.
Objetives
The aim was to determine the incidence and characteristics of TD-irAEs among patients with advanced cancer treated with ICIs in a real-life setting and to investigate the association between TD-irAEs and response to treatment.
Methods
A single-center retrospective analysis of TD-irAEs in patients with advanced cancer treated with ICIs. We analyzed the development of TD and its association with the response to treatment assessed using RECIST v1.1 criteria. We calculated the odds of recurrence associated with TD-irAEs using multivariable adjusted regression and overall survival associated with TD-irAEs using multivariable adjusted Cox proportional hazards models.
Results
We included 238 patients (72% male; median age 69.5 years, range 63-76) with melanoma, lung or urothelial cancer, treated with Atezolizumab, Pembrolizumab, Ipilimumab and/or Nivolumab. Of them, 70 (29%) patients developed TD-irAEs in a median time of 69 days (range 41-181). The most frequent TD-irAEs was subclinical hypothyroidism (41%), followed by subclinical thyrotoxicosis (24%), overt hypothyroidism (17%) and hyperthyroidism (17%). Patients who developed TD-irAEs were younger ($P = 0.030$) than those who did not. No significant differences between groups were found for sex ($P = 0.145$) or type of primary tumor ($P = 0.051$). The incidence of TD-irAEs in patients treated with combination therapy (Nivolumab + Ipilimumab, 67%) was significantly higher than that in patients treated with any ICI in monotherapy. Compared with patients who did not develop TD-irAEs, those in the TD-irAEs group had a relative reduction of 77% (OR 0.23, 95% CI 0.11-0.47) in the risk of progression and of 47% in the risk of mortality (HR 0.53, 95% CI 0.36-0.80), independent of age, sex, primary tumor, or type of ICI treatment.
Conclusions
TDirAEs occur in nearly 30% of patients receiving ICI treatment. Most TD-irAEs were mild and easily controlled. The occurrence of TD-irAEs appeared to be associated with improved response to ICIs as well as improved survival. These findings may reinforce the clinical relevance of monitoring thyroid function, as such monitoring could be an independent prognostic indicator of antitumor response and survival among oncologic patients on ICI treatment.

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PS1-03-05

Thyroid dysfunction in head and neck squamous cell carcinoma patients after external radiotherapy: clinicopathological risk factors

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Background
Radiotherapy (RT) with or without chemotherapy is a common treatment for head and neck squamous cell carcinoma (HNSCC) patients and it can cause adverse effects, including dysfunctions of thyroid. The aim of this study was to identify thyroid dysfunction among patients submitted to external RT for treatment of HNSCC, with serial evaluation of thyroid function.
Material and methods
This is a retrospective longitudinal study of the follow-up of thyroid function in 285 HNSCC patients treated with RT alone or associated with chemotherapy and/or surgery.
Results
53.7% of 285 patients presented thyroid dysfunction, 44.9% of them maintained persistent dysfunction. The most common dysfunction was subclinical hypothyroidism ($n = 124$), of which 68.5% remained with subclinical hypothyroidism, 21% evolved to overt hypothyroidism, 0.8% presented central hypothyroidism, and 9.7% returned to the euthyroid state at the end of follow up. The mean time after RT for the occurrence of subclinical dysfunction was 17 months whereas for overt evolution it was 24 months. Type 2 diabetes mellitus, bulky lymph nodes, and treatment with RT without surgery were seen as risk factors for thyroid dysfunction development. Regarding the risk of progression of subclinical hypothyroidism, a direct correlation with TSH level was observed: all patients with TSH $\geq$ 7.5 mIU/mL evolved to primary overt hypothyroidism or remained in subclinical hypothyroidism, whereas among those with TSH $<$ 7.5 mIU/mL, 19.5% were euthyroid at the end of follow-up.
Conclusion
These data indicate the need for frequent monitoring of thyroid function in HNSCC patients treated with RT. Special attention should be given to the population at greater risk, such as those with type 2 diabetes mellitus, bulky lymph nodes, and treated with RT without surgery.

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PS1-03-06

The importance of determining the PTH level in the early phase of the assessment in elderly patients to exclude the early phase of hyperparathyroidism

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The Case Study
We report the case of a 68-year-old female referred to the E.R. department with severe neurological problems. Patient's neurological status revealed that patient was disoriented in time and place, with emotional irritability and an asymmetric eye fissure, and not feeling well without any obvious reason. A preliminary CT scan with I/V contrast was done and acute neurological damage was excluded. In the lab, there were: hypokalemia, hypomagnesemia, increased CRP, Ca was within upper normal limits, kidney and liver function tests, CBC and urine tests, and coagulation factors were normal. On the second day, the patient's condition gradually worsened. ABG was done: Ca- 2.62 mmol/l, Potassium 3.35 mmol/l. Developed fever, acute respiratory failure, arrhythmia, tachypnea and desaturation despite oxygen inhalation. She was transferred to the ICU and intubated. Cordarone 5-7 mg/kg/hr, as a part of an effective and safe drug, and Rivaroxaban were used to achieve sinus rhythm. And for febrile temperatures, antipyretic treatment was administered. On the third day, the MRI scan and lab tests were done. An MRI scan with I/V contrast showed lacunal ischemia (chronic) in the basal nuclei and large hemispheres bilaterally. After a thorough assessment, a neck mass was detected. With further assessment, it was identified as being of parathyroid origin. That scan showed a slightly asymmetric thyroid gland with nonhomogenous structure. On its right edge, dorsally, an oval-shaped, intensely contrasted nodule with a size of 1.0 x 0.6 cm was seen. Physicians ordered lab tests. Ca was elevated at 2.82 mmol/l, vit D3 was 17.10 ng/ml, ast 165.8, ALT - 70.4, GGT-59.0, creatinine was 184 mkmol/l, and PTH was set out and it was 1799 pg/ml. Due to the patient's severe condition, additional tests like scintigraphy was not done.
Conclusion
Our study showed that in elderly patients with neurological disturbances and upper normal limits or high calcium level should be determined PTH level on early phase of the assessment to exclude latent phase of hyperparathyroidism.

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PS1-03-07

Obesity and metabolic parameters are not dependent on TSH levels within normal range in young women with autoimmune thyroiditis on levothyroxine therapy

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Introduction
The relationship between thyroid function and obesity and associated metabolic parameters has been extensively investigated especially in patients with primary

hypothyroidism on levothyroxine replacement therapy. Current data show inconsistent results possibly influenced by some patients' characteristics such as sex, age, concomitant diseases and medications.
Objective
To assess the relation between thyroid function tests and BMI, fasting blood glucose, lipids in euthyroid premenopausal women on levothyroxine replacement and healthy women without other disorders or medication intake.
Patients and Methods
77 women with autoimmune thyroiditis on levothyroxine treatment and 249 age matched premenopausal healthy women were included in the study. All participants had TSH level within the reference range 0.4-4.2 mIU/l. The included women did not have any other significant medical conditions, including diabetes mellitus, were not taking medications other than levothyroxine, were all premenopausal not taking estrogen-containing drugs. TSH, FT4, fasting blood glucose and lipids were investigated, BMI was calculated after height and weight measurement.
Results
Women on levothyroxine had higher levels of TSH (2.44 ± 0.12 vs 2.00 ± 0.05 mIU/l, $P < 0.01$) and FT4 (11.56 ± 0.16 vs 10.91 ± 0.09 pmol/l, $P < 0.01$) compared to healthy women. No differences between BMI and the other tested parameters were estimated between the two groups. There were no significant correlations between TSH and BMI in women with autoimmune thyroiditis, slight positive correlation with total cholesterol was identified ($r = 0.232$, $P = 0.042$). FT4 levels showed significant negative correlation with total ($P = 0.001$) and LDL cholesterol ($P < 0.001$). In euthyroid control group TSH showed slight positive correlations with BMI, fasting blood glucose and LDL cholesterol. FT4 levels were negatively associated with total cholesterol ($P = 0.006$) and HDL cholesterol ($P = 0.003$). After adjustment for age there were no changes in the results in both studied groups.
Conclusion
Our results support other authors' findings that as long as TSH is kept within the reference range there is no increased risk of obesity and metabolic complications in patients with autoimmune hypothyroidism. It even might be suggested that those women have more favorable metabolic profile because of the higher FT4 levels. Adjusting the levothyroxine dose solely to decrease TSH to low-normal values is not considered beneficial and thus is not justified.

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PS1-03-08

The prevalence and characteristics of immune checkpoint inhibitors induced thyroid adverse events in korea: a nationwide cohort study, 2017-2020

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Objectives
Immune checkpoint inhibitors (ICIs) have demonstrated stunning effects in many cancer types albeit its immune-related adverse outcomes such as hypophysitis, adrenalitis, and thyroiditis. Despite the significant increase in ICIs use in Korea, there still is a lack of clarification about the actual prevalence and risk factors of ICI-associated thyroid diseases.
Methods
In this nationwide cohort study, 12,079 lung cancer patients were extrapolated from the Korean National Health Insurance Service-National Health Information Database (NHIS-NHID, 2017–2020) who received ICI treatment (ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) with no history of thyroid diseases (including thyroid cancer) or use of levothyroxine and anti-thyroid drugs (ATD). ICI-related thyroid disease was defined as levothyroxine or ATDs use after ICI treatment.
Results
The prevalence of ICI-induced thyroid adverse events was 4.7% (402/8557, 301 female and 101 male), with a mean age of 65.6 years (standard deviation $\pm$ 9.6). The median duration of ICI-induced thyroid adverse events was 3.0 months (interquartile range, 1.0–5.6 months). Multivariate regression analysis identified females and smoking as significant risk factors for ICI-related thyroid adverse events. The unadjusted risk ratio (RR) for overall mortality within 1-year after ICI therapy was 0.52 (95% confidential interval [CI], 0.44–0.60), and remained at 0.49 (95% CI, 0.45–0.62) after adjusting confounding factors. And the adjusted RR for cancer-related mortality was 0.51 (95% CI, 0.44–0.61) with statistical significance but the RR for cardiovascular-related mortality was 0.81 (95% CI, 0.10–6.83) with no statistical significance.
Conclusions
To our best knowledge, this is the first nationwide cohort study to identify the prevalence of ICI-associated thyroid disease in Korea. Unlike previous studies, our nationwide study demonstrates a lower prevalence of adverse outcomes. Overall, ICI-associated thyroid adverse events in patients with ICI therapy had favorable survival rates. We recommend further studies to identify genetic risk factors of ICI-related thyroid disease for personalized and precise treatment for patients who receive ICI therapy.

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PS1-03-09

Iodine nutrition in greenland: urinary iodine concentration during a 20-year period

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Background
Iodine nutrition relies on dietary intake. Marine foods are iodine rich, and they contributed markedly to the iodine intake among populations in Greenland. However, dietary habits are drifting away from the traditional diet dominated by iodine rich marine foods such as seal, whale, and seabirds. This led us to monitor iodine nutrition among populations in Greenland.
Methods
Cohort studies were conducted in 1998, 2008, and 2018 including 50-69, 50-79, and 50–89-year-olds in the capital city Nuuk in West Greenland, in the main city Tasiilaq, and in surrounding settlements in the rural Ammassalik district in East Greenland. Participants were randomly selected in Nuuk while all inhabitants in Tasiilaq and the surveyed settlements in East Greenland were invited. Participants filled in an interview-based questionnaire on demographic and iodine-related determinants. A spot urine sample was collected for iodine determination using the Sandell-Kolthoff reaction modified according to Wilson and van Zyl. This report includes data from the 10- and 20-year follow-up on the first iodine nutrition study conducted in 1998.
Results
Participation rates were 95%/80%/80% with 535/632/437 participants in 1998/2008/2018. Thus, a total of 1,604 participations comprised of 1,141 (535/397/209 in 1998/2008/2018) unique participants and 463 follow-ups in 2008 (235) and 2018 (228). Urinary iodine concentration (UIC) was below 50 μg/l in 43% of samples in 1998 and in 45% of samples in 2018. Median (25; 75 percentiles) UIC was 75 μg/l (35; 133 μg/l)/70 (40; 135)/108 (50; 205) /115 (59;226) in non-Inuit/Inuit in Nuuk/Tasiilaq/settlements in 1998, and 91 μg/l (59; 154 μg/l)/90 (55; 135)/74 (46; 129)/84 (48;164) in non-Inuit/Inuit in Nuuk/Tasiilaq/settlements in 2018.
Conclusion
The monitoring of iodine nutrition in Greenland during a 20-year period revealed stable trends with an overall similar iodine nutrition level between 1998 and 2018. However, dynamics within sub-populations were marked with a decrease in urinary iodine excretion among Inuit in rural part of Greenland while urban populations showed similar or slightly higher UICs.

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Nodules-surgery

PS1-04-01

Individualized approach to the patients with autonomously functioning thyroid nodules and normal TSH blood level

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Objectives
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 stimulating hormone (TSH) blood level.
Methods
In this study 127 cytological benign AFTNs in 113 pts (98 female and 15 male) with normal TSH 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 60 (range 35 - 90) years. AFTNs were located more frequently in the right thyroid lobe (71 nodules) than in the left lobe (56 nodules). In 18 pts a solitary AFTN has been found on ultrasonography and the other 95 patients had AFTNs in multinodular goiter. 14 pts had two AFTNs. On post I-131 therapy thyroid scan in 79 AFTNs complete therapy effect has been observed, but in 48 AFTNs a scintigraphycally partial effect has been noted. Statistical analysis showed a significant reduction in the thyroid ($P = 2{,}2516E\text{-}10$) and AFTNs ($P = 0{,}0038$) volume after J-131 therapy. TSH value significantly increased ($P = 3{,}734E\text{-}05$) and FT4 value significantly decreased ($P = 5{,}2476\ E\text{-}05$) after I-131 therapy. FT3 ($P = 0{,}3743$), anti-TPO ($P = 0{,}7633$) and anti-Tg ($P = 0{,}1947$) and anti-TSH receptor ($P = 0{,}1166$) values did not change significantly.
Conclusion
This study shows that radionuclide therapy with I-131 in pts with AFTN and normal TSH 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.

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PS1-04-02

Early voice problems assessment in post-thyroidectomy syndrome using vocal fatigue index and cepstral analysis

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Post-thyroidectomy syndrome is defined as postoperative problems after thyroidectomy without injury of recurrent laryngeal nerve, and including most common symptom such as vocal fatigue, loss of high-pitch, reduced vocal strength, reduced speaking fundamental frequency also can be presented. In a recent systemic review, F0, shimmer, and MPT was significantly deteriorated only in the early period and not in the late period after thyroidectomy. There have been several questionnaires for subjective voice problem after thyroidectomy; voice handicap index (VHI) and Voice symptom scale (VoiSS), and Thyroidectomy-related voice questionnaire (TVQ). Cepstral analysis is effective in the estimation of dysphonia severity even for highly dysphonic voice samples; CPP appears to correlate well with overall voice quality. In this study, we aimed to assess voice changes after thyroidectomy via subjective and objective parameters in early phase (post-operative 1 month). Totally 96 patients who underwent thyroidectomy without recurrent laryngeal nerve injury at our hospital between April 2018 and June 2022 were enrolled, and all of them performed voice analysis including VH, VFI, MDVP, and CPP preoperatively and postoperatively. There were 37 males and 59 females, and their mean age was 48.39 years old. Among them, 57 patients underwent lobectomy, and 39 patients (including lateral neck dissection in 7 patients) got total thyroidectomy. After 1 month of surgery, even GRBAS scale showed no changes, postoperative subjective voice scale (VHI, VFI) was significantly decreased ($P < 0.001$, $P = 0.002$, respectively). In the objective voice score of MDVP, shimmer and EGG score was significantly decreased, and LH ratio showed significantly increased. The VHI and VFI changes between preop and postop had correlation with CPP/a/ and voice range profile (VRP) high pitch. Dividing groups according to sex, only female group showed significantly discomfort after surgery in VHI, VFI, and VRP high pitch. The group highly complained about voice discomfort after surgery was correlated with VFI score, EGG, and VRP high pitch. In spite of negative results in perceptual analysis, subjective discomfort is present in the early postoperative days after thyroidectomy. Comparing VFI to VHI, VFI also be good predictable tools for assessment of patients' voice problem. In patients with voice discomfort, CPP would be a feasible parameter. Female patients more complained about their postoperative voice problem, and their high pitch voice can be impaired in early postoperative days. Further study was expected to be a large scale with long term follow-up periods.

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PS1-04-03

Elastographic evaluation of thyroid nodules in children and adolescents with hashimoto's thyroiditis and nodular goiter with reference to cytological/histopathological diagnosis

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Introduction
Hashimoto's thyroiditis (HT) is the most frequent cause of thyroid disfunction in children and its incidence is increasing. Although thyroid cancer is an uncommon childhood malignancy with a reported incidence of about 0.59 cases per 100,000, there are data suggesting the comorbidity of papillary thyroid carcinoma with autoimmune thyroiditis (AIT) in children. Ultrasound elastography is a non-invasive imaging, based on estimation of mechanical properties (elasticity) of the tissue, improving the differential diagnosis of thyroid nodules. In our study we aimed to determine the elastographic features of thyroid nodules in children and adolescents with AIT and nodular goiter in relation to cytological and/or histopathological diagnosis and to assess if the autoimmune process reduces the accuracy of elastography in nodule evaluation.
Materials and Methods
We examined 215 children (57 boys and 158 girls) with 261 thyroid nodules (143 non-AIT and 118 AIT) between February 2013 and September 2021. All patients underwent conventional ultrasound with elastography followed by fine needle aspiration biopsy (FNAB). Elastography parameters were acquired with Toshiba Aplio MX SSA-780A system and analyzed while comparing of the stiffness of the nodule (ROI 1) to the healthy tissue (ROI 2).
Results
Abnormal Strain Ratio (SR $\geq$ 5) was observed in 36 non-AIT nodules and 15 AIT nodules. Papillary thyroid carcinoma was diagnosed in 5 patients (2% of all investigated nodules), these were 3 non-AIT nodules and 2 AIT nodules. SR of malignant thyroid nodules was statistically higher than benign ones both in the group of non-AIT (6 ± 4 vs. 3.67 ± 2.62, $P = 0.024$) and AIT nodules (6.3 ± 0.01 vs. 2.92 ± 1.89, $P = 0.047$). Comparing non-AIT and AIT benign nodules SR was higher in non-AIT nodules (3.67 ± 2.62 vs. 2.92 ± 1.89, $P = 0.01$). The sensitivity and specificity of elastography for detecting malignant nodules in non-AIT was 67% and 76% respectivey and in AIT nodules 100% and 88% respectively. Elastography's NPV was 99% in non-AIT nodules and 100% in AIT nodules.
Conclusions
Autoimmune inflammatory process of the thyroid gland does not limit the use of elastography in the diagnosis of thyroid nodules in children.

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PS1-04-04

Volume reduction rate's predictors after radiofrequency ablation of benign thyroid nodules. a single-centre analysis

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Background
Ultrasound guided minimally invasive therapies are becoming increasingly popular for the treatment of symptomatic benign thyroid nodules. Efforts have been directed on the prediction of volume reduction as a measure of efficacy of the procedure. Aim of the present study is to identify predictors of 6-months volume reduction rate (VRR) after radiofrequency ablation of benign thyroid nodules.
Materials and Methods
We performed a retrospective single-centre analysis on consecutive patients who underwent radiofrequency ablation for benign thyroid nodules from January 1st 2015 to December 31st 2021. Volume reduction rates were calculated from the preprocedural baseline and collected along with clinical periprocedural and follow up data. Univariate and multivariate linear regression analyses were performed to identify predictors independently associated with the outcome.
Results
A total of 48 patients were included in the analysis, 64,6% of which had compressive symptoms. Median preoperative nodule volume was 16,5 cm3 [IQR 11,1-28,9]. A single patient suffered an intranodular haematoma which was managed conservatively. Symptoms cure was achieved in 77,4% of symptomatic patients, with a median 6 months VRR of 58,8% [IQR 41,7—70,7]. A multivariable linear regression model was computed ($P < 0.001$; F 7,71) which identified nodule American College of Radiology Thyroid Imaging Reporting and Data Systems (TIRADS) score, preprocedural nodule volume, a diagnosis of toxic or recurrent nodule and Body mass index (BMI) as independent predictors of 6 months VRR ($P = 0.006$, 0.005, 0.008 and 0.016 respectively). BMI increments were negatively associated with VRR (Coefficient -1,42; 0,016) but not with lower compressive symptoms cure rate at 1 year.
Conclusions
BMI, TIRADS score and nodule volume independently predict VRR although an association with lower symptoms cure rate was not demonstrated. This study adds to the body of literature exploring predictors of radiofrequency ablation efficacy, providing valuable information for clinicians. Prospective multicentre studies are needed to confirm our findings.

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PS1-04-05

Clinical significance of serum thyroglobulin and tumor volume in delayed surgery for thyroid follicular neoplasms

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Objective
Serum thyroglobulin doubling time (Tg-DT/DR) is a valuable marker for predicting recurrences/metastases and response to treatment in patients with well-differentiated follicular cell-derived thyroid carcinoma. Similarly, tumor-volume doubling time/rate (TV-DT/DR) is helpful in predicting tumor progression during active surveillance of papillary microcarcinoma and chemotherapy. However, no study has investigated the clinical significance of Tg-DT/DR and TV-DT/DR in patients with suspicious follicular neoplasms. The study aimed to examine the significance of Tg and TV in delayed surgery for thyroid follicular neoplasms
Methods
A total of 648 cases that were resected and diagnosed as follicular adenoma (567 cases) or follicular carcinoma (81 cases) between January 2019 and December 2022 were retrospectively examined. Of these, 281 cases (249 follicular adenomas and 32 follicular carcinomas) with a follow-up of more than one year were included in this study. Tg-DR and TV-DR were calculated based on the results of at least three preoperative measurements. TV was obtained from ultrasonic measurements in three directions. A positive anti-Tg antibody (TgAb) level was defined as >40.0 IU/mL.
Results
There were no significant differences in age, sex, tumor size, incidence of the oxyphilic type, or TV-DR. The interval between the initial presentation and resection was longer in follicular adenoma than in follicular carcinoma ($P < 0.05$). Serum thyroglobulin level (mean:762.7 ng/mL) of follicular carcinoma were significantly higher than that of follicular adenoma (mean:251.3 ng/mL) ($P < 0.0005$), and the trend was largely due to the TgAb-negative cases. The frequencies of serum Tg levels $\geq$1,000 ng/mL in follicular adenoma and follicular carcinoma cases were 3.6% and 15.6%, respectively. Tg-DR did not reveal significant difference between follicular adenoma and follicular carcinoma in both TgAb-negative and -positive cases. However, Tg-DR ≥ 1.0/year in TgAb-negative follicular carcinoma cases (12.5%) tended to be more frequently observed in TgAb-negative follicular adenoma cases (2.8%) ($P = 0.0548$). Among the non-oxyphilic types, Tg-DR ≥ 1.0/year showed a significant difference between follicular carcinoma and adenoma ($P < 0.05$), and the risk of malignancy in cases with Tg-DR ≥ 1.0/year was 50.0%. None of the parameters examined were significantly different in the oxyphilic type.
Conclusions
In patients undergoing follow-up for non-oxyphilic follicular tumors, a high serum Tg level ($\geq$1,000 ng/mL) and Tg-DR (≥ 1.0/year) may indicate malignancy. However, it should be noted that Tg level or TV-DR are not helpful in TgAb-positive cases. For the oxyphilic type, it was not possible to find parameters suggesting malignancy because of the small number of cases.

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PS1-04-06

Role of superb microvascular imaging in thyroid nodule risk stratification

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Introduction
Angiogenesis plays an important role in the growth and processes of tumors, often indicating neovascularity. However the role of vascularization in thyroid nodules observed with power or color doppler has always been debated. Therefore, most of thyroid nodules sonographic risk classification do not consider vascularization as an important features in predicting the risk of malignancy. In the last years a new vascular imaging technique, Superb Microvascular Imaging (SMI) has been developed and some studies suggested a diagnostic value in thyroid nodules.
Purpose
The aim of our study is to evaluate the role of SMI as an additional feature to ultrasound (US) risk stratifications proposed by the American Thyroid Association (ATA) in predicting the risk of malignancy.
Materials and methods
We evaluated 198 thyroid nodules selected for fine needle aspiration cytology (FNAC) and classified them according to ATA risk classification. Superb Microvascular Imaging was classified into four types and then grouped in Type 1-2 SMI and Type 3-4 SMI and Thy1 and Thy3 cytologies were excluded for the statistical analyses.
Results
According to the British Thyroid Association, FNAC was benign (Thy2) in 83.5% (111/133), and suspicious or malignant (Thy4/Thy5) in 16.5% (22/133) of the nodules. Based on ATA US risk assessment, thyroid nodules were classified into 'very low/low suspicion' ($n = 75$, 56.3%), 'intermediate suspicion'($n = 38$, 28.6%) and 'high suspicion'($n = 20$, 15.1%). The rate of Thy4/5 cytologies was 1.3%, 15.8% and 75% in 'very low/low suspicion', 'intermediate suspicion' and 'high suspicion' thyroid nodules, respectively ($P < 0.001$). The rate of Thy4/5 cytologies was 10.3% in Type 1-2 SMI and 30.2% in Type 3-4 SMI nodules ($P = 0.006$). At multivariate analysis, both ATA risk class ($P = 0.02$ for intermediate risk and $P < 0.001$ for high risk categories) and SMI ($P = 0.04$) were independently associated with risk of malignancy. Stratifying SMI categories and ATA US risk classes, SMI was not associated with an increased rate of malignancy in 'very low/low suspicion' and 'intermediate suspicion' US risk nodules, whereas, in 'high suspicion' thyroid nodules, the presence of Type 3-4 SMI was significantly associated with a higher rate of Thy4/5 cytologies (50% Type 1-2 SMI and 100% for Type 3-4 SMI, $P = 0.03$).
Conclusions
In these preliminary data, Type 3-4 SMI is associated with a significant higher rate of Thy4/5 cytologies. However, SMI seems able to improve the positive predictive value of ATA US risk stratification only in 'high suspicion' category.

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PS1-04-07

Completion thyroidectomy via robotic transoral vestibular approach - preliminary outcome report

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Introduction
Transoral Robotic Thyroidectomy (TORT) is progressively gaining its ground in robotic thyroid surgery. With accumulated techniques and developments, TORT can also be applied for completion thyroidectomy. We review our experience with the transoral robotic approach to completion thyroidectomy to evaluate the safety and surgical feasibility.
Methods
Consecutive patients receiving completion TORT operation were evaluated from a prospective database. Descriptive and quantitative data were analyzed.
Results
Completion TORT operations were performed on 10 patients between February 2017 and November 2020. There were seven female and three male patients with a mean overall age of 42.2±13.5 years. A mean overall interval between operations was 49.2±73.6 months and average operation time of completion TORT thyroidectomy was 148.3±19.7 minutes. No complications occurred in all ten surgeries, and no surgery was converted to open surgery.
Conclusion
We preliminary show the feasibility of completion robotic transoral thyroidectomy. From the initial results, it is suggested that completion lobectomy using transoral robotic approach is a safe and feasible method with excellent cosmesis and minimal adverse effect.

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PS1-04-08

Effects of low Vitamin D on calcium and phosphate metabolism and thyroid nodule stiffness

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Background
Vitamin D deficiency contributes to elastographic hardening of thyroid nodules in patients with hypothyroidism. In such patients, the nodules are elastographically consistent with type 3b. Vitamin D regulation promotes the transition of nodules from type 3b to type 3a.
Objectives
The objective of the present study is to determine the effect of low level of vitamin D on calcium and phosphate metabolism.
Methods
The research lasted for 1.5 to 2 years, more than 30 patients were examined, and whose average age was 35-60 years old. TSH was 4.5-10.2 mIU/l, FT4 level was 0.8-1.2 ng/dL, vitamin D 2-20 ng/dL, PTH ranged from 6.1 to 10.2Pg/ml, calcium was within the normal range. Elastography was performed on a TOSHIBA Apilo 500. Elastographic examination revealed 3b nodules in the thyroid gland. The patients were prescribed Levothyroxine depending on body weight and vitamin D_3 50,000 IU once a week.
Result
After 3-5 months of treatment, drug-induced euthyroidism, normalization of vitamin D and regulation of calcium and phosphate metabolism (TSH 0.5-1.5 mIU/l, vitamin D 40-60 ng/dL, PTH 3.1-4.5 Pg/ml) were diagnosed. Elastographic examination after 10-12 months revealed reduction of thyroid nodule stiffness and transition from type 3b to 3a.
Conclusion
The result of the research showed that the low levels of vitamin D can lead to the stiffness of thyroid nodules due to the disturbance of calcium and phosphate metabolism.

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PS1-04-09

Vocal morbidity related to the external branch of the suprerior laryngeal nerve following thyroidectomy

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Vocal morbidity related to the external branch of the superior laryngeal nerve following thyroidectomy
Objectives
Damage to the external branch of the superior laryngeal nerve (EBSLN) can cause a vocal morbidity following thyroidectomy. However its diagnosis is challenging. Here we aim to determine the vocal, endoscopic and acoustic characteristics of a damage of the EBSLN as well as factors associated to its occurrence.
Materials and methods
We conducted a prospective study that included patients who underwent a partial or total thyroidectomy between September 2021 and January 2022 and who did not present a pre-operative laryngeal dysfunction. A vocal assessment was performed at pre-operatively and post-operatively at day1, one month and 6 months. We confirmed the diagnosis of EBSLN damage based on endoscopic findings and determined the vocal alterations related to its damage.
Results
We included 51 patients. We did not perform a systemic identification of the EBSLN. We observed endoscopic signs in favor of a damage of the EBSLN in 9 patients that included the following: shortening, thickening and bowing of the vocal fold in respectively 77.78%, 33.33% and 11.11% of cases as well as shortening of the ary-epiglottic fold (11,11%) and deviation of the glottis axe towards the paralyzed side (11,11%). We did not any vocal symptom in 6 patients while three patients presented a decrease of the habitual vocal pitch, vocal fatigue and dysphonia. Fundamental frequency (F0) deceased in 6 patients post-operatively with respective F0 values of 267 Hz, 238 Hz and 242 Hz at the pre-operative, one-day and one-month post-operative assessments. However the decrease was not significant. We did not record a significant difference of the degree of F0 decrease in patients with or without a damaged EBSLN. Jitter and shimmer increased in 5 patients with a damaged EBSLN but the increase was not significant. The used hemostasis technique for the ligature of the superior pedicle, operator experience and goiter size were not associated the EBSLN damage.
Conclusion
A damage of the EBSLN can cause a vocal alteration following thyroidectomy. Its clinical manifestation can remain unnoticed while endoscopic findings are neither constant no pathognomonic. Acoustic findings included a decrease of F0 and an increase of jitter. We did record any factor significantly associated with an increased risk of a damage of the EBSLN. Here we emphasize on the importance of suspecting a damage of the EBSLN in the case of a vocal alteration with normal vocal fold mobility.

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Thyroid hormone diagnostics 1

PS1-05-01

Functional thyrotropin receptor autoantibodies in women with thyroid autoimmunity and the impact of ovarian stimulation

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Background
Thyroid autoimmunity (TAI) is the most important cause of hypothyroidism in the general population, and its prevalence is higher in women of subfertile couples.[1] Women pregnant after an assisted reproductive technology (ART) with TAI carry a higher risk of a first trimester miscarriage rate compared to women without TAI. Several reasons could be underlying such as thyroid dysfunction, older age, an immune imbalance, and the presence of thyrotropin receptor antibodies (TSHR-Ab) that might impede the development of the corpus luteum (the ovarian hypothesis).[1,2] TSHR-Ab can be stimulating (TSAb) or blocking

(TBAb) and be present in women with TAI and/or be induced by the ovarian stimulation procedure (OS).[3]
Aim
In this prospective pilot study, we determined the presence of functional TSHR-Ab before and after OS in ten women with TAI and different causes of subfertility and in one woman without TAI.
Methods
TSH-R-Ab were measured with two established TSAb and TBAb cell-based reporter bioassays with luciferase release as readout according to manufacturer's instructions (Thyretain®, Quidel, USA). The cAMP-response element (CRE)-dependent luciferase expression levels was quantified in a luminometer.[3] In addition, the two new TSAb and TBAb bioassays (Turbo^{TM}, Quidel) utilize a novel cAMP biosensor that is an engineered form of firefly luciferase. Using this biosensor, luciferase activity is proportional to intracellular cAMP levels. Analyses were performed before, during and at the end of the OS.
Results
Mean (SD) age of the women was 38.8 ($\pm$ 3.2) years, median (IQR range) BMI 22 (20-28) kg/m^2, OS cumulative OS dose 1413 (613-2925) IU/l. Median TSH, FT4 and TPO-Ab serum levels were 2.33 (2.23-2.61) mIU/l, 16.8 (14.4-18.5) pmol/l and 152 (86-326) kIU/l, respectively. Fifty percent of women were treated with levothyroxine. During OS, oestradiol levels increased from 40 (26-56) ng/l to 963 (383-5095) ng/l; $P < 0.01$. Using four different bioassays, no functional TSHR-Ab were detected before or after OS, independent of the method used.
Conclusions
In women with TAI, TSHR-Ab were not detected prior or after OS. The results do not favour the ovarian hypothesis as a cause of increased miscarriage in subfertile women with TAI.
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PS1-05-02

Abstract withdrawn

PS1-05-03

Usefulness of real-time quantitative microvascular ultrasonography for differentiation of graves' disease from destructive thyroiditis in thyrotoxic patients: prospective study

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Background
The purpose of this study was to measure the ability of Microvascular ultrasonography (MVUS), which is a third-generation Doppler technique developed to increase sensitivity, to distinguish Graves' disease (GD) from destructive thyroiditis (DT).
Methods
This prospective study included a total of 167 patients from October 2020 to January 2023. Of them, 85 were patient with GD. All ultrasonography examinations were performed using microvascular flow technology (MV-Flow^{TM}). In the middle of study, there was a software upgrade of the ultrasound machine. The analysis was conducted before (cohort 1, 99 people, Graves 47) and after (cohort2, 68 people, Graves 38) the upgrade and for entire population. The color and power Doppler (CD and PD), and MVUS images were semi-quantitatively graded according to blood flow patterns. On the MVUS images, vascularity indices (VIs), which were the ratio (%) of color pixels in the total grayscale pixels in a defined region of interest, were obtained automatically. Receiver-operating characteristic curve analysis was performed to verify the diagnostic performance of MVUS.
Results
The area under the curve (AUC) for CD, PD, MVUS and MVUS-VI was 0.785, 0.824, 0.820 and 0.852 respectively for entire population. The optimal cutoff value of the MVUS-VI was 27.35% for distinguishing GD and DT with 81.2% sensitivity and 82.9% specificity. For cohort 1, the AUC of MVUS-VI was 0.815 and for cohor2, was 0.821.
Conclusion
In a real time and quantitative manner, MVUS-VI could be helpful to differentiate GD from thyroiditis in thyrotoxic patients, compared to conventional Doppler images.

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PS1-05-04

Higher titer of thyrotropin binding inhibitor immunoglobulin was associated with higher level of free thyroxine in graves' disease

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Background
The acitivity of the TSH receptor stimulating antibody is known to be associated with Graves' eye disease. However, the association between antibody titer and thyroid function was not significant, in previous studies. Taking into account the continuous changes in antibody titer and thyroid function during treatment, the association between thyroid function and clinical factors needed to be analyzed using panel analysis.
Methods
A total of 210 patients who visited and were treated in a tertiary hospital between 1999 February and 2019 May were included in this study. The patients were treated with methimazole according to their thyroid function status. Thyroid function test and thyrotropin binding inhibitor immunoglobulin (TBII) titer were measured at regular visit. We excluded patients who had relapsed after remission or underwent surgery or radioactive iodine treatment. Because the distribution of TBII was right skewed, TBII titer was transformed to base-10 logarithm. We performed panel analysis to evaluate the effect of factors on free T4 level during treatment period.
Results
The mean age of the patients was 43.4 $\pm$ 14.5, male patients were 86 (40.9%) and females were 124 (59.1%). At first diagnosis, mean of free T4 was 3.46 $\pm$ 1.83 ng/dL, and median of TBII was 10.2 (IQR: 5~23.99). The dose of methimazole at the time of diagnosis was 18.5 $\pm$ 10 mg a day. In the panel analysis for the free T4 level, the patient's age showed a negative association (Coef [95% CI] = -0.007 [-0.010 - -0.004]), and TBII showed a positive association (Coef [95% CI] = 0.272 [0.227 – 0.317]). However, sex and dose of methimazole did not show significant association with free T4 level.
Conclusion
In this study, we observed the positive association between TBII titers and free T4 levels in panel analysis. In the future, further studies using long-term follow-up clinical data are warranted to find associated factors for clinical course of Graves' disase.

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PS1-05-05

Multicenter, 5-assay comparison of thyrotropin receptor blocking antibodies

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Background
Thyrotropin receptor (TSH-R) blocking autoantibodies (TBAb) are present in 10-15% of patients with autoimmune thyroid disease (AITD). TBAb are functional and clinically relevant. This multicenter study compares the sensitivity and specificity of five immunoassays for the measurement of TBAb and introduces a novel and ultra-rapid TBAb bioassay.
Methods
Serum samples from AITD patients were tested with two TSH-R binding immunoassays (Cobas e411, Roche and ALINITY I, Abbott), an established cell-based TBAb reporter bioassay (Thyretain®, QuidelOrtho) with expression of a Luciferase transgene as readout and a new 'TurboTM' TBAb bioassay (QuidelOrtho) with a readout that is based on a cyclic AMP-activated luciferase. A Passing-Bablok regression and intra- and inter-assay validations were performed. All samples were also tested for stimulatory TSH-R-Ab (TSAb, Thyretain®).
Results
Of 1011, unselected, consecutive AITD patients (Graves' disease and Hashimoto's thyroiditis), 131 patients and 212 samples were TBAb positive. Median age was 33 years (25/75 percentile 13/48 years) and female: male ratio was 2.9:1. Of 212 samples, 149 (70.3%), 47 (23.1%) and 16 (7.5%) were hypothyroid, euthyroid and hyperthyroid, respectively. Thyroperoxidase and thyroglobulin autoantibodies were present in 136 (64.2%) and 70 (33%) samples, respectively. The five TSH-R-Ab assays were negative in 90 control subjects devoid of autoimmune thyroid and endocrine disorders. In contrast, the TurboTM cAMP TBAb, Luciferase TBAb and the binding assays detected TBAb in 212 (100%), 168 (79%) and 138/180 (65.1%) samples, respectively (Chi-square test $P < 0.001$). The TurboTM TBAb bioassay highly correlated with thyroid function ($P = 0.007$). Furthermore, the magnitude of percentage inhibition in both TurboTM and Luciferase TBAb bioassays correlated with TSH-R-Ab binding assay positivity (both $P < 0.001$). Seventeen of 212 (8%) samples showed dual TSH-R-Ab positivity in the Turbo TBAb and TSAb bioassays, while 11 (5.2%) samples showed dual positivity for TSAb and TBAb in all four bioassays. The two TBAb bioassays positively correlated (Spearman's r $=0.8$, $P < 0.001$). All bioassay measurements were done in duplicate. Intra-assay validation demonstrated adequate precision at 92% and 44% inhibition (serum TBAb positivity) with very low (3.95% inhibition) and low (6.5% inhibition) standard deviation (SD), respectively. Inter-assay validation showed 92% and 44% inhibition with SD of 7.1% and 4.9% inhibition, respectively.
Conclusions
This is the largest reported collective of TBAb-positive samples in AITD. TBAb markedly affects thyroid function. The easy-to-perform TurboTM blocking bioassay detected significantly more TBAb than the established immunoassays demonstrating higher analytical performance and clinical utility in the management of AITD patients.

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PS1-05-06

Predictive value of us doppler and microvascular imaging in differentiating benign and malignant thyroid nodules

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Objective
In this study, we investigated the utility of Doppler and microvascular imaging in diagnosing benign and malignant thyroid nodules according to the TI-RADS (Thyroid Imaging Reporting and Data System) and pathologic subtypes of thyroid malignancy.
Methods
Total 113 pathologically confirmed thyroid nodules ($n = 72$ (63.7%) benign, $n = 41$ (36.3%) malignant) from103 patients who visited for evaluation of thyroid nodules in single tertiary referral center between Feb. 2022 and Sep. 2022 were retrospectively included in this study. Two experienced radiologists reviewed US findings including color Doppler and microvascular pattern and scored using 4-scale visual analysis in consensus. US patterns of all nodules were categorized based on Korean thyroid imaging reporting and data system (K-TIRADS).
Results
The malignant nodules consist of 32 papillary carcinomas, 8 follicular variant papillary carcinomas and 1 lymphoma. The mean diameter of the nodules was 1.5 $\pm$ 1.1 cm (range 0.5 ~ 5.6 cm). All thyroid nodules were described with US lexicon proposed by K-TIRADS, and all US lexicons were significantly different between benign and malignant nodules ($P \leq 0.08$). Color Doppler score was also significantly different between benign and malignant nodules ($P < 0.000$). The nodules were categorized as benign ($n = 1$, 0.9%), low suspicion ($n = 39$, 34.5%), intermediate suspicion ($n = 43$, 38.1%), and high suspicion ($n = 30$, 26.5%). In subgroup analysis, there were no significant differences in color Doppler and microvascular imaging between benign and malignant nodules that were categorized as low and intermediate suspicion category. However, among the high suspicion nodules, benign nodules showed significantly higher vascularity scores when compared with malignant nodules ($P = 0.018$ in Doppler and $P = 0.051$ in microvascular). Classic PTC showed lower vascular scores in color Doppler and microvascular imaging while follicular variant PTC showed higher vascular scores.
Conclusion
Doppler and microvascular imaging can be helpful in differentiating benign and malignant thyroid nodules, especially for highly suspicious US featured thyroid nodules.

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PS1-05-07

Real-Time assessment of the beneficial role of artifical intelligence-based computer assisted diagnosis (AI-CAD) of thyroid nodules on ultrasound

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Objective
The purpose of this study is to evaluate and compare the effectiveness of artificial intelligence-based computer-assisted diagnosis (AI-CAD) in diagnosing thyroid malignancy by inexperienced physicians and experienced radiologist.
Methods
A total of 201 thyroid nodules from 192 patients was simultaneously evaluated by physician and radiologist using real-time ultrasound. After implementing AI-CAD, they reassessed the thyroid nodules. If necessary, the diagnosis was changed by referring to the AI-CAD results. Diagnostic performances of them with or without AI-CAD were calculated and compared.
Results
The sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating characteristics (AUROC) was analyzed with/without AI-CAD assistance. Without AI-CAD, the area under the receiver operating characteristics curve (AUROC) of the radiologist (0.799) was higher than that of the inexperienced physician (0.704). With the assistance of AI-CAD, the AUROC increased to 0.814 for the radiologist and 0.729 for the inexperienced physician. Both of radiologist and inexperienced physician showed increased sensitivity (70.37% vs 73.33%, 75.56% vs 80.74%), diagnostic accuracy (76.62% to 78.61% vs 72.64% to 75.62%), PPV (93.14% to 93.40% vs 81.60% to 82.58%), NPV (59.60% to 62.11% vs 56.58% to 62.32%) with aid of AI-CAD, while specificity remained unchanged (89.39% vs 65.15%).
Conclusion
The diagnostic performance in differentiating thyroid nodules can be further improved with the assistance of AI-CAD, regardless of the level of experience, particularly for inexperienced physicians.

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PS1-05-08

The risk of thyroid eye disease is increased following covid-19 vaccination

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Objectives
During the Covid-19 pandemic caused by the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2), vaccination has been widely adopted. Both SARS-CoV-2 infection and Covid-19 vaccines have been associated with several thyroid disorders. We studied the risk of Thyroid Eye Disease (TED) following Covid-19 vaccination.
Methods
This self-controlled-case-series study, validated model in assessing vaccine safety, included 98 consecutive patients (71 females and 27 males, mean-age 50 years) who attended our tertiary referral centre for new-onset (n =90) or reactivated (n =8) TED occurred in the period Jan 2021–Aug 2022, during the Covid-19 vaccination campaign launched in late 2020. Ninety-one (93%) patients had Graves' disease, 5 (5%) euthyroid TED and 2 (2%) Hashimoto's thyroiditis; 54/98 (55%) had a positive family history for thyroid/autoimmune disorders. For each vaccinated patient, we calculated person-days in time-windows after each dose, defined as 'exposed' if TED onset/reactivation occurred 1-28 days after vaccination and 'unexposed' if occurring outside such time-window. Poisson regression models were fitted to calculate incidence rate ratio (IRR) and 95% confidence-intervals (CI) of exposed vs unexposed. Sensitivity analyses were conducted considering only new-onset TED, gender, age, smoking, Covid-19 vaccine doses type and number and different exposed periods (29-56 and 57-84 days).
Results
Covid-19 vaccines were administered in 81 (83%) and never in 13 (13%) patients; data were missing in 4 patients. Of the 81 vaccinated subjects, 25 (31%) developed TED 1-28 days after vaccination (exposed) and 56 (69%) outside such time-window (unexposed). The IRR for TED was 3.24 (CI 2.01-5.20) overall and 5.29 (CI 2.71-10.3) in patients below 50 years of age. Gender and smoking did not modify the association between TED and vaccination, also when considering cases of disease new onset only. The TED risk seemed unrelated to the type or number of doses administered and progressively reduced over time following vaccination (P-trend 0.01). The TED severity was similar across the study subgroups. SARS-CoV-2 infection occurred in 23/98 (23%) patients during the study period and seemed not associated with TED.
Conclusions
The risk of TED development or reactivation is significantly increased shortly after Covid-19 vaccination, especially in subjects of less than 50 years of age. Possible mechanisms include spike protein interaction with the widely expressed ACE-II receptor or its cross-reactivity with thyroid self-proteins, and immune reactions induced by adjuvants. Until more safety data about Covid-19 vaccines will be available, caution and strict monitoring of individuals undergoing vaccination is suggested, especially if young and at risk of developing thyroid autoimmunity.

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PS1-05-09

Dried blood spot thyroglobulin in newborns as a surrogate biomarker for monitoring of iodine status of the population

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Background
Thyroglobulin (Tg) is a promising index of iodine status in pregnant women and children. The present study aimed to test a new strategy facilitating the monitoring of iodine status using Tg dried blood spot (DBS) in newborns.
Methods
Pregnant women were recruited in the third trimester of pregnancy at the Erasme Hospital in Brussels, Belgium. Thyroglobuline concentrations and urine iodine concentrations (UIC) were determined in pregnant women and newborns. A cord blood sample was collected to measure cord plasma Tg ($Tg_{\mathbf{CP}}$) and Tg in DBS ($Tg_{\mathbf{C\text{-}DBS}}$) at delivery. After delivery, a urine sample from the mother and the newborn was collected during the 2nd to 5th day of the life of the newborn, and three drops of blood were collected to determine neonatal Tg ($Tg_{\mathbf{N\text{-}DBS}}$) and TSH.
Results
Median UIC in pregnant women was 118 (68-205) µg/l (n =462) and 112 (69-172) µg/l (n =303) in newborns. The median serum Tg in the third trimester of pregnancy was 19 (11-32) µg/l (n =334), median $Tg_{\mathbf{CP}}$ was 53.6 (33.2-81.0) µg/l, median $Tg_{\mathbf{C\text{-}DBS}}$ was 32.4 (19.3-49.0) µg/l (n =294), and median $Tg_{\mathbf{N\text{-}DBS}}$ was 36.9 (25.2-59.9) µg/l (n =384) (P < 0.001). Maternal serum Tg was significantly and positively correlated with plasma and Tg-DBS in newborns (P < 0.05). Maternal and newborn UIC were also significantly and positively associated (r= 0.22, P < 0.001). Finally, $Tg_{\mathbf{CP}}$ (r=-0.23, P = 0.001) and $Tg_{\mathbf{C\text{-}DBS}}$ (r=-0.21, P = 0.003) but not $Tg_{\mathbf{N\text{-}DBS}}$ were negatively associated with UIC of newborns but not with maternal UIC.
Conclusion
Our results show that Tg concentrations in cord blood are negatively associated with newborns UCI but not with UIC of mildly iodine-deficient pregnant women. These data suggest, therefore, that newborns Tg are highly sensitive in detecting variations in iodine status.

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Thyroid Cancer clinical 1

PS1-06-01

Components of collaborative thyroid care clinics in the mississauga-halton regions in ontario, canada

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Background
The concept of collaborative thyroid care clinics (or networks), have been established over the last two decades, in many parts of the world.
Objective
What are the main available components of collaborative community-based integrated thyroid programs in the Mississauga-Halton regions [West Greater Toronto Area (GTA), Ontario, Canada], that can provide opportunities for streamlining thyroid care?
Method
Reviewing the available local resources through relevant websites (https://www.mississaugahaltonhealthline.ca) and comparison to the established benchmarks through literature review. A systematic literature search was performed using PubMed/Google Scholar databases, with several combinations of MeSH terms. Bibliography mining was also done on relevant articles to be as inclusive as possible.
Results
The main components of collaborative thyroid clinics from literature search are: thyroid ultrasound clinics, endocrinologists, thyroid fine needle aspiration (FNA)/cytology facilities, thyroid surgery/pathology facilities, radioactive iodine treatment/nuclear medicine, radiation therapy and medical oncology treatment facilities. Availabilities of the aforementioned resources in the Mississauga-Halton regions community: Resources available in both community-based and hospital-based settings: thyroid ultrasound centers (more than 30), endocrinologists (more than 20). Resources only available in hospital-based settings: thyroid FNA/cytology facilities (5-6 sites), thyroid surgery/pathology facilities (3 sites), radioactive iodine treatment/nuclear medicine (3 sites), radiation therapy and medical oncology treatment facilities (3 sites). Target population: Mississauga-Halton regions, Ontario, Canada [Health region, December 2017]: 1,164,740 persons [https://www12.statcan.gc.ca/census-recensement/2016]
Potential benefits of collaborative thyroid programs in the Mississauga-Halton regions community:

- streamlined treatment pathways and reduction in duplication of services
- shorter timeframes to interventions, concurrent consultations, less travel time, reduction in healthcare access disparities
- improved coordination of care and data sharing/access to information
- educational and research opportunities for health professionals

Conclusion
Collaborative thyroid care clinics present many potential positive outcomes for patients, healthcare providers and the health care system. They also have the potential to reduce healthcare costs, wait times, and health disparities, and can lead to evidence-based/data driven healthcare delivery.

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PS1-06-02

Long-Term outcomes following initial therapy in differentiated thyroid cancer (DTC) in china: DTCC 2nd stage study analysis 2014-2022

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Objectives
We previously reported the outcome of 1-year follow-up of 2013 DTC patients in the DTCC (differentiated thyroid cancer in China) 1st stage Study. Using the retrospectively gathered information, we sought to observe the long-term follow-up and prognosis of these patients with DTC undergoing thyroid surgery.
Methods
This multicenter, noninterventional study was conducted at eight tertiary hospitals across China. Data from the patients with more than five years of follow-up from the date of signing the informed consent form (ICF) in the DTCC 1st study were collected retrospectively. Eligible patients were those recruited into DTCC 1st study with intermediate risk or high risk of recurrence. We categorized the patients into five groups according to a time-weighted average of serum TSH (TW-TSH): lowest (<0.1 mIU/l), below (0.1-0.5 mIU/l), in the lower half (0.5-2 mIU/l), in the upper half (2-4 mIU/l), and above (>4 mIU/l) the reference range.
Results
1262 patients (mean age 48 years) who have completed follow-up were analyzed. After a median follow-up of 6.5 years (range, 1.0-8.3 years), the recurrent disease was observed in 33 patients (2.6%), five patients died (0.4%), and 11 patients (0.9%) had reoperation or multiple surgeries. Of the 1178 patients with sufficient follow-up data, 89.0%, 4.6%, 2.5%, and 3.9% were classified as having an excellent response, biochemical incomplete response, structural incomplete response, and indeterminate response during the first postoperative visit in this study, respectively. By univariate analysis, no difference was demonstrated in DFS (disease-free survival) according to the surgical extent (Total/near-total thyroidectomy vs. other, $P = 0.74$); a similar lack of difference was seen in radioiodine (RAI) treatment application (RAI vs. no RAI, $P = 0.65$). Based on the Cox model, no association was observed between TW-TSH and DFS in the overall cohort ($P = 0.07$). However, patients with TW-TSH in the lower half showed improved DFS compared with those with a TW-TSH above the reference range (risk ratio [RR] 0.37, $P = 0.01$).
Conclusions
This was the first large-scale retrospective study of how patients with DTC in China are treated in actual clinical practice. The results show that the recurrence rate is low; the reason may be that high-volume surgeons in top tertiary hospitals conducted the surgeries, and nearly all patients underwent lymph node dissection during the initial surgery.

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Clinical and surgical challenges of local relapse of papillary thyroid carcinoma (PTC)

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Aim
The assessment of the disease course and selected clinicopathological factors associated with recurrence risk and the effectiveness of surgical treatment of PTC patients.
Material and Methods
The retrospective analysis of 260 PTC patients selected from 403 patients operated on for recurrent thyroid cancer between 2002 and 2018 was performed. All statistical analyses were done using the programming environment R (v. 4.0.2).
Results
PTC patients differed in terms of the primary cancer stage. Stage T3 was predominant (40.4%) followed by stage T1 (33.1%). Lymph node metastases occurred in 167 patients (64.2%), while distant metastases in 2 (0.8%). The 5-year overall survival (OS) was 100% and the 20-year OS survival exceeded 80%. 113 patients (43.5%) were operated on for recurrence more than once. They had a significantly worse OS ($P = 0.038$). The highest percentage of complete recovery (94.6%) was achieved in patients reoperated on once only ($P < 0.001$). The 5-year disease-free survival (DFS) was 60% and the 15-year DFS was 30%. The best DFS was reported in pT1a patients. DFS was not significantly different in patients staged pT1b, while it was significantly worse in stage pT2. Worse DFS was observed in older patients (age ≥ 55; $P < 0.0001$), in males ($P = 0.004$), and in patients whose thyroglobulin (Tg) levels on TSH stimulation assessed after surgery for the first recurrence exceeded 10 pg/ml ($P < 0.0001$). In univariate analysis, the factors associated with higher recurrence risk included male sex ($P = 0.005$), age ≥ 55 years ($P < 0.001$), primary tumor diameter of 2-4 cm ($P = 0.001$) and >4 cm ($P = 0.021$), and postoperative Tg levels >10 ng/ml ($P < 0.001$). Significant factors in the multivariate analysis included tumor size of 2-4 cm ($P = 0.004$), lymph node metastasis ($P = 0.046$), high Tg levels ($P = 0.001$) and radicality of the first surgery ($P = 0.043$). In the Cox regression analysis, the independent prognostic factors affecting the risk of recurrence included primary tumor diameter of 2-4 cm ($P = 0.004$), Tg levels >10ng/ml ($P < 0.001$), lymph node metastases ($P = 0.046$) and radicality of the first surgery ($P = 0.043$).
Conclusions
The significant adverse influence of primary tumor diameter (2-4 cm) on the prognosis seems to be an argument against limitation of the extent of surgery in PTC patients staged cT2N0M0 as proposed by ATA. The study confirms the significance of high postoperative Tg levels as an independent prognostic risk factor associated with locoregional recurrence. The inconclusive results of the significance of other clinicopathological factors warrant further studies.

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PS1-06-04

Predictive factors for central neck compartment lymphnodes metastases' in sporadic medullary thyroid cancer patients

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Introduction
Total thyroidectomy (TT) plus central neck compartment (CC) lymphnode dissection is still the recommended initial gold standard treatment for medullary thyroid cancer (MTC), even in the absence of a pre-surgical positive neck US evidence of lymphnode metastases. Considering the risk of surgical complications of this prophylactic surgery and the low rate of histologic finding of CC lymphnode metastases, a more tailored lymphnode' surgery should be proposed. Aim of this study was to analyze the presence of possible predictive risk factors for the presence of CC lymphnode metastases in patients with sporadic MTC
Patients and methods
Data from 280 sporadic MTC patients, followed at our Institution from 2000 and 2018, were retrospectively analyzed. All underwent TT and prophylactic CC lymphnode dissection, while lateral dissection was performed only according to the pre-surgical US findings. Univariate analysis with chi-square test and multiple logistic regression analysis were applied to identify the clinico-pathological features associated with CC lymphnode metastases
Results
170/280 (60.7%) patients were female and 110/280 (39.37) were male. The mean age at MTC diagnosis was 54.72 ± 13.82 years. At the end of follow-up, 209/280 (74.6%) patients were cured, while 60/280 (21.4%) showed a biochemical/structural persistence of disease. CC lymphnode metastases were histologically found in 82/280 patients (29.3%). At the univariate analysis, the absence of tumor capsule

($P < 0.001$), the presence of intrathyroidal ($P < 0.001$)/extrathyroidal extension ($P < 0.001$), multifocality ($P < 0.001$), neoplastic embolization ($P = 0.001$), higher pre-surgical serum calcitonin levels ($P = 0.016$) and bigger tumor diameter ($P < 0.001$) were associated with the presence of CC lymphnode metastases. At the multivariate analysis, only the absence of tumor capsule (OR 4.13 [95% CI 1.78-9.59] $P = 0.001$), the presence of extrathyroidal extension (OR 5.06 [95% CI 1.99-12.8] $P = 0.0006$), multifocality (OR 4.17 [95% CI 1.67-10.41] $P = 0.002$) and tumor diameter (OR 1.95 [95% CI 1.46-2.6] $P < 0.0001$) were confirmed as independent predictive risk factors. We separately analyzed the subgroup of 131 microMTC. At the univariate analysis the absence of tumor capsule ($P < 0.001$), the presence of intrathyroidal ($P < 0.001$)/extrathyroidal extension ($P = 0.02$) and multifocality ($P = 0.002$) were associated with CC lymphnode metastases. At the multivariate analysis, multifocality was the only independent risk factor associated with a 5-time greater risk (OR 5.63 [95%CI 1.95-16.4] $P = 0.001$].
Conclusions
According to our data, the histological prevalence of CC lymphnode metastases in sporadic MTC patients is below 30%. The absence of tumor capsule, the presence extrathyroidal invasion, tumor multifocality and tumor diameter were found as the independent predictive risk factors for CC metastases, while in microMTC only multifocality was associated with higher risk of CC metastases

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PS1-06-05

Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha & beta testing

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Background
Patient decision aids (PtDAs) are structured clinical tools that facilitate shared decision making. Two important treatment decisions for patients with differentiated thyroid cancer (DTC), which could benefit from PtDAs, are: 1) the extent of surgery decision in patients with low-risk DTC and 2) the decision to start or delay starting the treatment with Tyrosine Kinase Inhibitors (TKIs) in patients with advanced tumors.
Material and methods
PtDAs for these two decisions were developed using the International Patient Decision Aids Standards (IPDAS) quality criteria in an iterative process of prototype development, via alpha and beta testing by patients and physicians. Information content of the PtDAs was based on the available literature, current guidelines and patients' needs, preferences and values.
Results
The web-based PtDAs underwent two rounds of alpha testing, revisions and a beta testing. The PtDAs have the same structure, consisting of six steps, being a general introduction, information about the treatment options, comparing the treatment options, knowledge questions, a values clarification exercise, and saving the information. The alpha testing ($n = 8$ patients, $n = 10$ physicians) showed that the PtDAs were highly acceptable and usable for decision making. Results of the beta testing in 20 patients showed that two patients did not use the PtDA, the other 18 patients found that the PtDAs were readable ($n = 17$) and helpful ($n = 14$) for decision making. All patients recommend using the PtDAs.
Conclusions
Evidence-based PtDAs were created for patients with DTC for two different treatment decisions. Our final version was judged to be clear, balanced and helpful in decision making.

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PS1-06-06

Papillary thyroid carcinoma associated with thyroiditis: about a series

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Introduction
The association between papillary thyroid carcinoma and thyroiditis was first reported in 1955 by Daily, in 2023 if this association is well established, it still continues to be talked about. Does cancer precede thyroiditis or does thyroiditis induce cancer and when the two combine does cancer have a better prognosis?
Material and methods
We report a prospective study carried out in a hospital center in Algeria between 2020 and 2022 which included 267 papillary thyroid cancers, of which 97 (36.3%) of the patients had thyroiditis. 85 (87.6%) of the patients who had an association with thyroiditis were women with a sex ratio of 3.29; their average age was 42.79 +/- 1.16 years. In a situation of thyroiditis, the tumor size was smaller (OR 0.51), with less vascular invasion (OR 0.39) but more multifocality (OR 1.75) compared to patients who didn't have thyroiditis.
Discussion
The association of papillary thyroid cancer with thyroiditis has generated many studies around the world, however it's difficult to make comparisons between them because of their heterogeneity; however, our study seems to agree with the results obtained by a majority of studies already published.
Conclusion
In our study, the association of papillary thyroid cancer with thyroiditis seems to be a better prognostic factor.

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PS1-06-07

Thyroid cancer in ukrainian children during 35 years after the accident at the chernobyl nuclear power plant

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Background
According to the statistics of the Ministry of Health of Ukraine, before the accident at the Chernobyl nuclear power plant, the incidence of thyroid cancer in children under 14 years of age was on average 0.04 per 100,000 children, however long-term consequences of the accident have not been analyzed.
Material and methods
We studied the incidence of thyroid cancer during the last 35 years in Ukraine in children under the age of 14 and 18 y.o. based on the statistics of the Ministry of Health of Ukraine.
Results
Ten years after the Chernobyl accident, the incidence of thyroid cancer in children increased 10 times in children under 14 years of age. Then this indicator gradually decreased and in 2006-2010 reached its lowest level. But, starting from 2010, the incidence of thyroid cancer began to increase again and almost 35 years after the accident, it again reaches critical indicators and remains at a high level. The incidence of thyroid cancer in children under the age of 18 during the last 10 years has remained at the level of 0.48 per 100,000 with the largest number of thyroid cancer cases occurring in children from the most contaminated regions after the accident. Some decrease in the incidence rate in 2019-2020 may be due to the COVID pandemic and restrictions of the movement of children for a complete examination and surgical treatment. During the period 2002-2021, thyroid cancer was diagnosed and operated on in 174 children under the age of 18
Conclusions
Since the largest number of cancer cases during the last 10 years was among children from the regions that were the most contaminated after the accident in 1986, and whose parents were exposed to negative radiation exposure, we can assume a cumulative remote effect on the formation of cancer in the second generation of victims of the Chernobyl accident

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PS1-06-08

Hypertension during lenvatinib for advanced thyroid cancer: a diagnostic and therapeutic algorithm for its management

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Background
Hypertension (HTN) is the most frequent adverse event during treatment with Lenvatinib (LEN) for advanced Radioactive Iodine-Resistant Thyroid Cancer (RAI-R TC), but data on its best therapeutic management are limited.
Objectives
To assess incidence, features and best management of LEN-related HTN in a consecutive single tertiary-care Centre.
Methods
Evaluation included 29 patients treated with LEN, followed for a mean time of 29.8 months (6-77 months).
Results
After a mean follow-up of 6.8 months, HTN was recorded in 76% of cases, as a de novo appearance in half of them. HTN significantly correlated with LEN dose ($P = 0.011$), and was of grade 1, grade 2 and grade 3 in 5%, 50% and 45% of patients, respectively. The majority (77%) of patients with HTN developed proteinuria, although no correlation was found ($P = 0.187$). Moreover, there was no correlation between HTN and patients clinical-pathological features or any other Adverse Event (AE), except for diarrhoea ($P = 0.025$). Specifically, patients with or without any pre-existing cardiovascular disease had a similar incidence of HTN during LEN, thus excluding the impact of this potential predisposing factor. Regarding tumour response according to RECIST Criteria 1.1, Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) during LEN treatment were not significantly different between patients who developed and patients who did not develop HTN (respectively: $P = 0.291$, log-rank $P = 0.217$, log-rank $P = 0.150$). After evaluation by a dedicated cardiologist, medical treatment was introduced in 21/22 patients: 1/21 in monotherapy and 20/21 multi-therapy. Calcium channel blockers (CCBs) were used in 81% of patients, either in monotherapy (5% of cases) or, in case of poor blood pressure control, in association with other anti-hypertensive drugs as ACE-inhibitors (ACE-i) or Beta-blockers (BB) (14%), with Angiotensin Receptor Blockers (ARB)/ACE-i + other anti-hypertensive drug (43%) or with a total of 4 anti-hypertensive drugs in 24% of patients. The firstly introduced drug was in most cases a CCB due to its effect on vasodilation; if necessary, an ACE-i/ARB was added, also for its effect on proteinuria. Hypertension control was obtained in 19/22 patients. No patient had to reduce or discontinue LEN treatment due to HTN.
Conclusion
HTN is a frequent and early adverse event in patients on LEN treatment. We suggest a diagnostic-therapeutic algorithm to be applied in clinical practice to allow efficient HTN control and improve patient compliance, reducing LEN discontinuation.

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PS1-06-09

Four cases of anaplastic thyroid carcinoma

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Introduction
Anaplastic thyroid carcinoma (ATC) carries an extremely poor prognosis. The reported median survival time is 3-9 months and one year survival rate is 18-20%. Here we report 4 cases of ATC.
Case reports
Case 1: An 82 year-old female presented with rapidly progressive anterior neck swelling. She underwent hemi-thyroidectomy and D1 dissection. Pathological diagnosis was ATC, T4aN0. External beam radiotherapy (EBRT) to the whole neck was administered. Because lung metastasis was detected four weeks after the surgery, she received weekly paclitaxel. Although partial response was observed, paclitaxel was discontinued due to the myelosuppression. She died of a respiratory failure 13 months after the surgery.
Case 2: A 54 year-old male presented with hoarseness. He underwent hemi-thyroidectomy and D1 dissection. Pathological diagnosis was poorly differentiated carcinoma, T4aN1a. Neck and lung metastasis was detected seven months after the surgery and he underwent total thyroidectomy and D1 dissection. Pathological diagnosis was ATC, T4bN1a. He received EBRT and weekly paclitaxel for eleven months. Although partial response was observed, paclitaxel was discontinued due to the patient's will. He died 13 months after the second surgery.
Case 3: A 70 year-old female presented with anterior neck swelling. She underwent total thyroidectomy, D2 dissection, and tracheostomy. Pathological diagnosis was ATC, T4aN1bM1. She received EBRT and weekly paclitaxel. Although stable disease was observed, she died of tracheal bleeding 6 months after the surgery.
Case 4: A 74 year-old female presented with anterior neck swelling. She underwent total thyroidectomy and D2 dissection, followed by adjuvant I-131 therapy. Retropharyngeal lymph node and lung metastasis were detected 2 years after the surgery. Fine needle aspiration cytology indicated ATC. Lenvatinib was administered for seven months. Although partial response was observed, she died due to massive bleeding from the tumor.
Discussion
Although NCCN guideline recommends paclitaxel as one of the systemic therapy regimens for ATC, paclitaxel is not covered by the public health insurance in Japan. Iwasaki *et al* reported a survival benefit of lenvatinib compared with palliative therapy including weekly paclitaxel. A meta-analysis by Huang *et al* showed a meaningful but limited clinical efficacy of lenvatinib for ATC. A careful administration is required to avoid massive bleeding when the lesions are close to large vessels.
Conclusion
A Randomized controlled trial with a sufficient sample size is needed to confirm the efficacy and safety of lenvatinib for ATC compared with paclitaxel.

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Thyroid Cancer Diagnosis 1

PS1-07-01

Elevated CRP and leukocytosis at diagnosis, but not elevated ESR, are prognostic markers in anaplastic thyroid cancer

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Objectives
Anaplastic thyroid carcinoma (ATC) is one of the malignancies with the highest mortality among all cancers. Immune cells are highly abundant in ATC tumors and increased infiltration with tumor-associated macrophages is associated with decreased survival. We hypothesize that systemic inflammatory markers are also associated with survival in patients with ATC and are more elevated in ATC compared to poorly differentiated thyroid carcinoma (PDTC).
Methods
Clinical and biochemical data were retrospectively collected from patients with ATC or PDTC that were treated at our hospital between 1999 and February 2023. Patients with inflammatory or infectious comorbidities were excluded. Inflammatory markers at diagnosis were compared between ATC and PDTC patients and survival was compared between patients with and without systemic inflammation.
Results
Seventy-two ATC patients and 26 PDTC patients were included. As expected, median survival in PDTC patients was significantly longer than in ATC patients (51 [95%-CI: 12-89] months vs 3 [1-5] months respectively). C-reactive protein (CRP, mean concentrations 50.4 vs 6.9 mg/l, $P<0.001$), erythrocyte sedimentation rate (ESR, 47.5 vs 21.7 mm/hour, $P=0.007$), absolute white blood cell count (WBC, 13.7 vs 8.0 x10^9/l, $P<0.001$) and the percentage of patients with distant metastases at diagnosis (56.3% vs 40.7%, $P < 0.001$) were all significantly higher in ATC patients when compared to PDTC patients. Albumin concentrations, neutrophil-to-lymphocyte ratio (NLR) and age at diagnosis were not significantly different between both patient groups. Within ATC patients, CRP concentrations ($r= -0.558$, $P<001$), WBC ($r= -0.405$, $P=0.001$), distant metastases ($r= -0.326$, $P=0.006$) and NLR ($r= -0.394$, $P=0.006$) at diagnosis were significantly correlated with survival, while sex, albumin and ESR were not. Within ATC patients, the subgroup of patients with elevated CRP at diagnosis had a significantly longer survival than patients without elevated CRP (median survival 1 [0-2] and 10 [0-23] months respectively, $P=0.009$). The same was true for ATC patients with and without leukocytosis at diagnosis (median survival 1 [0-2] and 5 [0-14] months respectively, $P=0.004$). On the contrary, median survival of ATC subgroups with and without elevated ESR were not significantly different. In a Cox regression model with the variables CRP concentration, WBC and distant metastases at diagnosis, both CRP concentration and distant metastases at diagnosis were significantly correlated to survival.
Conclusion
Systemic inflammation is more prevalent in ATC when compared to PDTC. Elevated CRP and leukocytosis at diagnosis are prognostic markers in ATC patients.

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PS1-07-02

Optimal cut-off values of protrusion angle of tumor on sonography (PATOS) system to predicting extrathyroidal extension in papillary thyroid carcinoma according to location

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Background
Extrathyroidal extension (ETE) is an important factor to determine treatment strategy of thyroid cancer. The purpose of this study was to present a new method to predict ETE in papillary thyroid carcinoma (PTC).
Methods
This study included 1,481 patients with PTCs. The ETE was classified into minimal and gross ETE. Using an protrusion angle of the tumor on sonography (PATOS) system, we calculated optimal cut-off values to predict ETE according to tumor location. And we compared diagnostic performance with previous ETE predicting methods.
Result
The optimal cut-off value to predict anterior ETE was 41.5° and 49.4°, minimal and gross ETE, prospectively. The optimal angle to predict posterior ETE was 39.8° and 54.6°, minimal and gross ETE, each. And the optimal cut-off value to predict tracheal ETE was 88.0° by the PATOS system. The diagnostic performance showed competitive results with previous methods.
Conclusions
The new method for predicting ETE proposed in this study which is PATOS system could be an alternative method.

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PS1-07-03

Comparison in ultrasonography (US) features and the korean-thyroid imaging reporting and DATA system (K-TIRADS) of isthmic and lobar papillary thyroid carcinomas (PTC)

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Objective
This study aimed to compare US features and K-TIRADS categories for diagnosing isthmic and lobar PTCs.
Methods
From January 2009 to December 2012, 163 patients who underwent thyroid surgery and were confirmed with a postoperative histopathological diagnosis of isthmic PTC were retrospectively included. Fifty-nine patients were excluded because their tumor size was < 0.5 cm, lack of preoperative thyroid US images, poor US image quality, and uncertainty between US findings and histopathological results. Eventually, 104 patients with isthmic PTC (88 female and 16 male; age range, 25–75 years; mean $\pm$ SD, 46.9 $\pm$ 9.9 years) were included in the study group. The control group comprised of 145 patients (127 female and 18 male; age range, 29–86 years; mean $\pm$ SD, 48.4 $\pm$ 10.9 years) who underwent thyroid surgery from January to April 2013 for a classic type of PTC, with the largest diameter being ≥ 0.5 cm and located in the thyroid lobe. A single radiologist retrospectively reviewed the US features and K-TIRADS categories of each nodule using a picture archiving and communication system.
Results
Most cases of isthmic (95.2%; 99/104) and lobar PTC (96.6%; 140/145) belonged to K-TIRADS category 5. Of the 104 patients with isthmic PTC, 95 and 9 cases were that of primary and non-primary cancers, respectively, whereas all 145 patients with lobar PTC had primary cancers. Isthmic PTC showed a lower prevalence of non-parallel orientation than lobar PTC (23.1 and 71%, respectively), whereas both isthmic and lobar PTC showed a high prevalence of microcalcification (69.2 and 79.3%, respectively) or irregular (spiculated/microlobulated) margin (93.3 and 95.2%, respectively). Nodule orientation was the only US feature statistically different between the two groups ($P < 0.0001$). There was no significant difference in patient age, sex, nodule size, composition, echogenicity, microcalcification, irregular(spiculated/microlobulated) margin, and K-TIRADS category ($P > 0.05$).
Conclusions
Most cases of isthmic and lobar PTC belong to K-TIRADS category 5, and only the nodule orientation parameter was different between isthmic and lobar PTC. Therefore, K-TIRADS may be useful in the diagnosis of both isthmic and lobar PTC.

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PS1-07-04

Role of ultrasound in predicting tert promoter mutation in follicular thyroid carcinoma

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Purpose
Telomerase reverse transcriptase (TERT) promoter mutations are associated with tumor aggressiveness. The purpose of our study was to demonstrate the ultrasonographic (US) features of TERT promoter-mutated follicular thyroid cancer (FTC) and to evaluate their predictive performances.
Materials and methods
Total 63 patients who had surgically confirmed FTC between August 1995 and April 2021 were included in this study. All of them were available for analysis of preoperative US findings and TERT promoter mutation results. Genomic DNA to identify TERT promoter mutations was extracted from archived surgical specimens. Logistic regression analysis was performed to compare US findings between TERT promoter-mutated and wild-type FTCs.
Results
Of 63 patients with FTC, 10 patients (15.9 %) had TERT promoter mutation. TERT promoter-mutated FTCs demonstrated significantly different US suspicion category compared to wild-type FTCs ($Ps = 0.0054$ for K-TIRADS and 0.0208 for ACR-TIRADS), with a trend toward increasing prevalence of high suspicion category (40.0 % for both K-TIRADS and ACR-TIRADS; Ps for trend $= 0.0030$ for K-TIRADS and 0.0032 for ACR-TIRADS). Microlobulated margin and punctate echogenic foci were independent risk factors related to TERT promoter mutation of FTC (odds ratio 9.693, 95% confidence interval 1.666–56.401, $P = 0.0115$ for margin; odds ratio 8.033, 95% confidence interval 1.424–45.309, $P = 0.0182$ for punctate echogenic foci). There were no significant differences in composition and echogenicity for TERT promoter-mutated and wild-type FTCs.
Conclusions
TERT promoter-mutated FTC are categorized more frequently as high suspicion by K-TIRADS and ACR-TIRADS. Based on US findings, independent risk factors for TERT promoter mutation of FTC are microlobulated margin and punctate echogenic foci.
Clinical Relevance/Application
TERT promoter mutations are closely associated with tumor aggressiveness and poor clinical outcomes in patients with thyroid cancer. The results of this study suggest that TERT promoter mutation tests should be performed in FTC patients with US features, including microlobulated margin and punctate echogenic foci.

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PS1-07-05

Ultrasonographic prediction of tumor invasiveness in follicular thyroid carcinoma: based on the who classification and tert promoter mutation

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Background
The purpose of this study was to assess the role of ultrasound (US) in predicting tumor invasiveness in follicular thyroid carcinoma (FTC) based on the World Health Organization (WHO) classification and telomerase reverse transcriptase (TERT) promoter mutation.
Materials and Methods
This retrospective study included 54 surgically confirmed FTC patients who underwent preoperative US and TERT mutation analysis. The WHO classification consisted of minimally invasive (MI-FTC), encapsulated angioinvasive (EA-FTC), and widely invasive (WI-FTC) types. The alternative classification was composed as follows: Group 1 (MI-FTC; EA-FTC with wild type [WT]-TERT), Group 2 (WI-FTC with WT-TERT), and Group 3 (EA-FTC with mutant [M]-TERT; WI-FTC with M-TERT). Each nodule was categorized based on the US pattern according to the K-TIRADS and ACR-TIRADS. For statistical analysis, the Jonckheere-Terpstra and Cochran-Armitage tests were used.

Results
Among the 54 FTCs, there were 29 (53.7%) MI-FTCs, 16 (29.6%) EA-FTCs, and 9 (16.6%) WI-FTCs. The alternative classification included 42 (77.8%) Group 1, 5 (9.3%) Group 2, and 7 (13.0%) Group3. Neither benign nor low suspicion US category was assigned to WI-FTC and alternative groups 2 and 3. In both classification groups, lobulation, irregular margin, and final assessment category showed significant differences (all $ps < 0.04$) and incidences of lobulation, irregular margin, and high suspicion category had a trend to increase with the increasing tumor invasiveness (all ps for trend < 0.006). In the WHO groups, hypoechogenicity differed significantly among the groups ($P = 0.0112$) and tended to increase in proportion as tumor invasiveness increased (P for trend $= 0.0145$). Meanwhile, in the alternative groups, so did punctate echogenic foci ($P = 0.0256$, P for trend $= 0.0245$).
Conclusion
Increasing tumor invasiveness in FTC based on the WHO classification and TERT promoter mutation is significantly correlated with the probability of displaying malignant US features using both K-TIRADS and ACR-TIRADS.
Clinical Relevance/Implications
A recent study proposed molecular marker-based risk stratification of FTC using TERT promoter mutations and WHO classification to better predict clinical outcome. Our study suggests that US prediction of tumor invasiveness in FTC is highly correlated with the WHO morphological classification as well as newly proposed TERT promoter mutation-based risk stratification.

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PS1-07-06

Validation of ct-based risk stratification systems for lymph node metastasis in patients with thyroid cancer

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Objective
To evaluate computed tomography (CT) features for diagnosing metastatic cervical lymph nodes (LNs) in patients with differentiated thyroid cancer (DTC) and propose CT-based risk stratification system modified from the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) guidelines.
Materials and Methods
A total of 463 LNs from 397 patients with DTC who underwent preoperative CT staging and US-guided fine needle aspiration of LNs were included. The CT features of each LN were evaluated: presence of a hilum, cystic change, calcification, strong enhancement, and heterogeneous enhancement. Multivariable logistic regression analysis was performed to identify independent CT features associated with metastatic LNs, and the diagnostic performance of each CT feature was evaluated. LNs were classified into probably benign, indeterminate, and suspicious categories according to K-TIRADS, and the malignancy risk of each category malignancy risk was calculated.
Results
The absence of a hilum, strong enhancement, calcification, and cystic change were independent CT features associated with metastatic LNs in patients with DTC. Strong enhancement, calcification, and cystic change showed moderate to high specificity (70.1–100%) and positive predictive value (91.8–100%). The absence of a hilum showed high sensitivity (97.8%) but low specificity (34.0%). When LNs were classified according to K-TIRADS guidelines, the malignancy rates of the probably benign, indeterminate, and suspicious groups were 6.7%, 13.2%, and 90.9%, respectively. Our proposed modified CT criteria excluding heterogeneous enhancement from the four K-TIRADS suspicious features gave malignancy rates of 6.5%, 17.0%, and 92.5% for probably benign, indeterminate, and suspicious categories, respectively.
Conclusion
CT features of absence of a hilum, strong enhancement, calcification, and cystic change were independently associated with metastatic LNs in patients with DTC. Our modified CT criteria provided better risk stratification of LNs than the current K-TIRADS guidelines. Our study results may provide a basis for revising CT-based LN classification in future guidelines.

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PS1-07-07

Macrofollicular variant of papillary thyroid carcinoma: ultrasonographic findings and clinical implications

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Objectives
The macrofollicular variant of papillary thyroid cancer (MFV-PTC) is a rare subtype often lending to a challenging diagnosis. This study evaluated the ultrasonographic (US) features and clinical implication of MFV-PTC.
Methods
Records of 14 patients histologically diagnosed with MFV-PTC at our institution over a period of 16 years were retrospectively reviewed. Preoperative US features, Bethesda categories determined by fine-needle aspiration (FNA) or core needle biopsy (CNB), and final pathology were assessed in all patients with MFV-PTC.
Results
Most nodules were noted as solid isoechoic on US and were categorized as low suspicion in 12 cases and intermediate suspicion in two cases. The median tumor size was 1.2 cm (range, 0.6–5.6 cm). Of the 14 MFV-PTC cases, 11 underwent FNA or CNB. Four (36.4%) with Bethesda category II or III underwent the follow up because of benign looking appearance on US and benign results in subsequent CNBs. However, the patients underwent delayed surgery (31.3 months, range 12–41 months) because of serially increased tumor size. Patients with seven nodules diagnosed as Bethesda type IV, V, and VI underwent subsequent surgery. Gross extrathyroidal extension into subcutaneous fat tissue and lateral lymph node metastasis were noted in a patient who underwent follow-up. No distant metastases or recurrence was detected.
Conclusion
MFV-PTC is representative of a benign sonographic appearance of PTC variants. Serial tumor growth is the only suspicious finding for MFV-PTC because FNA or CNB is often false negative.
Keywords
Thyroid nodule; Ultrasonography; Papillary thyroid carcinoma; Variant

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PS1-07-08

Abstract withdrawn

PS1-07-09

Clinical significance of tumor size in gross extrathyroidal extension to strap muscles(T3B) in papillary thyroid carcinoma

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Background
It has been studied that larger tumor size in T3b has a worse prognosis than T3b with smaller tumor size. The present study aims to compare the clinicopathological characteristics among modified T categories and clarify the significance of tumor size in T3b on the DSS of differentiated thyroid carcinoma(DTC).
Methods
A total of 6282 patients with DTC who underwent thyroid surgery at a single center were retrospectively analyzed. Patients with T1, T2, T3a, and T3b categories were included according to the 8th edition of the AJCC/UICC TNM staging system. In the modified T categories, T3b was divided into T3b-1 ($\leq$2 cm) and T3b-2 (2–4 cm), and T3b-3 ($>$ 4 cm). Disease-free survival (DFS) and Disease-specific survival(DSS) were compared among all T categories.
Results
In the total cohort of 6282 patients, T1, T2, T3a, T3b-1, T3b-2, and T3b-3 were 3353 (88.1%), 339 (5.4%), 39 (0.9%), 239 (3.8%), 90 (1.4%), and 20 (0.3%), respectively. There were no differences in DSS between T1 and T3b-1 (P = 0.319). However, there were significant differences in DSS between T2 and T3b-2, and between T3a and T3b-3 ($P < 0.001$, $P = 0.001$, respectively).
Conclusions
These results indicate that the tumor size of T3b may affect DSS, which decides AJCC/UICC TNM staging system. T3b($\leq$2 cm) showed no significant difference in mortality compared to T1. A modified stage that moves T3b($\leq$2 cm) to T1 and includes only T3b($>$2 cm) to T3b may show more efficient performance than the current stage.
Keywords: T3b, tumor size, modified T category, Differentiated thyroid carcinoma
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Translational 1

PS1-08-01

Predictors of radioiodine (RAI)-avidity restoration for NTRK fusion-positive RAI resistant metastatic thyroid cancers

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Introduction
Two-thirds of metastatic differentiated thyroid cancer (DTC) patients have RAI-resistant disease, resulting in poor prognosis and high disease-related mortality. Current studies of individualized therapy with different MAPK inhibitors report restoring RAI-avidity in 50 – 70% of *BRAF* and *RAS* mutated and thyroid cancers with no detected driver mutation. Five recent case reports of rare *NTRK* and *RET-PTC* fusion-positive metastatic, RAI-resistant thyroid cancers described restoration of RAI-avidity during treatment with NTRK or RET inhibitors. However, the concurrent presence of *TERT* promoter mutation is associated with poor RAI-avidity in distant metastatic DTC. We report the outcome of two *NTRK* fusion-positive patients after treatment with the NTRK inhibitor Larotrectinib.
Case Reports
An 83-year-old male and a 31-year-old female presented with T4a tumours with RAI-resistant lung metastases. The female patient demonstrated a negative diagnostic I-123 whole body scan (WBS), whereas the male patient exhibited rising thyroglobulin (TG) 7 months after initial RAI treatment and a negative post-treatment I-131 WBS. The male presented with an *ETV6-NTRK* fusion-positive tumour harbouring an additional *TERT* promoter mutation c.1-124C$>$T. Larotrectinib 100 mg b.i.d resulted in a TG decrease from 5.6 to 1.9 ng/mL and a size reduction of pulmonary metastases 1 year post-treatment. However, diagnostic I-123 WBS at 3 and 12 months post-Larotrectinib were negative for reinduction of RAI-uptake. Alternatively, the female patient with a *TRP-NTRK1* fusion-positive tumour (and negative for *TERT* promotor mutations) was treated with Larotrectinib 100 mg b.i.d, resulting in a TG decrease from 6.0 to 1.7ng/mL, and reduction in size and improvement in FDG/PET avidity of pulmonary metastases, 7 months post-treatment. Diagnostic I-123 WBS showed reinduction of RAI-avidity in the lung metastases, and she subsequently received 150 mCi I-131. The post-therapy scan showed prominent uptake in multiple lung metastases. Thyroid Differentiation Score derived from primary tumour RNAseq (mean of log2 of fold changes for mRNASeq read counts of 16 thyroid differentiation genes) was -0.287 for the *TERT* positive and -0.060 for the *TERT* negative tumour, respectively. The Apical Iodide Transporter (*SLC5A8*) and the Sodium-Iodide Symporter (*SLC5A5*) are characterized by a 2.5 fold and a 2.4 fold upregulation in the *TERT* negative compared to *TERT* positive tumour, respectively.
Conclusion
Similar to the association of RAI resistance with the co-occurrence of *TERT* and *BRAF* mutations, the co-occurrence of *TERT* mutations and *NTRK* fusions may also contribute to re-sensitization failure, in addition to advanced age, male sex, and T stage.
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PS1-08-02

Transcriptomic analysis reveals tumor microenvironment plays important role in nodal metastasis of papillary microcarcinomas

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Objectives
Attempts have been made to identify markers for aggressive disease in papillary microcarcinomas (PMCs), but genetic alterations identified in PMCs have failed to distinguish tumors with high-risk features. Thus, we aimed to identify candidate markers associated with lateral node metastasis (N1b) in patients with PMC through a transcriptomic analysis.
Methods
Bulk RNA sequencing was performed in 26 matched tumor and normal thyroid tissue samples (N0, n =14; and N1b, n =12). Analyses of principle component analysis (PCA), differentially expressed genes (DEGs), and functional enrichment were performed. To further explorer distinct tumor microenvironment (TME), EcoTyper, deconvolution tool, was applied.
Results
In PCA, PC2 axis divided tumor and normal thyroid tissue, but N1b tumor was not distinguishable from N0 tumor. We identified 631 DEGs between N1b and N0 PMCs (213 upregulated genes and 418 downregulated genes). The most significantly upregulated genes in N1b PMCs, including *NECTIN4, NOX4, PDLIM4, COL11A1, MMP11*, and *POSTN*, are related to tumorigenesis, adhesion, migration, and invasion. Functional enrichment analysis showed that DEGs were mainly enriched in the pulmonary fibrosis idiopathic signaling pathway, TME pathway, wound healing signaling pathway, and inhibition of matrix metalloproteases, and the activation of these pathways in N1b PMCs were predicted. Furthermore, deconvolution analyses revealed that N1b PMCs has a unique TME with abundant fibroblasts, and epithelial cells, and lymphocyte deficient, which are linked to higher risk. Consistently, fibroblast marker genes such as *COL10A1, COL3A1, POSTN, MMP11, VCAN, TNFAIP6, LOXL2, FN1*, and epithelial cell marker genes such as *NOX4, MFAP2, TGFVBI, TNC, ICAM1, CXCL8, CSF2* were highly expressed in N1b PMCs compared to N0 PMC or normal thyroid tissue.
Conclusions
Transcriptomic analysis revealed that N1b PMC show the activation of TME pathway and a distinct TME with a high abundance of fibroblasts and epithelial cells compared to N0. Therefore, these TME state could be potential target for N1b PMC and lead to better stratification for high-risk PMC with lateral node metastasis.
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PS1-08-03

Immunocytochemical staining for HBME-1 expression in the "diagnostic search" of differentiated thyroid cancer

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The objectives
To evaluate the diagnostic efficiency of the HBME-1 expression test on cytological samples with Bethesda categories III, IV, and V in the differential diagnosis of thyroid nodular lesions.
Materials and methods
The data of 14 patients with thyroid nodular lesions and cytological Bethesda categories III, IV, and V (" gray zone ") were analyzed. The HBME-1 expression was determined by the results of immunocytochemical (IC) and immunohistochemical (IHC) staining with mouse monoclonal antibodies against human HBME-1: Group I (n =9) - HBME-1 positive, Group II - HBME-1 negative. The HBME-1 expression grade was calculated as the sum of the score for staining intensity and cytoplasmic positive cells square (0 points – colorless, 1 - weakly pronounced yellow, 2 - moderately pronounced yellow, and 3 - brightly pronounced brown) and the score for the percentage of positive cells (0 - 0%; 1–25%; 2 - 26–50%; 3 - 51–75%; 4 - 76–100%) in the IHC sample. HBME-1 positive result was considered with an IHC score >6 points.
Results
According to the postoperative histological staining, the following diagnoses were made: nodular goiter (NG) – 6 and 0, follicular tumor of uncertain malignant potential (FT-UMP) – 3 and 1, differentiated thyroid cancer (DTC) – 0 and 4 (papillary TC – 3, follicular TC – 1) in the I and II groups, respectively. Patients with Bethesda III (n =5) were postop diagnosed: Group I (n =4) - NG; Group II (n =1) – FT-UMP. Patients with Bethesda IV (n =5): Group I (n =3) - NG was in 2 patients and FT-UMP - in 1; Group II (n =2) - DTC (papillary TC -1, follicular TC - 1). Bethesda V (n =4) cytology: Group I (n =2) with FT-UMP; Group II (n =2) with DTC (papillary form). ROC analysis showed that the positive predictive value (PPV) of the HBME-1 expression test was 80% (CI 83.4% -96.4%), and diagnostic efficiency - 92.9% (CI 66.1% - 99.8%). These results suggest the great potential of the test, however, due to the limited observations, CI (confidence intervals) are very wide. More accurate values require additional studies on larger samples.
Conclusions
HBME-1 can serve as an immunocytochemical marker for differentiating benign and malignant thyroid nodules. Its use will help reduce the number of unnecessary surgeries for benign tumors, improving patients' quality of life and reducing the burden on medical services.

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PS1-08-04

Association between BMI and Brafv600E mutation status may differ by primary tumor size

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Introduction
The prevalence of B-type Raf kinase (BRAFV600E) mutation in PTC has been observed in 30% to over 80%, and it seems that the mutation occurred in the early stage of thyroid carcinoma progression which precedes histological change. Based on previous reports, high body mass index (BMI) is considered a thyroid cancer risk. However, it is unclear whether high BMI has a certain association with the BRAFV600E mutational status. We assess whether high BMI is associated with higher BRAFV600E mutational risk.
Materials and Methods
We screened 6,558 papillary thyroid carcinoma (PTC) patients who had BRAFV600E test result between January 2009 and December 2017. After exclusion, 6,442 PTC patients were enrolled. We used logistic regression to assess the association between BMI and BRAFV600E mutational risk. Also, we categorized patients into two groups according to the primary tumor size.
Results
Of the 6,442 patients, 5,105 patients (76.2%) had BRAFV600E mutation, and 4,957 patients (76.9%) were female. Median BMI was 23.8 (21.6 – 26.2) kg/m2. Primary tumor size was ≤1 cm in 4,226 patients, and >1 cm in 2,212 patients. BRAFV600E mutational status was significantly associated with high BMI only in primary tumor size >1 cm (OR 1.035; 95% CI 1.004 – 1.006; P = 0.025). No clear association was found in the primary tumor size ≤1 cm (OR 1.004; 95% CI 0.98 – 1.028; P = 0.740). The pattern of odds ratio (OR) plots were similar in each group (primary tumor size ≤1 cm, and >1 cm) after adjusting with age, alcohol, and smoking status.
Conclusion
Higher BMI seems positively associated with BRAFV600E mutational status in primary tumor size >1 cm. However, the association between BMI and BRAFV600E mutation status may differ by primary tumor size.

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PS1-08-05

Can tert promoter mutation be a poor prognostic factor in undifferentiated thyroid carcinoma?

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Background
Telomerase reverse transcriptase (TERT) promoter mutation is a poor prognostic factor in differentiated thyroid carcinoma(DTC). It is thought to play a role in the transformation process to undifferentiated thyroid carcinoma(UTC), but its role as a prognostic factor in UTC is unclear. Therefore, in this study, we investigated whether the TERT promoter mutation acts as as an independent poor prognostic factor in UTC.
Methods
Among patients diagnosed with UTC from 1995 to 2020 at Samsung Medical Center, 28 patients who underwent TERT promoter mutation test were enrolled. Clinical features, including survival rate, were compared between patients with positive and negative in TERT promoter mutations. The overall survival(OS) was verified by the Kaplan-Meier method, and the evaluation of factors affecting survival was verified by the multiple regression analysis method [HR (95% CI)].
Results
The median age of 28 patients with UTC was 68.5 years (50.0~79.0), and 19 patients (67.9%) were female. In 16 patients (57.1%), there was coexistence or history of DTC. The median tumor size was 4.5 cm (0.8~11.0). There was no patient with stage IVA, whereas 12 patients(42.9%) with IVB, and 16 patients(57.1%) with IVC. Aggressive treatment (combination of surgery, radiotherapy and systemic treatment including tyrosine kinase inhibitor) was performed in 10 patients (35.7%). The median OS was 6.9 months (0.4~39.5), the 1-year OS was 32.1%, the 2-year OS was 21.4%, and the 3-year OS was 14.3%. TERT promoter mutations were found in 10 patients (35.7%). There was no difference in the clinical characteristics (age, gender, coexistence or history of DTC, tumor size, stage, pathological findings, etc.) between the TERT promoter mutation positive group and the negative group. However, more active treatment was performed in the TERT promoter mutation positive group. (60.0% vs. 22.2%, P = 0.04). The average survival time of the TERT promoter mutation positive group, which received more active treatment, was 9.1 months (0.4 to 39.5). It was longer than that of the negative group (6.1 months (0.4 to 39.0)), but was not a significant difference (P = 0.43). The 1-year survival rate was 40% in the TERT promoter mutation positive group, higher than 28% in the negative group, but it was not a significant difference. When multiple regression analysis was performed to find prognostic factors affecting OS, age [2.60 (1.08–6.26)], lymph node metastasis [5.72 (1.58–20.70)], and distant metastasis [2.59 (1.06–6.32)] came out as significant prognostic factors (P < 0.05), whereas TERT promoter mutation was not [0.89 (0.27–2.93)].
Conclusion
In this study, unlike DTC, TERT promoter mutation was not an independent poor prognostic factor in UTC.

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PS1-08-06

Comparative cyto-histological genetic profile in a series of differentiated thyroid carcinomas

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Introduction
Ultrasound-guided fine-needle aspiration cytology (US-FNAC), the gold standard method to distinguish benign from malignant thyroid nodules, is the most accurate, cost-effective and minimal invasive preoperative test, aiming to resolve patient management. However, up to 30% of US-FNACs are classified as indeterminate nodules, making difficult to avoid unnecessary surgeries. Molecular tests may contribute to refine the preoperative diagnosis of thyroid nodules.
Aim
The aim of this study was to compare the cyto-histological genetic profile (TERTp, BRAF and RAS (NRAS, HRAS and KRAS)), by using a paired series of cytology and histology samples, and to establish whether the molecular profile defined by US-FNAC is reliable to further characterize thyroid nodules and their biologic behavior.
Material and methods
The series was composed by a cytology and corresponding formalin-fixed paraffin-embedded (FFPE) tissue from 259 patients with thyroid nodules that underwent surgery between 2012 and 2020. The genetic alterations were examined by PCR/Sanger sequencing. The association of the genetic alterations with clinicopathologic features was evaluated.
Results/Discussion
Our series included 80.7% females (median age 55y, min18-max84). Cytology was non-diagnostic in 5.8%, benign in 18.2%, indeterminate in 39% and malignant in 37.1%; Histology was benign in 19.3% and malignant (differentiated thyroid carcinoma (DTC)) in 80.7% nodules, including papillary thyroid carcinomas (PTCs) in 180 cases. The indeterminate nodules correspond, in histology, to 23 benign (22.8%) and 78 malignant lesions (77.2 %). Mutation frequencies in cytology and histology specimens were, respectively, TERTp: 3.7% vs. 7.9%; BRAF: 19.5% vs. 25.1%; NRAS: 4.5% vs. 7.7%; HRAS: 4.9% vs. 7.4%; KRAS: 1.6% vs. 2.4%. Mutations in 96.5% of cytology and in 95.2% of histology were identified in PTCs. In indeterminate nodules, mutation frequencies in cytology and malignant histology were: TERTp: 4.3% vs. 11.1%; BRAF: 7.2% vs. 13%; RAS: 14.4% vs. 24.5%. The discriminative ability of mutations regarding DTC diagnosis showed 100% of specificity although with low sensitivity. A good cyto-histological agreement was obtained for molecular alterations (total cases 92.2%, k=0.67 and indeterminate nodules 91.9%, k=0.61), suggesting that molecular analysis in US-FNAC may anticipate the molecular profile of the tumor. Several statistically significant associations between the clinicopathological and molecular features of the tumors were found; TERTp and BRAF mutations were associated with extra thyroidal invasion, lymph node and distant metastases; RAS mutations were associated with presence of capsule. Although with low discriminative ability to exclude malignancy, genetic profile confirms malignancy in US-FNAC and contribute to refer patients to surgery.

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PS1-08-07

The role of metabolic markers, TYG and TYG-BMI indices in predicting the risk of thyroid cancer

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Introduction and Objective
Thyroid cancer (TC) is the most common endocrine tumor with a growing incidence worldwide. However, diagnostics using ultrasound research methods do not allow to unambiguously determine the type of thyroid lesion and make a precise diagnosis in early stages. The results of recent studies indicate the metabolic changes occurring in cancer cells. Various molecular biomarkers and indices (TYG, TYG-BMI) may indicate the onset of development and progression of thyroid cancer. The main aim of our study was to evaluate the role of metabolic markers and TyG, TyG-BMI indices as potential predictors of thyroid cancer.
Methods
A retrospective cohort study was conducted with the analysis of patient histories. Inclusion criteria were patients aged 18 to 85 years who were operated on for suspected thyroid cancer with a histologically verified diagnosis of thyroid cancer. Statistical analysis was carried out in the IBM SPSS Statistics 26.0 program.
Results
Data was collected from 155 patients (22 men and 133 women) aged 18 to 85 years (Mo=56, Me=58) with a mean body mass index of 28,47 [24,91; 32,21]. According to the results of histological examination, patients were divided into a group with thyroid cancer (32 patients (20.5%)) and a group with benign thyroid lesions (123 patients, 79.5%). 75.9% (120 patients) were exposed to Bethesda 1-3 and 24.1% (35) to Bethesda 4-6. A comparative analysis of metabolic markers in the studied groups was carried out: the level of LDL was significantly higher in the group with thyroid cancer (median - 3.42 [2.53; 4.2]) than in the group without cancer (2.58 [1.9; 3,4]). The mean TSH level was higher in the group with thyroid cancer (1.92 [1.15; 2.51]) compared with the group of benign diseases (1.43 [0.7; 1.8]), and the groups also differed in age (TC - 51.5 [41; 58.3], benign lesions - 61 [51; 67]). No association with triglyceride levels, TyG and TyG-BMI was found ($P = 0.738$; 0.529; 0.519, respectively).
Conclusion
A higher risk of malignant thyroid cancer is associated with higher levels of TSH, LDL and younger age. Our study did not reveal any relationship between the TyG, TyG-BMI indices and the risk of thyroid cancer, which may be due to a small sample of patients.

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PS1-08-08

The role of micrornas to the diagnosis of differentiated thyroid carcinomas

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Introduction
Several studies recommend the use of molecular tests for a complete diagnosis of malignancy in thyroid carcinomas (TC). The study and identification of molecular markers in thyroid will contribute to a personalized and effective treatment of the patients. The development of TC has been associated with the activation of oncogenes that are implicated in the cell signaling pathway, interfering in cancer promotion and outcome. Moreover, the repertoire of microRNAs (miRNAs) in TC has been recently identified as being important in tumor development and progression. The assessment of miRNAs expression represents a promising area of study in cancer.
Aims
This study aims to evaluate the role of miRNAs (miR146b, miR221, miR222 and miR15a) expression and the molecular association with genetic alterations (*TERT*p, *BRAF* and *RAS* (*NRAS*, *HRAS* and *KRAS*)) in the improvement of differentiated thyroid cancer (DTC) diagnosis.
Material and methods
For the relative quantification of miRNAs expression, a total of 83 thyroid samples, composed by formalin-fixed paraffin embedded (FFPE) samples of 12 benign and 71 malignant tumors (DTC) were selected. MicroRNA expression was assessed for miR146b, miR221, miR222, and miR15a by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) and the results were analyzed using the $2^{-\Delta\Delta CT}$ method. The discriminative ability of miRNAs expression regarding DTC diagnosis was evaluated using the area under the Receiver Operating Characteristic Curve (AUC). Cut-off values maximizing sensitivity were obtained. The association of miRNAs expression and genetic alterations was evaluated.
Results/Discussion
All four analyzed miRNAs showed a tendency to be over expressed in malignant tumors when compared with benign lesions. Corresponding discriminative abilities regarding DTC diagnosis were: miR146b (AUC 0.81, 95%CI 0.71-0.91), miR221 (AUC 0.74, 95%CI 0.64-0.84), miR15a (AUC 0.77, 95%CI 0.66-0.88), and miR222 (AUC 0.66, 95%CI 0.55-0.77). Cut-offs were 1.05 for miR146b with sensitivity (se) 82.5 and specificity (sp) 66.7, 1.35 for miR221 (se=71.8, sp = 73.3), 1.35 for miR15a (se=72.5, sp = 66.7), and 0.84 for miR222 (se=69.4, sp = 53.3). Our data reveals a significant statistical association between higher expression levels of all miRNAs, but miR15a, with *BRAF* mutation ($P < 0.001$), suggesting a connection of this mutation with miRNAs expression, in accordance with other studies. Although this study had a

limited sample size, three of the miRNAs showed a good discriminative ability in DTC. The association between the miRNAs profiling and molecular analysis could be useful for an accurate diagnosis of DTCs.

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PS1-08-09

Identification of rare braf variants in thyroid nodules

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Objectives
The substitution *BRAF* p.V600E is the most common genetic cause of the papillary thyroid carcinoma (PTC) and represents more than 95% genetic variants in *BRAF* gene. Other rare variants in the *BRAF* gene include other substitutions (e.g. p.K601E), small deletions or insertions close to codon 600. The aim of this study was to analyze a large cohort of thyroid nodules for rare genetic variants in the *BRAF* gene.
Methods
A total of 1282 fresh frozen thyroid tissues collected from 2003 to 2023 were screened for alterations of *BRAF* exon 15 by next generation sequencing. The cohort consisted of 837 PTC, 45 low-risk tumors, 36 oncocytic and follicular carcinomas (FTC), 7 poorly differentiated carcinoma, 17 anaplastic carcinomas and 323 benign tissues. The exon 15 of the *BRAF* gene was analyzed by next generation sequencing using the Nextera XT Sequencing Kit (Illumina) or Thyro-ID (4 bases). The VarSome software was used to interpret detected variants.
Results
Pathogenic variants in *BRAF* gene in 413 samples including the rare *BRAF* alterations in 14 samples - 11 PTC (1.3%), two benign nodules (0.6%) and one FTC (2.8%) - were detected. Eight various variants were detected. The most common were p.K601E, V600_K601delinsE and p.T599dup in four, three and two patients, respectively, followed by p.T599_V600insEAT, p.V600E+p.Q609E, p.A598_T599insI, p.V600_S605delinsEG and VKS600-2DFT in one case only. Except for p.K601E in one FTC and one benign nodule and p.T599dup in one benign nodule, other rare variants were found exclusively in PTC. The variants were evaluated as pathogenic or likely pathogenic using ACMG Classification. In one patient, pathogenic variant c.3140A>G p.(His1047Arg) in PIK3CA gene along with *BRAF* p.A598_T599insI variant was detected, in other patients with rare *BRAF* variants, no pathogenic variants in other main genes were detected.
Conclusions
The rare *BRAF* variants represented 3.4% of *BRAF*-positive thyroid nodules and their detection is only possible by sequencing. Except for p.K601E and p.T599dup, other rare variants were found exclusively in PTC. *Supported by AZV NU21-01-00448 and MH CZ RVO 00023761.*

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Thyroid Cancer Basic

PS1-09-01

Thyroid cancer and endocrine disruptive chemicals: a case-control study on per-fluoroalkyl substances (PFAS)

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Objectives
The worldwide incidence of thyroid cancer (TC) is increasing at an alarming rate in the last decades and environmental pollution has been suggested to be involved in this rise. Some environmental pollutants, namely endocrine disruptive chemicals (EDCs), have been linked to endocrine system disruption, including thyroid dysfunction, and increased risk of cancer. Among EDCs, per- and polyfluoroalkyl substances (PFAS) are widely used in many industrial and consumer products, including common household goods, and have raised global concern as persistent organic pollutants that threaten ecosystems and human health. To date few studies, mainly focused on high-risk populations, reported an association between PFAS and TC. The present case-control study aims to evaluate the possible association between serum PFAS concentrations and risk of thyroid cancer.
Materials and methods
We recruited 224 participants, of which 112 patients with a diagnosis of TC in the last five years and 112 sex and age-matched controls with no known history of thyroid diseases, primitive gonadic diseases, or other malignancies. Blood samples were taken from all participants and serum concentrations of some legacy PFAS were measured using liquid chromatography coupled to mass spectrometry. The possible association between serum PFAS levels and the risk of thyroid cancer was explored by the odds ratio (OR) and 95% confidence intervals (CI).
Results
The median age of case and control populations was 50 (range 20-89) and 51.5 (range 19-86) years respectively, with 77.7% of female participants in both groups. Among PFAS tested, perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA) were detected in more than 95% of samples, with a median concentration of 0.5, 1.8, 4.1 and 0.4 ng/ml respectively. On the other hand, perfluorodecanoid (PFDA) were detected in 42,9% of participants, with a median concentration of 0.1 ng/ml. After the adjustment for some confounder variables, a positive association between PFDA and the presence of thyroid cancer was observed (OR= 1,96, $P = 0.024$) in subjects with measurable levels of PFDA. On the contrary, a negative association was found for PFHxS (OR= 0.31, $P = 0.021$).
Conclusions
This study shows, for the first time, a positive association between PFDA exposure and thyroid cancer, suggesting that it may be considered as a risk factor for TC development. On the contrary, an inverse correlation was found with PFHxS, as previously reported, likely due to a potential reverse causality.

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PS1-09-02

The absence of TSHR-GPER heteromers is a potential marker of thyroid cancer

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Thyroid cancer is the most common type of endocrine tumor and reaches the peak of incidence between the age of twenty and fifty years. It has 4-fold higher prevalence in females than males, suggesting that estrogens and their receptors could be involved in thyroid cancer pathogenesis. Previous studies demonstrated allosteric interference operated by G protein-coupled estrogen receptor (GPER) to molecules structurally similar to the thyroid-stimulating hormone (TSH) receptor (TSHR), like the follicular-stimulating hormone (FSH) receptor (FSHR). Given these evidences, we hypothesize that GPER may interact with TSHR, modulating proliferative signals in thyroid cells. Mechanistic experiments evaluating TSHR/GPER heteromers and signaling were performed on papillary thyroid carcinoma (K1), follicular thyroid epithelial (Nthy-ori 3-1) and COS7 (control) cell lines, and confirmed in papillary, follicular, and anaplastic tumors *vs* healthy primary thyroid tissues by immunofluorescence (IF) and proximity ligation assay (PLA). Cell lines were co-transfected with specific plasmids to evaluate effects on the TSH-induced activation of Gαs and Gq protein-associated transduction pathways, under TSHR/GPER co-expression. Cell lines were treated with 300 nM TSH and 730 pM estradiol. Intracellular levels of cAMP and calcium ion (Ca^{2+}) increase were measured by bioluminescence resonance energy transfer (BRET), while intracellular IP1 increase was evaluated by homogeneous time resolved fluorescence (HTRF). Results were compared by Kruskall-Wallis test ($n = 6$; $P < 0.05$) and corrected by Dunn's post-hoc test. We found TSHR/GPER co-expression and physical interaction in healthy thyroid follicles using two different methods (IF and PLA), and confirmed these results in cell lines by BRET and HTRF. Surprisingly, no GPER expression was found in histological sections of papillary, follicular and anaplastic thyroid cancer, as confirmed by the absence of IF signal and heteromers. In TSHR expressing cell lines, TSH activated Gαq-mediated signals, i.e. IP1 ($n = 6$; $P < 0.05$) and Ca^{2+} ($n = 3$; $P < 0.05$), while it was not under TSHR/GPER co-expression. Control experiments with Gq and PLC inhibitors, i.e. YM-254890 and U73122, confirmed GPER-like inhibition of TSH-induced IP1 production. Instead, the presence of GPER unaffected TSH/GαS-mediated cAMP production ($n = 6$; $P \geq 0.05$). Cell treatment with estradiol and GPER antagonist (5 μM; G15) had no effects ($n = 6$; $P \geq 0.05$), revealing that GPER inhibits TSHR/Gq pathway regardless of ligands. GPER/TSHR heteromers drive potentially protective effects in thyroid cells, while the lack of GPER unlock TSH/Gq-dependent proliferative intracellular pathways in tumor cells. This data suggests that lack of GPER may be related to thyroid tumor pathogenesis.

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PS1-09-03

Prophylactic bilateral central neck dissection does not improve the short term response to surgery and radioiodine ablation in differentiated thyroid cancer

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Background
The use of prophylactic central neck dissection, especially for low-risk differentiated thyroid cancer, is still very variable from center to center. Obviously, central dissection does allow more complete staging of cancer, including identification of metastases not detectable on preoperative ultrasound. However, it could lead to higher risk of hypoparathyroidism. Above all, it is not entirely clear whether the identification of metastases of the central compartment and the consequent more aggressive treatment leads to a substantial benefit in terms of risk of recurrence and/or survival.
Methods
Retrospective analysis of patients in follow-up for thyroid cancer (histological diagnosis between 1978 and 2021) at an academic endocrinology unit. Among 693 subjects, only those treated with total thyroidectomy with or without bilateral central neck dissection (BCND) were considered. Subjects treated also with laterocervical lymphadenectomy, or with monolateral central neck dissection or diagnosed with medullary carcinoma were excluded. BCND and non- BCND groups were compared for post-surgical complications, post-surgical thyroglobulin (Tg) serum levels, outcome of post-dose whole body scintigraphy after radioiodine ablation (RAI), response to rh-TSH test. Comparisons between groups were performed with the non-parametric Mann-Whitney U-test or Chi-squared test for categorical data.
Results
106 subjects were treated with BCND and 322 subjects were not. BCND group had higher but not significant rate of post-surgical complications (8.5% vs 4.4%, $P = 0.412$), mainly persistent hypoparathyroidism. The 67% of BCND group and the 36% of non-BCND underwent RAI. Among them, BCND had lower Tg serum levels before RAI (8.99 ± 52.96 vs 92.59 ± 748.52 ng/ml) but significance is lost after correction for TgAb positivity. Groups did not differ for positivity at post dose whole body scintigraphy. At the rh-TSH test, performed 12 months after ablation, groups did not differ either in baseline Tg (BCND 0.26 ± 1.06 vs non-BCND 0.48 ± 2.14 ng/ml, $P = 0.491$) or stimulated Tg (BCND 0.56 ± 2.16 vs non-BCND 1.26 ± 8.40 ng/ml, $P = 0.354$). Stimulated Tg was <1 ng/ml in 93% of BCND and 87% of non-BCND ($P = 0.276$).
Conclusions
In subjects treated for differentiated thyroid cancer, performing BCND together with thyroidectomy does not seem to improve the short-term response to surgery and RAI. Our retrospective data provide no indication of long-term response, so further studies are needed.

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PS1-09-04

Development and pre-clinical validation of next-generation sequencing gene panel to detect clinically relevant mutations in thyroid cytological and histological samples

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Objectives
Molecular techniques are becoming increasingly important for the management of thyroid nodules. In particular, next-generation sequencing (NGS) can assess multiple predictive biomarkers simultaneously, enabling more accurate pre-operative risk stratification for patients with indeterminate fine-needle aspirates and identifying specific molecular alterations for targeted therapy in patients affected by advanced, radioactive iodine refractory carcinomas. To meet these needs, we developed and validated a custom NGS gene panel (Nexthyro) designed to identify clinically relevant mutations implicated in thyroid oncogenesis.
Methods
Our panel covers 265 mutations in 15 genes and 161 gene fusions, specifically targeting mutations in BRAF, EIF1AX, GNAS, HRAS, IDH1, KRAS, NF2, NRAS, PIK3CA, PPM1D, PTEN, RET, DICER1, CHEK2, TERT promoter, and fusions in RET, BRAF, NTRK, PAX8/PPARγ, ALK, and ROS1. The analytical sensitivity was assessed by extracting both DNA and RNA from two different cell lines: 1) gDNA OncoSpan (Horizon Diagnostics [HDx]), which harbours 386 variants in 152 genes, including those detected by our panel, and 2) LC-2/ad (Dr. Miguel Angel Molina-Vila, Laboratory of Oncology, Pangaea Oncology, Spain) which harbor RET gene fusions. The nucleic acids were mixed with wild-type cell lines reaching serially decreasing dilution points (Table 1). Each dilution point was tested twice to assess the reproducibility of the results.
Results
All samples were successfully analysed and the limit of detection (LOD) of the mutated allele was established at 2% for both DNA alterations and RNA fusions. These results were successfully replicated in the same NGS run (Table 1).
Conclusions
Our custom NGS gene panel demonstrated high reproducibility and analytical sensitivity. Further validation using cytological and histological routine samples, which is currently underway. is necessary to evaluate implementation in clinical practice. **Table 1**. Dilution point, mean fusions RNA read counts and allele frequency of DNA mutations. For each dilution point, the results from the two different set of NGS tests were compared in order to show their analytical reproducibility.

Table 1

DNA/RNA DILUITION POINT	RNA (MEAN FUSIONS READ COUNTS)		DNA (MUTATED ALLELE FREQUENCY)	
100%	1399	1329	58%	60%
50%	368	350	26%	24%
20%	212	225	14%	12%
10%	126	130	6%	8%
2%	103	107	3%	2%
0%	0	0	0%	0%

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PS1-09-05

Inactivating mutations of TP53 and resistence to tyrosine-kinase inhibitors in patients affected with aggressive thyroid cancer

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Objectives
Well differentiated thyroid cancers (WDTC) are generally sensitive to first line treatments or eventually to tyrosine kinase inhibitors (TKIs). However, a part of WDTC together with poorly differentiated (PDTC) and anaplastic (ATC) thyroid cancers are particularly aggressive and refractory to all treatments, TKIs included. Since TKIs resistance is proven to be related with the presence of *TP53* mutations in other tumours, and *TP53* alterations are frequently detected in aggressive thyroid cancer (TC), we aimed to investigate the possible correlation between *TP53* mutational status and resistance to TKIs in patients with aggressive TC.
Methods
The molecular analysis of *TP53* was performed in a cohort of 30 patients bearing aggressive TC (24 WDTC and 6 PDTC/ATC) and treated with TKIs by Sanger sequencing.
Results
TP53 mutations were detected in 7/30 (23.3%) tumour tissues (3 WDTC and 4 PDTC/ATC) and fall within exons 5-8 encoding the DNA binding domain of the protein. Three mutations were already reported in TC (p.C135Y, c.626_627delGA, p.Q192X), 4 reported in other solid or haematological malignancies (p.M133R, p.C135F, c.722_724delTCC, p.H214Y) and 1 never reported in any tumour (c.866_867delTC). Interestingly, patients harbouring *TP53* mutations were significantly more resistant to TKI compared to the wild type ones (86% vs 22%, $P = 0.0045$). It is worthy to note that the only patient with a *TP53* mutation responsive to TKI carried a partially functional missense mutation (p.H214Y), as reported in the IARC *TP53* database. Patients with undifferentiated TC (PDTC and ATC) were more frequently mutated in *TP53* than those with WDTC (66.7% vs 12.5%, $P = 0.0157$) and were more frequently resistant to TKIs than the WDTC group (83% vs 29%, $P = 0.0256$). Among WDTCs, those with *TP53* mutations tended to be more frequently unresponsive, and among undifferentiated cases, those with *TP53* mutations were totally unresponsive, suggesting that the resistance to TKI therapy might be correlated to the presence of *TP53* mutations regardless of the grade of differentiation.
Conclusions
We demonstrated for the first time in TC a correlation between the presence of inactivating mutations in *TP53* gene and the development of resistance to TKI therapy in patients harbouring aggressive thyroid cancers. The testing for these mutations could be considered as a prerequisite to be obtained when deciding the opportunity to start or not a treatment with TKIs.

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PS1-09-06

Targeting the DNA damage response kinase CHK1 in TP53-mutated thyroid cancer: *in vitro* studies

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Objectives
Differentiated TCs are generally sensitive to first line treatments and tyrosine kinase inhibitors (TKIs). However, part of them along with undifferentiated TC, namely Anaplastic (ATC) and Poorly Differentiated (PDTC), are aggressive and show refractoriness to tyrosine-kinase inhibitors (TKIs) treatments. A correlation between resistance to TKIs and inactivating *TP53* mutations was proven in TC by our group, consistent with data obtained in other tumors. To find a novel therapeutic strategy for aggressive TC, we aimed to investigate the DNA damage response (DDR) pathway, where p53 plays a crucial role. Indeed, since the combined lack of function of two DDR players can induce cancer cell death by synthetic lethality, the pharmacological inhibition of a DDR molecule in tumors lacking p53 function is a promising strategy currently studied and clinically tested in several solid and hematological malignancies.
Methods
MMT cell viability assay, western blot and immunofluorescence analyses were used to characterize the DDR pathway in response to a DNA damaging agent in a panel of TC cell lines with known *TP53* mutational status, and to evaluate the inhibitory effect of Prexasertib, a highly selective Chk1 kinase ATP-competitive inhibitor, on Chk1 kinase activity.
Results
The *in vitro* characterization of the DDR showed the presence of genomic instability predominantly in *TP53*-mutated cell lines. Interestingly, Chk1 kinase resulted strongly activated in response to the genotoxic agent Doxorubicin (DOXO) in *TP53*-mutated cell lines (FRO, SW1736, B-CPAP and HTC/C3) as compared to the wild-type lines (TPC-1, K1 and IHH-4). Therefore, we tested the effect of Prexasertib (PX) on our TC cell lines and found that it was able to inhibit 50% of cell proliferation (IC50) at less than 10 nM concentration in all p53-deficient cell lines. Moreover, combined treatments with low concentration of PX (4nM) and IC25 DOXO showed remarkable decrease in *TP53*-mutated TC cell proliferation with respect to single treatments, without affecting healthy thyroid cell viability, as demonstrated treating patient-derived normal cultured thyrocytes.
Conclusions
Our data showed, for the first time in TC, that Chk1 may be a suitable target for novel treatment strategies in p53-deficient aggressive TC.

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PS1-09-07

Familial papillary thyroid carcinoma as a new clinical entity

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Background
Familial papillary or follicular thyroid carcinoma is a rare, nonmedullary thyroid carcinoma characterized by the presence of the disease in two or more first-degree relatives. With the worldwide increasing rate of papillary thyroid carcinoma (PTC) in the recent years, the familial form of the disease (FNMTC) has also become more common than previously reported, however remains less well described clinical entity. Here we report a case of PTC in identical twins.
Case presentation
The index case was a 41-year-old male who referred to our clinic in December 2021 with complaints of fatigue, shortness of breath, high blood pressure, weight gain. On physical examination he had normal vital signs except for tachycardia; The thyroid hormone report was standard and the neck ultrasound revealed presence of nonpalpable <1 cm hypoechoic solitary nodule with irregular margins, vertical orientation, highly vascularized, corresponding to TIRADS IV category. Then, FNAB was performed with the BETHESDA VI report. The patient underwent total thyroidectomy and bilateral neck dissection. Histopathological report of papillary microcarcinoma with microscopic extrathyroid extension, lymphangio and perineural invasion. The patient's family members were worried, and we performed neck ultrasound in identical twin brother. He was also diagnosed with PTC. The patient underwent total thyroidectomy with bilateral neck dissection, and received radioactive iodine (100 mCi each) treatment.
Conclusion
Our case is important because it raises awareness of a rare disease and represents an interesting challenge for clinician. Many controversies are associated with the management of FNMTC. The decision to screen members of FNMTC kindreds with thyroid ultrasound is neither recommended nor discouraged but we strongly recommend that the first degree relatives should be considered for screening.

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PS1-09-08

Overexpression of activated focal adhesion kinase correlates with adverse clinicopathological factors of papillary thyroid carcinoma

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Objective
Focal adhesion kinase (FAK) is non-receptor tyrosine kinase that has been shown to affect cell motility, adhesion, invasion, cell survival, proliferation and de-differentiation. Its increased expression has been reported for various types of malignancies and is associated with cancer progression. However, there are less information regarding its posttranslational form, phosphorylated at Tyrosine 397 (pY397-FAK), which represents a key event for complete protein activation. In order to determine the possible role of the activated form of FAK in progression of papillary thyroid carcinoma (PTC), we analyzed expression levels of pY397-FAK. We aimed to investigate its presence in tumor and adjacent normal thyroid tissue and its localization in tumor cells, as well as its expression levels in relation to clinicopathological parameters of PTC patients.
Material and methods
Proteins were extracted from 68 snap-frozen malignant and 14 corresponding non-malignant adjacent thyroid tissue for the purpose of pY397-FAK expression analysis by western blot method. Immunohistochemistry was also applied with the aim of investigating the localization of pY397-FAK in terms of presence in the cytoplasm, membrane and nucleus. All the expression levels were correlated separately with the clinicopathological parameters, to test the prognostic capacity.
Results
Densitometric analysis of western blot results showed that the levels of pY397- FAK are significantly higher in the malignant tissue than in paired non-malignant ($P < 0.001$). We detected the presence of pY397- FAK in all three compartments, with the strongest staining observed in the cytosol. Nuclear staining was noticed in 26.5% (18/68) of the cases. Furthermore, we detected nuclear staining predominantly in the follicular variant of PTC. Western blot analysis revealed that increased expression of pY397-FAK correlated with lymph node metastasis, degree of tumor infiltration, extrathyroid invasion, pT, pTNM and tumor aggressiveness. Immunohistochemistry displayed similar results in terms of cytoplasmic and membranous staining, except that high expression of pY397-FAK originating from cytoplasm significantly correlated with intraglandular dissemination as well. Moreover, the best results have been achieved when the mean score (mean values of cytoplasmic, membranous and nuclear scores) was used for the statistical analysis.
Conclusions
Our results showed that post-translational modifcation of FAK is important event during malignant progression of PTC and that its elevated expression is promising candidate in prognostic assessment. The mean pY397-FAK immunohistochemical score displayed the best performances in stratification of highrisk PTC patients.

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A novel somatic genetic alteration in sporadic medullary thyroid carcinoma

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Introduction
Medullary thyroid carcinoma (MTC) is a malignant thyroid tumor originating from parafollicular C-cells. Most of MTCs (75%) are sporadic while remaining are hereditary. The hereditary form of MTC is a consequence of the mutation of the proto-oncogene RET (Rearranged During Transfection). Somatic mutations of the RET gene are also present in 40%-70% of the sporadic form of MTC (sMTC). Somatic mutations are also observed in the RAS genes and very rarely in

the BRAF gene. Gene fusions are usually not observed and are rarely reported in MTCs. There are currently two reports describing single medullary thyroid carcinoma specimens in which gene fusions have been detected. According to recent advances in targeted therapies, it is important to identify new potential molecular targets for management of advances and metastatic MTCs. Therefore the aim of this study was to investigate the gene rearrangements and gene variants in tumor tissue of sporadic medullary thyroid carcinoma.
Method and samples
The sporadic MTC tumor tissues of 40 patients were analyzed using Archer library kit and the MiniSeq Illumina sequencing system. For the fusion gene analysis, RNA was isolated from the fresh frozen tissues samples which were collected intraoperatively. RNeasy Micro Kit (Qiagen) were used. The bioinformatics analysis was performed with the Archer Analysis software v. 7.0.0-4 and own bioinformatic pipeline.
Results
RET and RAS genes mutation were predominantly present in sporadic MTC tumor cells. Fusion of ALK gene with long non-coding RNA transcript was detected in 3 samples. Both genes involved in the fusion are located on chromosome 2 and are in an adjacent location, what might be the case of a "read-through" fusion. This fusion has previously been detected in glioblastoma multiforme and Ewing sarcoma cell lines.
Conclusions
Fusion genes in sporadic MTC is rare however ALK fusion gene is observed at low frequencies. The role of this alteration in the carcinogenesis of sporadic medullary thyroid carcinoma requires further investigation.

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Thyroid Gland, Iodine & Autoimmunity Basic

PS1-10-01

Targeting interleukin-11 signaling, an emerging patholgical mediator in thyroid eye disease

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Objectives
Thyroid eye disease (TED) is considered a fibroinflammatory disease with pathology related to both inflammatory and fibrotic disease processes. IL-11 is a fibroinflammatory cytokine that is linked to tissue fibrosis of the lung, skin, heart, kidney and liver. Recently, IL-11 was identified as a possible disease modifier in TED. IL-11 levels are increased in TED patient plasma, in correlation with disease severity, and IL-11 stimulates phenotypic switching of orbital tissue-derived cells to pro-fibrotic myofibroblasts. We have further evaluated the role of IL-11 in the activation of human TED patient derived orbital fibroblasts to determine if IL-11 may play a pathologic role. LASN01 is a fully human, clinical stage antibody to IL-11R which potently blocks IL-11 signaling and is an investigational therapeutic agent for fibroinflammatory diseases. We have investigated the ability of LASN01 to reverse IL-11 driven pathologies in TED.
Methods
Orbital adipose/connective tissue was obtained from control ($n = 2$) and TED patients ($n = 7$) following orbital decompression surgery and used to isolate orbital fibroblasts (OFs). The effects of IL-11R blockade with LASN01 on the release of hyaluronic acid, a driver of TED progression, cell proliferation, and collagen expression were examined in response to stimulation with IL-11 or other stimuli. Cellular expression/release of IL-11 and IL-11R were also compared between control cells and TED-derived orbital fibroblasts.
Results
IL-11 gene expression is increased in TED fibroblasts relative to control cells and is induced by fibroinflammatory mediators IL-1β and TGFβ. IL-11 induces proliferation of TED OFs as well as secretion of hyaluronan (HA). LASN01 can effectively block IL-11 induced proliferation and HA production by TED-derived OFs. Although some donor variability was observed, LASN01 can inhibit IGF-1 stimulation of orbital fibroblasts and may affect the pathway downstream of the FDA approved therapeutic agent, teprotumumab.
Conclusion
LASN01 has the potential for differentiated therapeutic efficacy through the inhibition the IL-11R and the inhibition of HA release and anti-fibrotic activity. LASN01 is worthy of further investigation as a potential treatment of TED.

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PS1-10-02

Decreasing iodine intake among pregnant faroese women

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Introduction
Iodine is essential for thyroid funciton and severe deficiency adversely affects the developing brain. A raised and sufficient intake is particularly important during the pregnancy. Iodine sources include sea foods and sea salt, and it is available as a dietary supplement. The former was previously important to the Faroses diet but the intake of traditional Faroses foods is decreasing with at likely parallel influence on the iodine intake. Currently, there is no knowledge about the iodine status of pregnant women in the Faroe Islands. We thus aimed to determine the iodine intake among pregnant Faroese women.
Method
From June 2020 through April 2022, 672 eligible women were enrolled in early pregnancy, and 647 donated a morning spot urine sample and answered two questionnaires: one that pertained to demographic information and an iodine-specific questionnaire. Iodine concentration in urine (UIC) was determined using the Sandell-Kolthoff reaction modified according to Wilson and van Zyl.
Results
The participation rate was 63%. Median UIC was 110 µg/l (IQR 76 µg/l – 176 µg/l), and 43% had UIC <100 µg/l. Factors important for UIC <100 µg/l and <150 µg/l included age, intake of iodine containing vitamins or supplements within 48 hours, fish dinner, eggs, and the previous week's fish cold-cut (OR, 0.3 – 0.9; *P*-values, 0.09 – <0.001). Cheese, milk products, seabirds and higher educational levels were positively associated with iodine nutrition among pregnant Faroese women. Gestational age, smoking, alcohol intake, BMI, and place of living did not associate with iodine intake levels. UIC decreased during data collection from a median UIC of 117 µg/l (IQR (84-183 µg/l) in June–November 2020, to 101 µg/l (IQR 68-143 µg/l) in December 2021–April 2022 ($P = 0.004$).
Conclusion
Overall, Faroese pregnant women were iodine depleted with 43% having an UIC <100 µg/l. However, the majority of those with UIC in the lower range were younger women, and the iodine nutrition had a distinctly decreasing trend coforming to the ongoing changes in dietary habits among younger women who tend to consume less iodine-rich foods. Hence, we recommend continuous monitoring of the iodine intake in pregnant women.

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PS1-10-03

Characterization of anti-thyroglobulin antibodies epitopes in patients with hashimoto's thyroiditis in areas with normal and excessive iodine intake

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Introduction
An increase in dietary iodine uptake, from insufficient to borderline values, induces the unmasking of a hidden epitope on thyroglobulin (Tg). No data about the effect of an excessive iodine intake on the expression of Tg epitopes recognized by human TgAb are available.
Objective
To compare the expression of TgAb epitopes in sera of Hashimoto's thyroiditis (HT) patients from areas with adequate, slightly and markedly excessive iodine intake.
Methods
Inhibition of Tg-TgAb binding was evaluated in HT patients from Italy (Ita, n. 12) , Nagasaki (Nag, n. 11) and Sapporo (Sap, n. 11). Median urinary iodine in these cohorts is 124, 363 and 1015 µg/l. Tg-TgAb binding was inhibited by 4 recombinant human Tg-Ab Fabs that recognize Tg epitopes A, B, C and D. The ability of each AbTg-Fab to inhibit Tg-TgAb binding was evaluated by an immunoenzymatic method. 50 µl/well of TgAb-Fab (or culture medium) was incubated with 50 µl of serum (diluted to provide a final OD of ~ 1.0). The inhibition by TgAb-Fab was calculated from the OD values for serum TgAb alone - serum TgAb + TgAb-Fab and expressed as a percentage of serum TgAb alone.
Results
Levels of inhibition were similar for TgAb-Fab A (Ita: 47 ± 9%; Nag: 41 ± 11%; Sap: 32 ± 10%, $P = 0.095$) and TgAb-Fab B (Ita: 31 ± 11%; Nag: 36 ± 11%; Sap 37 ± 7%; $P = 0.561$), different for TgAb-Fab C (Ita 26 ± 5%; Nag: 40± 12%; Sap 31 ± 7%; $P = 0.015$) and TgAb-Fab D (Ita: 24 ± 7%; Nag 34 ± 8%; Sap 31 ± 10%; $P = 0.025$, Kruskal-Wallis). In pairwise comparison, the level of inhibition was lower in Ita sera by TgAb-Fab C ($P = 0.009$ vs Nag) ($P = 0.037$ vs Sap) and by TgAb-Fab D ($P = 0.027$ vs Nag) ($P = 0.017$ vs Sap, Mann-Whitney).
Conclusions
Levels of TgAb of HT patients are higher in areas with excessive iodine intake. We have previously shown that a rise in urinary iodine from 86.5 to 112.5 µg/l induced the unmasking of epitope B on Tg. A further increase (up to 363 µg/l) induces a higher expression of epitopes C and D. An additional increase (up to 1015 µg/l) does not lead to a different recognition of the 4 epitopes. Likely, other epitopes, in addition to the 4 identified by our TgAb-Fabs, are recognized by TgAb from Japanese HT patients.

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PS1-10-04

Nutritional iodine status & thyroid homeostasis in pregnant women from iodine-deficient environments in india

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Ample literature exists on thyroid functioning and adjustments in Iodine-sufficient pregnant women. But information from endemic-iodine zones is meagre. In this study we attempt to understand how the thyroid copes with the dual challenge of iodine deficiency posed by physiological status of pregnancy and that by Iodine-deficient environment.
Objective
To compare TSH and FT4 profiles and their mutual correlation in iodine-deficient and iodine-sufficient subjects during progressive trimesters of pregnancy.
Methods
Study design: Epidemiological observational survey. Study populations were derived from rural Himalayan foothills in two States Uttarakhand UK, Bihar. BR. Blood & urine samples collected from women 18-45years. UK $n = 125$, longitudinal study. BR $n = 425$ cross sectional. Information on socioeconomic status, maternal thyroid history, dietary-iodine intake, smoking habits and BMI were generated. IEC approval & informed consent were taken. On the first visit, using UIC as biomarker (WHO) pregnant women were categorised into iodine-sufficient (ISS, > 150 ug/l) and Iodine-deficient subjects (IDS, < 150 ug/l). Table 1 summarises results.
Results
UIC significantly declined in UK longitudinal study despite 77% iodised-salt use. FT4 declined and TSH increased ($P < 0.001$) in both IDS and ISS, in UK & BR. TSH and FT4 levels were near-normal. 'r' was higher in IDS from UK (r=0.51, 0.66, 0.61) as well as BR (0,72, 0,65, 0.636) as compared to that in ISS (UK r= 0.17,0.24,0.27 and BR r= 0.07,0.12,0.04) in Trimester I, II, III.
Conclusion
The pituitary-thyroid axis appears to become more sensitive in iodine deficiency resulting in near normal levels of free thyroxine despite consistent UIC decline. Also UIC may not be an ideal biomarker of iodine-deficiency. Intramural grant from SRHU o JS, ACS & AK and UGC JRF to SLT are acknowledged.

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PS1-10-05

A relationship between thyroid disorders and chronic rhinosinusitis: a nested case-control study using national health screening cohort

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Abstract: PS1-10-04

Table 1. Measures of thyroid function and iodine nutrition in Iodine-deficient & iodine-sufficient pregnant women from 8 & 10 villages drawn from Himalayan foothills in States of Uttarakhand & Bihar respectively.

	Tri I (n) Mean ±se	Tri II (n) Mean ±se	Tri III (n) Mean ±se	Tri I Median	Tri II Median	Tri III Median
UK IDS		3.11±0.12 (78)	3.90±0.13 (78)	2.18	2.93	3.46
TSH mIU/l	2.34±0.12 (78)					
FT4 pm/l	14.69+0.30 (78)	12.74+0.29 (78)	11.09+0.27 (78)	14.41	12.5	10.54
UIC ug/l	(78)	(78)	(78)	138	128	108
UK ISS		2.76±0.14 (47)	3.41±0.14 (47)	2.25	2.85	3.44
TSH mIU/l	2.25±0.17 (47)					
FT4 pm/l	15.09±0.36 (47)	13.26±0.33 (47)	11.70±0.26 (47)	14.85	13.1	11.85
UIC ug/l	(47)	(47)	(47)	161	133	118
BR IDS		3.64±0.10 (147)	4.21±0.09 (160)	2.17	3.32	4.0
TSH mIU/l	2.62±0.12 (68)					
FT4 pm/l	14.25±0.3 (68)	12.37±0.2 (147)	11.4±0.2 (160)	14.47	12.4	11.2
UIC ug/l	(68)	(147)	(160)	80	80	84
BIHAR ISS		3.83±019 (16)	3.96±0.25 (17)	3.05	3.80	3.70
TSH mIU/l	2.99±0.21 (31)					
FT4 pm/l	13.94±0.4 (31)	11.87±0.7 (16)	11.48±0.6 (17)	13.67	11.6	11.0
UIC ug/l	(31)	(16)	(17)	168.5	172	170

NOTE: UK = Uttarakhand longitudinal study, BR = Bihar, cross-sectional study IDS = Iodine-deficient pregnant subjects, ISS = Iodine-sufficient pregnant subjects.

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Thyroid hormones influence other organs as well as nearly all parts of the human body, so thyroid hormone imbalance can cause diverse problems in the human body. Chronic rhinosinusitis (CRS) is one of the most common diseases among patients visiting otorhinolaryngology clinics, and CRS can be divided into two different subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRS and thyroiditis are common diseases related to autoimmune features; however, there have been few studies on their correlation. The purpose of this study was to examine the relationship between thyroid conditions and CRS in a matched cohort in a study performed inside the Korean National Health Insurance Service-Health Screening Cohort (2002–2015). With 24,096 control individuals, 6024 CRS patients were 1:4 matched for age, sex, household income, and region of residence. Conditional logistic regression was used to examine the effects of a prior history of thyroid disease, including hypothyroidism, hyperthyroidism, thyroiditis, autoimmune thyroiditis, and Graves' disease. Subgroup analyses were performed in regard to the presence of nasal polyposis. Univariate analysis (all $P > 0.05$) revealed that there was no difference between the CRS group and the control group in the prevalence of a history of hypothyroidism (2.8% vs. 1.8%), hyperthyroidism (2.0% vs. 1.5%), thyroiditis (1.1% vs. 0.8%), autoimmune thyroiditis (0.4% vs. 0.3%), and Graves' disease (0.3% vs. 0.2%). In the multivariate-adjusted model, hypothyroidism was linked to CRS (odds ratio [OR] 1.25, 95% confidence interval [CI] 1.00–1.57). After being categorized according to the presence or absence of nasal polyps, thyroid disorders were not statistically significantly linked with CRS in the subgroup analyses. Our study reported a statistically significant association between hypothyroidism and CRS. Future studies are required to fully elucidate the relationship between thyroid diseases and CRS, including the mechanisms underlying this association.

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PS1-10-06

Reference range of maternal thyroid hormones from rural himalayan foothills (TEHRI CLUSTER): a cross sectional study

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Background
It is well established that during pregnancy, normal physiological changes occur concomitant with an enhanced metabolic demand for thyroxine/iodine. If dietary iodine intake is sufficient, normal equilibrium is achieved. With deficient iodine intake, the demand not being met, it is believed that pathological alterations occur leading to maternal thyroxineaemia and impaired growth and neurodevelopmental disorders in the offspring. However, there are very few studies with respect to uterine history of thyroid hormones in iodine deficient area. Present study is an attempt in that direction. Trimester wise hormonal profiles have been provided.
Objective
To establish trimester specific reference ranges of Thyrotrophin(TSH) & Free Thyroxine (T4), dietary iodine & Urinary Iodine Excretion(UIE) levels.
Method
This study involved population drawn from tehri cluster viz., District Hospital Tehri(30.3809° N, 78.4374° E), CHC Devprayag (30.1584° N, 78.5989° E) and CHC Belashwar (29.9831° N, 78.5278° E). Blood and urine samples collected from pregnant ($n = 570$) and non pregnant ($n = 300$) subjects. Information on socioeconomic status, maternal thyroid history, dietary-iodine intake, smoking habits and BMI were generated. IEC approval & informed consent were also taken.
Results
All mothers used iodisided salt (26.33 ± 9.08 ppm) had BMI and BP within normal range. None of then were smokers. Table 1 depicts the results of the study
Conclusion
The UIC values observed in population reflected marginally mild iodine deficiency (ID) as per WHO norms, despite adequate iodisation level. However thyroid hormone profile was near normal indicating an apt handling of marginal ID.

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Table 1. Reference range of TSH and FT4 in pregnant and non pregnant subjects from Tehri Cluster.

Parameter	Status	Range (5-95percentile)	Range (2.5-97.5 percentile)	Mean ± SEM
TSH (mIU/l)	NP ($n = 300$)	0.46-3.74	0.36-4.56	1.73 ± 0.060
	Tri I ($n = 167$)	0.46-3.26	0.32-3.73	1.60 ± 0.066
	Tri II ($n = 274$)	0.47-3.59	0.36-4.56	1.65 ± 0.079
	Tri III ($n = 81$)	0.58-3.89	0.28-4.94	1.73 ± 0.105
FT4 (ng/dl)	NP ($n = 300$)	0.48-3.6	0.15-4.28	4.65 ± 2.830
	Tri I ($n = 167$)	0.63-2.9	0.47-3.56	1.72 ± 0.055
	Tri II ($n = 274$)	0.63-2.91	0.39-3.67	1.64 ± 0.046
	Tri III ($n = 81$)	0.65-3.38	0.34-4.50	1.77 ± 0.075
UIC (μg/l)	NP ($n = 300$)	106-189	104-198	100*
	Tri I ($n = 167$)	104-191.6	103-197.8	148*
	Tri II ($n = 274$)	104.8-189	102-198	155*
	Tri III ($n = 81$)	104-196.6	104-198	147*

* median

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PS1-10-07

Aryl hydrocarbon receptor (AHR) polymorphisms may contribute to the genetic susceptibility to hashimoto's thyroiditis (HT), favouring the onset of the autoimmune disorder when exposed to pollutants

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Objectives
The interaction between genetic predisposing factors and environmental triggers is crucial for the development of HT. In last decades, the steady rise in frequency of HT in developed countries pointed to a strong influence of changing environmental factors, including increased pollution. Air pollutants, like dioxins and polycyclic aromatic hydrocarbons, are ligands of the aryl hydrocarbon receptor (AHR). This ligand-activated transcription factor, involved in pollutants detoxification, is a key modulator of anti-oxidant defences and immune responses, acting as a regulator of T-reg and Th17 cell differentiation. Aim of this study was to investigated if AHR polymorphisms may contribute to the genetic susceptibility to HT.
Patients and Methods
We evaluated the presence/distribution of specific and characterized polymorphisms of AHR gene, rs2066853 in exon 10 and rs10249788 in the promoter region, in 100 unrelated HT patients (90 F; mean age 50 ± SD 17 yr) and 100 unrelated sex- and age-matched healthy controls (HC). The sample size was estimated considering a power of 0.8 and an alpha value of 0.05. All subjects were caucasian non-immigrant, born and stably living in the same geographic area, including a high polluted area hosting a petrochemical complex and not-polluted rural and coastal areas. DNA was extracted from whole blood of each subject. The genotyping of AHR gene was performed by means of Restriction Fragment Length Polymorphism (RFLP) assay and nucleotide sequencing analysis. For all DNA datasets, genotype frequencies were in Hardy–Weinberg equilibrium.
Results
The polymorphism rs2066853 (G > A) was found in 2 HT patients in heterozygous condition, and in no HC. The SNP rs10249788 (C > T) was identified in 20/100 HT patients and in 8/100 HCs (all heterozygous C/T). The SNP frequency distribution was significantly different between HT patients and HCs ($P < 0.05$), and the OR value (> 3) of heterozygous (C/T) genotype showed a significant correlation with the disease ($P < 0.05$). Statistical analysis of covariate variables demonstrated the SNP

rs10249788 (C>T) was significantly and independently associated with family history of HT and thyroid function ($P < 0.05$). Noteworthy when evaluating its frequency distribution with respect to the area of residence, we found a significant difference between patients residing in areas with environmental issues and those living in non-polluted areas of the same province ($P < 0.05$).
Conclusions
We provide the first evidence that the SNP rs10249788 (C>T) is associated to Hashimoto's thyroiditis, showing a significant correlation with exposure to environmental pollutants. AHR polymorphisms could contribute to genetic susceptibility to HT, modulating AHR expression.

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PS1-10-08

Thyroid-Resident memory T-cells specific for SARS-COV-2 are enriched in patients with thyroid disorders related to covid-19

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Objectives
SARS CoV-2 infections have been associated with the onset of classic subacute thyroiditis (SAT) or atypical SAT, observed in 10-15% of patients hospitalized for severe COVID19 disease (COV-A-SAT) and characterized by absence of neck pain, mild thyrotoxicosis associated with non-thyroidal illness syndrome and thyroiditis-like areas which may persist in the thyroid gland up to 12 months following SARS-CoV-2 infection, despite normalization of thyroid function. Little is known about thyroid anti-viral immune responses and the aim of the study is to define the role of circulating and thyroid-resident T-cells in COV-A-SAT patients.
Methods
T-cells derived from peripheral blood and thyroid (by fine-needle aspiration) samples of 13 unvaccinated COV-A-SAT patients, 6 patients developing classic SAT following COVID19 vaccination and no previous SARS-CoV-2 infection (VAX SAT), 6 patients with ATD (3 spontaneous and 3 following COVID19 vaccination) and 15 COVID19-naïve healthy donors (HD) were analyzed by multi-dimensional flow cytometry, UMAP and DiffusionMap dimensionality reduction and FlowSOM clustering. SARS-COV2-specific T-cells were identified by cytokine production induced by SARS-COV2-derived peptides and with COVID peptide-loaded HLA multimers after HLA haplotyping.
Results
COV-A-SAT patients showed activated Th1 and cytotoxic CD4+ and CD8+ effector T cells four months post-infection, which acquired a quiescent memory phenotype after eight months. Anti SARS CoV-2-specific CD4+ and CD8+ T-cell responses were detectable in peripheral blood four months post-infection, but were reduced after eight months. CD4+ and CD8+ tissue-resident memory cells (TRM) were present in the thyroid gland of COV-A-SAT patients, and circulating CXCR3+T-cells were identified as their putative precursors. SARS-CoV-2-specific T-cells were enriched in the thyroid and acquired a TRM phenotype eight months post-infection. Thyroid-resident TRM cells were also found in VAX-SAT and ATD patients, but no HD. Interestingly, we observed that HLA DRB1*13 was significantly over-represented in the total cohort of 13 COV-A-SAT patients as compared to healthy haplotyped donors. Moreover, there was also a significantly more frequent expression of HLA-B*57, suggesting that they may represent a genetic risk factor to develop COV-A-SAT.
Conclusions
Patients with thyroid disorders induced by severe Covid-19, in particular COV-A-SAT patients, show a prolonged systemic anti-viral effector T-cell response and the generation of COVID19-specific TRM in the thyroid target tissue. Such prolonged immune response may be in part responsible for the persistence of thyroiditis-like areas up to 12 months. Thyroid-resident TRM cells seem involved in thyroid disorders, both COVID19 related or not. The association of COV-A-SAT with specific HLA haplotypes suggests a genetic predisposition and a key role for T-cells.

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PS1-10-09

Analysis of T- and B- lymphocytic infiltrate of target tissues in patients with graves' disease and orbitopathy

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Objectives
In Graves' disease (GD) and Graves' orbitopathy (GO) self-reactive lymphocytes escape immune tolerance, although the underlying mechanisms are not fully understood. We aimed to characterize the immune signatures of target tissue-resident lymphocytes in relation to GD and GO.
Methods
Lymphocytes were derived from blood and ultrasound-guided-fine-needle aspiration (US-FNA) of thyroid and neck lymph nodes (LNs) of the following patients: 13 GD (newly diagnosed or relapsed), 7 GD with active GO (GO-A; ongoing orbital inflammation), 14 GD with inactive GO (GO-I; absent orbital inflammation), 6 Hashimoto's thyroiditis (HT), 15 non-autoimmune multinodular goiter (MNG) and 3 healthy donors (HD). Lymphocytes were also isolated from orbital tissues of 5 patients with Dysthyroid Optic Neuropathy (DON) and 6 GO-I after orbital decompression. Lymphocytes were immunophenotyped by flow cytometry (FACSymphonyTM cytometer) with a 21 surface/intracellular staining panel. Intracellular cytokines were detected following stimulation with PMA and ionomycin.
Results
In LNs, thyroid and PBMCs patients, GD, GO and HT groups show increased T regulatory cell (Treg) numbers when compared with HD. However, in PBMCs of patients with GO-A, Tregs show a lower production of IL-10. Patients with GD and GO present in both thyroid and LNs an increased number of T follicular helper cells (Tfh), as well as a reduction of the Germinal Center-B/Germinal Center-Tfh ratio. B and T lymphocytic infiltrates were found in all analyzed orbital tissues. Our preliminary results show that in DON patients the number of intra-orbital CD19+ B cells is increased compared to GO-I patients.
Conclusions
By neck LN and thyroid sampling with US-FNA we were able to immunophenotype patients with thyroid autoimmune disease. By also studying lymphocytes directly isolated from the orbital tissue, we were able to detect more specific tissue-resident lymphocytes. The increase in Treg cells in patients with thyroid autoimmunity could indicate an attempt by these cells to suppress the altered immune response, or a compensatory consequence of their dysfunction, as observed in GO-A patients. Furthermore, thyroid autoimmunity, especially GD and GO, appears to be characterized by an increase of Tfh cells. Intra-orbital B and T infiltrate characterize GO and may correlate with disease severity, as shown in patients with DON. The extension of this analysis to a larger number of patients will further validate our findings and allow identification of specific immune signatures of GD and GO.

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Poster Session 2: Miscellaneous 2

PS2-11-01

Temporal pattern of thyroid function changes in patients with cured and not cured adrenocorticotropin (ACTH)-Dependent Hypercortisolism

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Context
Chronic hypercortisolism is known to impact the hypothalamus-pituitary-thyroid (HPT) axis, through a disruption of both thyrotropin-releasing-hormone and thyroid-stimulating hormone (TSH) release. These changes, in turn, are responsible for reduced triiodothyronine (T3) and thyroxine (T4) synthesis and secretion, eventually resulting in central hypothyroidism (C-Hypo). However, data on magnitude and timing of recovery of the above abnormalities are still controversial.
Objective
To evaluate:i)the frequency of C-Hypo at diagnosis in patients with ACTH-dependent hypercortisolism;ii)short- and mid-term dynamic changes of thyroid function parameters following implementation of appropriate surgical and/or medical therapy.
Methods
We retrospectively reviewed records from consecutive patients affected with hypercortisolism due to ACTH-secreting pituitary adenoma and ectopic ACTH syndrome (EAS). Included were patients with no known primary thyroid dysfunction, who had been serially tested for thyroid function parameters (TSH, free-T4 [FT4], free-T3 [FT3]) upon hypercortisolism confirmation (T_0), and at 3 (T_1), 6-9 (T_2), and 12-15 (T_3) months after surgery/medical therapy had been performed/started.
Results
Forty-five patients (35 females,10 males, median age 41yrs, range 12-74) affected with ACTH-secreting pituitary adenoma ($n = 41$; microadenoma 92.7%) and EAS ($n = 4$) were included in the study. C-Hypo was diagnosed at T_0 in 8/45 (17.8%) patients (FT4 10.5 ± 1.6 pmol/l; FT3 4.0 ± 0.7 pmol/l; TSH: M $\pm$ SD 0.9 ± 0.6 mU/l). Compared to C-Hypo patients, patients without C-Hypo had higher FT4 levels (15.3 ± 2.6 pmol/l, $P < 0.001$) at T_0, whereas both TSH and FT3 concentrations were similar (TSH 1.3 ± 1.1 mU/l, $P = 0.56$; FT3 4.5 ± 1.0 pmol/l, $P = 0.45$). At T_1, 33/45 (73.3%) patients achieved remission of hypercortisolism and 12/45 (26.7%) were persistently hypercortisolemic. TSH concentrations increased significantly between T_0 and T_1 in cured patients (1.11 ± 0.63 vs 2.05 ± 1.35 mU/l, $P < 0.001$) but not in not-cured patients (1.89 ± 1.63 vs 1.84 ± 1.10 mU/l, $P = 0.78$). Similarly, FT3 significantly increased in cured patients only (4.31 ± 0.99 vs 5.47 ± 0.91 pmol/l, $P = 0.001$). No changes in FT4 concentrations were found between T_0 and T_1 in both cured and not-cured patients. Finally, a significant reduction in FT4/FT3 ratio was observed in cured patients (3.53 ± 0.81 vs 2.57 ± 0.72 pmol/l, $P = 0.002$). No significant changes were observed in thyroid function parameters in the further follow up in either cured (T_2 $n = 36$; T_3 n $= 40$) and not-cured patients (T_2 $n = 9$;T_3 $n = 5$).
Conclusions
Our data are consistent with an inverse correlation between hypercortisolism and thyroid function parameters before and after therapeutic control. The observed different behavior in FT3 and FT4 levels following remission of hypercortisolism may be related to recovery of the inhibitory effect of hypercortisolism on deiodinase activity.

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PS2-11-02

Resistance to thyroid hormone alpha: outcomes of twelve years of thyroxine therapy

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Objectives
In 2011, we described the first case of Resistance to Thyroid Hormone due to a mutation in thyroid hormone receptor a (RTHα) in a six year old child with features of congenital hypothyroidism but near-normal thyroid function tests. Here, we report outcomes following twelve years of thyroxine therapy in this patient.
Methods
Colonic contractility, intestinal transit time, growth, resting energy expenditure, heart rate and biochemical parameters were measured serially during thyroxine treatment. Neurologic, cognitive and neuroimaging phenotypes at age 8 and 17yrs were compared.
Results
Following thyroxine therapy, delayed intestinal transit time (>72hrs) normalised, with absent colonic contractile activity being restored. Short stature has significantly improved (height – 3.0 SDS at age 6yrs vs – 0.6 SDS at age 18yrs), with greatest change in lower segmental height (- 3.0 SDS to -1.0 SDS). Thyroxine therapy is required in high (3.8 mg/kg) dosage to normalise resting energy expenditure (baseline $<2^{nd}$ centile; currently 25-50^{th} centile), but biochemical hyperthyroidism (TSH <0.03mU/l, FT4 54 pmol/l (RR 10-21), FT3 21 pmol/l (RR 3.5-6.9) has not raised serum sex hormone binding globulin levels (baseline 146 nmol/l (RR 40-140); currently 118 nmol/l) or average heart rate (2011: 83 bpm; 2023: 78 bpm). Deficits in visual perception, visuo-motor integration, speed of information processing and motor coordination (all $< 1^{st}$ centile) persist. Previous localised reductions in density of white matter tracts have resolved; changes in brain volume (including previous cerebellar involution) are being assessed.
Conclusions
In childhood RTHα, thyroxine therapy to normalise metabolic rate remedies growth retardation and slow intestinal transit. Ongoing educational support, targeted at overcoming persistent neurocognitive deficits, may enable the patient to achieve her full potential.

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PS2-11-03

Evaluation of advanced end glycation products (AGES), their solube receptors (SRAGE) and the components of oxidative stress in patients with hashimoto's thyroiditis on levothyroxine substitution

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Background
Advanced glycation end products (AGEs) are heterogenous group of irreversible chemical moieties originated from non-enzymatic glycation and oxidation of proteins, nucleic acids, and lipids. The engagement of AGEs with their chief cellular receptor (RAGE) activates signaling pathways contributing to the progression of chronic diseases like autoimmune thyroiditis, type 2 diabetes mellitus and its complications. Soluble RAGE (sRAGE) prevents AGE-RAGE

interaction in a competitive manner. Paraoxonase 1 (PON1) is an antioxidant enzyme with reduced activity in several autoimmune diseases.
Subjects and Methods
We investigated the association between serum AGE, sRAGE and paraoxonase-1, aryl esterase activity (ARE); and thyroid function in 73 Hashimoto's thyroiditis patients (HT) on levothyroxine (LT4) substitution, and in 83 age, BMI and gender-matched healthy controls. The serum AGEs levels were determined by autofluorescence on a multi-mode microplate reader, and the serum sRAGE levels by ELISA method. Serum PON1 paraoxonase and aryl esterase activity were detected spectrophotometrically.
Results
Mean AGE level was lower (10.71 vs 11.45 AU/μg protein; $P = 0.046$), while mean sRAGE level was higher (923 vs 755 pg/mL; $P < 0.0005$) in the serum of HT patients than the controls. AGE correlated with age, while sRAGE correlated negatively with BMI in both groups. We found negative correlation between AGE and fT3 levels (r=-0.32; $P = 0.006$) and sRAGE and TSH levels (r=-0.27; $P = 0.022$) in HT patients, while we failed to find association between AGE, sRAGE and parameters of thyroid function in the control group. Among patients AGE and RAGE levels showed no correlation with paraoxonase or aryl esterase activity of PON1.
Conclusion
According to our results in HT patients lower TSH and higher fT3 levels within the reference range is accompanied by a favourable AGE/RAGE balance. The levels of AGE and RAGE seem to be not associated with PON1 activity in LT4-treated HT patients. Further investigations are needed to confirm these results.

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PS2-11-04

Behavior of thyroid function tests in a brazilian elderly population using big data

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Behavior of thyroid function tests in a Brazilian elderly population using Big Data
Introduction
Interpretation of thyroid function data has changed over the last decades with several groups demonstrating changing in the thyroid axis with aging, particularly with a progressive increase in age-related TSH. With the proliferation of studies with large datasets, termed Big Data, sample sizes are no longer a challenge, and the possibility of using clinical laboratory databases to evaluate this population becomes a practical and innovative solution.
Objetive
The aim of the present study is to determine the behavior of TSH and free T4 (fT4) levels (in two different methods) for a population over 60 years old using the database of thyroid function tests from Fleury Laboratory in Brazil.
Methods
Data from 8.694.807 blood samples were retrospectively analyzed and filtered first for the TSH analysis using concentration within the reference values of free T4 (fT4), negative anti-thyroid antibodies and the absence of medication use. Thereafter, the same sample was analyzed for two different methods of fT4 (fT4a-Roche Diagnostic and fT4b-Beckman Coulter). The statistical analyzes were performed using R software. Wilcoxon / Kruskal-Wallis test was used to compare concentrations of TSH among two age groups, from 18 to 59 years old (under-60), and over 60 up to 107 years old (over-60). For the FT4 analysis, reference values for each group in each method were obtained through bootstrapping. Results From the initial group, 42.477 TSH samples were selected to be studied. TSH levels was similar in both sexes, but with noticeably difference between the age-groups increasing with age in the 95th upper limit: 6.86 (60-69 years), 7.92 (70-79) and 10.46 mUI/l (over 80 years). For fT4a, 10.038 samples and for fT4b, 658.267 samples were analyzed, and an increase in the levels of fT4 were observed between the age groups, raising from 1.5 ng/dL in the group 18-59 years-old to 1.82 ng/dL in the group over 80 years old for fT4a and from 1.0 ng/dL to 1.4 ng/dL for fT4b for the same age groups.
Conclusions
Increase of both TSH and fT4 with age is well documented in literature and this large database analyzed through big data techniques was able to identifies the same phenomenon in the Brazilian population. This data could be helpful to determine age specific thyroid function tests values that will improve diagnosis of thyroid disease in elderly patients and possibly avoid overdiagnosis of subclinical hypothyroidism in this population.

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PS2-11-05

Sensitivity to thyroid hormones and cardiometabolic risk in euthyroid obese children: A cross-sectional study

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Background
The typical biochemical phenotype related to obesity, that is high serum TSH within normal range, low/normal free thyroxine (FT4) and increased free triiodothyronine (FT3) levels, can be interpreted as a resistance to thyroid hormones. It is unclear the role played by thyroid hormones in the pathogenesis of metabolic derangement associated with obesity.
Aim
To investigate the association between thyroid hormones sensitivity and cardiometabolic risk factors in a cohort of euthyroid obese youths.
Material and Methods
This is a single-center, cross-sectional, observational study on children with euthyroid obesity. Each patient underwent clinical and auxological examination and laboratory workup including an Oral Glucose Tolerance Test (OGTT) and the measurement of serum TSH, FT4, FT3 and lipid profile. We measured the parameters representing central and peripheral sensitivities to thyroid hormones (Thyroid Feedback Quantile-based Index (TFQI), TSH Index (TSHI), Thyrotroph Thyroxine Resistance Index (TT4RI), Parametric Thyroid Feedback Quantile-based Index (PTFQI) and FT3/FT4 ratio, respectively), and we compared them in different subgroups of patients according to the TSH level, the presence/absence of insulin resistance and the severity of obesity; finally, we evaluated the association with some cardiometabolic risk factors.
Results
Four hundred ninety-one Caucasian euthyroid obese children and adolescents (age 9.93 ± 2.90) were recruited. Two hundred twenty-five subjects (45.8%) had a high-normal TSH level (TSH 2.3-5.0 mU/l), 315 subjects (64.2%) were severe obese (BMI standard deviation (SD) > 2.5 according to the WHO reference). Two hundred sixty-one subjects (53.1%) had insulin resistance defined by HOMA-IR > 2.5 in prepubertal children and > 4 in pubertal ones. Severe obese children as well as subjects with high-normal TSH had higher FT3/FT4 ratio values comparing with those with BMI < 2.5 SD and with low-normal TSH values, respectively. There were no differences in indices of thyroid hormones sensitivity between children with insulin resistance and those normoinsulinemic. On regression analysis, BMI-SD was positively associated with FT3/FT4 ratio values (B = 2.202, $P < 0.001$); area under the glucose curve and area under the insulin curve were positively associated with TT4RI (B = 1.110, $P = 0.034$; B = 7.670, $P = 0.001$ respectively); HDL values was negatively associated with TSHI values (B = -9.140, $P = 0.005$).
Conclusions
Higher values in resistance to thyroid hormones indices are associated with an unfavorable metabolic phenotype related to obesity. This evidence could suggest the potential role of sensitivity to thyroid hormones in the development of metabolic diseases.

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PS2-11-06

Thyroid disorders in the faroe islands: incidence of hyperthyroidism, hypothyroidism, and structural abnormalities

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Objectives
Iodine intake affects the risk of thyroid disorders. This study aimed to calculate the overall incidence of thyroid dysfunctions and structural abnormalities in the Faroe Islands and to describe the relation to sex and age.
Methods
We performed a nationwide, register-based study covering all 54,000 inhabitants of the Faroe Islands between 2006 and 2018. Cases were identified and classified by thyroid dysfunction using redeemed prescriptions of thyroid medication. We used a grace period of 19 months (2004-2006) to prevent recurrences of previous thyroid prescriptions. Structural abnormalities were diagnosed using ultrasonic examinations and thyroid scintigraphy available from 2008 to 2018. A patient chart review by a senior endocrinologist consultant confirmed all cases. Thyroid test results were available from all patients to support the classification of incident cases. ICD-10 diagnosis supported the diagnosis when available.
Results
We identified 1,152 individuals newly diagnosed with thyroid disease from 2006-2018, of which 990 (86%) cases received thyroid medication. The incidence of hypothyroidism was 112 per 100,000 person-years with a female:male ratio of 3:1, and 82% hosted a thyroid-peroxidase-autoantibody. The incidence of hypothyroidism increased with age in both women and men, and it decreased between 2008 and 2018 from 99 to 62 per 100,000 person-years ($P < 0.001$). The incidence of hyperthyroidism was 55 per 100,000 person-years with a female:male ratio of 3:1. Graves' disease was the most frequent subtype of hyperthyroidism (49%), followed by multinodular toxic goitre (17%). Additionally, 11% were categorised as TSH-Receptor-Antibodies positive mixed type. Atoxic structural abnormalities (goitre, nodules, and cysts) were identified in 27 per 100,000 person-years, with a female-male ratio of 6:1. The occurrence of structural abnormalities was relatively stable throughout the study period.
Conclusions
A relatively high incidence of autoimmune thyroid disease was seen in the Faroese population. Results suggest that the pattern of thyroid disease is changing from that of iodine replete to iodine-deficient populations. The improved insight into the patterns and trends supports the work towards better care for those affected by thyroid disease. Our evaluation warrants continuous monitoring of thyroid disease occurrence among populations in the North Atlantic.

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PS2-11-07

Abstract withdrawn

PS2-11-08

Strange changes in thyroid hormone metabolism in post-covid patients in ajara

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Background
The pandemic has led to the development of strange and inexplicable disorders in various organs and systems, which do not fit into the existing standard of diagnosis and treatment of the disease. This was especially reflected in the metabolism of the thyroid gland. The aim of the study was to study the metabolism and changes of thyroid hormones in post-covid patients. (The study includes the results of two clinics)
Materials and Methods
In the post-covid period, from January 2021 to December 2022, 450 patients were examined. Normal age is from 18 to 65 years. 350 of them are women and 100 are men. In 47 cases, strange disorders of the metabolism of thyroid hormones were detected. These patients were separated into a new group. Demographic data of patients: age, gender, diagnosis. The level of TSH, Ft4, anti-TSH receptors was also evaluated.
Results and discussion
The data of 47 primary patients were studied within the framework of the study. Average 18 to 55 years old, 18 men and 36 women. Ultrasound, all patients had shown thyroid volume normal or hypoplasia, without structural changes. Covid-19 were infected with all of them and had been vaccinated with various vaccines. TSH of patients ranged from 0.1 to 1.3 (norm 0.5 to 5.0 mIU/l) Ft4 to 0.9 to 1.2 (0.7 to 1.9 ng/dL). Anti-TSHR —— TRAb: 1.78-1.89 (norm < 1.75 IU/l)
Conclusion
Research questions:
1. Is this the real Graves?
2. Is it the impact of covid?
3. Should antithyroid treatment be prescribed?

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PS2-11-09

Thyroid dysfunctions in covid-19 patients: impact on in-hospital outcomes and long-covid symptoms

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Context
A variety of thyroid disorders have been documented in COVID-19 patients, including non-thyroidal illness syndrome (NTIS), subacute thyroiditis (SAT) and thyrotoxicosis.
Objectives
To investigate the relationship between thyroid dysfunctions observed during hospitalisation and COVID-19-related morbidity and mortality.
Study design and setting
Prospective cohort study on patients admitted in a tertiary hospital for COVID-19 pneumonia. Thyroid function tests (TFTs) and thyroid autoantibodies were assessed during hospitalisation and 4 months after discharge (FU1).
Patients and Methods
We enrolled 376 patients between March 2020 and June 2021, including 121 subjects requiring intensive care unit (ICU). Sixty-eight and 13 patients were excluded because they were affected with thyroid diseases or were taking amiodarone.
Results
None of the 295 patients included in the study had subacute thyroiditis during hospitalisation. An undiagnosed primary hypothyroidism was found in four patients (1.3%), two of them with positive TPO-Ab. A transient reduction of TSH, fT3 and fT4 levels compatible with NTIS was found in 62 (21%), 67 (23%) and 14 (5%) patients, respectively. Treatment with steroids during or before the admission did not significantly influence these findings. Thirty-seven out of 295 (13%) patients died during hospitalisation. Risk factors for in-hospital mortality were age > 65, obesity, history of cardiac disease, severe ARDS, disseminated intravascular coagulation, cardiac complications, coinfections, liver dysfunctions, low T4 and low T3 levels ($P < 0.05$), but not low TSH levels. Conversely, age > 65, history of cardiac diseases or Parkinson's disease, severe ARDS requiring intubation, coinfections and low T4 were risk factors for decreased patients' autonomy after hospitalisation. After discharge 104/258

(40%) of participants decided to withdraw from the study. At FU1, the remaining 154 patients had normal TFTs, except two men with borderline high TSH (<5 mU/l) and negative TPO- or Tg-Ab. TRAb were negative in all patients. None of patients with negative thyroid autoantibodies at admission developed thyroid autoimmunity at FU1. Long-COVID symptoms including fatigue, dyspnea and palpitations, cognitive dysfunctions, depression, balance instability, taste and smell dysfunctions, hair loss were reported by 88/154 (57%) patients at FU1. Interestingly, age > 65 years and low TSH during admission, but not low T3 or T4 were significantly associated with long-covid symptoms such as asthenia and muscular weakness ($P = 0.012$ and 0.048), but not with neurological or cognitive impairment. Females reported symptoms of long-COVID more frequently than males ($P = 0.008$).

Conclusions

Biochemical finding in euthyroid patients with severe SARS-CoV 2 infections correlate with in-hospital outcomes and long-term consequences of COVID-19.

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Nodules 1

PS2-12-01

Radiofrequency vesus ethanol ablation for single-session treatment of benign cystic thyroid nodules: a short-term retrospective study

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Objective

This study aims to compare 1-month's efficacy and safety of single-session ethanol ablation and radiofrequency ablation for treating both purely cystic nodules and predominantly cystic thyroid nodules

Materials and Methods

This short-term retrospective study was approved by the Ethics Committee of the Institutional Review Board of Danang Family hospital, and written informed consent for procedures was obtained for all patients. 39 patients who presented with cystic thyroid nodules and met inclusion criteria were extracted from the computerized medical records. The internal fluid of cystic thyroid nodules was aspirated as much as possible. Ethanol ablation was performed using 18-gauge needles with 99.5% ethanol, and RFA used a cooled-electrode RFA system and 18-gauge internally cooled electrodes via the trans-isthmic approach, moving-shot technique. Nodule volume, therapeutic success rate, the largest diameter, thyroid function tests, and complications were evaluated and compared before and after treatment in each group

Results

Among 39 patients, 17 patients were undergone EA (mean age of 47.35 years; the proportion of female of 76.5%; purely thyroid cyst percentage of 41.4%) and 22 patients were undergone RFA (mean age of 46.63 years; the proportion of female of 86.4%; purely thyroid cyst percentage of 54.5%). Both treatment techniques showed a significant reduction of the largest diameter and nodule volume ($P < 0.05$) without complications. RFA reduced nodule volume and the largest nodule size greater than EA treatment at 1-month post-ablation ($P < 0.05$). In addition, the therapeutic success rate in the RFA group was higher than in the EA group.

Conclusion

Both RFA and EA treatment with single-session confirm the efficacy and safety for cystic thyroid nodules at 1-month follow-up, RFA reduced greater in nodule volume and the largest nodule size than the EA treatment. Thus, the therapeutic success rate in the RFA group was higher than in the EA group.

Keywords

Radiofrequency ablation, ethanol ablation, cystic *thyroid nodules, efficacy and safety*

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PS2-12-02

Efficacy and safety of single-session radiofrequency ablation in treating benign thyroid nodules: A short-term prospective study

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Objective

The aims of this study are to evaluate the safety and efficacy of RFA in the treatment of benign thyroid nodule(s) and to find independent factors related to the volume reduction rate of the nodule(s).

Materials and methods

This short-term prospective study from a single medical center was conducted on 93 benign thyroid nodules in 93 patients treated with RFA. Two basic techniques were used: the trans-isthmic approach, moving-shot technique. Clinical and ultrasonography examinations were performed at 1; 3 months follow-up after the treatment session. Primary outcomes included volume reduction ratio (VRR) at 1 month and 3 months follow-ups; Secondary outcomes were therapeutic success rate and complications. Multiple linear regression analysis was used to determine independent factors associated with VRR.

Results

A final sample of 78 patients with 78 nodules, given participant rate 83.8%, (included 60 solid nodules, 16 predominantly cystic nodules, and 2 thyroid cysts) was followed for 3 months. The mean volume reduction ratio was 41.47% and 64.72% after 1 month and 3 months follow-ups, respectively. The therapeutic success rate was 30.8% at 1 month and 84.6% at 3-month follow-ups. Symptom score and cosmetic score improved significantly. There was no change in thyroid function tests. Two minor complications (transient voice change) were found. The multiple linear regression analysis showed that the internal component of the nodules significantly related to the VRR during the 3 months follow-up ($\beta = 23.00$; 95%CI (7.59 - 38.45)).

Conclusion

RFA was demonstrated as a safe and effective option for benign thyroid nodules treatment. It can be used as an alternative treatment with encouraging results.

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PS2-12-03

Malignancy risk stratification and subcategorization of intermediate suspicion thyroid nodules: A retrospective multicenter validation study

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Objective

To determine whether the Korean-Thyroid Imaging Reporting and Data System (K-TIRADS) 4 nodules can be subcategorized by ultrasonography (US)-based stratification of malignancy risk, and to evaluate the diagnostic performance of the modified biopsy criterion based on the subcategorization of the K-TIRADS 4 category in a multicenter cohort.

Materials and Methods

A total of 1,541 K-TIRADS 4 nodules (≥ 1 cm) with final diagnoses were included in the study. The association of US features with malignancy was assessed in the overall K-TIRADS 4 nodules and each subgroup nodule. The US criteria for subcategorization of the K-TIRADS 4 nodules were developed based on the US features, which significantly increased the malignancy risk among the K-TIRADS 4 nodules. The diagnostic performance of biopsy criterion 1 (size cut-off of 1 cm), biopsy criterion 2 (size cut-off of 1.5 cm), and modified biopsy criterion 3 (size cut-off of 1 cm for K-TIRADS 4B and 1.5 cm for K-TIRADS 4A) were evaluated in the K-TIRADS 4 nodules.

Results

US features of marked hypoechogenicity, macrocalcification, and the presence of two or three suspicious US feature significantly increased the malignancy risk of the K-TIRADS 4 nodules. The K-TIRADS 4 nodules could be subcategorized as K-TIRADS 4 B (higher risk) and K-TIRADS 4A (lower risk) according to the US criteria. The modified biopsy criterion based on the subcategorization of K-TIRADS 4 nodules reduced the unnecessary biopsy rate for malignancy by 22.5% compared with criterion 1 ($P < 0.001$) and increased the sensitivity by 29.6% compared with criterion 2 ($P < 0.001$).

Conclusion

The K-TIRADS 4 nodules were subcategorized as K-TIRADS 4B (higher risk) and K-TIRADS 4A (lower risk) based on US features and increasing malignancy risk. Modified biopsy criterion 3 can be complementarily used for biopsy criterion 2 in patients who require higher diagnostic sensitivity for malignancy.

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PS2-12-04

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: What we have to know

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The inclusion of the less aggressive follicular form of papillary thyroid cancer (PTC) is associated with an increase in the incidence of the condition, with the follicular variant of PTC being the most common of all variants. The majority of individuals with the encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) are treated as though they have classic thyroid cancer, despite the availability of mounting evidence to contradict the aforementioned. According to numerous research, a certain type of noninvasive- EFVPTC (NI-EFVPTC) demonstrated poor histopathologic diagnostic reproducibility and has received aggressive treatment similar to that of a classical thyroid neoplasm. Therefore, to replace the term NIEFVPC, a new nomenclature for these tumors, called "noninvasive follicular thyroid neoplasm with papillary-like nuclear characteristics" (NIFTP), was introduced in the year 2016. The present paper explores this recently introduced terminology, clinical, histologic, and molecular features, and diagnostic criteria.

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PS2-12-05

Diagnosis of malignany in surgery after rf ablation of benign thyroid nodule

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Background
Some regrowing nodules after radiofrequency ablation (RFA) of symptomatic large benign thyroid nodules are revealed as malignancies in surgery. The aim of the study was to assess the ultrasound (US) characteristic of thyroid nodules diagnosed as cancer later, the predictive factors for cancer after RFA, and the prevention methods for these cancers to avoid RFA.
Materials and Methods
The medical records of 22 thyroid nodules with 18 patients who underwent RFA for debulking symptomatic benign thyroid nodules between 2008 and 2016 and followed by surgery were reviewed. We investigated pre-RFA characteristics of thyroid nodules and change in follow-up after RFA and final surgical pathology.
Results
Final malignancies were confirmed in seven of 22 RFA-treated nodules. Pre-RFA mean maximal diameter was significantly greater in malignant nodules than benign nodules (3.89 ± 0.98 cm vs 5.23 ± 1.52 cm, $P = 0.04$). There was no difference in regrowth interval between benign and malignant nodules (56.00 ± 36.00 months vs 47.14 ± 33.66 months, $P = 0.48$). Volume reduction rate at 12-month was lower in malignant nodules than benign nodules ($51.16 \pm 13.81\%$ vs $73.68 \pm 20.15\%$, $P = 0.08$). Pre-RFA benign confirmation of all seven malignant nodules were used with two US-guided fine needle aspirations (FNA) except for one using US-guided core needle biopsy (CNB). Using CNB, all regrowing ablated nodules confirmed as malignancy after RFA were diagnosed as suspicious for follicular neoplasm. The histology of the malignant nodules in surgery after RFA was follicular thyroid carcinoma except for one follicular variant of papillary thyroid carcinoma.
Conclusion
Symptomatic large thyroid nodules confirmed as benign before RFA should be considered for false negative FNA, and the possibility of regrowth after RFA is high. When considering retreatment of regrowing nodules, reconfirmation with CNB prevents the diagnosis of cancer from being delayed.

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PS2-12-06

Assessment of an artificial intelligence-based decision support system in the thyroid nodule evaluation in clinical practice

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Objective
To evaluate the impact of a decision support system (DSS) based on artificial intelligence (AI) -KoiosDS- on ultrasound (US) image analysis and risk stratification in thyroid nodules.
Material and methods
Retrospective US study of all thyroid nodules with histologic (AP) result from June 2020 to December 2021. Diagnostic performance of US with ACR-TIRADS, by six endocrinologists and DSS, before and after the use of AI was evaluated.
Results
A total of 172 patients (83.1% women) with a mean age of 52.3 ± 15.3 years were evaluated. The maximum nodular diameter was 2.9 ± 1.2 cm, with 10.7% being malignant. 81.4% and 24.5% of the nodules classified by DSS as ACR-TIRADS 3 and 4, respectively, were reclassified into lower risk categories with AI When performing a ROC curve to assess the diagnostic performance of endocrinologists and DSS against the AP diagnosis, a mean increase in the area under the curve (AUC) after the use of AI was observed for endocrinologists (AUC = 0.730 vs. 0.790, $P < 0.001$) and IP (AUC = 0.696 vs. 0.735, $P < 0.001$). When evaluating the impact of AI on diagnostic accuracy, we observed an improvement in mean sensitivity (S) (82.75% vs. 88%), specificity (S) (35.25% vs. 50.25%), a high negative predictive value (NPV) (94.5% vs. 96.75%) and an increase in positive predictive value (PPV) (13.5% vs. 17.75%). When analyzing the degree of agreement in the US characteristics, we observed a mean increase in concordance with the use of AI in all ultrasound patterns, especially echogenicity (kappa 0.456 vs. 0.642; $P < 0.001$). As well as an improvement in the mean correlation between the endocrinologist's ACR TIRADS scores after the use of AI ($r = 0.678$ vs. 0.801, $P < 0.001$). When estimating the DSS as a learning tool for the endocrinologists in the first 25 image evaluated by the endocrinologist compared to the last 25, an improvement in the degree of agreement after using the AI was observed in the assessment of all the ultrasound features, particularly echogenicity (kappa 0.474 ± 0.244vs0.698 ± 0.111; $P < 0.001$).
Conclusion
The use of AI in an Endocrinology Department was associated with an overall improvement in the diagnostic ability of US, as well as an increase in S, E, NPV and PPV. AI reclassified more than half of the nodules with intermediate ACR TIRADS into lower risk categories. All US ACR-TIRADS patterns increased the degree of agreement and interindividual variability were reduced with the use of AI. AI proved to be a useful learning tool in the evaluation of thyroid nodule.

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PS2-12-07

A prospective study on a short course of lugol's solution in toxic nodular goiter

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Objective
Preoperative iodine therapy due to toxic nodular goiter (TNG) is discouraged as iodine may cause an aggravation of hyperthyroidism. In Graves' disease iodine has been used for a century but little data is available on iodine treatment in TNG. We aimed to examine if a short course of iodine treatment is safe to administer in TNG.
Method
20 patients with TNG with persistent subclinical to mild hyperthyroidism were included at our tertiary care center of Endocrinology. This was a non-randomized open label intervention without controls. All participants were treated with Lugol's solution 5 % (Potassium Iodide) 3 drops thrice daily p.o. for ten days, in total 603 mg iodine. Heart rate, TSH, free T4 (fT4) and free T3 (fT3) concentrations before (day 0) and after treatment (day 10) were measured. Thyroid hormone levels were also measured at two time points during the course of treatment to discover possible

exacerbation of hyperthyroidism. Heart rate and thyroid hormones before and after treatment were compared using the non-parametric Wilcoxon signed-rank test for paired data. Any possible adverse reaction was reported.
Results
Median age was 63.5 years, interquartile range (IQR) 56 – 68. Female to male ratio 19:1. Peripheral hormone levels decreased and TSH levels increased. Differences in TSH, fT4, fT3 levels were statistically significant. The difference in heart rate was not statistically significant. No exacerbations of hormone levels were noticed in any of the participants during treatment. Six participants (30 %) reported symptoms related or possibly related to treatment (gastrointestinal symptoms, headache). All symptoms were classified as mild and temporary. All participants completed the study although one ingested $<$ 80 % of the doses (77%).
Conclusions
In this prospective intervention study on toxic nodular goiter we found that a short course of Lugol's solution was safe to administer. The reported adverse reactions were mild and temporary. This indicates that Lugol's solution might be an option for preoperative treatment when antithyroid drugs are not tolerated.

Variable	Reference	Lugol day 0 Median (IQR)	Lugol day 10 Median (IQR)	*P*-value
Heart rate		72 (56 - 68)	73 (68 - 79)	0.11
TSH	0.3 - 4.2 mU/l	0.07 (0.02 - 0.2)	0.3 (0.15 - 0.6)	0.0002
Free T4	12 - 22 pmol/l	17 (15.5 - 19)	14 (12 - 15.5)	0.0003
Free T3	3.1 - 6.8 pmol/l	5.4 (5.1 - 5.9)	4.1 (3.8 - 4.5)	0.0002

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PS2-12-08

Practice of low risk papillary thyroid cancer treatment: Active surveillance vs immediate surgery

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Background
Active surveillance (AS) has been widely accepted as a safe option in the treatment of low risk papillary thyroid microcarcinoma (PTMC) in recent years on the basis that its prognosis is not inferior to immediate surgery. However, clinicians as well as patients are still hesitant in actually choosing AS over immediate OP as treatment. Our aim was to investigate the factors in choosing treatment options in low risk PTMC.
Method
Seoul National University Bundang hospital (SNUBH) is a participant of Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro) which started in 2016. Adults aged more than 18 years who visited SNUBH with newly diagnosed thyroid nodules between May 1, 2016 and October 5, 2018 were recruited (n =1923). Patents with papillary thyroid microcarcinoma 1 cm or less, with US guided fine needle aspiration (FNA) or Core needle biopsy (CNB) results of suspicious of malignancy or malignancy, Bethesda category V or VI were enrolled (n =901).
Results
692 patients (538 Female 77.7%) with low risk PTMCs with a median age of 43 years (range 18–80) were analyzed. Patients having Graves' disease requiring operation or RAI (n =1) or high risk features of suspected organ involvement (n =155), clinical or pathological Lymph node involvement or distant metastasis (64), or poorly differentiated histology or variant with poor prognosis (n =0) were excluded from analysis. AS was selected in 191 (27.6%) and OP in 501(72.4%) patients. There was no difference in the proportion of females in the AS and OP groups (74.3% vs 79.0% P = 0.184). The mean of the initial ultrasonic maximum diameter was 0.71 cm (range 0.2-1.0 cm, median 0.7 cm). The initial size of the nodules was larger in the OP group than in the AS group (mean, 0.72 cm vs 0.67 cm P = 0.000). The mean of the initial size of the nodules was larger in the 70s and 80s (n =11, 0.90 cm) compared to the rest of the age group showing, 10s to 20s(n =53): 0.73 cm, P = 0.179; 30s(n =199): 0.71 cm, P = 0.194; 40s(n =211): 0.70 cm, P = 0.210; 50s(n =160): 0.71 cm, P = 0.195; 60s(n =58): 0.70 cm, P = 0.216; (n =11): 0.90 cm). The older groups tended to select AS more than the younger groups, especially those over the age of 50 (24.0 % vs 34.9%, P = 0.002). 90.3% of the low-risk PTMC patients who were enrolled in MAeStro and 4.5% of those who were not chose AS.
Conclusion
AS was more easily selected when enrolled in the prospective study comparing between AS and immediate surgery in low-risk PTMC patients, MAeSTro. Multidisciplinary management through study enrollment was an important factor for the selection of AS.

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PS2-12-09

Pediatric patients with goiter and normal thyroid function: US findings related to underlying autoimmune thyroid diseases

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This study was conducted to investigate and compare thyroid ultrasonography (US) findings in pediatric patients with goiter and normal thyroid function with positive or negative thyroid autoimmunity. From 2000 to 2020, we reviewed initial thyroid US images in 33 autoimmune thyroid diseases (AITDs) patients and 52 non AITD patients. Our review of the images focused on thyroid parenchymal hypoechogenicity and heterogeneous echopattern subdivided into 2 groups according to severity: hypoechogenicity 1 and 2 (HO1 and HO2) and heterogeneity 1 and 2 (HE1 and HE2). HO1 and HE1 were observed more frequently in the non AITD group (86.5% and 42.3%, respectively), while HO2 and HE2 were observed more frequently in the AITDs group (36.4% and 81.8%, respectively). More patients in the AITDs group showed change of both US groups and thyroid function state within the follow-up periods than in non AITD group (33.3% and 5.77%, respectively). Pediatric patients with underlying AITDs showed more severe parenchyma hypoechogenicity and heterogeneous echopattern compared with non AITD patients with goiter and normal thyroid function.
Key words: ultrasonography, goiter, pediatric, thyroid function

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Surgery

PS2-13-01

Does presence of deranged thyroid hormone impact the post-surgery outcomes in the patients undergoing CABG procedure?

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Introduction
It is well established fact that the thyroid gland and heart have diverged from the same ancestral origin, thus have close metabolic relationship. Any alteration in the thyroid hormone profile, either hyper or hypo thyroid conditions may lead to manifestation of cardiac diseases. In routine clinical procedures abnormalities in the thyroid hormone levels were commonly observed in the cases of chronic heart failures.
Objective
To Evaluate and compare pre/intra/post-operative parameters of subjects with/-without thyroid undergoing CABG to study the impact of thyroid hormones on their post-operative outcomes.
Method
A tertiary care hospital-based study was planned to enroll the patients undergoing for the CABG. The subjects above the age of 18 years with Indian nationality were chosen for the study. The other inclusion criteria were subject undergoing CABG, able to give informed consent and free from other comorbid conditions including pregnancy. The study was approved by the Institutional Ethics Committee. Total 560 subjects were qualified for the study. Selected subjects were further divided into three groups (Hypothyroid, Hyperthyroid and Euthyroid) based on their thyroid hormone status after confirmation from practising endocrinologists. Their samples and data were collected and analysed using MS Excel and SPSS.
Results
The Euthyroid subject group has a mean value of 3 hours ICU stay which is less than the mean ICU stay of hypothyroid (5 hours) and hyperthyroid (4 hours). For the Euthyroid subjects average stay in the hospital was 10 days whereas for the group of subjects having thyroid, either hypothyroidism or hyperthyroidism the average length of stay in the hospital was for 12-14 days. Average ionotrope usage by Euthyroid group was 3.4 hrs whereas for hypothyroid and hyperthyroid group it was 3.8 hrs and 3.7 hrs respectively. Ventilator support needed by Euthyroid group was 16 hrs whereas for hypothyroid and hyperthyroid was 18 hrs.

Conclusion
The subjects groups without thyroid shows better post-operative outcomes as compared to the groups of subjects having altered thyroid status. Thyroidism, either hypothyroidism or hyperthyroidism impacts post-operative outcomes of subjects undergoing coronary artery bypasss surgery. Therefore, altered thyroid levels may be an indicator of poor outcomes post-surgery.

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PS2-13-02

Comparison of voice outcome according to the degree of thyroidectomy skin flap

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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 noiseto-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.

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PS2-13-03

Clinical application of pectoralis nerve block ii for flap dissection-related pain control after robotic transaxillary thyroidectomy: preliminary results of a randomized controlled trial

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Purpose
Few studies have examined the clinical utility of ultrasonography-guided pectoralis nerve block II (PECS II) during wide flap dissection of SP robot-assisted transaxillary thyroidectomy (SP-RATT). This study presents preliminary results of a randomized controlled trial.
Methods
A total of 48 adult patients (aged $\geq$ 20 years) who underwent elective SP-RATT (including lobectomy) or total thyroidectomy from November 2022 to February 2023 at Seoul St. Mary's Hospital (Seoul, Korea). The patients were divided into a block group (n =22) and no-block group (n =26). Pain was measured using a visual analog scale (VAS) at 4, 24, and discharge day after surgery, and the requirements for rescue painkillers in the post-anesthesia care unit and ward were recorded. The Korean version of quality of recovery-15 questionnaire (QoR-15) was used to assess quality of recovery after surgery.
Results
The demographic variables were comparable between the two groups. The block group had significantly lower VAS scores at 4 h postoperatively (3.0 $\pm$ 2.2 vs. 4.5 $\pm$ 2.3, $P = 0.024$). However, no significant group difference was observed after 24 h and at discharge day. The block group had lower VAS scores within 1 day of surgery than the no-block group, which experienced significant pain relief only after postoperative day 1. The block group required fewer painkillers in the post-anesthesia care unit than the no-block group. There was no statistically significant differences between the two groups in all items of the QoR-15K. However, the block group showed relatively higher scores in the pain item.
Conclusions
PECS II may serve as a new pain relief modality and valuable addition to the current multimodal analgesic strategy for patients undergoing SP-RATT.
Keywords
PECS II block, robotic surgery, transaxillary, thyroidectomy, visual analogue scale, randomized controlled trial

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PS2-13-04

Multifocality is not a risk factor for recurrence after thyroid lobectomy: A study of 1,684 patients with differentiated thyroid cancer

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Background
We evaluated the impact of the multifocality on post-lobectomy recurrence in patients with differentiated thyroid cancer (DTC).
Methods
We analyzed 1,684 patients with DTC who underwent thyroid lobectomy from 2008 to 2015 using logistic regression models to calculate the relative risk on post-lobectomy recurrence.
Results
Tumor diameter increased from 4.9 mm to 8.1 mm and the proportion of extrathyroidal extension (ETE) and multifocality progressively increased from 2008 to 2015 (2.1% to 24.3% and 4.2% to 22.8%: respectively). During the 88.6-month follow-up period, 67 (3.98%) recurrences and 2 (0.12%) deaths were observed. There were 269 (16.0%) multifocal DTC cases; 265 multifocal papillary thyroid cancer (PTC) and 4 collision tumors. There was no significant difference between the multifocal and unifocal groups in terms of the proportion of recurrences (5.2% vs. 3.7%, $P = 0.262$) and distant metastasis (0.4% vs. 0.1%). Logistic regression analysis revealed a positive nodal ratio (PNR) above 42.0% (OR=3.56) to be the unique and potent risk factor for DTC recurrence. Conversely, tumor diameter greater than 7.5 mm, age $<$ 42.5 years, ETE, and multifocality were not risk factors. A PNR above 42.0% and N1a stage were potent risk factors on the Kaplan-Meier analysis. Tumor diameter greater than 7.5mm and age $<$ 42.5 years were equally significant risk factors. Contrariwise, multifocality and ETE were proven to not be risk factors for DTC recurrence after thyroid lobectomy (Log-rank $P = 0.099$ and $P = 0.126$, respectively).
Conclusion
Multifocality is not a risk factor for DTC recurrence after thyroid lobectomy and should not be considered an indication for immediate completion or total thyroidectomy.

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PS2-13-05

Survey results comparing transoral thyroidecotmy to open thyroidectomy

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Introdcution
The number of patients who undergo transoral thyroidectomy has increased with the recent progress in thyroid surgery techniques and increasing number of

patients concerned about cosmetic effects. This study aimed to compare transoral endoscopic thyroidectomy survey results with those of open thyroidectomy and to determine whether any differences existed between the two groups.
Methods
One hundred patients who underwent thyroidectomy performed by a single surgeon at Gangnam Severance Hospital (Seoul, South Korea) were enrolled. Before and after surgery, the Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, 15-Item Quality of Recovery, and Post-traumatic Stress Disorder Checklist surveys were administered. Patients with insufficient survey data were excluded
Results
No differences existed between the transoral and conventional thyroidectomy groups in the scale scores, except for the HADS-Depression survey scores. The Hospital Anxiety and Depression Scale-Depression scores of the transoral endoscopic thyroidectomy and open thyroidectomy groups were 4.22 ± 0.781 and 5.52 ± 0.84 (P value $<.05$ (.039)). In the multivariable analysis adjusted for age and weight differences between the conventional and transoral groups, no differences existed between the groups in the survey scores, including the Hospital Anxiety and Depression Scale-Depression scores.
Conclusions
No differences existed between the transoral endoscopic thyroidectomy and open thyroidectomy groups in the survey scores, except for the Hospital Anxiety and Depression Scale-Depression scores. Thus, postoperative stress about pain and the degree of recovery that patients feel after surgery were similar between the transoral endoscopic thyroidectomy and open thyroidectomy groups.

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PS2-13-06

Prospective implementation of thyroid lobectomy recommendations and thyrospec molecular testing for bethesda III and IV nodules and impact on surgery

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Objectives
In May 2016, the local thyroid cancer tumor group proposed and adopted specific thyroid lobectomy recommendations based on the 2015 ATA guidelines. ThyroSPEC molecular testing was introduced for all Bethesda III and IV lesions in August 2020. The goal of this study was to evaluate the implementation of the ATA lobectomy guidelines and the introduction of ThyroSPEC molecular testing on rates of upfront total thyroidectomy (TTx), diagnostic lobectomy for Bethesda I-IV (DxL), therapeutic lobectomy for Bethesda V-VI or high-risk/malignant molecular mutation (TxL), and completion thyroidectomy (CTx) by reviewing data from a tertiary thyroid cancer referral setting.
Methods
Data were collected from a prospective thyroid cancer database from April 2017 to October 2022. Patients with non-differentiated thyroid cancer, those who underwent subtotal thyroidectomy, no surgery, or who had undergone surgery at an outside center were excluded. Patients were classified as having TTx, DxL, TxL, or CTx.
Results
A total of 724 differentiated thyroid cancer patients were included in this study. There were 531 (73%) TTx and 193 (27%) lobectomies as the initial surgery, with 107 (55%) patients undergoing DxL, and 86 (45%) patients undergoing TxL. CTx was most often indicated due to postoperative findings of ATA intermediate or high recurrence risk thyroid cancer. 56/107 (52%) of the DxL patients underwent CTx, with 39/63 (62%) occurring pre-ThyroSPEC and 17/44 (39%) occurring post-ThyroSPEC ($P < 0.05$). Of the TxL, 26/86 (30%) underwent CTx, with a similar rate pre- and post-ThyroSPEC (29% and 32%, $P = 0.788$). Meanwhile, there was an increase in upfront TTx from 28% pre-ThyroSPEC to 47% post-ThyroSPEC ($P < 0.05$) for Bethesda III and IV nodules, with 12 patients with Bethesda III or IV undergoing upfront TTx due to malignant molecular markers or high-risk mutations in the post-ThyroSPEC group. There was also an increase in initial lobectomies (DxL and TxL) that did not require CTx from 14% to 22% ($P < 0.05$) pre- and post-ThyroSPEC.
Conclusions
The introduction of specific thyroid lobectomy recommendations and ThyroSPEC molecular testing resulted in an increase in upfront total thyroidectomies due to malignant molecular markers or high-risk mutations and a decrease in patients requiring completion thyroidectomy post lobectomy. This translates to more patients receiving an appropriate diagnostic or therapeutic surgery upfront and fewer second operations for completion thyroidectomy. This decreases the cost to the patient in terms of anxiety, time off work, and need for recurrent surgery, as well as cost to the health care system.

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PS2-13-07

Abstract withdrawn

PS2-13-08

The effect of surgery extent on vocal alteration following thyroidectomy

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Objectives
Vocal alteration can occur following thyroidectomy with or without a damage of laryngeal nerves. Multiple factors can increase the risk of vocal alteration. We aim to determine the impact of surgery extent on vocal symptoms and endoscopic and acoustic findings.
Materials and methods
In this prospective study, we evaluated the vocal alteration in patients undergoing a partial (PT) or total thyroidectomy (TT). We performed a vocal assessment pre-operatively and at one-month post-operatively; it was based on vocal symptoms, Voice Handicap Index 10 score (VHI-10), laryngeal endoscopy and acoustic parameters. We compared vocal assessment results in the TT and PT groups. We also determined if central neck dissection (CND) was associated to an increased vocal alteration.
Results
We included 51 patients in the study. They underwent a TT or PT in 50.98% and 49.02% respectively. Surgery included a CND in 11 patients either bilateral (17,65%) or unilateral (3,92%). The presence of a vocal fatigue was significantly more encountered in the TT group. The value of VHI-10 score, jitter and shimmer were significantly more increased in the TT group while the Harmonic to noise ratio (HNR) was significantly more decreased in the TT group (table 1). We did not note a significant association between CND and the following parameters: VHI-10 score, vocal fatigue, dysphonia and recurrent laryngeal nerve palsy, jitter, shimmer, mean fundamental frequency (F0) and HNR alteration.
Conclusion
TT was associated to a worse vocal outcome in comparison to PT with significantly higher jitter, shimmer and lower HNR values. VHI10 score was also slightly more altered following Total thyroidectomy but without causing a significant handicap. CNT did not affect vocal outcomes.

Table 1: Vocal alteration following partial and total thyroidectomies

Vocal assessment method	Partial thyroidectomy ($n = 26$)	Total thyroidectomy ($n = 25$)	P value
VHI10 score	0 [0.14]	2 [0.28]	**0,049*** **
Vocal symptoms			
- Dysphonia	21.05%	36.84%	0,238*
- Vocal fatigue	11.76%	52.63%	**0,005****
Endoscopic findings			
- RLN palsy	5.26%	11.11%	0,5*
Acoustic parameters			
- F0	243.31 [152.8;33.94]	214.83 [130.94;361.48]	0.509****
- Jitter	0.011 [0,0041;0,031]	0,017 [0,0028;0,06]	**0.028*****
- Shimmer	0.1 [0.05;0.19]	0.13 [0.065;0.23]	**0.038*****
- HNR	14.37 [6.19;21.74]	9.51 [3.95;15.5]	0.001****

VHI10(Voice Handicap Index10), F0(fundamental frequency), RLN(recurrent laryngeal nerve) Statistical test: *Fisher, **chi-square, ***Student,****Mann-Whiteny

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PS2-13-09

Body mass index and postoperative morbidity after thyroid surgery: findings from a large retrospective cohort study

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Background
Obesity is a major public health issue frequently associated with increased complication rates after elective general surgery. Previous reports on complications after thyroid surgery in obese patients were performed on selected cohorts. In this study, we sought to explore the relationship between Body Mass Index (BMI) and postoperative morbidity after thyroid surgery in a large cohort of consecutive patients.
Materials and Methods
A single-centre retrospective analysis was conducted on patients who underwent total or partial thyroidectomy with or without central or lateral compartment dissection at a tertiary referral endocrine surgery unit between January 1st 2020 and October 31st 2021. Clinical and postoperative data was collected including postoperative haemorrhage (PH), severe hypocalcemia (<7,5 mg/dL at day 1) (PSH), recurrent laryngeal nerve palsy (RLNP) and wound infection (WI) rates along with surgery duration (SD) and postoperative stay (POS), which were treated as outcome measures. Univariate and multivariate linear and logistic regression analyses were performed and results were adjusted for confounders relevant to each outcome measure.
Results
A total of 656 consecutive patients were included (77,7% male; 22,3% female), with a median BMI of 24,8 Kg/m2 [IQR 22,3 – 27,5]. The BMI distribution among patients was 51,8% lower than 25 kg/m2, 34,3% between 25 and 30 kg/m2 and 13,9% above 30 kg/m2. Total thyroidectomy was performed in 90,1% of cases while central and lateral compartment dissection was performed on 11,4% and 2% of patients, respectively. Thirtyone patients (4,7%) underwent additional parathyroidectomy for associated primary hyperparathyroidism. Postoperative hemorrhage PH, PSH, RLNP, and WI rates were 0,6%, 19,5%, 3,8%, and 1,2%, respectively, with a median POS of 2 days [IQR: 2-2]. When adjusted for relevant confounders BMI was not found to be a predictor of PH, RLNP, WI, SD and POS (all $p > 0.05$). However, when adjusted for central compartment dissection, thyroidectomy extension, age, gender, parathyroidectomy, Graves' disease and chronic thyroiditis, BMI was found to be an independent predictor of PSH (OR 0,93; $P = 0.06$).
Conclusions
This study found that higher BMI values are not associated with an increased rate of major complications after thyroid surgery. Additionally, higher BMI values are independently associated with decreased rates of PSH. The protective role of BMI should be thoroughly investigated due to its potential value in tailoring preoperative calcium and vitamin D supplementation.

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PS2-13-10

Transoral robotic thyroidectomy for thyroid diseases - lessons learned from a 1000 consecutive procedures

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Background
To evaluate the technical feasibility, effectiveness, and safety of transoral robotic thyroidectomy (TORT), using the da Vinci system through analysis of our series of 1000 consecutive patients.
Method
A review of a prospectively designed database at our institute from September 2012 to February 2022 revealed a series of 1000 consecutive TORT patients with preoperative diagnosis of various thyroid diseases. Clinicopathologic characteristics and surgical outcomes were analyzed.
Results
All except one operation were performed successfully without open or laparoscopic conversion. There were 895 hemithyroidectomies, 8 isthmusectomies, and 97 total thyroidectomies. The mean total operation time and console time were 179.03 ± 42.81 and 112.40 ± 37.07 minutes, respectively. There were 45 postoperative complication events including infection, mental nerve injury, flap injury, transient vocal cord palsy, delayed hematoma, and oral commissure tearing. The mean duration of hospitalization for patients after the operation was 2.6 ± 0.9 days. The average tumor size was 0.88 ± 0.65 cm for malignant tumor and 2.65 ± 0.92 cm for benign nodules, while the average number of retrieved lymph nodes were 5.49 ± 4.1.
Conclusion
This study is the largest single-institution experience to demonstrate that TORT can be applied safely and effectively for patients with thyroid disease.

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Case Reports 1

PS2-14-01

A case of congenital "hypothyroidism"

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Introduction
Neonatal screening for congenital hypothyroidism is considered a major cornerstone in making early diagnosis and starting therapy in neonates. This is a very important step to prevent the consequences of untreated hypothyroidism including mental retardation and developmental delay. Neonatal screening is usually conducted by screening the level of T4 with or without TSH level. Confirming the diagnosis of hypothyroidism is a very important step before starting therapy.
The case
A 6-week-old male presented for evaluation of congenital hypothyroidism. He was diagnosed by neonatal State screen for a reported low T4 and was started on Levothyroxine therapy of 10 micrograms po daily at the age of two weeks. He has been irritable and had diarrhea in the past ten days which persisted despite changing the milk formula. His physical examination revealed tachycardia and brisk reflexes. Laboratory obtained during the visit findings showed: TSH 0.003 uIU/ml (0.6 -3.75 uU/ml): 0.003 mIU/l T4 5.1 ug/dl (4.5-12 ug/dl): 65.64 nmol/l Free T4 3.2 ng/dl (0.8- 1.9 ng/dl): 41.2 pmol/l Based on clinical presentation and laboratory results, thyroxine-binding globulin (TBG) deficiency was suspected and confirmed by an additional laboratory test, the Levothyroxine therapy was discontinued, the parents were educated about the diagnosis, and repeated thyroid function tests obtained one month later revealed normal TSH and Free T4.
Conclusion
Positive neonatal screening tests need to be confirmed with repeated laboratory tests before starting therapy. Making the correct diagnosis of neonatal congenital hypothyroidism is a very important step too. Understanding the differential diagnosis of normal TSH Low T4 is essential. When the Free T4 level is normal, considering and confirming TBG deficiency diagnosis is essential since over-treatment with Levothyroxine can cause craniosynostosis. If the free T4 level is low, considering secondary congenital hypothyroidism is needed while obtaining full pituitary work -up including the evaluation of the ACTH-Cortisol axis. Early treatment with Levothyroxine in this case may unmask adrenal insufficiency. The neonatal thyroid screen interpretation requires a detailed understanding of the thyroid function tests normal values in the first weeks of life.

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PS2-14-02

Thyrotoxicosis in a patient with turner syndrome: radioactive iodine therapy

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Introduction
Turner syndrome (TS) is a chromosomal disorder affecting female and characterized by complete or partial monosomy of the X chromosome. These genetic changes lead to the abnormalities in growth and development and increase

the risk of autoimmune diseases, including those affecting the thyroid. Thyroid pathology in TS may include autoimmune thyroiditis, hypothyroidism, thyrotoxicosis (Graves disease, AIT in the hyperthyroid state). Thyrotoxicosis is the clinical syndrome of excess circulating thyroid hormones. One of the main causes of thyrotoxicosis is Graves' disease (GD), an organ-specific autoimmune disease caused by the production of stimulating thyrotropin receptor antibodies. There are three treatment options for thyrotoxicosis: anti-thyroid drugs, radioactive iodine and thyroidectomy. A personalized approach to disease management is especially important in cases of genetic diseases.
Methods
We present a clinical case of a patient with TS and GD, who has been referred to a radiologist at the Department of Radionuclide Therapy of Endocrinology Research Center. The patient was diagnosed with congenital hypothyroidism at neonatal screening, but thyroid hormones therapy was initiated aged three. Based on the survey, GD was diagnosed aged twenty one. Anti-thyroid drug therapy was started, which resulted in toxic hepatitis. Taking into account intolerance to anti-thyroid drugs, radioiodine therapy (RAIT) has been recommended.
Results
RAIT led to hypothyroidism throughout 2 months with decreasing of thyrotoxicosis symptoms and levels of liver enzymes.
Conclusion
Nowadays, the pathophysiological aspects of more frequency prevalence of thyroid autoimmune pathology in patients with TS are not clearly understood. RAIT for patients with GD on the background of TS or another chromosomopathy should be considered individually with taking into account potential risks of radioactive iodine complications. Also, it is important to investigate the influence of RAIT on liver function.
Keywords
Turner syndrome; autoimmunity; Graves' disease; radioiodine therapy; chemical and drug induced liver injury
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PS2-14-03

Two cases of radioactive iodine refractory malignant struma ovarii with nras mutation

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Background
Struma ovarii is a germ cell tumor of the ovary containing $\geq$ 50% thyroid tissue and malignant struma ovarii (MSO) is a very rare disease containing papillary or follicular thyroid carcinomas (FTC). There is no consensus on optimal management for patients with MSO and no data on radioactive iodine (RAI) responsiveness. Here, we report two cases with RAI refractory MSO with NRAS mutation detected by next-generation sequencing (NGS).
Case 1
A 25-year-old nulligravida patient underwent laparoscopic salpingo-oophorectomy due to a 5.7 cm mass in the left ovary. Pathological examination revealed an MSO (FTC) and additional exploratory laparotomy found multiple metastatic FTC in the peritoneum. She underwent total thyroidectomy and 200 mCi of RAI therapy. There was no RAI uptake in multiple peritoneal nodules on post-therapeutic whole-body scan (WBS) and her stimulated serum thyroglobulin (Tg) level was 826 ng/mL NGS analysis identified NRAS Q16K mutation.
Case 2
A 44-year-old patient (gravida 2) underwent laparoscopic right ovarian cystectomy for a 10.5 cm mass. The pathology was poorly differentiated thyroid carcinoma arising in MSO and she underwent a hysterectomy and bilateral salpingo-oophorectomy. The pathology confirmed the residual MSO without invasion of adjuvant tissues. Adjuvant RAI therapy (150mCi) was done after total thyroidectomy of the normal thyroid gland and there was no abnormal RAI uptake in the pelvic cavity. Eight months later, peritoneal seeding of MSO was detected in FDG-PET scan with serum Tg increase from 31.6 ng to 66.5 ng/mL RAI refractoriness was confirmed after an additional 200 mCi of RAI therapy. She underwent additional surgery for the increase of peritoneal mass with colon invasion. NRAS Q16K mutation was also confirmed by NGS analysis in this patient.
Conclusion
RAI therapy is an important treatment option for patients with metastatic MSO after the initial surgical approach and total thyroidectomy. However, some MSOs may be less differentiated and not respond to RAI. Future studies are required to guide the optimal therapeutic approach for RAI refractory MSO based on the driver mutation.
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PS2-14-04

Diagnosis and management of a thyrotoxicosis storm on unknown hyperthyroidism

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Introduction
In the spectrum of endocrine emergencies, thyroid storm is one of the most critical complications. Recognition and appropriate management of life-threatening thyrotoxicosis is vital to prevent the high morbidity and mortality that may accompany this disorder. The incidence of thyroid storm has been noted to be less than 10% of patients hospitalized for thyrotoxicosis; however, the mortality rate secondary to thyroid storm ranges from 20 to 30%. We report in this work, the case of a patient with unknown Grave disease, who had a thyreotoxicosis storm after cholestectomy.
Observation
52-year-old patient, 20 days before his thyrotoxicosis storm, our patient presented with acute pancreatitis on vesicular lithiasis, which required the realization of a cholecystectomy, our patient did not show any clinical sign of thyrotoxicosis before surgery, but the occurrence of a hypertensive peak, tachycardia at 147 beats/min and significant dyspnea, a thyroid assessment was carried out, returning in favour of hyperthyroidism with a TSH level $< 0.01\mu$ui/ml and an FT4 level: 69 pmol/l, the electrocardiogram found an atrial fibrillation, the diagnosis of a thyroid storm was retained on clinical and biological criteria (scored at 50 according to the Wartofsky score) and the patient was transferred to an intensive care unit, where he received appropriate management. Subsequently, our patient received radical treatment for his hyperthyroidism.
Conclusion
Thyrotoxicosis and thyroid storm represent a critical diagnostic and therapeutic challenge to the clinician. Recognition of life-threatening thyrotoxicosis and prompt use of medications aimed at halting the thyrotoxic process at every level is essential to successful management. A set of therapeutic weapons exist: the treatment aimed at stopping synthesis of new hormone within the thyroid gland, halting the release of stored thyroid hormones from the thyroid gland, preventing conversion of T4 to T3, and providing systemic support of the patient. All of which can stop the thyroid storm and save the patient from critical complications. Once this transition occurs, definitive therapy of thyrotoxicosis can be planned.
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PS2-14-05

28 years of thyroid eye disease reactivations

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A male patient, currently 64 years old, was diagnosed with TED (Thyroid Eye Disease) in 1993 when he underwent surgery for "exophthalmos" in both eyes (likely decompression surgery), followed by surgery to correct diplopia. He underwent a total thyroidectomy one year later. For ongoing "activity" of thyroid and TED patient received radioiodine ablation in 1995 and 1997. At that time, he also received "some pulses" of methylprednisolone and long-term per oral prednisone treatment. He also reported treatment with cyclophosphamide – however, we could not confirm it. For the first time, he was seen at our University clinic in 2016 for five years of ongoing problems with lids edema, eye tiredness, occasional ptosis of the upper eyelid, tearing, and redness, without diplopia. Due to the unusual course of TED, we excluded myasthenia gravis and IgG4-related disease. For recurrent progressions of TED since 2016, he had received at our clinic pulses of methylprednisolone with a cumulative dose of 7,5g, three times 100 mg Rituximab, prolonged per oral therapy with prednisone and one-year treatment of cyclosporine. While on cyclosporine, he developed exposure keratopathy, which required tarsorrhaphy. In October 2022, he was switched to

Tocilizumab 162 mg s.c. weekly and we have started to see dramatic changes in his appearance (decreased swelling, decreased redness, and improved eye motility). His TSI (Thyroid Stimulating Immunoglobulin), which was till Tocilizumab (at least since 2016), all the time above the detection threshold (>40 mIU/l) started to decrease. This work was supported by the Ministry of Health of the Czech Republic - Conceptual development of research organization (FNOL, 00098892) and grant no. NU21J-01-00017.

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PS2-14-06

Amyloid goiter in patient with mediteranian fever

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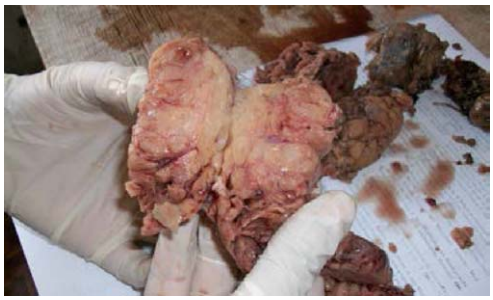
Introduction
The thyroid gland is affected by amyloidosis in 50% of cases in primary amyloidosis and80% in secondary amyloidosis.
Case report
The patient, male, born in 1976 was admitted to the department of endocin Surguary of the Astghik Medical Center, Armenia complaining of general weakness, feeling of compression and heaviness in the neck (cervical discomfort), cough, shortness of breath, swallowing difficulty. When the patient was 12 years old diagnosed Mediteranian Fever. The following findings have been determind.
Conclusion
Thyroid amyloidosis is a rare disease. The presence of dense rough surface progressing in size goiter, often leads to the assumption of thyroid cancer. Note that in spite of the atrophy of the glandular tissue of the thyroid gland, the patient had not expressed disturbances of hormonal status (euthyroid state). This fact may be related to powerful compensatory properties of the thyroid gland

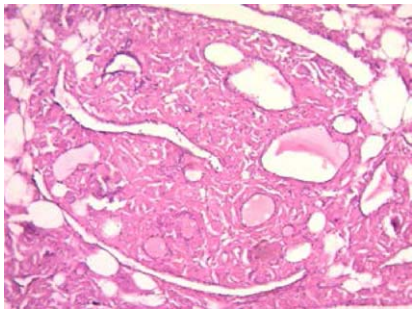
Test	Result	Normal range
TSH	1.1 uIU/ml	0.27-4.2 uIU/ml
FT4	1.5 ng/dl	0.93-1.7ng/dl
T3	0.9 ng/ml	0.80–2.0 ng/ml
Thyroid gland ultrasound	Expressed diffuse changes of the thyroid gland with total amyloid fibrous transformation of thyroid tissue with sharply depleted vascular pattern. Right lobe: volume – 184.6 cm3, left lobe: volume – 168.5 cm3, isthmus – 10.9 mm.	

Macro-preparation on cut.



DS. Mediterranean Fever, Amyloid goiter
Thyroidectomy was performed.

Micro-preporation



Amyloidosis of the thyroid gland: vessel walls sharply thickened by deposits of amyloid in them. Hematoxylin and eosin.

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PS2-14-07

Primary thyroid mucoepidermoid carcinoma with extensive pulmonary metastasis

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Mucoepidermoid carcinomas (MECs) are the most common malignant tumors of the salivary glands. Primary thyroid MECs are extremely rare (about 0.5% of all thyroid malignancies) and, in the majority of cases, are associated with an indolent biologic potential and excellent long-term prognosis. We present the case of a 67-year-old man, with a recently growing anterior cervical mass, associating dyspnoea and fatigue. Thyroid ultrasound revealed an inhomogeneous, hypoechoic mass in the left lobe and multiple pathologic bilateral adenopathies, of up to 3 cm. Cervical and thoracic CT showed a heterogenous mass comprising left thyroid lobe and isthmus, of about 3/6 cm, with a cranial extension which encapsulates the larynx, without an obvious invasion of the laryngeal cartilages; in the lower part, the tumor extends to the left anterior and superior mediastinum and has mass effect on the esophagus. There were multiple nodules in both lungs' parenchyma compatible with metastasis. The patient was referred to the surgical department and one of the pathological lymph nodes was removed. Histological exam revealed malignant infiltration with ovoid, round and polygonal tumoral cells, eosinophilic cytoplasm, round and ovoid, nucleolated nuclei, pale chromatin, in an island and cribriform pattern. Immunohistochemistry tests showed tumoral cells diffusely positive for CK19, P63, TTF1, PAX8 and negative for thyroglobulin, CD5, Chromogranin A and Synapto, Ki67 positive in 15% of tumoral cells. The diagnosis was metastasis from primary thyroid mucoepidermoid carcinoma. Due to worsening of respiratory symptoms the patient was referred to the pneumology clinic, where he unfortunately passed away just 4 weeks after the initial presentation for endocrinological evaluation.
Conclusions
Although they are usually considered tumors with favorable evolution, sometimes thyroidal MEC may present in an advanced, metastatic stage, associated with a poor prognosis.

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PS2-14-08

Thyrotoxic periodic paralysis: report of two cases

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Introduction
Hypokalemic periodic paralysis (HPP) belongs to a group of inherited diseases called channelopathies, whose main manifestation include painless muscle paralysis. There are also acquired forms of HPP secondary to hyperthyroidism, called thyrotoxic periodic paralysis (TPP). It's prevalence is markedly higher in men.
Case Reports
Case 1. 34-year-old Venenzuelan man, without medical history. He consults in the emergency department due to sudden onset of ascending paresthesia and limb weakness, associated to nausea and vomit. He reported intermittent tremor and heat intolerance. Laboratory findings demonstrated severe hypokalemia (1.3mEq/l). He was transferred to ICU for aggressive hypokalemia management, promptly recovering full neurological function after normalizing serum potassium. He didn't develop arrhythmias. On physical examination, he was clinically hyperthyroid with diffuse goiter. Further laboratory showed a suppressed TSH <0.015, with an elevated fT4 (5.35 ng/dl, normal value (NV) up to 1.79), and T3 2.8 ng/dL (NV up to 1.69). Ultrasound showed chronic thyroiditis. TRAb: 35 IU/l (NV <0.55). Methimazole was started. At follow up, he remains stable, euthyroid and neurologically asymptomatic.

Case 2. 32-year-old Chilean man with history of hypertension treated with losartan. He was referred to the emergency department due to limb weakness, with inability to stand up, associated with dyspnea, palpitations, and chest pain. He referred a 20 kg weight loss with preserved appetite, heat intolerance, diaphoresis and progressive weakness. An EKG was performed showing sinus tachycardia with a prolonged PR and QT interval, ST segment depression, and a prominent U wave. Physical examination revealed slight tremor, palpable thyroid without nodules, and hyperdynamic aortic murmur. Initial laboratory tests showed severe hypokalemia (1.6mEq/l). After aggressive correction, patient had full neurological recovery. TSH levels were <0.015, T3 2.95 ng/dL and fT4 4.37 ng/dL and TRAb 8.12 IU/l. Ultrasound showed chronic thyroiditis. Methimazole was started and has remained asymptomatic ever since.

Conclusions

TPP is a rare disease, but it should be considered in a patient with painless muscle weakness and hypokalemia. Aggressive correction is imperative to avoid malignant arrhythmias.

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PS2-14-09

Lowering of circulating thyroxine levels in graves' disease resulting in rhabdomyolysis: A less known complication in management of graves' disease

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Thyrotoxicosis causing hypokalaemic paralysis is a known complication among Asians, Myopathy as a result of thyrotoxicosis or caused by antithyroid drugs (ATD) is rare. Myositis, resulting in a rise in creatinine kinase levels (CK) is commonly seen in overt hypothyroidism, however, rapid lowering in circulating thyroid hormone levels during the treatment of Graves' disease could result in myalgia and elevated CK levels. This complication needs to be actively diagnosed when patients are symptomatic for muscle pain after initiation of ATD therapy in Graves' disease. The following case of Graves' who started on carbimazole (CMZ) developed myositis secondary to relative hypothyroidism illustrates this phenomenon. A 23-year-old lady presented to the Emergency Department with myalgia and muscle cramps without weakness. She had been diagnosed by primary care to have Graves' disease 2 months earlier, having presented with clinical and biochemical hyperthyroidism. Labs: (FT4 [Free Thyroxine] >100 pmol/l [Reference Interval (RI): 12 – 22], TSH [Thyroid Stimulating Hormone] <0.005 mIU/l [RI: 0.27 – 4.2]) and high titres of TSH receptor antibody (6.2 IU/l [RI: <1.8]). She had been treated with CMZ 20 mg twice a day, which improved her thyrotoxicosis but resulted in a rapid lowering of FT4 within a month. Her symptoms had developed a month after starting CMZ, which had already been adjusted to 15 mg daily with FT4 8.1 pmol/l and TSH 0.020 mIU/l at the point of review. CK was elevated at 2300 U/l (RI: 24 – 200). Systems review was unremarkable and renal function was normal, with no other cause of myositis identified. CK and myalgia improved with hydration and reduction of CMZ dose to 5 mg daily. Thyroid hormone has multiple effects on skeletal muscle, and there have been increasing reports of myositis after treatment of Graves' disease. While the mechanism remains unknown, associations with ATD and relative hypothyroidism have been suggested. Given that patients on treatment are generally on ATD and have reductions in levels of thyroid hormone, etiology is difficult to determine. As musculoskeletal complaints are common in patients with hyperthyroidism, relative hypothyroidism-induced myositis may be more common than reported. Anticipating this condition will allow clinicians to intervene with early dose reduction to alleviate myositis. Reduction of ATD doses with close monitoring instead of discontinuing treatment or extensive investigation may be a prudent course of action.

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Hyperthyroidism

PS2-15-01

A prospective, observational study on the effect of an ablative vs a conservative approach for the treatment of graves' hyperthyroidism in patients with moderate-to-severe, active graves' orbitopathy

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Objectives

Optimal treatment for Graves' hyperthyroidism (GH) in patients with moderate-to-severe, active Graves' orbitopathy (GO) remains to be established. There is debate on whether a conservative (antithyroid drugs, ATDs) or an ablative approach (radioactive iodine, RAI, or surgery, Tx)has to be preferred. The aim of the present study was to investigate whether these different approachesresult in a different outcome of GOfollowing intravenous glucocorticoids (ivGCs).

Methods

The study design entailed enrollment of 52 consecutive patients with relatively recent onset ($\leq$ 18 mo.) GH and moderate-to-severe, active GO. Following adequate counseling, patients were asked to freely choose between an ablative (RAI for ultrasound thyroid volume $\leq$ 30 ml, Tx for volume >30 ml) or a conservative approach, to be then treated with ivGCs (12 weekly infusions of methylprednisolone; cumulative dose: 4.5 g). Primary outcome was the overall outcome of GOat 24 weeks (composite evaluation). Secondaryoutcomes were: 1) outcome of single eye features: 2) quality of life (GO-QoL); 3) GO worsening at 24 weeks.

Results

Of 52 patients enrolled, 48 completed the 24-week evaluation, 23 in ablation group (22 treated with RAI and one with Tx) and 25 in ATDs. The two groups did not differ for baseline parameters (sex, age, smoking habits, BMI, thyroid volume, thyroid function, LDL-cholesterol, GO features, TSH-receptor autoantibodies and GO-QoL). The proportion of overall GO responders at 24 weeks was greater in ablation group (47.8% vs 16% in ATDs; OR 4.81; 95% CI from 1.25 to 18.5; $P = 0.028$). There was a trend to a greater proportion of proptosis, clinical activity score (CAS) and eye duction responders in ablation group, although the difference did not reach significance. On the same line, there was a trend to a greater proportion of GO-QoLresponders in ablation group. Only one patient (4.3%) worsened in ablation group compared with 3 (12%) in ATDs, with no statistical difference. Forty-eight mild adverse events (20 in ablation and 28 in ATDs group) in 36 patients (16 in ablation and 20 in ATDs group) were recorded, of which 19 related to ivGCs and 14 related to thyroid treatment (6 in ablation and 8 in ATDs group), with no difference between groups.

Conclusions

An ablative approach for GHtreatment seems to result in a better overall outcome of GOfollowing ivGCs, without a greater proportion of GO worsening. Further, randomized clinical trials are needed to confirm our observations.

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PS2-15-02

Grip strength in newly diagnosed hyperthyroidism

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Introduction

Grip strength is a valuable biomarker of an individual's biological age. Weak grip strength is a key component of sarcopenia and frailty and is associated with subsequent poor health, disability and mortality. Skeletal muscle is one of the major target organs of thyroid hormones. Hyperthyroidism may affect skeletal muscles qualitatively and quantitatively, to the extent of developing muscle weakness and myopathy. There are few studies investigating grip strength in patients with newly diagnosed hyperthyroidism.

Aim

The aim of this study is to assess the association of hyperthyroidism with grip strength. To achieve our goal, we set the following tasks: to compare grip strength between healthy females and women with newly diagnosed hyperthyroidism and to look for correlation between anthropometric or thyroid parameters and grip strength.

Materials and Methods

We evaluated 90 women over the age of 18, divided into 2 groups: group A ($n = 45$) women with newly diagnosed untreated hyperthyroidism (autoimmune thyroid disease or toxic nodular goiter) and group B ($n = 45$) - healthy females of

the same age. We evaluated anthropometric parameters, laboratory tests of TSH, free T3 (FT3), free T4 (FT4), TPO-Ab and TRAb. Grip strength was analyzed using a hand-held dynamometer. Statistical analysis was performed by SPSS version 18 for Windows. We used statistical grouping of the data, descriptive methods, Pearson correlation and T-test for statistical hypotheses.
Results
Grip strength testing showed approximately twice as much weakness in hyperthyroid women (16.67 ± 5.96 kg) compared to euthyroid ones (33.82 ± 10.22 kg). There were significant positive correlations between handgrip strength and weight, waist and hip circumferences and BMI. With the reduction of TSH from normal to hyperthyroid values, the grip strength also decreased (p 0,001; r 0,658). As expected, the same, but negative trend between FT3 and grip strength was observed (p 0,013; r -0,274). With the immunological evolution of the disease from euthyroidism to autoimmune hyperthyroidism, expressed by the rise of TPO-Ab and TRAb, a significant reduction of grip strength was observed. In conclusion, hyperthyroidism may affect the skeletal muscles qualitatively and quantitatively. Grip strength in hyperthyroid women is significantly affected by the autoimmune thyroid disorder.

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PS2-15-03

Does iodine fortification affect the risk of atrial fibrillation in incident hyperthyroidism?

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Objectives
Iodine fortification (IF) induces an initial increase followed by a decrease in the incidence of hyperthyroidism in the population. Also, the sex-, age-, and subtype distribution of hyperthyroid cases changes after IF. The risk of atrial fibrillation (AF) in hyperthyroid patients is influenced by these factors. Therefore, we aimed to examine how the association between incident hyperthyroidism and atrial fibrillation was affected by an IF increasing the population intake from moderate-mild iodine deficiency to low-adequacy.
Methods
Incident hyperthyroid patients were included at the date of first in- or outpatient diagnosis, and AF within 3 months before to 6 months after the index date was identified by in- and out-patient hospital diagnoses in Danish nationwide registers, 1997-2018. The relative risk (RR) of AF each calendar year (reference year: 1997, IF introduced in 2000) was analyzed by Poisson regression models adjusted for age, sex, educational level, geographic region, and comorbidities.
Results
Overall, out of 62,201 patients with incident hyperthyroidism, 7.66% (95%CI 7.45-7.87) had AF. There was a non-significant increased risk during the first years after IF followed by a gradual decrease in the risk of AF to RR 0.72 (95%CI 0.52-0.79) in 2017. There was no statistically significant difference in the development in the risk of AF by sex, age group, or region (moderate vs mild iodine deficiency before IF).
Conclusions
Results indicate that IF may reduce the risk of concomitant AF in hyperthyroid patients. If these results are confirmed, IF may not only reduce the population incidence of hyperthyroidism but also reduce the burden of morbidity in remaining hyperthyroid patients.

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PS2-15-04

THY-PRO 39 questionnaire in gravès disease patients after therapy

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Introduction
Graves' disease is the leading cause of hyperthyroidism in the adult population. Antithyroid drugs (ATD) are the first choice worldwide, however, after an initial treatment course of 18-24 months, almost 40-50% will relapse. In these cases, current guidelines suggest a second course or prolonged use of ATD as an option. Recently, the study of quality of life (QOL) has obtained great importance, since the QOL in hyperthyroid patients is very affected. However, there are scarce data on QOL in patients after the treatment of Graves' disease.
Objectives
The objective of the study was to evaluate the QOL using the Thy-PRO 39 questionnaire in Graves' disease patients who relapsed after an initial ATD course and were treated with radioiodine (RAI) or a second course of ATD.
Materials and Methods
Fifty-one patients with Graves' disease relapse were evaluated, in the euthyroid state, according to the Thy-PRO 39 questionnaire (validated for the Brazilian population) and divided according to the treatment. Group 1: patients on the second course of ATD; Group 2: patients treated with RAI followed by levothyroxine supplementation. Group 3: was represented by patients in remission.
Results
In Group 1 ($n = 30$), mean age was 56 ± 14 years, mean serum TSH = 2.49 ± 1.66 uUI/ml, and mean serum FT4 = 1.12 ± 0.25 ng/dL mean period of treatment with ATD was 75 ± 66 months, 10% of the patients were current smokers. In Group 2 ($n = 21$), mean age was 55 ± 12 years, mean serum TSH = 2.40 ± 1.47 uUI/ml, and mean serum FT4 = 1.25 ± 0.41 ng/dl, 14% of the patients were current smokers. In Group 3 ($n = 10$) mean age was 53 ± 15 years, mean serum TSH = 2.39 ± 1.12 uUI/ml, and mean serum FT4= 1.28 ± 0.25 ng/dL. There were no patients with history of smoking, current or previous. The mean clinical activity score at the evaluation was 0 ± 1 for all groups, and no differences between the groups regarding age, TSH, and FT4 were found. Regarding patient symptoms about goiter; hypo and hyperthyroidism; eye; tiredness; cognitive complaints; anxiety; depression; emotional susceptibility; impact on emotional and daily life the three groups showed similar results three groups showed similar results.
Conclusion
The Thy-PRO 39 questionnaire showed no difference among the three studied groups. A second course or prolonged use of ATD provides the same quality of life as RAI treatment plus levothyroxine.

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PS2-15-05

Resting heart rate monitoring for optimized treatment of hyperthyroidism - the pulsar-study

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Objectives
Graves' disease (GD) is a common cause of hyperthyroidism. An increased heart rate (HR) is a hallmark of elevated thyroid hormones (TH). In a prospective observational study we monitored HR continuously with wearable fitness trackers to evaluate the correlation between HR and TH levels and the relevance of HR monitoring for clinical management of patients with GD.
Methods
Seventeen outpatients with newly diagnosed or relapsed GD starting anti-thyroid drugs (ATD) were recruited for this study. Patients were invited to the endocrine outpatient clinic at the University Hospital Basel for five visits three to five weeks apart. At inclusion, they received a wearable fitness tracker for continuous HR monitoring during the study. At each visit we measured clinical parameters, downloaded data from the device, performed an ECG and determined serum TH levels (TSH, fT3, fT4). We assessed hyperthyroid symptoms with a questionnaire and adjusted ATD dose.
Results
Fifteen of the seventeen patients were female. Mean age was 37.1 ± 12.9 years. At baseline, all participants were hyperthyroid with a suppressed TSH. The peripheral TH were elevated with a mean fT4 of 38.3 ± 21.2 pmol/l and a mean fT3 of 15.7 ± 9.3 pmol/l. The mean resting HR was 82.0 ± 11.2 bpm. With ATD

treatment TH decreased significantly over the course of the study, fT4 dropped to 14.8 ± 6.3 pmol/l and fT3 decreased to 5.2 ± 1.9 pmol/l. In parallel, the resting HR declined to 67.1 ± 9.2 bpm ($P < 0.0001$ and p for trend < 0.0001 for all parameters). Levels of fT4 and fT3 correlated significantly with resting HR when analyzed over all participants ($R^2 = 0.67$ for both fT4 and fT3). Many physiological factors influence HR and the individual normal range of TH. To account for these inter-individual differences and to assess the relation between TH level and HR in more detail, we analyzed the individual HR and TH data using a nonlinear model based on an exponential growth equation. For most patients this function achieved a very good fit between the predicted and the actual TH values for any given HR. The median coefficient of determination (R^2) for fT4 was 0.81 (IQR 0.66 to 0.94) and 0.87 (IQR 0.70 to 0.95) for fT3.

Conclusion

We can demonstrate a strong relation between TH levels and continuously monitored resting HR in patients with GD. The course of HR and TH levels can be modelled in individual patients. Wearable devices could potentially be used to tailor treatment of GD to the needs of the individual patient.

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PS2-15-06

Factors influencing early outcome of radioiodine treatment in patients with graves' disease

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Aim

In Graves' disease (GD) the goal of radioiodine (I-131) application is the elimination of hyperthyroidism. The reported success rate 1 year after treatment is up to 90%. The aim of this retrospective study was to assess the factors influencing the early outcome 3 months after I-131 treatment of GD patients in an iodine sufficient area.

Materials and Methods

We reviewed medical records of GD patients who received I-131 therapy between January 2013 and December 2017. In all patients antithyroid drugs were discontinued at least 3 days before I-131 application. Prior I-131 therapy, uptake of iodine-123 (I-123) at 20-hours or technetium-99m-pertechnetate (Tc-99m) was measured. During follow-up, thyroid function was evaluated up to 3 months after I-131 application and time to occurrence of hypothyroidism was established. Patients' characteristics influencing the early outcome of I-131 treatment were estimated, p value of < 0.05 was considered statistically significant.

Results

We evaluated 849 GD patients (660 females and 189 males) aged between 16 and 91 years (mean age, 50.4 ± 17.0 years). The median I-123 uptake, measured in 37.8% (321/849) patients, was 69.0%, and the median Tc-99m uptake, measured in 62.2% (528/849) patients, was 3.18%. The median treatment I-131 activity was 623 MBq I-131 (range, 436-1123 MBq). Follow-up data were available for 91.6% (778/349) patients. At 3 months after I-131 application we confirmed hypothyroidism in 81.6% (635/778) patients, hyperthyroidism in 14.1% (110/778) and euthyroidism in 4.3% (33/778) patients. Hypothyroid patients were younger than hyperthyroid and euthyroid patients (49.1 ± 16.7 years, 55.7 ± 17.4 years and 57.8 ± 17.0 years, respectively, $P < 0.001$), with a higher proportion of females (chi-square = 6.6, $P = 0.04$). Their median I-123 uptake was higher (72.2%, 62.5% and 33.0%, respectively, $P = 0.02$), but their Tc-99m uptake did not differ (3.20% and 2.78% and 2.98%, respectively, $P = 0.38$). In hypothyroid patients applied I-131 activity was lower (587 MBq, 737 MBq and 728 MBq, respectively, $P < 0.001$). Mean time to hypothyroidism was 2.3 ± 0.9 months. There was a significant correlation between time to hypothyroidism and younger age ($r = -0.087$, $P = 0.03$), but no correlation was confirmed with I-123 uptake ($r = -0.004$, $P = 0.95$), Tc-99m uptake ($r = -0.017$, $P = 0.73$) or applied I-131 activity ($r = -0.007$, $P = 0.86$).

Conclusion

More than 80% of GD patients develop hypothyroidism already within 3 months after I-131 therapy. This outcome is more frequently associated with younger age, female sex and higher uptake of I-123. Careful monitoring of patients following I-131 application is necessary to identify and treat the early outcome in a timely manner.

References: none

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PS2-15-07

Immunogenetics markers of graves' disease relapse after antithyroid treatment

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Introduction

The choice of treatment for Graves' disease (GD) requires a comprehensive assessment of the patient's condition and the risk of recurrence. The aim of our study was to evaluate the association of immunological and genetic markers with GD recurrence after antithyroid treatment.

Methods

We conducted a case-control study. The study included 63 patients with GD who received antithyroid treatment. After at least 12 months of withdrawal patients were divided into two groups: 1. GD remission ($n = 18$); 2. GD relapse ($n = 45$). All patients have undergone a laboratory examination, the study of polymorphic markers of the *CTLA4, TSHR* genes was performed by polymerase chain reaction. Statistical analysis of the results was carried out using SPSS 26.0. A P value < 0.05 was considered statistically significant.

Results

The level of TRAb at the time of discontinuation of therapy was significantly higher in the group with GD relapse - 5.05 [0.84; 24.08] than in the group with GD remission – 1.0 [0.5; 1.88] ($P = 0.033$). 37.9% of patients with GD relapse and 15.6% with GD remission had a hereditary predisposition to GD ($P = 0.006$). An active Graves' ophthalmopathy (GO) was more common in the group with GD relapse - 23 (53.5%) than with GD remission - 14 (77.8%) ($P = 0.025$). Carriage of the *GG* genotype polymorphism of the *TSHR* gene was more frequent in patients with GD remission - 38.1% compared with patients with GD relapse - 10.3% ($P = 0.009$). There was not significant difference in polymorphic markers of the *CTLA4 gene*.

Conclusions

Several risk factors for relapse are identified. A higher level of TRAb, history of active GO, hereditary predisposition to GD are associated with relapse of GD. The result of our study shows association of *TSHR* gene polymorphism with GD remission after antithyroid treatment.

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PS2-15-08

Extended pharmacometrics computer model utilizes heart rate to monitor thyroid function in adults with graves' disease under carbimazole monotherapy

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Objectives

Graves' disease (GD) is characterized by variable disease severity at diagnosis and variable disease activity during follow-up. Antithyroid drugs (ATD) such as carbimazole (CMZ), methimazole or propylthiouracil are the first-line treatment. Current guidelines recommend a range of ATD starting dose according to GD severity, followed by dose titration until euthyroidism is reached and a maintenance dose for a specific patient is established. As thyroid hormones have a strong positive chronotropic effect, heart rate (HR) turns out to be a useful

clinical marker to monitor thyroid activity under pharmacotherapy. The aim of this study was to extend recently developed clinically practical pharmacometrics (PMX) computer model characterizing individual disease activity and describing the relation between free thyroxine (FT4) and tachycardia in pediatric patients with GD with various GD severity under CMZ monotherapy to adults with or without receiving beta blockers.
Methods
Retrospectively collected clinical (resting HR during consultation) and laboratory data from adults with GD during the first 120 days of treatment at University Hospital Basel, Switzerland, were analyzed. PMX computer model was developed in the non-linear mixed effects modeling framework consisting of differential equations linking FT4 kinetics with HR dynamics, accounting for inter-individual variability, and incorporating clinically relevant individual patient characteristics. GD severity groups were defined based on FT4 at diagnosis according to current guidelines.
Results
Data from 37 adults with GD with at least 2 HR measurements (68% female, median age 42 [IQR 35, 55] years, and 25 mild, 8 moderate, and 4 severe GD at diagnosis, 54% receiving beta blockers) with 203 FT4 measurements and 129 HR measurements, 122 paired measurements, were analyzed and used for model development. At diagnosis, patients showed a median FT4 of 38.3 [IQR 32.3, 54.1] pmol/l, and a median HR of 94 [IQR 81, 118] bpm. Final PMX model accurately predicted individual disease dynamics for each GD patient during the first 120 days of treatment accounting for clinically relevant covariate effects, such as age, gender, and GD severity.
Conclusion
Developed clinically practical PMX computer model predicts individual HR and disease dynamics under CMZ monotherapy with or without receiving beta blockers. This computer model is expected to facilitate personalized pharmacotherapy and has the potential to mitigate risk for under- or overdosing of ATD in patients with GD. Prospective randomized validation trials are warranted to further validate and fine-tune computer-supported personalized dosing in GD patients.

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PS2-15-09

Long-term follow-up after antithyroid drug treatment withdrawal in patients with the first episode of gravès disease: a retrospective cohort study in spain

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Background
Despite a high relapse rate, antithyroid drugs (ATDs) remain the first-line therapy of Graves' disease (GD). Long-term follow-up studies of GD in Spain are scarce. Our aims were to identify clinical differences between patients who relapsed vs those who attained remission and to describe the relapse rate of GD after ATD withdrawal.
Methods
We analyzed patients with the first episode of GD who were treated with ATDs during 2010 - 2020, in a third-level hospital in Madrid, Spain. Relapse was defined as overt clinical and biochemical hyperthyroidism after the withdrawal of ATDs. Categorical and continuous variables were analyzed by chi-squared test and independent samples t-test. ROC analyses were used to determine relapse cutoff values for each of the quantitative variables. The cumulative risk of relapse during follow-up was estimated using the Kaplan–Meier approach.
Results
During a median follow-up time of 4.2 years (1.2 – 6.8), 105 (38.5%) patients experienced a relapse. Fifty-four (51.4%) relapses occurred during the 1st year, 20 (19%) during the 2nd, 11 (10.5%) during the 3rd, 9 (8.6%) during the 4th and the remaining 11 (10.5%) during the following 6 years. The majority of relapses occurred during the first and second year, 0.0172 relapses per patient-month and 0.0074 relapses per patient-month, respectively. Cutoff values to predict relapse were fT4 $\geq$2.5 ng/dl, fT3 $\geq$5.07 pg/ml, TRAb $\geq$ 6.33 U/l, age $\geq$ 50.1 years and a thyroid volume of $\geq$ 27.7ml for males and $\geq$ 12.2 for females.
Conclusions
In our population, female sex, Graveś orbitopathy and smoking were associated with relapse of GD. The majority of relapses occurred during the first 2 years but maintained a considerable rate until the 4th year after ATD withdrawal.

		Remission	Relapse	
Numbers		168	105	
Male sex, n (%)	32 (11.7)	25 (14.5)	7 (6.7)	0.040*
Age at diagnosis, years	46.1 (36.4 – 53.9)	45.6 (36.4 – 51.9)	46.8 (36.9 – 56.4)	0.379
Thyroid volume, mL	13.6 (8.8 – 19.5)	13.6 (8.8 – 19.7)	13.2 (8.8 – 18.9)	0.709
fT4, ng/dL	2.47 (1.83 – 3.46)	2.45 (1.72 – 3.64)	2.5 (1.9 – 3.2)	0.501
fT3, pg/mL	6.75 (4.77 – 10.57)	6.76 (4.54 – 10.52)	6.48 (5.1 – 10.7)	0.707
TRAb, U/l	5.60 (3.16 – 11.3)	4.97 (3.08 – 10.21)	6.6 (3.61 – 12.9)	0.393
Graves' orbitopathy, No. (%)	37 (13.7)	16 (9.7)	21 (20)	0.016*
Smoking, No. (%)	44 (18.7)	26 (17.8)	18 (20.7)	0.035*
Treatment duration, months	18.4 (14.6 – 22.9)	17.9 (13 – 21.8)	19.4 (16.8 – 23.5)	0.043*

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Thyroid Cancer Clinical 2

PS2-16-01

Follicular thyroid cancer in lenvatinib therapy complicated by tracheoesophageal fistula treated with pharyngo-laryngo-esophagectomy and definitive tracheostomy

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Lenvatinib is a tyrosine kinase inhibitor (TKI), approved for the management of locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer (DTC). A side effect of this drug is the tracheoesophageal fistula, described in 14.7% of patients. When this side effect is present, the interruption/withdrawn of the TKI is required and in this case no valid therapeutic options are described. We present the case of a 63-year-old woman patient with thyroid follicular carcinoma (FTC) with lung metastases, treated with Lenvatinib, stable for ten years. For the appearance of dysphagia, odynophagia and chronic cough, the patient performed a whole-body computed tomography (CT) which confirmed a locoregional recurrence, in retrotracheal space, with the presence of air bubbles. Bronchoscopy and radiography of the esophagus with contrast medium documented saliva leakage into the trachea, confirming the tracheoesophageal fistula. For these reasons, Lenvatinib was interrupted, and an enteral nutrition by nasogastric tube was started. Four months later the suspension of Lenvatinib, the patient had a progression on local disease and lung metastases with concomitant increase of the serum Thyroglobulin levels (TG) (4042.91 mg/l vs 1882.25) and, despite enteral nutrition, the patient had a weight loss (10 kg). Since a significant PD occurred in the neck and since the patient complained a strong discomfort due to the presence of naso-gastric tube and to the weight loss, after a multidisciplinary evaluation, she underwent to the surgery of pharyngo-laryngo-esophagectomy, gastric anastomosis and definitive tracheostomy. The patient gradually resumed to feed orally, with a referred by patient improvement of her quality of life. One month later the surgery, in consideration of the stability of the clinical conditions, the patient restarted Lenvatinib. Eight months later the surgery and seven from TKI beginning, the CT showed remission of loco-regional disease and a partial response of lung disease with a reduction of TG (1,424 mg/l vs 2.927). Although the TKI therapy, the patient had a weight increase (5 kg). This was the first case of DTC with tracheoesophageal fistula treated with surgery. The surgical treatment allowed not only the local control of the disease but also the possibility to start again systemic treatment with Lenvatinib. The present case also demonstrates that local treatment, despite highly invasive, could improve the subjective perception of quality of life.

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PS2-16-02

BIG data analysis of secondary cancer risk according to thyroid cancer in patients with lipid metabolic disease

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Lipid metabolism diseases are continuously increasing due to lifestyle changes, and many studies have reported that the incidence of other cancers increases in these diseases. Thyroid cancer occurs frequently, and its prognosis is good; therefore, there are many survivors. In this study, we aimed to confirm whether thyroid cancer itself affects the risk of secondary cancer in patients with lipid metabolic disease and the factors affecting this risk through analysis of institutional data and big data from the Korea National Health Insurance system. In both data, patients were extracted through the diagnosis of lipid metabolic disease, and the risk of secondary cancer was compared according to the presence or absence of thyroid cancer. In the analysis of institutional data, the risk of secondary cancer increased by approximately two-fold compared to that in patients without thyroid cancer. Interestingly, the risk of secondary cancer was not significantly increased in the patient group with both non-alcoholic fatty liver disease and dyslipidemia. In the nationwide cohort, univariate and multivariate analyses indicated that hazard ratios of thyroid cancer were 1.329 (95% confidence interval [CI], 1.153–1.533) and 1.301 (95% CI, 1.115–1.517), respectively. In the risk analysis of individual cancers, lip, tongue, mouth, lung, bone, joints, soft tissue, skin, brain, and male cancers and lymphoma showed significantly increased hazard ratios after the occurrence of thyroid cancer. As a result of analysis according to thyroid hormone replacement, analysis of institutional data showed that the risk of secondary cancer decreased with long-term use. In the population-based cohort analysis, 261,598 patients who underwent surgery for thyroid cancer were included. Among them, 11,790 patients had a second primary cancer and 47,160 patients without secondary primary cancer were matched. The average dose of thyroid hormone also increased the adjusted odds ratio (OR) in both low ($\leq$ 50 μg, OR 1.29, CI 1.12–1.48) and high ($>$ 100 μg, OR 1.24, CI 1.12–1.37) doses. Analyzing over time, the adjusted OR of second primary cancer was increased compared to patients without thyroid hormone administration, especially in short ($\leq$ 1 year) duration, 1.29 (CI, 1.12–1.48), and long ($>$ 5 years) duration, 1.24 (CI, 1.12–1.37). Thyroid cancer in patients with dyslipidemia or non-alcoholic fatty liver disease might be a valuable factor for predicting the development of other cancers, and insufficient and excessive thyroid hormone replacement might be linked to increased secondary cancer in patients undergoing thyroidectomy.

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PS2-16-03

The incidence of thyroid cancer in europe: A meta-analysis

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Background
The incidence of thyroid cancer (TC) has been increasing in recent years while mortality has remained stable. The cause of this increase is unclear, although several hypotheses have been proposed. While the increased incidence may only be apparent due to increased testing, there is data that suggest that there may be a real increase in incidence related to different risk factors. The aim of this meta-analysis was to determine the current incidence of TC in Europe.
Methods
A literature search was performed using MEDLINE and SCOPUS databases looking for studies published between January 2017 and December 2021 using the keywords *thyroid cancer, prevalence, incidence, epidemiology* and *Europe*, which yielded 525 studies. After excluding papers with insufficient or inadequate information, 53 studies were further evaluated. Of those, only 15 fulfilled the inclusion criteria and were subsequently analysed. We performed random-effect meta-analysis using MedCalc software. Meta-analysis was performed on all TC and on each histotype (papillary, follicular, medullary, and anaplastic) separately.
Results
TC mean incidence (95% CI) per 100,000 person-years was 10.2 (6.3-15.0); for women and men, 15.4 (10.4-21.4) and 5.0 (3.5-6.8), respectively. The incidences for histotypes (total, women and men) were: papillary 6.0 (2.4-11.3), 11.7 (6.0-19-3), 4.2 (2.4-6.4); follicular 1.1 (0.9-1.4), 1,8 (1.7-1.9), 0.8 (0.7-0.8); medullary 0.5 (0.4-0.6), 0.6 (0.4-0.8); and anaplastic 0.2 (0.1-0.3), 0.2 (0.2-0.3), 0.2 (0.1-0.2).
Conclusions
To the best of our knowledge, this study is the first to offer an overview of the current incidence of TC in Europe and provides information on the incidence of all histotypes of TC as well. In all cases, the incidence in women was higher than in men. The incidence of papillary TC was found to be the highest among the different histological types, followed by follicular, medullary, and anaplastic. The results are consistent with the global trend of increasing incidence of papillary TC.

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PS2-16-04

A rare association: graves's disease and thyroid cancer with hyperfunctioning lung metastasis

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Introduction
The association between thyroid cancer and thyrotoxicosis is rare and, in particular, autonomous hyperfunctioning metastasis of differentiated thyroid cancer (TC) are seldom described, with a prevalence of 0.71%. Althought most hyperfunctioning metastasis are derived from follicular thyroid cancer (FTC), metastasis from papillary thyroid cancer (PTC) have been also reported. Bone metastasis account for the majority of cases. Hyperfunctioning TC metastasis have been rarely associated with anti-TSH receptor antibodies (TRAbs).
Clinical case
A 53-year-old male patient came to our attention in April 2018 for a non-toxic multinodular goiter. Because the dominant nodule (4 cm) was indeterminate at high risk (TIR3B according to the Italian classification of 2023), thyroidectomy was suggested but the patient refused it. Four years later, after the appearance of asthenia, palpitations, weight and hair loss, hyperthyroidism with positive TRAbs (19.2 UI/l, n.v. $<$1.5) was diagnosed, and anti-thyroid drug (methimazole) and beta blocker were started. CT scan confirmed the multinodular goiter and showed suspicious cervical lymphadenopathies and lung metastasis. In October 2022, the patient underwent total thyroidectomy and central and lateral cervical lymph-nodes dissection. Histology showed a poorly differentiated thyroid cancer associated with classical subtype multifocal papillary TC (positive for somatic mutation in *NRAS gene* and in *TERT promoter*), with multiple metastatic lymph-nodes [T3a(m)N1bM1]. Treatment with LT-4, suggested at discharge, was tapered down two months later, due to thyrotoxicosis. Still, thyrotoxicosis persisted, TRAbs were still positive (15 U/l), and methimazole was re-started and titrated up to 40 mg/day. In February 2023 the patient underwent 131-I treatment (81 mCi), after methimazole had been withdrawn for two days. Post-therapeutic SPECT-CT scan, performed ten days later, showed lymph-node and lung metastasis, which were avid of radioiodine. The patient was still hyperthyroid with positive TRAbs, at high title (19.60 UI/l). A month after 131-I treatment the levels of thyroid hormones started falling and methimazole was decreased to 15 mg/die.
Conclusions
We present the case of a patient with hyperfunctioning lung metastasis from thyroid cancer, with positive TRAbs. We hypothesize that TSH receptor expressed on the metastatic cells is activated by serum TRAbs, leading to the production of thyroid hormone and persistent hyperthyroidism.

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PS2-16-05

Quality of life in differentiated thyroid cancer survivors in bulgaria

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Objectives
To evaluate the quality of life (QoL) in patients with differentiated thyroid cancer (DTC) by a validated thyroid-specific questionnaire and to identify factors with significant impact on the QoL.

Methods
Two hundred DTC patients, treated in one tertiary center, were recruited in the study. One year after the thyroid surgery, they completed the QoL Cancer Survivor Instrument – Thyroid version questionnaire. The questionnaire assessed their physical, psychological, social and spiritual well-being. Additional data were collected about the participants' comorbidities, tumor characteristics and treatment, educational level and marital status.
Results
Eighty-four percent of the patients were female and the median age of the study group was 41 years (IQR, 33-52). The majority of the DTCs (99.5%) were papillary thyroid cancers with predominance of TNM stage I and II cases. The reported overall QoL was 6.9/10 (5.9-7.6), with 0 indicating the worst QoL. The scores for each of the assessed subscales were: 7.5 (5.9-8.6) for physical, 5.9 (4.6-7.2) for psychological, 8.4 (7.4-9.3) for social and 5.7 (4.9-6.5) for spiritual well-being. The greatest discomfort in the physical state was caused by: fatigue (6.0, IQR 3-8), cold or heat intolerance (6.5, IQR 4-10), dry skin/hair problems (7.0, IQR 3-10), and sleep changes (7.0, IQR 4-10). The lowest individual QoL score was observed for the distress by the initial diagnosis (1.0, IQR 0-5). The participants did not report a significant effect of the disease and treatment on their professional performance and daily routines. The females reported worse overall QoL than the males ($P = 0.02$). In the females were observed lower total physical and psychological subscale scores than in the males ($P < 0.001$; $P = 0.01$, respectively). Female sex was the only factor which significantly decreased the overall QoL of the study participants ($P < 0.001$).
Conclusions
Despite the excellent long-term prognosis, DTC had negative impact on the survivors' QoL. Understanding the specific difficulties and concerns of DTC patients as well as identifying the factors that contribute to their decreased QoL could improve the postoperative care.

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PS2-16-06

Prevalence, screening and clinical implications of thyroid cancer in patients with acromegaly: A cohort study

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Objective
Thyroid cancer (TC) screening in acromegaly is a controversial topic. The Endocrine Society opposes routine TC screening in acromegaly patients without a palpable nodule, and the American Thyroid Association does not consider acromegaly to be a high-risk condition for developing TC. However, acromegaly is associated with an increased risk of TC, and some centers opt for thyroid ultrasound screening even in the absence of palpable thyroid nodules. Being one of the supporters of this strategy, we aimed to present the characteristics of our acromegaly patients with a diagnosis of differentiated TC.
Methods
This was a single-center retrospective cohort study. Among our registry of 395 adult acromegaly patients diagnosed between 1998 to 2022, thirty-one (17 female, 14 male) with a histopathological diagnosis of differentiated TC were evaluated.
Results
The prevalence of differentiated TC in our acromegaly cohort was 7.8%, with a slight female predominance (55%). The mean age ($\pm$standard deviation) at the onset of acromegaly symptoms and at acromegaly diagnosis were 38.3 ± 12.1 and 41.8 ± 11.4 years, respectively. The mean time between the two occasions was 3.1 ± 4.2 years. The mean age at TC diagnosis was 47.5 ± 10.5 years. The mean time since acromegaly diagnosis to TC was 5.7 ± 6.8 years. Three patients were diagnosed with TC within the two years prior to being diagnosed with acromegaly, three were diagnosed within a year of being diagnosed with acromegaly, and seven were diagnosed >10 years after being diagnosed with acromegaly. None of the patients had consistently normal IGF-I levels until TC diagnosis. Twenty patients (64.5%) had multiple fine needle aspiration biopsies until being diagnosed with TC. Except for one patient, all were treated with total thyroidectomy; the remaining patient underwent hemithyroidectomy. The mean tumor size was 1.3 ± 1.2 cm, ranging between 2 mm to 5 cm. The most common TC subtype was papillary TC (29, 93.5%). Fifteen patients had multicentric, while ten had bilateral TCs. Cervical lymph nodes were involved in three patients. Vascular invasion and positive surgical margins were identified in three and two patients, respectively. Fifteen patients received radioactive iodine treatment, with a median dose of 100 mCi (range: 50-150 mCi). In four patients, there was another primary malignant neoplasm in addition to TC. There was no TC-related death.
Conclusions
Papillary TC is common in acromegaly patients. While routine thyroid nodule screening has the disadvantage of increasing the risk of overdiagnosis, thyroid ultrasound monitoring would be beneficial, particularly in patients with persistently elevated IGF-I levels.

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PS2-16-07

Tumor lysis syndrome during neoadjuvant selpercatinib treatment for medullary thyroid cancer

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Selpercatinib is a specific RET inhibitor, highly effective in the treatment of advanced RET-mutant medullary thyroid carcinoma (MTC). The consequences of selpercatinib administration in MTC patients who have not undergone thyroid surgery are still unknown. We report the case of an 84-year-old man undergoing investigations for worsening diarrhea and weight loss. Upon a neck ultrasound scan and blood exams that pointed out high levels of both calcitonin (CT, 20.583 ng/l) and carcinoembryonic antigen (CEA, 246 μg/l), he was diagnosed with locally advanced MTC. The Next-Generation Sequencing analysis identified the somatic RET M918T mutation. Due to the patient age, his comorbidities, and the tumor burden, surgery was excluded and neoadjuvant treatment with selpercatinib 160 mg twice per day was started. The US examination and blood exams performed after two weeks of treatment displayed a significant reduction of both primary and metastatic lesions, along with a considerable decrease of both CT and CEA. During the fourth week of treatment, the patient experienced weakness, nausea, vomiting, oliguria, and blunted consciousness. Blood exams detected severe hypocalcemia, hyperphosphatemia, hyperkalemia, hyperuricemia, and acute kidney injury on pre-existing chronic kidney disease (CKD). As the Cairo-Bishop criteria were satisfied, a tumor lysis syndrome (TLS), secondary to the systemic anti-tumor therapy, was diagnosed. Accordingly, the patient withdrew selpercatinib and received high-volume intravenous expansion with crystalloid fluids, along with the administration of calcium, rasburicase, phosphorus- and potassium-binding agents. Nevertheless, he experienced renal function worsening and life-threatening metabolic abnormalities. After unsuccessful treatment with furosemide and ethacrynic acid, he underwent intermittent renal replacement therapy. After nine days of dialysis, a significant clinical improvement was obtained, leading to replacement treatment interruption. Upon discharge, the patient re-started selpercatinib at the dose of 80 mg twice per day. After 11 months, the patient is still well tolerating the treatment, renal function is stable and neither new manifestations of TLS nor any other AE appeared. Tumor lesions were further reduced and stable, with stable serum levels of CT and CEA. To the best of our knowledge, this is the first case report of selpercatinib-induced TLS during treatment of MTC. The case is of particular interest also due to the long-term stability of the MTC obtained in a patient who was not operated on. This evidence could pave the way for future application of selpercatinib in this subset of patients.

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PS2-16-08

Lobectomy outcomes in patients with low-risk differentiated thyroid cancer: oncologic and safety outcomes at a swiss tertiary referral center

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Background
Recent guidelines recommend lobectomy (LOB) when compared to total thyroidectomy (TTX) as the preferred approach for patients with low-risk differentiated thyroid cancer (DTC). Major advantages are the avoidance of lifelong hormone replacement therapy and the absence of any risk for contralateral recurrent laryngeal nerve palsy and postoperative hypoparathyroidism with no or minimal increased risk for adverse oncological outcomes. However, this limited approached still has not been universally adopted.
Methods
We performed a retrospective analysis of prospectively collected data of consecutive patients with DTC undergoing thyroid surgery between July 2015 and June 2022 at our tertiary referral center. Patients were stratified low, intermediate and high-risk according to the ATA guidelines and staged according to the current TNM classification. Treatment recommendations were made by the local thyroid board and generally based on the 2015 ATA guidelines and 2019 Swiss recommendations. Patients were followed every 6 to 12 months by neck ultrasound. Data on oncological and safety outcome were analyzed and are presented by descriptive statistics.
Results
277 patients (74.7% females, median age 50.3 years, range 16-80 years) underwent thyroid surgery for DTC with 146 (52%) assigned to the ATA low-risk group. The median follow-up time was 2.36 years. 118 (42.6 %) of low-risk patients were treated with LOB (62.7% pT1a, 28.8% pT1b, 8.5% pT2). Patients treated with TTX (10.7% pT1a, 42.9% pT1b, 46.4% pT2) 28 (19.2%) received additional radioiodine (22 adjuvant, 6 remnant ablation). In the LOB group no recurrence was observed and 1 patient treated with TTX and adjuvant radioiodine was suspicious for a structural relapse. In the LOB group 43 (36.4%) patients met recommended TSH goals with no additional levothyroxine replacement. Transient RLNP occurred in 3 patients (2.5%) of the LOB and 1 patient (3.6%) of the TTX group. Transient hypoparathyroidism occurred in 4 (14.3%) of the TTX group.
Conclusion
In patients with low-risk DTC lobectomy does not carry an increased risk fur recurrence, obviates the need for lifelong thyroid hormone replacement in the majority of patients and should be reinforced as the preferred surgical strategy.
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PS2-16-09

A rare case of late folliculate of the lower limbs secondary to vandetanib
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Introduction
Vandetanib is a multikinase inhibitor of the family of EGF receptor inhibitors whose main indication is medullary thyroid cancer at the locally advanced or metastatic stage. It is associated with cutaneous toxicity represented mainly by acneiform eruptions and hand-foot syndrome appearing a few weeks after the start of treatment. Folliculate is rare We report a rare case of late chronic folliculate of the lower limbs secondary to vandetanib.
Observation
77-year-old patient treated with vandetanib for an inoperable multimetastatic advanced stage (nodal, hepatic, pulmonary and bone) medullary thyroid carcinoma. Early on, he presented with a hand-foot syndrome resolved by doxycycline and topical corticosteroids. At eight months of treatment, an eruption of very inflammatory, itchy and painful papulo-pustular lesions of the lower limbs appears, made up of a polymorphic inflammatory infiltrate located around the pilosebaceous follicle on histology. Slowly favorable evolution under systemic corticosteroid therapy, doxycycline and anxiolytics.
Discussion
We report a rare case of late folliculate under vandetanib. This atypical presentation has been described in rare observations (three to date). Poorly individualized in the literature, this clinical picture is distinguished from acneiform eruptions which are early and of low intensity predominant on the face and trunk, while late folliculate preferentially sits on the limbs and its onset is delayed, the lesions are of greater size, inflammatory, with pruritus and pain.
Conclusion
Late chronic folliculate of the limbs secondary to vandetanib is rare and not very serious and can break social and family ties.
Keywords: Vandetanib, MCT, Folliculate, Lower limbs
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Thyroid Cancer Diagnosis 2

PS2-17-01

The 2017 bethesda system for reporting thyroid cytopathology: the experience of a tertiary center
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Objectives
The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a validated and widely used tool for thyroid nodules triage. Studies reporting on the frequency of each Bethesda category are scarce, and there are wide discrepancies in the reported results between the various centers. Our aim was to register all cytological reports of the thyroid fine needle aspiration biopsies (FNAB) reviewed in the Cytology Department of a tertiary hospital during a calendar year, and to compare them with the literature and the TBSRTC recommendations.
Methods
We reviewed 448 reports of thyroid FNAB performed under ultrasound guidance and reported at the Cytology Department of the University Hospital of Patras from 1/1 to 31/12/2022.
Results
Table 1 shows the percentages of each TBSRTC category in all FNAB samples examined, in those reported by the most experienced cytologist and in those reported by all other cytologists, the percentages reported in the literature and the expected percentages according to the TBSRTC recommendations. In the samples examined by the most experienced cytologist, there were significantly less reports of categories I and III, and significantly more reports of category II. Of the 30 patients with category III FNAB, thyroidectomy was recommended to 5 due to TIRADS V sonographic appearance of their nodules (3 surgeries done so far: 2 papillary carcinomas, 1 follicular tumor of uncertain malignant potential), and repeat FNAB was recommended to the rest.
Conclusions
The percentages of cytological diagnoses in thyroid FNAB material per TBSRTC category in our center were similar to the expected according to the TBSRTC recommendations. Increased experience of the reporting cytologist was associated with more Bethesda II and less Bethesda I and III reports.

Table 1 Percentages of reports per TBSRTC category for the population studied, literature data and TBSRTC recommendations

	All samples	Most experienced cytologist	All other cytologists	Literature data	TBSRTC
n	448	275	173		
I	97 (21.7%)	43 (15.6%)	54 (31.2%)*	1.2 – 20.1%	2 – 20% (ideally <10%)
II	307 (68.5%)	215 (78.2%)	92 (53.2%)*	23.5 – 87.5%	60 – 70%
III	30 (6.7%)	8 (2.9%)	22 (12.7%)*	0.8 – 27.2%	3 – 6% (ideally <7% or <10%)
IV	1 (0.2%)	0	1 (0.6%)	2.9 – 16.8%	-
V	3 (0.7%)	2 (0.7%)	1 (0.6%)	0.8 – 37.2%	-
VI	10 (2.2%)	7 (2.5%)	3 (1.7%)	2.3 – 19.5%	3 – 7%

* $P < 0.001$ vs most experienced cytologist

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PS2-17-02

Monocentric validation of the 'thyroid risk score' (TRS) in a large series of indeterminate thyroid nodules

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The diagnosis of indeterminate thyroid nodules is a challenge in cytopathology practice. To increase the diagnostic accuracy in these cases, we previously set up a 'thyroid risk score' (TRS), derived from the sum of the scores assigned to: cytology + EU-TIRADS classification + nodule size + molecular profile. In the present study we prospectively validated the reliability of the TRS in the clinical practice. From 2018 to 2022 we evaluated 354 indeterminate nodules (210 Bethesda class III and 144 class IV) before surgery. Genetic analysis was performed by a custom NGS target panel able to analyze most of the mutations involved in thyroid cancers in 11 genes on DNA and 10 recurrent gene fusions on cDNA. Genetic alterations were detected in 66/354 nodules (19%). Forty-three mutated (65%) and 48 non-mutated nodules (17%) were submitted to surgery. Furthermore, 23 cases with a low suspicious TRS (<6) underwent thermal ablation. The remaining cases are waiting for surgery (TRS ≥ 6 or compressive goiter), or are under ultrasonographic follow-up (TRS <6 or refusing surgery). The risk of malignancy (ROM) associated to different genetic variants was: BRAF and RET/PTC3 100%, TERT 60%, RAS 0-50%, EIF1AX and PAX8/PPARG 0%. The ROM in operated lesions increased paralleling to the calculated TRS: $4<$TRS≤ 6 (low suspicion), $6<$TRS≤ 8 (intermediate suspicion), and TRS >8 (high suspicion) resulted associated to a ROM of 14, 43 and 100%, respectively. ROC curves confirmed the previous identified score >6.5 as the best threshold to differentiate between malignant and benign nodules ($P < 0.001$), with a sensitivity of 76%, specificity of 78%, positive and negative predictive values of 70% and 82%, respectively and accuracy of 77%. This threshold showed a better performance in the differential diagnosis of nodules than either the various parameters included in the TRS. In conclusion, the TRS represents a useful approach to identify malignancy in indeterminate thyroid lesions, reducing unnecessary surgeries.

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PS2-17-03

Role of cervical ultrasound in the pre-operative evaluation of central compartment lymph nodes in thyroid cancer

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Background and Objective

In thyroid cancer (TC) central compartment (CC) neck dissection (CCND) should accompany thyroidectomy in case of clinical and/or cytological suspicion of lymph node (LN) metastases. Cervical ultrasound has been indicated as the first-line examination in the pre-operative staging of TC, although its diagnostic performance in evaluating CC LN is controversial. Proving that cervical ultrasound can accurately identify CC metastases would allow to use this exam to choose surgery extension, avoiding prophylactic CCND and its higher surgical risks. Aim of this study was to evaluate sensitivity (SS), specificity (SP) and diagnostic accuracy (DA) of preoperative cervical ultrasound in detecting CC LN metastases in TC patients referred to a high-volume center for thyroid diseases.

Methods

We enrolled patients undergoing total thyroidectomy and at least unilateral CCND for TC at our center between January 2010 and July 2022; we included only those for whom a preoperative cervical ultrasound aimed at the study of cervical LN was available. Histological examination was considered as the gold standard. The location in which staging ultrasound was performed (our center vs other centers) and the size of primary tumor were taken into consideration as variables potentially impacting study outcomes.

Results

198 patients were included. Most of them had preoperative ultrasound performed at our center (86%) and had a small tumor (57% T1, 14% T2, 28% T3). On preoperative ultrasound, CC LN were defined as suspicious for metastases in 45% of cases. On definitive histological examination nodal metastases were found in 55.5% of patients. SS, SP and DA of preoperative ultrasound were respectively 60.9%, 75% and 67.2%. SS and DA were higher in the group of patients who had preoperative ultrasound performed at our center (respectively 73% and 73.1%; $P < 0.001$); SS and DA were inversely correlated with primary tumor size, although this was not statistically significant (Table 1).

Conclusions

Preoperative cervical ultrasound presents some limitations in the correct local staging of TC patients, especially in the evaluation of CC lymphatic involvement. Our data highlight that, given the better SS and DA, it should be preferably performed in high-volume centers specifically dedicated to thyroid diseases; however, especially in case of larger primary tumors, prophylactic CCND should be taken in consideration.

Table 1 SS, SP and DA of preoperative ultrasound according to the size of the primary tumor

	T1	T2	T3	*P*-value
SS	65.5%	58.3%	53.7%	0,5
SP	73.7%	75%	80%	0,8
DA	69.6%	67.9%	60.7%	0,507

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PS2-17-04

PRO-gastrin-releasing peptide as an additional screening marker in the diagnostic work up for medullary thyroid carcinoma

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Background

Patients with medullary thyroid carcinoma (MTC), a neuroendocrine tumour derived from the parafollicular C-cells, often present with metastasized disease. Survival strongly correlates with stage of disease at diagnosis, illustrating the need for early diagnosis. Calcitonin (CT), a well-established tumour marker for MTC, is limited by a high rate of false positives in the screening phase. Promising new markers for MTC are procalcitonin (PCT) and progastrin releasing peptide (proGRP). Where literature has proven non-inferiority for PCT, evidence is lacking for proGRP. Previous studies looking into proGRP had small sample size, mostly retrospective design and large variability in reported sensitivity, specificity and cut-off value. Therefore, the present study prospectively evaluated the clinical performance of proGRP in a large series of patients with pathology proven diagnosis of MTC vs other thyroid disease.

Methods

Serum samples from 278 patients that underwent total thyroidectomy for either benign thyroid disease ($n = 117$), differentiated and other thyroid carcinomas (non-MTC) ($n = 137$) or MTC ($n = 24$) were collected before surgery. Serum proGRP and PCT concentrations were measured using Lumipulse G1200 (Fujirebio), CT

was measured using Immulite 2000XPi (Siemens). Cut-offs for CT (10 pg/mL) and PCT (0.15 ng/mL) were based on literature. Cut-off for proGRP (100 pg/mL) was based on previous studies and validated in a local cohort.
Results
Median proGRP concentration (300.5; 69.7 – 1249.8) was significantly higher in MTC compared with benign thyroid disease (30.3; 23.9 – 38.2) and non-MTC (27.1; 21.9 – 34.5) ($P < 0.001$). Despite, having a good specificity of 99.6%, sensitivity of proGRP was low (70.4%). Therefore, proGRP did not perform better than CT in discriminating between MTC and benign thyroid disease or non-MTC in a screening setting. As expected, PCT performed as good as CT with a sensitivity off 100% and a specificity of 98.5% (CT sensitivity and specificity were 100% and 98.8% respectively). Combining proGRP and CT lead to a perfect specificity (100%), but decreased sensitivity even further (69.2%).
Conclusion
ProGRP alone does not perform better as a screening marker for MTC than CT. Furthermore, there is no added value of combining proGRP and CT in a two-step approach in cases where calcitonin concentration is inconclusive. This study supports the evidence in literature for PCT as a tumour marker in MTC, with PCT having clear advantages over CT given the better (pre-) analytical characteristics, such as inter-assay comparability and protein stability.

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PS2-17-05

18F-DOPA-PET/ct in medullary thyroid cancer patients with biochemical incomplete response

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Objectives
PET/CT scan with ^{18}F-fluoro-dihydroxyphenylalanine (^{18}F-DOPA) is an emerging useful tool in medullary thyroid cancer (MTC) patients. The question whether ^{18}F-DOPA-PET/CT could be useful in MTC patients with biochemical incomplete response (BiR) is to clarify.
Methods
Fifty-three MTC patients with BiR performed ^{18}F-DOPA-PET/CT scan between May 2021 and December 2022 after having performed total body CT scan with i.v. contrast, all with negative or indeterminate findings.
Results
Most of patients were females (60.4%). The median age at the diagnosis was 47 years. Sixteen (30.2%) patients had familial form of MTC. When ^{18}F-DOPA-PET/CT was performed [median 37 months (IQR: 102-196.5) from diagnosis], the median serum calcitonin (CTN) value was 399 (165-1135) pg/mL. ^{18}F-DOPA-PET/CT result was negative in 15/53 (28.3%) cases. Conversely an uptake of the radiotracer was observed in 38/53 (71.7%) cases. CT scan was negative in 20/53 (37.7%) while in the remaining 33 (62.3%) patients, indeterminate findings were underlined. When comparing the two imaging procedures, they were both negative in 11 (20.8%) cases. In 9 (16.9%) cases of negative CT scan, ^{18}F-DOPA-PET/CT was positive in the neck and in 2 case in the liver. Among 33 patients with indeterminate findings at CT scan, 29 showed uptake at ^{18}F-DOPA-PET/CT (neck in 25, mediastinal lymph node in 5, bone in 4, liver in 4 and 2 in lung), while 4 were negative. When we analyzed the concordance between the two procedures (uptake of ^{18}F-DOPA in the same sites of indeterminate lesions described at CT scan), 9 patients showed a concordance, while 3 patients a discordance (uptake of ^{18}F-DOPA in other sites than those described at CT scan). The other 17 patients showed a partial concordance, most of whom (11/17 – 64.7%) had more indeterminate lesions at CT scan than ^{18}F-DOPA uptake.
Conclusions
In most of the cases of MTC patients with BiR and negative or indeterminate findings at CT scan, ^{18}F-DOPA-PET/CT scan revealed radiotracer-enhancing lesions. Therefore, in this setting of uncertain diagnostic imaging and detectable CTN values, ^{18}F-DOPA-PET/CT can be helpful to better define the nature of indeterminate lesion at CT scan. It is worth to note, however, that although these findings are effective in improving the follow-up of the disease, we did not experience any change in the clinical management, because of the small size of the lesions.

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PS2-17-06

Impact of lymphovascular invasion on otherwise low-risk papillary thyroid carcinomas: A retrospective and observational study

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Background
Presence of venous vascular invasion is a criterion of intermediate risk of recurrence in papillary thyroid carcinoma (PTC). However, the presence and type of vascular invasion (lymphatic or venous) is often underreported and its impact on PTCs without other risk features remains unknown.
Objective
To evaluate the impact of both lymphatic and venous invasion on the risk of recurrence/persistence on otherwise low-risk PTCs.
Methods
Retrospective study including patients with otherwise low-risk PTCs but with vascular invasion, diagnosed between 2013 and 2019. The persistence/recurrence during the follow-up was evaluated. Pathology was reviewed to confirm the presence of lymphovascular invasion and determine the type of invasion.
Results
A total of 141 patients were included. Lymphovascular invasion was confirmed in 20.6%. After surgery, 48.9% ($n = 69$) of the patients received radioactive iodine (RAI). The median follow-up time was 4 [3-6] years. Overall, 6 (4.2%) patients experienced persistent/recurrent disease in the neck, including 3 with lymphovascular invasion, confirmed as "only lymphatic". Overall, patients with tumors harboring lymphovascular invasion had significantly more persistent/recurrence disease compared with those without lymphovascular invasion (10.3% vs 2.7%, $P = 0.1$), especially in the subgroup of patients not treated with RAI (20% vs 1.6%, $P = 0.049$) [OR 15.25, 95% CI 1.24-187.85, $P = 0.033$].
Conclusion
Lymphovascular invasion, including lymphatic invasion only, is associated with a sensibly higher risk of persistent/recurrent disease in otherwise low-risk PTCs, namely in patients not treated with RAI. Lymphatic invasion could have a role in risk-stratification systems for decision making.

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PS2-17-07

Correlation of three thyroglobulin assays in the management of differentiated thyroid cancer (DTC) patients

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Correlation of three thyroglobulin assays in the management of differentiated thyroid cancer (DTC) patients
Introduction
Thyroglobulin(Tg) is the main biochemical marker of DTC. Usual immunometric assays(IMA) are prone to interference by autoantibodies which can lead to erroneous results. LC-MS/MS has been described as an assay that may provide accurate results, however the literature reported up to 40% of undetectable rates in patients with positive thyroglobulin antibodies(TgAb) and structural disease.

Objective
To compare three different Tg assays in patients with positive and negative TgAb.
Methods
129 patients with negative (97) and positive TgAb (32), had Tg measured by LC-MS/MS assay(Tg-MS) with functional sensitivity of 0.7 ng/mL and at least one of the 2 IMAs (by Beckman^{R} and Roche^{R}) with FS of 0.1 ng/mL. Negative TgAb samples were considered when TgAb were negative at least by two Methods Roche ^{R}; Siemens^{R} and AntiTgII Siemens^{R}. The correlation between assays was assessed using Spearman's correlation coefficient and Deming linear regression. Strength of the correlations were determined by the McBride scale: $r < 0.90$ poor; $r = 0.90$ to 0.95 moderate correlation; $r = 0.95$ to 0.99 is substantial; $r > 0.99$ almost perfect
Results
Comparing the performance of Tg-MS and Tg-IMA in samples with negative TgAb, the overall concordance of positive and negative results between Tg-IMAs and Tg-MS was 91.8% (89/97) when the FS of each assay was used. The concordance between Tg-Roche and Tg-Beckman was 99% (just one sample discordant). Method comparison between the Tg-IMAs and Tg-MS in TgAb negative specimens correlated well: correlation coefficient between Tg-MS and Tg-Beckman was r 0.950; Tg-MS and Tg-Roche were r 0.956; and the best correlation coefficient was seen between Tg-Beckman and Tg-Roche (r 0.982). On the other hand, comparing the performance of Tg-MS and Tg-IMA in samples with positive TgAb ($n = 55$) undetectable results of Tg were observed in 20/32 patients (62.5%) in IMAs and in 22/32 (68.8%) in the LC-MS/MS assay. The overall concordance in TgAb positive samples between Tg-IMAs and Tg-MS was 87.5% (28/32). Tg-IMAs agreement was 96.4% (27/28). Correlations between Tg-IMAs and Tg-MS were worse than observed in negativeTgAb patients. The correlation coefficient between Tg-MS and Tg-Beckman was r 0.875 and between Tg-MS and Tg-Roche was r 0.878. Correlation between Tg-Beckman and Tg Roche was better (r 0.965)
Conclusion
The 3 assays correlated well in negative TgAb samples but had poor correlation between IMAs and LC-MS/MS assays in the TgAb positive samples. Therefore, efforts should be done to develop assays able to measure Tg in TgAb positive samples.
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PS2-17-08

Characteristics of incidental pappillary thyroid microcarcinomas detected by various nuclear medicine imaging techniques

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Objective
The prevalence of incidentally discovered papillary thyroid microcarcinoma (iPTMC) has increased with the expanded use of diagnostic imaging, including nuclear medicine imaging techniques. While iPTMC appears to have a better prognosis than non-incidental PTMC, it was suggested that thyroid carcinomas that were incidentally discovered during 18F-fluorodeoxyglucose positron emission tomography/computer tomography (FDG PET/CT) or parathyroid scintigraphy may have poor prognostic features, with no particular emphasis on iPTMCs. The aim of this study was to assess and compare the histopathologic characteristics of iPTMCs discovered via various nuclear medicine imaging methods.
Methods
Patients with PTMC who had a confirmed histopathological diagnosis between 2014 and 2023 were evaluated retrospectively. Among a total of 957 subjects with PTMC, 59 were incidentally discovered during diagnostic imaging using nuclear medicine techniques including thyroid scintigraphy ($n = 27$), parathyroid scintigraphy ($n = 11$), or FDG PET/CT ($n = 21$) that were performed for causes unrelated to thyroid carcinoma.
Results
iPTMCs discovered by either FDG PET/CT, parathyroid or thyroid scintigraphy represented 6% of all PTMC. The indications for using FDG PET/CT was to stage different cancers ($n = 19$) or find the primary location of a metastatic cancer ($n = 2$), while parathyroid and thyroid scintigraphies were to determine the origins of hypercalcemia and thyrotoxicosis, respectively. The mean patient age was 53.6 ± 12.2 years, and 65% ($n = 39$) were female. The cytological examinations were mostly reported as BETHESDA category III or V. Total thyroidectomy was performed in 93% ($n = 55$) of the cases, with central lymph node dissection in twelve. In histopathological examination, most of the cases had follicular subtype ($n = 18$) while seven patients had tall cell subtype. iPTMC size was greater than 5 mm in 68% of cases, and cervical lymph node metastasis was detected in 15%. iPTMCs discovered by FDG PET/CT showed higher rates of multifocality, capsular invasion, cervical lymph node involvement and extrathyroidal invasion than those discovered by parathyroid or thyroid scintigraphy; however, only extrathyroidal invasion reached statistical significance. HBME-1, CK-19, and Galectin-3 expressions were comparable between cases discovered by FDG PET/CT and other methods, whereas loss of CD-56 expression was prevalent in cases detected by FDG PET/CT. In two cases where FDG PET/CT was used to identify the primary origin of a metastatic cancer, scalp and thoracic vertebral lesions were biopsied to identify papillary thyroid cancer metastases.
Conclusions
Patients with PTMCs usually have a good prognosis. However, based on the results of this research, which looked at a subset of iPTMCs identified using nuclear medicine imaging methods, we concluded that iPTMCs found during FDG PET/CT may have poor prognostic characteristics, leading to more frequent extrathyroidal invasion and even distant metastases.
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PS2-17-09

Clinical application of grading system in sporadic medullary thyroid carcinoma patients

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Introduction
Despite its neuroendocrine origin, only recently an international study group proposed a dedicated grading system (IMTCGS) for medullary thyroid carcinoma (MTC). IMTCGS is an independent and powerful tool able to predict disease specific survival (DSS) as well as distant metastasis-free (DMFS) and locoregional recurrence-free survivals (LRFS), regardless of other risk factors, including staging.
Objectives
To evaluate the performance of IMTCGS in predicting DSS, DMFS and LRFS in a series of sporadic MTC divided according to different clinical presentations (stage I-II, stage III, stage IVa/b and stage IVc).
Methods
Pathologic and clinical features of 303 patients with sporadic MTC, all surgically treated at the Endocrine Surgery Unit and followed at the Endocrine Unit of the University Hospital of Pisa, from 2000 to 2018, were collected. All samples of the primary tumors were re-evaluated by an expert pathologist to be able to characterize high-grade and low-grade tumors according to IMTCGS criteria.
Results
174/303 (57.4%) patients were female and the median age at diagnosis was 54 (IQR 44-65). According to AJCC 8th edition, 175 (57.8%) cases were classified in stage I-II, 55 (18.2%) in stage III, 42 (13.9%) in stage IVa/b, and 31 (10.1%) in stage IVc. During a median follow-up of 79 months (IQR 35-133), patients with high-grade tumors showed lower DMFS and LRFS ($P < 0.001$) than low grade ones. When dividing patients according to stage, high-grade significantly helped to identify those who had lower DMFS and LRFS in stage I-II and III ($P < 0.05$). However, no differences in DMFS and LRFS between high-grade and low-grade tumors were observed in stage IVa/b cases ($p > 0.05$) Twenty-eight patients (9.2%) died for cancer related causes in a median time of 119 months (IQR 70-165). Patients with high-grade tumors showed a lower DSS ($P < 0.001$) compared with low-grade. However, when dividing patients according to the initial stage, no difference in DSS were observed between high-grade and low-grade in all the 4 subgroups analyzed ($p > 0.05$)
Conclusions
In our series, the clinical usefulness of grading system in sporadic MTC patients seems to be limited. The presence of distant and latero-cervical lymph nodes metastasis at diagnosis overcomes the prognostic role of grading system for DMFS, LRFS and DSS. Conversely, in lower stages (I, II and III), then with lower risk of recurrence and mortality, patients with high-grade tumors had worst prognosis.
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Treatment 1

PS2-18-01

Role of radiofrequency ablation in the treatment of symptomatic distant metastasis of thyroid cancer

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Objective
To evaluate the effectiveness and safety of ultrasound-guided RFA for symptomatic distant metastasis of DTC.
Methods
The medical records of 12 patients who underwent RFA for palliative treatment of 18 symptomatic distant metastases from thyroid cancer between January 2008 and December 2020 were analyzed. All patients were assessed for their degree of discomfort, and were evaluated periodically as outpatients, clinically, and by imaging and serologic markers.
Results
Of the 18 tumors treated, 9 were soft tissue metastases, and 9 were bone metastases. The mean size of the treated tumor was 5.3 cm (range, 1.7-10.7 cm). All patients had complaints of pain and/or bulging before RFA. After RFA, the patients reported a subjective improvement in symptoms related to 11 out of the 18 metastatic tumors (61.1%). Nine out of 18 tumors decreased in size with a mean SRR of 0.43% $\pm$ 0.22%. There were no major complications during the treatment or follow-up period related to RFA. After a mean follow-up duration of 37.4 months, 5 patients had progression of the tumor, 4 patients had a stable tumor status, and 3 patients died due to pneumonia.
Conclusions
RFA can be used as palliative therapy to relieve the symptoms caused by metastatic tumors; however, it has a limited role in improving the overall prognosis in patients with distant metastasis from thyroid cancers.

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PS2-18-02

Abstract withdrawn

PS2-18-03

A systematic drug repurposing approach for anaplastic thyroid cancer

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Anaplastic thyroid cancer (ATC) is the most aggressive and lethal form of thyroid cancer. ATC rarely develop as ex-novo lesions, but rather evolves from pre-existing well-differentiated thyroid cancer (DTC) through a de-differentiation process that leads cells to acquire an aggressive phenotype. ATC are refractory to radiotherapy, having lost the expression of Sodium-Iodine Symporter, and often also to standard chemotherapy. Moreover, debulking surgery is frequently difficult, thus these patients remain with no effective therapeutic options. Drug Repurposing aims to discover new clinical indications for existing drugs. The application of this approach may represent an alternative and efficient strategy to identify ready-to-use new treatments for rare diseases, such as ATC. We hypothesized that re-programming the ATC cells toward a more differentiated phenotype should mitigate aggressiveness and restore sensitivity to standard therapies, thus we applied a systematic drug repurposing approach based on gene expression. To overcome the rarity of ATCs samples, we collected data from 7 public GEO patient sample datasets and analyzed them to identify a differential Gene Expression Signature (dGES) describing the transition DTC-ATC. Gene Ontology analysis highlighted that Up-regulated genes were enriched in cell migration, motility and mitotic-related processes, while Down-regulated genes were enriched mainly in thyroid hormone generation, cell-cell junctions and adhesion. These observations confirmed the validity of our analysis. Then, this dGES was used to query the Connectivity Map, a database of gene expression signatures induced by hundreds of compounds. To identify a list of drugs virtually able to induce a signature opposite to our query, thus to revert the DTC-ATC transition, we retrieved small molecules with a connectivity score $<$-90. This score was re-calculated to consider the weight of the most represented Perturbagen Classes, then compounds were re-ranked. The obtained 69 compounds were prioritized through manually curated data mining. 8 candidates emerged and undergo an in-vitro screening, in three different ATC cell lines. Due to early toxicity, 2 molecules were excluded and for the remaining 6 IC50 were calculated, and proliferation/cytotoxicity assays were performed. The results excluded 3 other compounds, and another one was excluded since it had no effects on cell morphology. The 2 remaining drugs, a CDKi and an AURKi, will be further assessed for their biological effects on ATC cells, alone and in combination with standard chemotherapeutics. Results will allow us to identify a drug, able to restrain ATC aggressiveness and refractory, which is also already used in clinical practice, thus providing an effective ready-to-use therapeutic option.

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PS2-18-04

Comparative effectiveness of selpercatinib vs standard treatment in patients with medullary thyroid cancer: An interpatient analysis from libretto-001

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Objective
Head-to-head data comparing selpercatinib, a highly selective and potent *RE* arranged during Transfection (*RET*) kinase inhibitor with CNS activity, to standard treatment of *RET*-altered medullary thyroid cancer (MTC; cabozantinib or vandetanib) is currently unavailable. This *post-hoc* comparative effectiveness analysis of data from the phase 1/2 LIBRETTO-001 trial compared investigator-assessed outcomes among patients with *RET*-mutated MTC treated with selpercatinib, but naïve to cabozantinib and/or vandetanib (selpercatinib arm), vs outcomes among patients previously treated with cabozantinib and/or vandetanib, who may have also received other systemic therapy including multikinase inhibitors (MKI) in first-line (1L) prior to trial enrollment (comparator arm).
Methods
Data obtained from case report forms in the LIBRETTO-001 trial (15 June 2021, data cutoff date) were assessed retrospectively. Patients aged $\geq$12 years, diagnosed with advanced or metastatic *RET*-mutated MTC, and Eastern Cooperative Oncology Group Performance Status score 0 to 2 were included. The index date was the date of initiation of selpercatinib treatment for the selpercatinib arm and the date of initiation of 1L MKI treatment for the comparator arm. Time to treatment discontinuation (TTD), time to next treatment or death (TTNT-D), and time to progression (TTP) were compared between the cohorts after propensity score-based matching (1:1 using baseline covariates) to estimate treatment effect. Kaplan-Meier analyses with log-rank test were performed for TTD, TTNT-D, and TTP, followed by Cox proportional hazards regression model to estimate relative efficacy, presented as hazard ratios (HR) and 95% confidence intervals (CI).
Results
From the 277 total patients, 142 and 135 were included in the selpercatinib arm and comparator arm, respectively. Both the arms had 135 patients after matching. Overall, baseline patient characteristics were similar between the arms after

matching, except for brain metastases (selpercatinib arm 2.2% vs comparator arm 7.4%; $P < 0.05$). The selpercatinib arm demonstrated significantly longer TTD (HR 0.13 [95% CI 0.08, 0.20]), TTNT-D (HR 0.03 [95% CI 0.01, 0.08]), and TTP (HR 0.11 [95% CI 0.06, 0.18]) than the comparator arm.

Conclusion

The current analysis suggests selpercatinib use is associated with improved outcomes and may be more efficacious compared to standard therapies for patients with advanced or metastatic *RET*-mutated MTC. Further information will be obtained from the ongoing phase 3 LIBRETTO-531 trial.

Table 1

Outcome in months	Selpercatinib arm, median (95% CI) ($n = 135$)	Comparator arm, median (95% CI) ($n = 135$)	HR (95% CI)	*P*-value
TTD	Not reached (NR, NR)	14.0 (11.8, 16.7)	0.13 (0.08, 0.20)	<0.0001
TTNT-D	Not reached (NR, NR)	16.1 (14.0, 18.8)	0.03 (0.01, 0.08)	<0.0001
TTP	Not reached (NR, NR)	15.2 (12.6, 18.0)	0.11 (0.06, 0.18)	<0.0001

NR – Not Reached

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PS2-18-05

The first experience of laser interstitial thermotherapy in the treatment of patients with nodular goiter and cytology tbsrtc iv

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The objective was to evaluate the short-term results of the laser interstitial thermotherapy (LITT) application in the treatment of patients with nodular goiter and cytology TBSRTC IV category.

Materials and methods

In 2021-2023, ultrasound-guided LITT was performed on 21 patients with nodular goiter and cytology TBSRTC IV. Laser type - GaAlAs Diode Laser (VELAS II-30F). The wavelength was 1064 nm, and the emission mode - continuous. Power at the 1st session was 3.4 (3.3; 3.5) W, at the 2nd - 3.4 (3.4; 3.45) W, $P = 0.58$. The energy at the 1st session was 510.0 (352.0; 784.5) J, the 2nd - 408 (258, 770.5) J, $P = 0.31$. Twenty-six LITT sessions were performed: Group I ($n = 12$) - 1 session, Group II ($n = 6$) - 2 sessions. Volume-reduction rate (VRR) and cytological smears at control TFNAB were evaluated. A positive result has been considered at VRR $\pm$ 70.0% and the absence of atypia in control smears. The average follow-up period was 4.0 (3.0; 6.3) months.

The results VRR after 1 LITT session ranged from 12.4% to 99.10%, after the 2nd LITT session at 1st control - min. - 85.7%, max. - 100.0%, at the 2nd control – 96.55%. The frequency of patients with VRR $\pm$ 70.0% in Group I was 75.0%, and in Group II – 100.0%, $P = 0.52$. Binary logistic regression analysis did not reveal a statistically significant relationship between the frequency of VRR $\pm$ 70.0% and the number of sessions or energy delivered to the node, $P = 0.34$. After LITT at control TFNAB in Group I, the frequency of TBSRTC IV was 20% ($n = 1$), and TBSRTC II – 80.0% ($n = 4$). In group II, TBSRTC IV – 40.0% (n = 2), TBSRTC III – 40.0% (n = 2), and TBSRTC II – 20.0% (n = 1). The study groups did not differ statistically significantly in the frequency of TBSRTC II, III, and IV after LITT, $P = 0.13$. The average values of DAP-IV activity before LITT in patients of Group I was 6.0 (3.25, 8.0), after LITT – 0.0 (0.0, 3.5), $P = 0.068$. In Group II, DAP-IV before LITT was 0.0 (0.0; 6.5), and after LITT – 3.0 (1.5; 6.0), $P = 0.581$.

Conclusions

Laser interstitial thermotherapy can be an effective method of treatment for patients with nodular goiter and a cytology TBSRTC IV. However, to obtain more valid results, a study should be conducted on a larger sample. The research proceeds.

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PS2-18-06

Prognostic model of the rate and risk of papillary thyroid cancer local metastases based on preoperative clinical and ulrasonic predictors

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Introduction

Papillary thyroid cancer (PTC) is an indolent tumor with low malignancy potential. However, occult synchronous cervical lymph node metastases (CLNM), which may lead to a high risk of local recurrence, are still present in 20–40% of patients. The low diagnostic efficiency (< 47%) of the neck ultrasound in central lymph node metastases detection leads to the development of alternative ways of occult CLNM prediction in patients with PTC. The objective is to develop a prognostic model based on preoperative clinical and ultrasound predictors for the assessment of the papillary thyroid cancer local metastasis risk.

Materials and methods

The perioperative data of 301 patients were analyzed: 117 patients with CLNM, diagnosed after surgery; 184 patients - without CLNM. Five factors were determined as the most significant CLNM predictors: 1) subcapsular location; 2) tumor size; 3) ill-defined margin; 4) microcalcifications; 5) age. The prognostic model was created on the basis of binary logistic regression using the statistical analysis program StatPlus, version 7 (AnalystSoft Inc.). An MS Excel template was created to automate the calculation process.

Results

Regression coefficients calculations were performed:

Indicator	Regression coefficient β
b_0	-2,009
b_1	-0,039
b_2	0,114
b_3	1,033
b_4	1,215
b_5	0,590

The probability of metastases detection was calculated by the formula:
$P = 1/(1 - e^{-y})$, where **e** - the Euler's number, y - obtained by regression equation, i.e.:
$y = -2.009 - 0.039*X1 + 0.114*X2 + 1.033*X3 + 1.215*X4 + 0.590*X5$
X are binary variables (presence or absence of the feature): X_1 - age (years), X_2 - tumor size (threshold value is $\geq$ 10 mm), X_3 - subcapsular location, X_4 - ill-defined margin, and X_5 - microcalcifications. The resulting prognostic model had sensitivity – 61.5 % (95% CI 52.1-70.4); specificity – 83.7 % (95% CI 77.6-88.7); diagnostic efficiency – 75.1 % (95% CI 69.8-79.9). The models quality was assessed ($n = 50$): sensitivity – 53.7 %, specificity – 77.1 %, and diagnostic efficiency - 70.0%. The values of the selected indicators were within the calculated 95% CI. The values of the selected indicators were generally within the calculated 95% CI, however, the model needs further improvement on a larger sample size.

Conclusions

The practical application of the suggested prognostic model may improve the outcomes of PTC management by preoperative predicting the risk of CLNM presence with an accuracy of 75.1%.

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PS2-18-07

Role of preoperative serum calcitonin and carcinoembryonic antigen in predicting surgical extent of lateral lymph node metastasis in medullary thyroid carcinoma: a multicenter study in korea

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Background
The optimal initial surgical extent for medullary thyroid carcinoma (MTC) remains controversial. Aim of this study was to evaluate the ability of serum calcitonin and carcinoembryonic antigen(CEA) to predict the extent of surgery needed in the lateral neck in patients with MTC.
Methods
This retrospective multicenter cohort study included data from patients with MTC surgically treated in the 6 tertiary medical centers in Korea from 1996 to 2022. We retrospectively reviewed data on preoperative level of calcitonin and CEA, primary tumor size, and the number and location of lymph node metastases (LNMs) in 203 patients with MTC.
Results
Lateral LNMs and initial distant metastasis was present in 75 patients (36.9%) and 8 patients (3.9%), respectively. The preoperative level of calcitonin and CEA in patients with lateral LNMs was significantly higher than that of patients with central LNMs (median calcitonin 960 pg/mL vs 133.8 pg/ml, median CEA 41.8 ug/l vs 9.3 ug/l, $P < 0.001$). The cutoff value of preoperative calcitonin and CEA for prediction of lateral LNMs was 403 pg/mL and 9.5 ug/l, respectively. The area under the curve (AUC) of calcitonin and CEA for prediction of lateral LNMs were 0.773 (95% CI: 709–0.837, $P < 0.001$) and 0.747 (95% CI: 0.679-0.815, $P < 0.001$). In multivariate analysis, factors associated with lateral LNMs were gross extra-thyroidal extension ($P = 0.002$), calcitonin ($\geq$ 50pg/mL) ($P = 0.006$), and CEA ($\geq$ 10 mg/l) ($P = 0.002$)
Conclusions
The preoperative level of serum basal calcitonin and CEA were correlated with disease extent and showed significant value for predicting the extent of LNMs. These results suggest that both preoperative basal level of calcitonin and CEA can be used to determine the optimal initial surgical extent for LN dissection in patients with MTC.

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PS2-18-08

Clinical practice guidelines for radiofrequency ablation of benign thyroid nodules and malignant thyroid cancers: A systematic review

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Objectives
Radiofrequency ablation (RFA) is considered an alternative treatment for benign thyroid nodules and malignant thyroid cancers. There were various clinical practice guidelines from international societies for ablation of benign thyroid nodules. Recently, RFA is becoming a promising treatment choice for recurrence thyroid cancer, and RFA is suggested as a minimally invasive treatment for low-risk papillary thyroid microcarcinoma (PTMC). Several international societies also proposed clinical practice guidelines for malignant thyroid cancers. Therefore, we systemically reviewed these clinical practice guidelines for benign and malignant thyroid RFA and compared the similarities and differences between them to identify a standard treatment strategy.
Methods
The Ovid-MEDLINE and Embase were searched and a manual search was conducted to identify articles for RFA of benign thyroid nodules and malignant thyroid cancers. Studies that included clinical practice guideline of benign and malignant thyroid RFA were included. We extracted data on the indication, pre- and post-procedural evaluation, techniques, efficacy, safety, preference and cost, and informed consent.
Results
Sixteen guidelines were included. These studies were guidelines developed by 10 international thyroid societies including the Korean Society of Thyroid Radiology (KSThR), three French thyroid associations, Italian scientific societies and Italian minimally invasive treatment of the thyroid, international multidisciplinary thyroid association, European Thyroid association (ETA), committee of Asian Conference on Tumor Ablation, American Association of Clinical Endocrinology (AACE), Thyroid Tumor Ablation Experts Groups of Chinese Medical Doctor Association, three German thyroid associations, and four professional Austrian thyroid associations. All guidelines suggested the clinical practice guidelines for ablation of benign thyroid nodules, and most societies except French thyroid associations and German thyroid associations suggested the malignant thyroid cancer RFA. Most guidelines were included indications, pre- and post-procedural evaluation, techniques, efficacy, and safety for thyroid RFA. Two societies, AACE and ETA, described the cost of benign and malignant thyroid RFA, and ETA only suggested the preference according to the patients' status.
Conclusion
Most guidelines were included the similar major contents for benign and malignant thyroid RFA. Systematic review of various guidelines for benign and malignant thyroid RFA can be help to establish the standard treatment strategy.

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PS2-18-09

Evaluation of real-world efficacy in lenvatinib and pembrolizumab treated poorly (PDTC) and anaplastic (ATC) thyroid cancer patients

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Anaplastic thyroid carcinoma (ATC) is a rare and aggressive malignancy with only limited effective systemic treatment options. The identification of actionable genetic lesions and its exploitation has expanded therapeutic approaches and especially for the subset of BRAFV600E mutated ATC (11-25%) combined BRAF- and MEK-inhibition indicated meaningful activity. Still, further effective therapeutic options are required for patients without identifiable driver mutations. The role of immunotherapy (IT) in this regard is an area of active interest. Recently, combined application of the multityrosine kinase inhibitor *Lenvatinib* and the PD1- inhibitor *Pembrolizumab* showed promising results in 6 ATC and 2 PDTC patients with detectable PD-L1 expression level (*ATLEP*) resulting in an implementation of a prospective trial (ATLEP II). An evaluation of 35 included patients (27 ATC, 8 PDTC) showed an ORR of 34.3% (12/35) with a median OS of 10.25 months in ATC patients. Here, we investigated real-word efficacy of an *in-house* cohort of *Lenvatinib* and *Pembrolizumab* treated poorly (PDTC) and anaplastic (ATC) thyroid cancer patients (ATC $n = 6$, PDTC $n = 4$) in a tertiary tumour centre. The objective response rate in ATC was 50% (3/6). Tree patients had partial response, and 3 patients had durable stable disease. The median overall survival since first application of IT was 10.5 months. The objective response rate in PDTC was 25% (1/4). The median overall survival since first IT administration was 20 months. Nine patients had tumour tissue available for PD-L1 expression testing and only in one sample, PD-L1 expression was $< 10\%$. Four patients (4/10) experienced an immune-related adverse event (grade 3 or higher). To conclude, in line with previous data, IT may represent an effective treatment option for a subset of PDTC and ATC patients with manageable toxicity in a *real-world* setting.

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Thyroid Hormone Transport & Metabolism Basic

PS2-19-01

Types 2 and 3 deiodinase are induced in blood cells of critical ill patients: Implications to nonthyroidal illness syndrome pathophysiology

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Dysregulation of types 2 and 3 deiodinases (D2 and D3) are present and profoundly alters the metabolism of thyroid hormones in the nonthyroidal iIllness syndrome (NTIS). The activation of this enzyme in peripheral blood cells can be one of the factors that alters the progression of this syndrome. However, the effect of oxidative stress on D3 expression in these cells from ill patients is unknown.

Objective

Evaluate the presence and variations of D3 expression in the granulocytes and lymphocytes cells of intensive care patients in ICU due to any disease.

Methods

Forty patients admitted to ICU due to any cause had their blood collected at admission and after seven days. Cells from whole blood were separated by different cell gradients and by flow cytometry. The total carbonyl content and GSH were used as a parameter of intracellular redox balance. D2 and D3 expression and locations was determined with *in situ* hybridization RNAscope.

Results

T3 levels were divided into three categories (T3 $<$ 35ng/dl, 35-60 ngd/l and $>$ 60ng/dL). Media was 31 ± 1.6, 47 ± 7.6 and 63.12 ± 3.14 ng/dL respectively. The formation of carbonyls, a marker of oxidative damage to proteins, was increased in both cell types (all $P < 0.0001$) in all patients, independently from admission cause. GSH levels were also diminished ($P < 0.001$). DIO2 and DIO3 expression were increased in activated granulocytes (by 5-fold each, $P = 0.002$) at admission. We observed a significant difference on D2 and D3 expression among dose patients from the groups of T3 $<$ 35 and T5 35-60ng/dL when compared to the expression observed in those patients with T3 $>$ 60 ng/dL RNAscope confirmed the presence of these enzymes in both granulocytes and mononuclear cells.

Conclusion

Critical disease induces D2 and D3 in defense cells, regardless the type of disease, contributing to diminishing circulating T3 levels.

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PS2-19-02

PResence of MCT8 and OATP1C1 in mouse endothelial cells is required for normal brain development and function

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Impaired TH transport across brain barriers results in severe TH deficiency in Mct8/Oatp1c1 DKO mice, leading to disturbed neuronal development, myelination as well as locomotor abnormalities. Although brain-barrier associated cells (i.e. endothelial cells, astrocytes, choroid plexus epithelial cells) have been shown to express both transporters, the cell-specific function of Mct8 and Oatp1c1 has still not been defined. Here, we generated and analysed mouse mutants that lack Mct8 and Oatp1c1 in endothelial cells only (= Endo del mice). For that purpose, conditional Mct8/Oatp1c1 flox animals were crossed with mice expressing Cre-recombinase under the constitutively active Tek2 promoter (= Tie2 cre). Endo del mice were born at the expected mendelian frequency and phenotypically indistinguishable from their control littermates. Immunofluorescence studies confirmed a cell-specific deletion of Mct8 in brain capillary endothelial cells while expression of Mct8 in choroid plexus, tanycytes as well as in neurons was not affected. Mct8 expression was also preserved in peripheral tissues such as liver and heart of Endo del mice. Immunofluorescence analysis of Endo del mice at postnatal day P12 revealed a strongly reduced number of inhibitory Parvalbumin-positive neurons in the cerebral cortex, similarly to the phenotype seen in global Mct8/Oatp1c1 deficiency. In contrast, myelination was less compromised in Endo del animals compared to global Mct8/Oatp1c1 DKO mice. Fluorescence *in situ* hybridization studies were conducted at the age of 4 months and revealed increased TRH expression in the paraventricular hypothalamic nucleus (PVN) similarly to the increase seen in DKO mice. Likewise, hybridization signal intensities for the TH regulated genes RC3, Klf9, Aldh1a1 showed decreased levels in Endo del mice as well as in DKO mice. Altogether, our data point to a sustained TH-deficient CNS in Endo del mice and thus underscore the critical role of Mct8 and Oatp1c1 in mediating TH transport across endothelial cells.

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PS2-19-03

Thyroid hormone metabolite 3-iodothyronamine (T1AM) as an effective repressor of microglia-mediated neuroinflammation

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Microglial dysfunction is one of the hallmarks and leading causes of common neurodegenerative diseases (NDD), including Alzheimer's disease (AD), Parkinson's disease (AD), and amyotrophic lateral sclerosis (ALS). All these pathologies are characterized by aberrant aggregation of disease-causing proteins in the brain, which can directly activate microglia, trigger microglia-mediated neuroinflammation, and increase oxidative stress. The availability of cell-permeable inhibitors of glial activation and neuroinflammation could represent a valid tool for the treatment or prevention of common NDD. Recently, 3-iodothyronamine (T1AM), an endogenous amine putatively derived from thyroid hormone (TH) metabolism, gained interest for its ability to promote neuroprotective effects in several models, including seizure-related excitotoxic damage, altered autophagy, amyloidosis and OGD-induced synaptic dysfunction. Nevertheless, T1AM's effects on microglial disfunction remain still elusive. In the present work we investigated whether T1AM could decrease the inflammatory phenotype (M1) of LPS/TNFα-stimulated human microglial cells (HMC3), promoting the transition to the protective M2 phenotype. Dose-response experiments, carried out by exposing HMC3 cells to pretreatment with increasing concentrations (0.1, 1, and 10 μM) of T1AM followed by LPS/TNFα treatment, revealed that T1AM causes a significant ($P < 0.05$) dose-dependent reduction of pro-inflammatory interleukin-6 (IL-6) secretion as compared to LPS/TNFα treated cells. A significant dose-dependent increase of anti-inflammatory interleukin-10 (IL-10) was also observed. Expression of TAAR1, T1AM's putative receptor, in HMC3 cells was also assessed by qPCR analysis, and no changes were observed after 24 h treatment with LPS/TNFα. Notably, TAAR1 was demonstrated to be a chief target of T1AM anti-inflammatory action in HMC3 cells. Indeed, we observed that T1AM protective effect against microglia-activation was abolished by co-administration of TAAR1 selective antagonist EPPTB (5 nM). Conversely, administration of TAAR1 agonist RO5166017 (1 μM) produced a reduction of pro-inflammatory IL-6 comparable to that previously observed after administering T1AM (1 μM). Since 3-iodothyroacetic acid (TA1), the major catabolite of T1AM, has been reported to be responsible for some effects elicited by T1AM treatment, we checked whether TA1 administration could also decrease the inflammatory phenotype of LPS/TNFα-stimulated HMC3 cells. We observed that TA1 administered at 0.1, 1, and 10 μM concentrations was not able to produce any significant effect on both IL-6 and IL-10 release from LPS/TNFα-stimulated HMC3 cells, suggesting that the induction of microglial transition from pro-inflammatory to anti-inflammatory phenotype is exclusively due to the action of T1AM through the interaction with the TAAR1 receptor.

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PS2-19-04

Repositioning of cefuroxime as novel selective inhibitor of the thyroid hormone activating enzyme type 2 deiodinase

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The iodothyronine deiodinases constitute a family of three selenoenzymes regulating the intracellular metabolism of Thyroid Hormones (THs, T4 and T3) and impacting on several physiological processes, including energy metabolism, development and cell differentiation. The type 1, 2 and 3 deiodinases (D1, D2, and D3), are sensitive, rate-limiting components within the TH axis, and rapidly control TH action in physiological conditions or disease. Notably, several human pathologies are characterized by deiodinases deregulation (e.g., inflammation, osteoporosis, metabolic syndrome, muscle wasting and cancer). Consequently, these enzymes are golden targets for identifying and developing pharmacological compounds endowed with modulatory activities. However, until now, the portfolio of inhibitors for deiodinases is limited and the few active compounds lack selectivity. Screening a collection of FDA-approved drugs against an in silico model of murine D2, we identified a list of molecules with the potential ability to interact with D2. Among them, we validated the cephalosporin Cefuroxime as a novel D2 specific inhibitor. Using isotopes for deiodination activity determination, we demonstrated that Cefuroxime has the remarkable ability to inhibit D2 enzymatic activity without perturbing D1 and D3 function. Interestingly, acting as a specific D2 inhibitor, Cefuroxime has anti-thyroidal action *in vivo*. Indeed, it blocks D2 activity in the D2-expressing tissues, as the brown adipose tissue, the skeletal muscle and the anterior pituitary. Notably, in our experimental settings, Cefuroxime inhibits the enzymatic activity of D2 without altering the systemic TH status when administered *in vivo* in euthyroid mice for 15 days. However, despite we show for Cefuroxime a very interesting inhibitory activity, highly specific for D2, its eligibility as negative modulator of D2 in human is unlikely, mainly as a consequence of its antibiotic activity, (long term toxicity, negative effect on human microbiota, risk of selection of Cefuroxime resistant bacteria). Notwithstanding, we think that the identification of a synthetic ligand endowed with specificity for D2 will allow the beginning of a drug optimization process toward the development of new hits that will maintain selectivity toward D2, while losing their antibiotic potential. In conclusion, these data prove a novel activity of the antibacterial drug Cefuroxime and demonstrate that this compound can be viewed as a potent modulator of the peripheral conversion of T4-to-T3, preventing the local amplification of the TH signal in pathophysiological conditions.

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PS2-19-05

Characterization of epcam in thyroid cancer biology by three-dimensional spheroids *in vitro* model

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Thyroid cancer (TC) is the most common Endocrine malignancy. Nowadays Undifferentiated Thyroid Cancers (UTCs) are still a lethal disease, mostly because of the lack of effective therapeutic options. The insurgence of therapy resistance and disease relapse is believed to be caused by a subpopulation of cancer cells with a stem-like phenotype and specific tumor-initiating abilities, the so called Tumor-Initiating Cells (TICs). Several markers have been identified and described over the years to detect TICs and allow the development of potential therapeutic approaches that could serve to specifically target these cells and promote the eradication of the tumor. In TC, TICs have been identified using precise *in vitro* and *in vivo* assays (e.g. sphere-forming assays and tumor grafts), variations of enzymatic activities, expression of well-known stemness markers and expression of membrane markers. In the present work, we provide more insight into the role that Epithelial Cell Adhesion Molecule (EpCAM), a known TICs marker in other epithelial tumors, may have in TC biology. This result was accomplished by the integration of TC tissues examination, through Western Blot and Immunofluorescence, and *in vitro* characterization of 2D and 3D models from FRO Anaplastic Thyroid Cancer (ATC) cell line. The main methodologies applied to obtain the 3D cultures are the hanging-drop and coating with poly(2-hydroxyethyl methacrylate) non-adhesive substrate. Our data demonstrated that EpCAM is subjected to an intense cleavage process in FRO-derived 3D tumor spheres, and that this model is representative of the variability of EpCAM expression and cleavage that we found in patient-derived tissue samples. We also demonstrated that the expression of EpCAM can be modulated by the regulation of its cleavage and that the integrity of the protein seem to be a crucial factor for the initial phase of the generation of the 3D spheres in FRO, postulating that the cleavage of the protein may occur in a second moment, induced by the ability of cells to adapt to variations in growth conditions and/or to the microenvironment within the spheres. Finally, we observed that EpCAM-expressing cells (EpCAM+) in FRO appeared to be more resistant than EpCAM- cells after treatment with Vemurafenib (PLX-4032), as well as FRO-derived 3D spheres with respect to adherent cells. In conclusions, EpCAM expression and cleavage may play a significant role in putative TC TICs biology and the most promising results should be validated on patient-derived samples.

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PS2-19-06

DIO2 and dehal1 are common targets of MIR-146B and PAX8 shaping a regulatory circuit that modulates the differentiated phenotype of papillary thyroid carcinomas

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Regulatory circuits involving miRNAs and transcription factors (TFs) are prevalent mechanisms of gene expression by which developmental and pathologic processes occur. MiR-146b is one of the most upregulated and abundant oncomiRNAs in papillary thyroid carcinomas (PTCs). We have previously shown that miR-146b and PAX8 regulate each other and share common target genes such as NIS, thus highlighting a miR-146b-3p/PAX8/NIS regulatory circuit that governs the differentiated phenotype of PTC. In this study, we found that DIO2 and IYD (DEHAL1), two thyroid iodide-metabolizing genes essential for thyroid differentiation, are also common targets of miR-146b and PAX8. Our ChIP-Seq characterization showed that DIO2 and IYD (DEHAL1) are downstream target genes that are positively regulated by PAX8 in the rat thyroid cell line PCCl3, and TSH strongly induces the upregulation of both DIO2 and DEHAL1. Our NGS analysis of PTC tumor samples as well as analysis of TCGA data sets, show a significant negative correlation between the expression levels of miR-146b and the levels of DIO2 and DEHAL1 ($r = -0.5$; FDR < 0.05 and $r = -0.6$; FDR < 0.05, respectively). We next analyzed the protein expression of DIO2 and DEHAL1 in a panel of 13 thyroid cancer cell lines finding a general downregulation for DEHAL1 and various levels of expression for DIO2. Bioinformatic prediction analysis shows that there are three and two binding sites for miR-146b-5p and -3p respectively in the 3'UTR of DEHAL1 and one binding site for miR-146b-5p in the 3'UTR of DIO2. Overexpression of miR-146b markedly decreases DIO2 and DEHAL protein expression in NTHY-ORI cell line and we are currently investigating whether miR-146b-5p is specifically targeting the 3'UTR of both genes. In conclusion, we provide further evidence that a TF-miRNA co-regulatory network based on miR-146b and PAX8 modulate genes essential for thyroid differentiation that may be exploited therapeutically in PTC.

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PS2-19-07

Absence of MCT8 and OATP1C1 in mouse oligodendroglia cells results in delayed myelination

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Inactivation of the thyroid hormone transporters Mct8/Oatp1c1 in mice causes a profound TH deficiency in the CNS due to an impaired TH transport across brain barrier cells. As oligodendrocyte maturation and myelin formation requires proper thyroid hormone (TH) signaling, Mct8/Oatp1c1 double knock-out (DKO) mice exhibit a persistent state of hypomyelination similar to the situation in

MCT8 deficient patients. Yet, to which extent proper myelination is dependent on the presence of Mct8 and Oatp1c1 in oligodendrocytes and/or their precursor cells has not been determined. Here, we studied myelination at different time points in Mct8/Oatp1c1 mutant mice that lack both transporters only in oligodendroglia cells (= OL CKO mice). For that purpose, conditional Mct8/Oatp1c1 mouse mutants were crossed with transgenic mice expressing cre-recombinase under the control of the oligodendroglia specific Olig2 promoter. OL CKO mice were phenotypically indistinguishable from their cre-negative control littermates and showed normal body weight and locomotor performance as assessed by beam walk and hanging wire test at the age of 4 months. Likewise, serum TH parameters as well as hypothalamic TRH expression were not altered. Analysis of the oligodendrocyte markers MBP and CNPase in the cerebral cortex of 4 months old animals revealed similar immunofluorescence signal intensities in OL CKO and control mice. However, at postnatal day P12, expression of both proteins was found to be significantly reduced in OL CKO mice suggesting a transient delay in myelination. Quantification of mature oligodendrocyte numbers by Olig2/CC1 co-immunostaining at P12 disclosed reduced numbers of double positive cells in OL CKO similar to DKO mice indicating a myelination defect in both mouse models. Altogether, our studies confirm an oligodendrocyte differentiation impairment in the absence of Mct8 and Oatp1c1. The comparison between DKO and OL CKO mice, with OL CKO mice still being able to sense local TH concentrations and only showing a transient delay in myelination, points to cell-autonomous and non-cell-autonomous impacts of both TH transporters. Ongoing studies are expected to disclose at which time points during development Mct8 and Oatp1c1 are required to ensure a normal commitment of precursor cells to the oligodendroglial lineage.

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PS2-19-08

Thyroglobulin detection in extracellular vesicles isolated from human plasma

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Objective
Detecting recurrence of differentiated thyroid cancer is performed by serial measurements of serum thyroglobulin (Tg) levels, however, in the presence of anti-Tg antibodies, this measurement is unreliable. Extracellular vesicles (EVs) are small membrane-enclosed structures, with a prominent role in cell-to-cell communication. All cell types release EVs and they can be isolated from various biofluids, while their cargo reflects the content of the cell of origin. Previous studies showed that EVs from bovine serum, FRTL-6 rat thyroid cell line conditioned medium and human urine all contain thyroglobulin. EVs isolated from human serum were not previously investigated for the presence of Tg. We performed a qualitative study to determine whether Tg can be detected in the EVs isolated from human plasma or serum of patients with thyroid diseases, in order to test a novel approach for measuring Tg segregated from anti-Tg antibodies.
Methods
We employed 4 samples for this analysis: one plasma sample from a healthy donor, 2 plasma samples from patients with thyroid nodules and one serum sample of a patient positive for thyroglobulin antibodies. Extracellular vesicles were isolated by differential ultracentrifugation. The size and the number of vesicles were determined with nanoparticle tracking analysis (NTA) and the characterisation of EVs surface markers as well as thyroglobulin detection was performed by means of Western blot.
Results
NTA analysis showed that the median size of particles in the extracellular vesicle-enriched preparations isolated from plasma or serum samples fell in the range of 90 – 110 nm, corresponding to the size of EVs. EVs-enriched preparation isolated from the plasma of thyroid nodule patients and serum of a patient with thyroglobulin antibodies were positive for the presence of thyroglobulin, while this protein was not detected in the sample from the healthy donor.
Conclusions
Thyroglobulin can be detected in the EVs-enriched preparation isolated from serum and plasma samples of patients suffering from thyroid gland pathophysiologies. Although preliminary, these results point out the possibility of efficiently bypassing the obstacles caused by Tg antibodies in serum Tg detection. Detecting thyroglobulin enclosed in vesicles that are actively secreted from the thyroid follicular cells holds promise as an innovative concept in diagnosing differentiated thyroid cancer recurrence. Quantitative studies on a large sample cohort are in progress.

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Thyroid Hormone Receptors Basic

PS2-20-01

Thyroid hormone receptor beta expression changes have a limited impact on non-alcoholic steatohepatitis progression

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Background and Aim
Thyroid hormone beta receptor (TRβ) agonists have shown promising results to improve non-alcoholic steatohepatitis in preclinical studies and clinical trials. However, a recent cross-sectional study on human liver biopsies found that TRβ expression decreases during non-alcoholic steatohepatitis (NASH), which may indicate developing thyroid hormone resistance and pose a challenge for TRβ agonists. We aim to study how the changes in TRβ expression impact NASH progression.
Methods
We investigated the alterations of TRβ in two animal models using a novel paradigm that combines choline-deficient high fat diet (CD-HFD) with thermoneutrality housing. To study NASH progression, C57BL/6 wild type or TRβ knockout mice were feed with control or CD-HFD at 4, 8, and 16 weeks. AAV8-mediated hepatocyte-specific TRβ in NASH wild type mice was used as gain-of-function approach. Histology, gene expression, body composition, metabolic parameters and thyroid hormone in serum were measured.
Results
We confirm that TRβ is reduced in mouse NASH, as in humans. Remarkably, treated mice lacking TRβ did not perform worse, but instead showed less liver fibrosis and decreased expression of NASH-associated genes. This effect was not due to the endogenous hyperthyroidism usually observed in TRβ knockout mice, as their thyroid hormone levels normalized at thermoneutrality. On the other hand, increasing TRβ expression in wildtype NASH mice using liver-targeted gene therapy did not result in any improvement in histology, gene expression, or metabolic parameters.
Conclusion
Taken together, our data suggest that downregulation of TRβ expression is not detrimental for NASH progression, and elevating TRβ during NASH without additional ligand does not have beneficial effects on hepatic health or overall metabolism. The findings therefore highlight the importance of targeting local ligand and not receptor availability and suggest that liver-specificity rather than isoform-specificity, might be of greater relevance for NASH treatment.

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PS2-20-02

Central actions of thyroid hormone: The role of the zona incerta

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It is well established that thyroid hormones (TH) possess the ability to regulate body temperature. Thermogenesis can be induced peripherally in fat and muscle, but the active hormone T3 can also act centrally in the brain to raise the body temperature via the sympathetic nervous system. In recent studies, T3 treatment in mice has been shown to elevate the body temperature even far below thermoneutrality. This indicates that the induced hyperthyroidism causes a state of pyrexia instead of hyperthermia and the body temperature set point is elevated. However, the brain region where TH can act to alter this body temperature set point is not yet known. Candidate regions have been identified using PET/CT scans of mice undergoing T3 treatment to show neuronal activation. Among them is the Zona Incerta (ZI), a region of the subthalamus, that has previously been indicated in body temperature control, as well as anxiety modulation. Thus, the goal of this research project is to investigate the role of TH signalling of the ZI in the control of body temperature and anxiety. To inhibit TH signalling, an adeno-associated virus expressing a dominant negative thyroid hormone receptor α1 was injected into the ZI using stereotaxic surgery. The results showed tendentially increased anxiety, as could be observed by higher corticosterone serum levels, as well as altered RNA levels of glucocorticoid target genes and an increased R amplitude in ECG. Moreover, inhibition of ZI TH signalling caused decreased body weight gain with no difference in neither food or water intake, nor energy expenditure. Along with an increased body weight loss during fasting, these findings suggest higher stress levels. However, inhibiting TH signalling in the ZI failed to lower the body temperature, as seen by radiotelemetry and infrared camera data. Collectively, the preliminary data gathered from this study indicates that ZI TH signalling contributes to stress and anxiety in mice but does not play a role in body temperature control.

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PS2-20-03

Epigenome-wide association study reveals cpg sites associated with thyroid function and regulatory effects on KLF9

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Thyroid hormones play a key role in cellular growth, development, and metabolism, and are known regulators of gene expression through genomic and non-genomic processes including DNA methylation. Using eight cohorts from the ThyroidOmics-Consortium and a standardized meta-analysis quality control pipeline, we conducted an epigenome-wide association study between blood-based leucocyte DNA methylation sites and thyroid hormones (TSH, free T3 and free T4) in up to 7,073 participants of European and African ancestry. Significant associations were replicated in independent samples. The validated findings were correlated with gene expression levels and genetic variants. Causal influence of thyroid hormones on the DNA methylation levels was assessed by Mendelian randomization. Epigenome-wide significant associations (P-value $<$ 1.1E-7) of 3 CpGs for free T4, 5 for free T3, and 2 for TSH were discovered and replicated (combined P-values $=$ 1.5E-9 to 4.3E-28). The associations included CpG-sites annotated to *KLF9* (cg00049440) and *DOT1L* (cg04173586) that overlap with all three traits with consistent effect directions. Associations were also found for CpG-sites in *FKBP5* for free T4, and at *CSNK1D/lINCO1970* and *LRRC8D* for free T3. Differences in circulating TSH levels have a causal effect on DNA methylation of *KLF9*. DNA methylation of cg00049440 in *KLF9* was inversely correlated with *KLF9* gene expression in blood. The CpG-site at *CSNK1D/lINC01970* overlapped with THRA binding peaks in liver cells. The total additive heritability of the methylation levels of the six significant CpG-sites is between 25% and 57%. Significant methylation QTLs were identified for CpG-sites at *KLF9*, *FKBP5*, *LRRC8D* and *CSNK1D/lINC01970.* We report novel associations between TSH, thyroid hormones and blood-based DNA methylation. This study advances our understanding of thyroid hormone action and serves as a proof-of-concept that similar integrations of EWAS and other omics techniques can provide a valuable tool for unravelling thyroid hormone signaling next to classical *in-vitro* and animal studies.

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PS2-20-04

Staying cool in the heat - the role of thyroid hormone receptor alpha in thermoregulation

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A normal thyroid status is crucial for correct tissue and organ function, including temperature homeostasis. The tissue-specific actions of thyroid hormone on body temperature regulation in humans and rodents are largely modulated via the nuclear thyroid hormone receptor TRα1. Consequently, mice expressing a mutant TRα1R384C display a reduced core body temperature at 22°C caused by excessive heat loss via the tail. Surprisingly, the hypothermic phenotype of TRα1 mutant mice cannot be rescued by housing the mice at 30°C which negates tail heat loss. The observed lack of a compensatory brown fat activation suggests that the central regulation of temperature homeostasis may be impaired in TRα1-mutant mice. Ultimately, we hypothesize that TRα1-mutant mice have a lower central body temperature set-point due to yet unknown actions of the mutant TRα1 in the brain. To test whether a mutant TRα1 in the brain contributes to a lower body temperature phenotype, we injected adeno-associated viral vectors carrying the dominant-negative TRα1R384C into the hypothalamus, targeting the POA an area known to be involved in whole-body thermoregulation. Interestingly, preliminary data suggests that the expression of dominant-negative TRα1 in the hypothalamus indeed lowers body temperature independent of caloric intake. Further experiments aim at dissecting the contributions of dominant-negative TRα1 in the brain on resting metabolic rate and other metabolic parameters.

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PS2-20-05

Human resistance to thyroid hormone beta operates via a mechanism requiring receptor binding to DNA

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Objectives
All known ($>$230) different mutations in thyroid hormone receptor β (TRβ) causing Resistance to Thyroid Hormone β (RTHβ), localise to three clusters within its hormone binding domain. Here, we report phenotypes and molecular studies in an unique family with RTHβ due to a mutation in the DNA binding domain (DBD) of TRβ.
Methods
We ascertained clinical and biochemical features in four children and their parents from this family. Following identification of the *THRB* variant by next generation sequencing, functional properties of the TRβ mutant were assessed *in vitro*. We studied expression of T3-regulated target genes (*KLF9, HR*) and lipid metabolism in mutation-containing hepatocytes derived from inducible pluripotent stem cells (iPSCs) of patients, generated *ex vivo*.

Results
A male child (P1, age 4.7yrs) and his sister (P2, age 17.5yrs) with intellectual disability, elongated facies, winged scapulae, epiphyseal dysgenesis (P1), sensorineural hearing loss, goiter, tachycardia and abnormal thyroid function tests (P1: FT4 45pmol/l (RR 10.5-21), FT3 20pmol/l (RR 4-8.1), TSH 4.95mU/l (RR 0.35-5.5; P2: FT4 31pmol/l, FT3 11pmol/l, TSH1.95mU/l) were homozygous for an aminoacid substitution (Arg158Leu, R158L) at a highly conserved residue in the TRβ DBD. In contrast, their parents and two other siblings, all heterozygous for R158L TRβ, had normal thyroid function tests and no clinical abnormalities. Although their cellular expression and nuclear translocation is preserved, R158L mutant TRβ1 and TRβ2 exhibit negligible T3-dependent activation or repression of reporter genes (DR+4 TKLUC, TSHαLUC). Loss of binding of R158L TRβ1 and TRβ2 to DNA correlates with reduced thermal stability of the mutant DBD *in vitro*. Correlating with clinical phenotypes, hepatocytes derived from homozygous, R158L mutant TRβ iPSCs, exhibit loss of target gene (KLF9, HR) expression and excess lipid accumulation, whereas target gene expression in heterozygous R158L mutant TRβ hepatocytes is preserved.
Conclusions
Receptor haploinsufficiency, due to a heterozygous, loss-of-function mutation in the TRβ DNA binding domain, does not cause RTHβ. Homozygosity for this receptor defect is associated with RTHβ and additional phenotypes that mirror features observed in the first recorded cases of the disorder with homozygous deletion of *THRB* (Refetoff *et al* 1967, PMID4163616)

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PS2-20-06

A cardiac developmental defect prevents thyroid hormone-induced tachycardia in the syndrome of resistance to thyroid hormone alpha

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Objectives
Thyroid hormones (TH) affect cardiovascular functions *via* direct actions on the heart and *via* indirect actions on central nervous system. Mutations in TH receptor α1 (TRα1) cause Resistance to Thyroid Hormone α (RTHα), a disorder characterized by hypothyroidism in TRα1-expressing tissues including the heart.
Methods
The current experiments aimed at investigating the role of peripheral and central TRα1-signalling by further phenotyping TRα1 mutant mice (harboring R384C mutant TRα1) and making use of several techniques including radiotelemetry, electrocardiogram, transcriptomic, DNA methylation as well as *in vivo* pharmacology.
Results
In long-term radiotelemetry, TRα1 mutant mice showed bradycardia, broader heart rate (HR) distribution and blunted response to pharmacological denervation as compared to wildtypes at 22°C, suggesting a poor autonomic control of HR. While HR distribution and autonomic control of HR ameliorated at 30°C, the bradycardic state persisted. Interestingly, a 12-day oral T3 treatment, which reactivates the mutant $TR\alpha_1$ function, did not induce tachycardia - a key feature in hyperthyroid wildtypes. Microarray analysis in hearts showed decreased levels of Hcn2 and Hcn4 in $TR\alpha_1$ mutant mice, which were reversed by T3 treatment. However, the expression of several calcium and potassium channels, responsible for the repolarization of cardiomyocytes, were irreversibly decreased and not restored by T3 treatment in adulthood, clearly pointing towards developmental defects and possibly accounting for the T3-resistant bradycardia observed in $TR\alpha_1$ mutant mice. In fact, exposure of $TR\alpha_1$ mutant mice to higher maternal TH concentrations in utero restored the expression of some of these genes, *via* the normalization of several differentially methylated CpG sites in cardiac DNA of $TR\alpha_1$ mutant adult mice. Moreover, electrocardiogram recordings in untreated $TR\alpha_1$ mutant mice revealed longer PQ and QT intervals, whereas T3-induced tachycardia in wildtypes was fully abolished by peripheral injection of 4-aminopyridine, a potassium channels blocker, together indicating atrial and ventricular abnormalities such as long QT syndrome, often observed in hypothyroid patients.
Conclusions
Our findings highlight that developmental actions of TRα1 can lead to a T3 resistant heart and demonstrate that the TH-mediated induction of Hcn2 and Hcn4 is not sufficient for tachycardia development.

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PS2-20-07

Local thyroid hormone action in T cells - shaping T cell immunity

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The systemic function of thyroid hormones (TH) is highly dependent on their local action in distinct cell populations. A major target of TH are immune cells, yet knowledge on the effect of TH on immune responses is still incomplete. Within this study we aimed to determine the impact of TH on T cells, key players of immune responses, in more detail. To this end, we analyzed the activation and function of T cells from mice lacking TRα ($TR\alpha^{0/0}$) or expressing a TRα mutant unable to bind to DNA ($TR\alpha^{GS/GS}$). Initial phenotypic analysis of naïve mice by flow cytometry revealed an increase in circulating $CD4^+$ T cells in $TR\alpha^{GS/GS}$ compared with WT mice. Moreover, $CD4^+$ T cells in the spleen of $TR\alpha^{GS/GS}$ mice displayed a migratory and activated phenotype. Interestingly, the frequency of regulatory T cells (Treg), an important anti-inflammatory subpopulation of $CD4^+$ T cells, was also elevated within $TR\alpha^{GS/GS}$ mice. This was accompanied by an increase in thymus-derived natural Tregs while $TR\alpha^{GS/GS}$ $CD4^+$ T cells also showed an enhanced differentiation into induced Treg during *in* vitro polarization. RNA sequencing analysis of isolated regulatory T cells from naïve mice indicated an activated phenotype of $TR\alpha^{GS/GS}$ Treg. Moreover, we could detect an enhanced activation of the NFκB pathway in $TR\alpha^{GS/GS}$ $CD4^+$ T cells based on RNA sequencing as well as protein analysis. Taken together, we show an altered T cell phenotype in $TR\alpha^{GS/GS}$ mice, characterized by an augmented Treg immunity, which might be associated with increase activation of the NFκB signaling. These results might provide a better understanding of local TH action in T cells as a prerequisite to further elucidate the role of TH imbalance for immune responses during infectious and non-infectious diseases.

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PS2-20-08

Immunophenotyping of mice with mutated thyroid hormone receptor alpha or beta

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The immune system is a major target of thyroid hormones (TH), as they have been shown to act on innate as well as adaptive immune cells affecting their proliferation, activation and survival. However, the local TH action within the immune system is still poorly understood. To improve our understanding of this interaction, we performed an immunophenotyping of mice at baseline using flow cytometry and ELISA. For this, we focused on mice with TRα or TRβ mutations leading to TR deficiency (KO strains) or impaired DNA binding (GS strains). Flow cytometric analysis of the main leukocyte populations in TRβKO and GS mice revealed only minor differences in the composition of circulating and lymphoid immune cells. Similarly, TRαKO and GS mice displayed only minor differences in the innate immune compartment. However, significantly elevated frequencies of circulating T cells were found in TRαGS mice, which was related to an increase in the $CD4^+$ but not the $CD8^+$ subpopulation. Nevertheless, both $CD4^+$ and $CD8^+$ T cells exhibited a distinct phenotype in TRαGS mice which could be linked to either T cell activation or T cell exhaustion. Overall our data suggest a minor effect of TRβ on immunity, as well as a minor role of both TR in the innate immune system. It should be noted that these data were obtained in a naïve state and therefore do not necessarily correspond to the situation after stimulation. Nevertheless, our results imply an important function of TRα in the adaptive immune response already at steady state. The impact of TRα action on the adaptive immunity upon activation requires further investigation.

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PS2-20-09

The relevance of histidine 175 in thyroid hormone receptor alpha 1 for co-repressor binding revealed by a family carrying a H175R variant

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Background
Resistance to thyroid hormone (TH) alpha (RTHα), caused by heterozygous mutations in THRA, is characterized by abnormal thyroid function tests and features due to tissue-specific hypothyroidism, including disproportional short stature, variable motor and cognitive defects, macrocephaly and macroglossia, constipation and anemia. Mutant receptors display defective T3 binding resulting in impaired transcriptional activity. Dominant negative inhibition of the WT receptor results from a failure of corepressor complex dissociation from mutant receptors. The residues interacting with corepressors and the mechanisms underlying dominant negative inhibition have not been elucidated.
Methods
We describe a family, carrying a heterozygous H175R TRα variant, that lack most classical features of RTHα, except short stature. *In vitro*, T3-dependent transcriptional activity of WT and H175R mutant TRα1 were measured using three TRE-luciferase reporters (MAL-DR4, PAL-IR0, F2-ER6) in Jeg-3 cells. T3-dependent cofactor (NCoR1, SMRT-γ and SRC1) interactions with WT and H175R mutant TRα1 were tested in mammalian two-hybrid assays and in co-immunoprecipitations. Artificial mutations (H175A, H175F, H175K) were generated to investigate the required amino acid properties at position 175.
Results
The H175R showed impaired T3-dependent transcriptional activity on all TRE tested (EC50 H175R vs WT: 5.4 [3.9-7.4] vs 0.28 [0.26-0.29] nM, $P < 0.001$ for MAL; 5.4 [4.7-6.2] vs 0.29 [0.19-0.43] nM, $P < 0.01$ for PAL; 1.21 [0.94-1.56] vs 0.23 [0.13-0.41] nM, ns for F2). However, when co-transfected with WT TRα1 we found no significant dominant negative effect for TRα1-H175R. In mammalian two-hybrid assays, recruitment of GAL4-SRC1 was concomitantly impaired (EC50 H175R vs WT: 207 [147-290] vs 0.53 [0.41-0.68] nM, $P < 0.001$). Strikingly, T3-induced GAL4-NCoR1 and GAL4-SMRT-γ dissociation curves showed complete absence of NCoR1 and SMRT-γ interactions with the H175R mutant, which was confirmed by co-immunoprecipitation. Substitution of His175 with Lysine (H175K), but not with Alanine or Phenylalanine (H175A and H175F), similarly reduced T3-dependent transcriptional activity and abolished corepressor recruitment.
Conclusion
Our data indicate His175 as an important residue for corepressor binding in human TRα1, compatible with previous *in vitro* studies using artificial mutants. The substitution for a large positively charged residue rather than the absence of His175 causes lack of corepressor binding to H175R TRα1. At present, it is unclear if the H175R variant is linked to the phenotype. Studies in animal models carrying this variant will be performed to address this question.

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Poster Session 3: Hypothyroidism

PS3-21-01

Patients' persistent symptoms during therapy for hypothyroidism: results from the "thesis"* collaboration. (*treatment of hypothyroidism in europe by specialists, an international survey)

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Background
Levothyroxine (LT4) is considered the standard of care for hypothyroidism, however 5-10% of hypothyroid individuals complain of persistent symptoms despite achieving biochemical euthyroidism on LT4.
Methods
17,247 thyroid specialists from 28 countries were invited to participate in a survey. It enquired about respondents' perceptions of the cause of hypothyroid-like persistent symptoms and how the prevalence of such complaints had changed over time. Geographic regions were defined according to the UN Statistics Division. Gross national income (GNI) information stems from https://data.-worldbank.org/.
Findings
The response rate was 32.9%. Persistent symptoms despite normal TSH while receiving LT4 treatment was reported to affect up to 10.0% of patients by 75.4% of respondents. Main assumed causes for symptom persistence included psychosocial factors (77.1%), comorbidities (69.2%), and unrealistic patient expectations (61.0%). Multivariate analysis showed that the prevalence of persistent symptoms in Eastern Europe (OR 0.44; 95% CI 0.37-0.52), Southern Europe (OR 0.49; 95% CI 0.41-0.59), and Western Asia (OR 0.74; 95% CI 0.57-0.96) was lower than Western and Northern Europe. A lower frequency of persistent symptoms was also associated with longer respondent clinical experience (OR 0.40; 95% CI 0.30-0.52). In contrast, being an endocrinologist (OR 1•93; 95% CI 1.51-2.48), working at a university center (OR 1.26; 95% CI 1.11-1.42) and having a high-volume practice (OR 1.26; 95% CI 1.10-1.44) were associated with higher estimates of prevalence of persistent symptoms. Most respondents perceived either a stable or increasing trend (40.9% and 28.4%, respectively). Multivariate analysis showed that compared to Western Europeans, Northern Europeans and Western Asian respondents reported an increasing, while Eastern Europeans reported a decreasing trend. An increasing trend was also reported by respondents with a private practice and those with a high-volume practice.
Interpretation
The majority of THESIS respondents attributed the persistence of hypothyroid-like symptoms to psychosocial factors. It could be postulated that the higher prevalence of persistent symptoms reported by the specialists in endocrinology who work in academic and tertiary level structures is possibly due to referral of unresolved clinical conditions to these structures. The prevalence of dissatisfaction in hypothyroid patients seems to be rather stable over time. However, the prevalence of dissatisfied patients is increasing in countries with higher GNI, like the northern region of Europe, while is reported as decreasing in regions with lower GNI, like the eastern area of Europe.

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PS3-21-02

Use of t3-containing treatments for hypothyroidism: results from the "thesis"* collaboration (*treatment of hypothyroidism in europe by specialists: an international survey)

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Background
Levothyroxine (LT4) monotherapy is the mainstay of treatment of hypothyroidism, but a sizeable minority of endocrinologists also use T3-containing treatments in some patients notwithstanding concern about their safety.
Methods
17,247 thyroidologists from 28 countries were invited to participate in a questionnaire survey. Geographic regions were defined according to the UN Statistics Division. Gross national income (GNI) information stems from https://data.worldbank.org/.
Findings
The response rate was 32.9%. LT4 was the initial treatment chosen by the majority (98.3%). Other options favored by a minority were: LT4 + LT3 1.2%; LT3 monotherapy 0.3%; desiccated thyroid extracts (DTE) 0.1%. A significant minority (42.4%) of respondents stated that they would never consider LT4 + LT3 combination treatment. LT4 + LT3 combination treatment was favored by 39.7% for patients with persistent symptoms, by 15.7% for a short period in patients recovering from protracted hypothyroidism. Multivariate analysis showed that LT4 + LT3 combination treatment was positively associated with a) being an endocrinologist compared to other specialties (OR 1.44; 95% CI 1.17-1.76); b) having a high-volume compared to low volume practice (OR 1.39; 95% CI 1.23-1.58); c) and working in countries with high compared to low GNI (OR 1.021; 95% CI 1.014-1.027). Conversely LT4 + LT3 combination treatment was negatively associated with a) respondent being male (OR 0.86; 95% CI 0.76-0.97), and b) working in Western Europe compared to other regions (OR 0.27; 95% CI 0.20-0.36). In addition, choice of T3-containing medication was significantly associated with respondents' view that LT4 alone cannot restore normal physiology and inversely associated with the view that patients' unrealistic expectations are the cause of persisting symptoms.
Interpretation
The vast majority of respondents considered LT4 as the first line of treatment, while a very small minority (1.7%) chose T3-containing treatments. The THESIS respondents' approach to LT3-containing treatments is in accordance with present evidence. Nearly all respondents stated that they would not use LT4 + LT3 combination as initial treatment, and only 40% would consider this therapy for persistent symptoms. Why this treatment option was more frequently recommended by endocrinologists who work in private practice, who are female, and who live in countries with higher GNIPC is unclear and requires further study. At variance with reports from the USA, DTE was nearly never recommended by THESIS respondents. This may reflect concerns about overtreatment, unphysiological fluctuations in T3 levels and variable potency and is consistent with available evidence and recommendations by professional guidelines.

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PS3-21-03

Tryptophan metabolism via kynurenine pathway in young women with hypothyroidism

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Objective
Hypothyroidism is one of the most common disturbances of thyroid function caused by a thyroid hormone deficiency, found predominantly in young women. The general slowdown of metabolic processes and low-grade chronic inflammatory state occurs in the broad spectra of clinical hypothyroidism manifestations. Although several risk factors of hypothyroidism have been identified, the exact pathogenic mechanisms remain unexplained. The conventional treatment of hypothyroidism is hormone replacement therapy with levothyroxine, one of the main prescribed drugs worldwide. The metabolism of tryptophan (TRP) via the kynurenine pathway (KP), affecting the immune system, contributes to numerous fundamental biological processes. Since the role of the above-mentioned metabolic pathway in hypothyroidism is unknown, the current study aimed to determine KP activity in young women with diagnosed hypothyroidism.
Methods
The study population consisted of 50 women with hypothyroidism treated with thyroid hormone replacement therapy (mean levothyroxine dosage of 1.09 ± 0.36 μg per kilogram of body weight per day, mean age 32.22 ± 9.68) and 33 healthy, age-matched women (CON). Serum levels of TRP, kynurenine (KYN), and its further metabolites: 3-hydroxykynurenine (3-HKYN), kynurenic acid (KYNA), anthranilic acid (AA) and 3-hydroxyanthranilic acid (3-HAA) were determined by HPLC (Agilent Technologies 1260 series LC system), with DAD and FLD detection. Statistical evaluation of the results was performed using STATISTICA, version 13.3.
Results
TRP concentrations in both groups were similar, while KYN and 3-HKYN levels were significantly elevated in the patients' group compared to CON ($P < 0.001$). The KYN/TRP ratio, which reflects the activity of the indole 2,3-dehydrogenase enzyme (IDO-1) involved in the conversion of TRP to KYN, was elevated in hypothyroidism compared to CON ($P < 0.05$). KYNA concentrations were decreased ($P < 0.05$), and KYNA/KYN ratio, which reflected kynurenine aminotransferase-1 (KAT-1) activity, was significantly lower in women with hypothyroidism compared to CON ($P < 0.01$). In contrast, AA levels were significantly higher in the patients compared to CON ($P < 0.0001$), whereas 3-HAA levels were comparable between both groups. In addition, the 3-HAA/AA ratio, indicating the transformation of AA to 3-HAA was significantly reduced in HT patients compared to healthy subjects ($P < 0.001$).
Conclusions
Young women with hypothyroidism manifest alteration of TRP metabolism through the kynurenine pathway. The accumulation of KYN, 3-HKYN, and particularly AA occurred, with simultaneously limited KYNA production. Disturbances in the balance between KYNA and AA formation may potentially impact the development of the indicated thyroid function disturbance, which requires further research.
Founding
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PS3-21-04

Autoimmune thyroid disease and hypothyroidism in patients with iron deficiency

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Background
Autoimmune thyroid diseases (AITD) are multifaceted conditions in which the thyroid gland is infiltrated by lymphocytes resulting in the production of thyroid-specific auto-antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). Iron deficiency (ID) is considered to be the most common nutritional deficiency worldwide and has multiple effects on thyroid metabolism.
Aim
The goal of this study is to measure the prevalence of autoimmune thyroid disease and hypothyroidism in patients with iron deficiency.
Methods
72 patients, aged 21-56 (all female) were included in the study. The complete blood count results of the patients mentioned above, revealed low levels of hemoglobin, hematocrit, MCV (mean corpuscular volume) and iron. A diagnosis of ID was concluded. Following the diagnosis, the levels of TSH, TPOAb and TGAb were checked to determine whether the patients were also suffering from AITD and hypothyroidism.
Results
After evaluating the test results, it was revealed that 43 of the women enrolled in the study had autoimmune thyroid disease and hypothyroidism. That is ≈60% of all the patients.
Conclusion
It can be concluded that ID has the possibility to affect thyroid function and therefore can be linked to AITD and hypothyroidism.

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PS3-21-05

The hypothyroid mothers' newborn repercussions in a semi-intensive care unit

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Thyroid hormones (TH) are responsible for maintaining metabolism. Its concentrations are fundamental during pregnancy and the first days of life, and its imbalance can generate early and late repercussions for the newborn.

Objectives
This study evaluates the relationship between maternal thyroid disease history impact on newborns and infants admitted to the semi-intensive care unit.
Materials and methods
Data were collected from a historical cohort of 1,400 newborns and infants admitted from January 2018 to December 2020. Malformed newborns, those with genetic syndromes and incomplete medical records were excluded. Information such as gestational age according to the Capurro index, Apgar score in the first and fifth minutes of life, sex, type of delivery, length of hospital stay, maternal Diabetes Mellitus and pregnancy hypertension were recorded. Instead, hypoglycemia, neonatal jaundice, respiratory distress, neonatal anoxia, infectious risk, and meconium aspiration were considered as outcomes. The data were analyzed by Chi-square (X2), relative risk (RR), ROC curve, and logistic regression.
Results
After exclusion, 1260 patients remain. We identified maternal hypothyroidism history associated with a lower weight (P-value < 0.003, RR: 4.3 - CI: 1.6 to 11.3) and lower Capurro (P-value < 0.005, RR: 3.5 - CI: 1.5 to 8.4). Hypoglycemia was the only outcome associated with maternal hypothyroidism (P-value < 0.001, RR: 4.9 - CI: 2.2 to 11.1). A multivariate analysis also identified it as an independent risk factor (P-value: 0.001, RR: 4.3 – CI: 1.8 to 10.5). Maternal Diabetes and hypertension were also independent predictors with a risk of 3.5 ($P < 0.001$, CI: 1.9 to 6.4) and 2.0 ($P = 0.010$, CI: 1.2 to 3.4), respectively.
Conclusions
The knowledge of the maternal thyroid history helps to predict repercussions for the newborn. We associated that history with a lower weight, lower gestational age (Capurro) and hypoglycemia outcome. In addition, maternal hypothyroidism, diabetes and hypertension were also independent risk factors for newborn hypoglycemia.

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PS3-21-06

Liquid Levothyroxine (L-T4; vs. Tablet L-T4) mantains more stable tsh levels in hypothyroid patients

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Hypothyroidism is usually treated with levothyroxine (L-T4), that is present in different formulation. We aim to assess if hypothyroid patients have a better control of thyroid-stimulating hormone (TSH) levels by following a L-T4 therapy in a liquid formulation, with respect to the tablet formulation. We enrolled seven hundred hypothyroid patients treated with liquid L-T4, and three hundred and fifty hypothyroid subjects receiving tablet L-T4 (both groups were matched by age and gender). All the enrolled subjects had normal circulating TSH levels at the basal evaluation, and did not report any malabsorption or drug interference issues. Patients were monitored for two years, and their serum TSH, FT3, FT4 levels were assessed after one and two years. At the first abnormal TSH value, we evaluated: 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. We registered the following results: after 1 year, TSH values were normal in 84 % 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 ($P < 0.05$). Hypothyroidism affects approximately 5% of the population, mostly of them are women and people over 60 years of age. Once reached stable TSH levels in the normal range, patients are monitored with an annual test of the TSH levels in order to adjust the therapy, if necessary. The maintainment of a stable TSH level in the normal range is very important, since large population studies showed an increased mortality in people with TSH in the hypothyroid range. Our data support the efficacy of liquid L-T4, with respect to tablet L-T4, in the maintainment of normal TSH levels in hypothyroid patients in the long term follow-up.

Keywords: Hypothyroidism, liquid L-T4, tablet L-T4, Hormone Replacement Therapy, Thyroid
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PS3-21-07

Assessing the risk of atrial fibrillation in hypothyroid women prescribed with liothyronine: A retrospective cohort study

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Background
Whether combination therapy of levothyroxine and liothyronine increases the risk of atrial fibrillation remains a topic of debate.
Objectives
The objective of this study was to investigate the risk of atrial fibrillation in individuals with hypothyroidism treated with a combination of levothyroxine and liothyronine.
Methods
We conducted a retrospective cohort study using individual-level linkage of Danish nationwide registries to identify women who claimed a prescription of liothyronine between 2017 and 2019. These cases were matched 1:1 with women treated with levothyroxine only, based on age-group, Charlson Comorbidity Index (CCI), educational level, and year of prescription. The primary outcome was a diagnosis of atrial fibrillation, and cases and controls were compared by use of Poisson regression models to estimate the incidence rate ratios (IRRs).
Results
This retrospective cohort study included 2,896 women who claimed a prescription of liothyronine, median age 53 years (interquartile range 45 to 60). Most women (98.9%) had no major comorbidities (CCI = 0), and 87.5% had a high school or higher education. The women were followed for a median time of 2.9 years, totaling 18,361 person-years of observation time. Six women treated with liothyronine (6.7 per 10,000 person-years) were diagnosed with atrial fibrillation, compared to four in the control group (4.2 per 10,000 person-years). However, no statistically significant increased risk of atrial fibrillation was found (Incidence rate ratio of 1.61 [95% CI 0.45 – 5.70])
Conclusions
The results of this study suggest that the risk of atrial fibrillation among women taking liothyronine is low, and the addition of liothyronine compared to levothyroxine treatment alone was not associated with an increased risk of atrial fibrillation. However, caution should be exercised in interpreting these results due to the relatively short follow-up period and the small number of events observed in this age-group of women.

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PS3-21-08

Consumptive hypothyroidism in a patient with metastatic melanoma: A case report on a new association

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Introduction
Consumptive hypothyroidism is a rare condition characterized by the aberrant expression and increased activity of thyroid hormone deiodinase type 3 (DIO3) in neoplastic tissue. This leads to an augmented conversion of thyroxine (T4) to the inactive reverse triiodothyronine (rT3). So far, most cases of consumptive hypothyroidism have been described in infants with hemangiomas.
Case presentation
We report the case of a 64-year-old woman with metastatic melanoma of the choroid that first presented with immunotherapy-induced thyroiditis (ipilimumab/nivolumab). Due to progression to hypothyroidism, she was started on L-thyroxine. Because of metastatic tumor progression, the patient received multiple local and systemic treatments including trametinib (MEK inhibitor), olaparib (PARP inhibitor), pembrolizumab (anti-PD-1), lenvatinib (multikinase inhibitor), binimetinib (MEK inhibitor), and finally autologous Tumor-Infiltrating Lymphocytes enriched for tumor antigen specificity (NeoTIL). After 2 years of L-thyroxine treatment, TSH values started to rise, and despite high doses of L-thyroxine (up to 6.1 mg/kg/jour) thyroid function never normalized. Low T3 levels and persistent hypothyroidism despite high doses of L-thyroxine and adequate compliance arose the suspicion of consumptive hypothyroidism. While the biochemical characterization remained incomplete due to

the passing of the patient, analysis of metastatic tumor tissue demonstrated very abundant overexpression of DIO3 by immunohistochemistry.
Conclusion
Consumptive hypothyroidism is a rare entity that must be considered in oncologic patients with hypothyroidism requiring high doses of L-thyroxine. Recent observations, including this case report, show that certain epithelial malignancies can also overexpress DIO3 and, hence, lead to consumptive hypothyroidism. Treatment consists of high doses of L-thyroxine, sometimes in association with liothyronine (LT3). The role of new forms of immunotherapy on DIO3 overexpression and the development of consumptive hypothyroidism needs to be further investigated.
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PS3-21-09

Efficacy of oral liquid l-thyroxine (L-T4) in controlling hypothyroidism in patients submitted to total thyroidectomy
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Tablet levothyroxine (L-T4) is the common treatment for hypothyroidism. We aim to investigate the efficacy of L-T4 in liquid formulation in patients recently subjected to total thyroidectomy (without malabsorption or drug interference), with respect to L-T4 tablets. Eighty patients were treated with L-T4 in tablets, whereas one hundred and sixty received liquid L-T4 at the same dosage (1.5 mg/kg/day). All patients started the therapy the day after thyroidectomy, and the drugs were assumed every day 30 min before breakfast. Serum thyrotropic hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were evaluated in a first control after 6 weeks, then in a second control after 12 weeks. We showed a significantly higher prevalence of patients in the hypothyroid range (TSH > 3.6 mcU/ml) under a L-T4 tablet therapy, with respect to those in treatment with the L-T4 liquid formulation. Furthermore, TSH values were significantly lower in the liquid L-T4 group, than in the tablet L-T4 group both at the first ($P < 0.05$), and at the second control ($P < 0.01$). FT4 and FT3 levels were not significantly different. Our results suggest that liquid L-T4 therapy leads to a better control of TSH levels in thyroidectomized patients, not reporting issues of malabsorption, gastric disorders, or drug interference.
Keywords: Hypothyroidism, total thyroidectomy, liquid L-T4, tablet L-T4, Hormone Replacement Therapy, Thyroid
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Nodules 2

PS3-22-01

Radiofrequency ablation of benign thyroid nodules: Value of the anterolateral hydrodissection technique
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Purpose
To evaluate the technical feasibility, efficacy, and safety of the anterolateral hydrodissection (ALHD) technique in radiofrequency ablation (RFA) for benign thyroid nodules.
Methods
Between November 2019 and April 2020, 39 patients underwent 41 sessions of RFA with ALHD technique for treatment of benign thyroid nodules. ALHD was performed with cold (0°C–4°C) 5% dextrose solution during RFA to minimize pain and secure sufficient safety margins from critical neck structures. The initial ablation ratio (IAR) was measured to evaluate the technique's efficiency. Ultrasound examinations, symptoms, and cosmetic scores were evaluated pre-procedure and at 6- and 12-month post-procedure. Procedure-related pain during RFA and complications were evaluated.
Results
The mean index nodule volume was 20.5 ± 21.6 ml. ALHD was technically feasible in all patients. The mean IAR was 90.7 ± 8.3%, and significant reductions in mean nodule volume were noted at 6- and 12-month follow-up ($P < 0.001$, 63.9 ± 19.0%, and 76.3 ± 18.9%, respectively). After the procedures, symptom and cosmetic scores showed significant improvement at 6- and 12-month follow-up ($P < 0.001$). Pain during the procedure was well-controlled with ALHD in all patients. There was no additional lidocaine injection after the initial use of 5–10 cc of lidocaine at the start of the procedure in all patients. Transient voice change was observed in one patient, but the patient recovered spontaneously within 30 minutes.
Conclusion
The ALHD technique was technically feasible in all patients and effective for achieving 90.7% IAR. The ALHD technique also had a pain-relieving effect, resulting in lower amount of lidocaine administration during the procedure.
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PS3-22-02

Abstract withdrawn

PS3-22-03

Determinants of hypothyroidism post-radioactive therapy in toxic adenomas and toxic multinodular goiter: A multicenter cohort study
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Introduction
The definitive treatment of hyperthyroidism caused by toxic adenoma (TA) and toxic multinodular goiter (TMNG) is ablative therapy with radioactive iodine (RAI) or surgical resection of the hyperfunctioning thyroid nodules. Hypothyroidism after RAI therapy is a common complication.
Objectives
To evaluate the prevalence and risk factors of hypothyroidism in patients undergoing RAI for AT and BMNT.
Methods
A Multicentre non-randomized cohort study was performed. Patients diagnosed with AT or TMNG who underwent RAI from January 2018 to November 2021 were eligible. The following inclusion criteria were used: > 18 years old, negative thyrotropin(TSH)-receptor antibodies and positive technetium-99m scintigraphy for hyperfunctioning adenomas. Patients with post-therapy resolution of clinical and biochemical hyperthyroidism (TSH > 0.4μUI/mL) were considered cured. Biochemical hypothyroidism was defined as TSH > 4.2 μUI/mL RAI activity was chosen based on thyroid volume and hyperthyroidism severity.
Results
One hundred-forty-eight patients (126 women) with AT ($n = 57$) and TMNG ($n = 91$) treated with RAI (activity between 5-20mCi), with a mean age of 65 ± 13 years, were admitted for analysis. Forty-five patients with TMNG presented with more than 3 hyperfunctioning nodules and 86.8% of TMNG patients had hyperfunction nodules in both thyroid lobules (bilateral disease). In the first year after RAI, 94,6% ($n = 140$) patients had biochemical cure of hyperthyroidism and 35.8% of patients developed hypothyroidism requiring levothyroxine supplementation. In the majority ($n = 32$; 60.4%) of patients who developed hypothyroidism, it manifested within the first 6 months after RAI therapy. The onset of hypothyroidism was more prevalent among women (*Chi-square test*: 36.5% vs 22.7%, respectively, *P*-value < 0.001) and more common in patients with the diagnosis of AT when compared with those with TMNG (*Chi-square test*: 42.1% vs 29.7%, respectively, *P*-value < 0.001). Moreover, patients with bilateral hyperfunctioning nodules presented with lower hypothyroidism rate than those

with unilateral thyroid disease (*Chi-square test*: 30.3% vs 39.1%, respectively, *P*-value <0.001). No difference in post-RAI hypothyroidism's prevalence was found regarding age, RAI activity, TSH or T4L levels at the diagnosis.
Conclusion
In this study, hypothyroidism after RAI in AT/TMNG presented in 35.8% of the patients. Hypothyroidism after RAI was more frequent in women, patients with a single hyperfunctioning adenoma and unilateral disease. This evidence may indict that ablative activity of RAI under normal-functioning thyroid tissue may have an impact on hypothyroidism incidence post-RAI therapy.

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PS3-22-04

Abstract withdrawn

PS3-22-05

Prevalence and incidence of thyroid nodule and its risk factors; a population-based prospective cohort study in iodine-sufficient area

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Objective
The aim of this study is to investigate the prevalence and incidence of thyroid nodules, and associated risk factors in population-based prospective cohort study.
Methods
We investigated the prevalence of thyroid nodules using the data of 3,104 adults aged over 50 years, who were enrolled in the Korean Genome and Epidemiology Study and performed thyroid ultrasonography (US) in 2011-2012. Individuals have been performed US every 2 years, during 8 years of follow-up. The incidence of thyroid nodules and associated risk factors were analyzed among adults who did not have thyroid nodule at baseline and followed-up with US more than once. We compared the incidence of thyroid nodules among 4 groups according to the changes of metabolic syndrome (MS) status during 8 years of follow-up: MS_0, adults who never had MS; MS_1, adults who developed to MS; MS_2, adults recovered from MS; MS_3, adults having MS consistently.
Results
The mean age of the study population was 64.9 $\pm$ 8.5 years, and 56.9% were women. The age-adjusted prevalence of thyroid nodules was higher in women: 0.3-0.59 cm, 15.6% vs 12.4%; 0.6-0.99 cm, 16.2% vs 7.7%; $\geq$1 cm, 20.9% vs 9.4%. The prevalence was also associated with older age, higher body mass index (BMI) and waist circumference (WC), and MS. The age-adjusted incidence was also higher in women: 0.3-0.59 cm, 25.2% vs 17.5%; 0.6-0.99 cm, 8.8% vs 5.2%; $\geq$1 cm, 2.1% vs 1.0%. In logistic regression model, the association between the MS and the prevalence of thyroid nodule $\geq$ 1 cm was significant (odds ratio [OR], 1.657, 95% confidence interval [CI] 1.334-2.057, $P < 0.001$). In cox regression models, MS still significantly increased the risk of the incidence of thyroid nodule, even after adjustment for age, sex, smoking, alcohol consumption, thyroid dysfunction (HR 2.169, 95% CI 1.128-4.173, $P = 0.020$). The risk for the incidence of thyroid nodules $\geq$1 cm was significantly higher in MS_3 group compared to that in the MS_0 group (HR 3.427, 95% CI 1.500-7.828, $P = 0.003$), in multivariable adjusted model.
Conclusion
To our knowledge, this was the first study reporting the prevalence and incidence of thyroid nodules based on the prospective cohort study in general population. MS increased the risk of prevalence and incidence of thyroid nodules independent of multiple variables.

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PS3-22-06

Italian guideline on the management of benign non-hyperfunctioning thyroid nodule causing compressive symptoms

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Aim
Diagnostic definition and therapeutic interventions for nodular thyroid disease represent a high healthcare cost and their consequences may have a negative impact on quality of life of patients. This guideline aims at providing a reference for the management of non-functioning, benign thyroid nodules causing local symptoms in adults outside of pregnancy. The purpose is to standardize the treatment, based on the evidence provided by the GRADE method and the expertise of a multidisciplinary expert panel.
Methods
Recommendations has been issued following the Methodological Manual for clinical practice guidelines developed by the Italian Istituto Superiore di Sanità, using the PICO approach (Population, Intervention, Comparison, Outcome). Efficacy of hemithyroidectomy with isthmectomy has been compared to total thyroidectomy, minimally invasive therapies, medical treatment, and no treatment. Based on the indications appointed by a multi-disciplinary panel, critical clinical outcomes were considered in the systematic review and formulation of recommendations.
Results
In patient with a benign non-hyperfunctioning thyroid nodule causing local symptoms, the therapeutic option must be proposed considering the clinical picture, the available resources and the preferences expressed by the patient. The recommended primary surgical treatment is hemithyroidectomy combined with isthmectomy, as long as no significant disease is detected in the opposite thyroid lobe. For patients with clinically significant disease in the opposite lobe, total thyroidectomy should be considered. Thermal ablation may be considered as an alternative to surgery in patients with a symptomatic, solid, benign, single, or dominant thyroid nodule. TSH-suppressive treatment with L-thyroxine or radioiodine treatment are not indicated as a routine treatment option. Percutaneous ethanol injection should be considered as the preferential therapeutic option in a patient with a single or dominant benign thyroid nodule with a cystic or predominantly cystic structure causing local symptoms.
Conclusion
The recommendations contained in this guideline will be revised within three years from the date of publication. A new systematic literature review will verify the availability of new evidence that may influence the strength of recommendations. According to the data at hand, adopting guideline recommendations would likely lead to a gradual decrease in the number of surgical procedures for benign thyroid nodular disease. This could result in fewer admissions to surgical departments for non-cancerous cases and expedited treatment for patients with thyroid cancer. Additionally, a decrease in indirect costs related to extended replacement therapy and handling of surgical complications may be expected.

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PS3-22-07

A pharmacoeconomic analysis from italian guidelines for the management of non-hyperfunctioning, bening thyroid nodules

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Background
Thyroid nodules are the most common endocrine pathology. Due to the widespread use of imaging modalities, mostly ultrasound, the incidental finding of thyroid nodules has increased, reaching a prevalence of 50-60% in adults. Diagnostic definition and therapeutic interventions represent thus an increasing cost for health system. In patient with benign thyroid nodule causing local symptoms, hemithyroidectomy with isthmectomy or total thyroidectomy are the recommended primary surgical treatment, depending on unilateral or bilateral disease localization, respectively. For patients with symptomatic, solid, benign, single, or dominant thyroid nodule, thermal ablation may be considered as an alternative to surgery.
Aim
To produce economic evidence in the context of the definition of guideline for the management of non-hyperfunctioning, benign thyroid nodules in Italian healthcare setting.
Methods
A systematic literature review and a survey among the guideline panel members were performed to address drivers that contribute to total cost of each therapeutic option.
Results
In Italy, during the last 20 years, an average of 40,000 thyroid surgeries (total or partial) have been performed each year, about one quarter of them for malignant diseases. One third of those operated on for a benign disease suffered from uninodular goiter or multinodular goiter with a clearly dominant nodule. The number of patients eligible for percutaneous ablative treatment could thus range from 8,000 to 10,000/year. The individual reimbursement by national health system (NHS) for thyroid surgery amounts to € 4211. Savings for each ablative treatment replacing hemithyroidectomy/total thyroidectomy can be estimated at € 2651 (the difference between € 4211 cost of thyroid surgery and € 1560 of an ablative treatment). Annual savings for the NHS would fluctuate from a minimum of € 7,953,000 to € 23,859,000 when ablative treatments will be fully operational.
Conclusions
While thyroid surgery is a standardized therapeutic procedure, the more recently introduced minimally invasive therapies with thermal ablation are less standardized. On considering the cost-utility profile, a reduction in the annual number of surgical interventions for benign nodular pathology (currently the main cause of thyroid surgery) is foreseeable in favor of minimally invasive treatments performed in day-hospital, sparing costs of operating room and hospital stay. This change should also generate a reduction in the occupation rate of surgical beds and faster accessibility to surgical departments for oncological operations.

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PS3-22-08

Natural course of benign thyroid nodular disease in a borderline iodine-sufficient area: 10-year retrospective follow-up data from a tertiary center

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Objective
Thyroid nodules are common in the population more than 90% are benign. Data about the long-term follow-up of benign nodular thyroid disease is limited. We aimed to clarify, clinical outcome, frequency and magnitude of volume changes in cytologically and/or sonographically benign nodules in long-term(> 5 years) follow-up and to determine the predictive features of nodule growth.
Methods
We retrospectively collected data of cytologically and/or sonographically benign 427 nodules from 221 euthyroid patients with 10 years of ultrasonographic follow-up(2004–2023) from the same tertiary center and sonographers. Thyroid autoantibody positivity, presence of more than 5 or confluent nodules that are difficult to interpret sonographically, were excluded. Nodule volume was calculated using the ellipsoid formula: a × b × c × 0.523.
Results
The volume change patterns of 427 nodules from 206 euthyroid patients (F/M = 3/2), with the mean age 50.2 ± 12.5 years] were analysed. Mean ± s.d.TSH at the initial visit was 1.7 ± 1.08 mIU/l. The median nodule volume was 0.47 (min-max = 0.03-28.24) ml. When the nodules were examined according to their echogenic patterns, 47%(n = 202) of the nodules were isoechoic, 25%(n = 107) hypoechoic, 20%(n = 85) mixed (iso-hypoechoic) and 8%(n = 33) hyperechoic. Regarding nodule structure, 39%(n = 165) of the nodules were solid and 61%(n = 262) were mixed. Concerning the location(longitudinal axis), 13%(n = 57) of the nodules were located in the upper third, 50% (n = 215) in the middle and 37%(n = 155) in the lower third. The percentage of nodule volume change at the 5th and 10th years were presented in Table 1. 70%(n = 153) of the nodules that grew in the first 5 years continued to grow in 5-10 years. 46% of the stable nodules and 30% of the nodules which decreased in volume in the first five years grew between 5-10 years. The growth pattern in the second 5 years was significantly different from the first 5 years(McNemar-Bowker test, P = 0.02). A generalized mixed linear model revealed that age at diagnosis, male gender and initial nodule volume were significant predictors for the nodule volume change (OR = 0.980 P = 0.037, OR:0.630 P = 0.040, OR:0.929 P = 0.019 respectively), where as echogenicity and location were not associated with nodule growth.
Conclusions
To our knowledge, this is the first 10-year retrospective follow-up of euthyroid benign nodular disease in the literature, we showed that young age, female gender and small initial nodule volume are predictive for increased nodule volume in long-term follow-up.

Table 1

	Follow-up at 5 year (n = 427)		Follow-up at 10 year (n = 427)	
Increase	n	%	n	%
Nodule vol ≥ 15%	220	52	257	60
Nodule vol ≥ 30%	172	40	238	56
Remain stable	85	20	38	8
Decrease				
Nodule vol ≥ 15%	122	29	132	31
Nodule vol ≥ 30%	89	21	108	25

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PS3-22-09

Percutaneous ethanol sclerotherapy for the treatment of benign cystic thyroid nodules: A 5 year-experience at a tertiary care hospital

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Objectives
Assess the efficacy and safety of ultrasound-guided percutaneous ethanol injection (PEI) for treating benign cystic or predominantly cystic-thyroid nodules (TN).
Methods
Retrospective analysis of all euthyroid patients treated with PEI for purely (>90% of cystic component) or predominantly cystic (50%-90% of cystic component) TN between January 2018 to February 2023. Efficacy was defined as 50% or greater reduction in pretreatment volume with no recurrence. Safety was considered as no or mild PEI-related complications. Patients with incomplete data were excluded.
Results
In this analysis, 55 patients were included, of whom 39 were female (70.9%) and the median age was 55 (±16) years. The most common complaint was a cosmetic issue in 33 patients (58.2%), and 9 patients (16.4%) were symptomatic (4 with dysphagia, 1 with dysphonia, and 3 with neck pressure). PEI was used in 34

(61.8%) patients with predominantly cystic nodules. The median largest diameter of the nodules was 39.0 (P25-75: 34-46) mm, and the median initial volume was 14.7 (P25-75: 8.6-24.5) mL. During PEI sessions, the median amount of fluid drained was 8.0 (P25-P75: 4-13) ml, and the median amount of ethanol instilled was 3.0 (P25-P75: 1.3-5.0) mL. Overall, reductions of TN volume >50% were achieved in 46 (83.6%) of the nodules with a median follow-up of 30.8 (13-43) months. This was achieved in a median time of 8 (1-27) weeks after the 1st PEI. Around 56.4% (31) of the nodules were successful after just one session. No statistical differences were found in the success of PEI and the type of nodule. All symptomatic patients went into remission. However, 4 (7.3%) of the nodules with initial success did end up recurring after 99 [55-153] weeks on median. One of these patients underwent surgery due to the nodule becoming almost completely solid with over 30mm in size, and histopathology revealed a benign diagnosis. Adverse reactions (AE) were reported in 8 (14.5%) patients and were mostly mild. Six patients complained of mild reactions: 5 experienced a burning sensation during PEI, and 1 developed a local hematoma. Two patients developed more serious AEs: dysphonia (which improved after speech therapy) and Horner syndrome.

Conclusion

In our experience, PEI is an effective and generally safe procedure. The technique leads to significant reductions in nodule volume, with lasting effects. Additionally, all symptomatic patients experienced improvement. Further investigation in larger studies is warranted, given the limitations of our single-center, small sample size study.

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Pregnancy

PS3-23-01

TSH elevation before or after a pregnancy according to unidentified maternal thyroid function and thyroid autoantibody status in the early pregnancy: A study of 13,664 danish pregnant women

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Objectives

One of the risk-based screening criteria for thyroid disease in pregnancy is previous abnormal thyroid function or thyroid autoantibody-positivity. We speculated on the frequency and results of thyroid function testing in women of fertile age as part of routine care before and after a pregnancy.

Methods

The North Denmark Region Pregnancy Cohort includes retrospective assessment of thyroid function and thyroid autoantibodies (ADVIA Centaur XPT, Siemens Healthineers) in stored biobank samples from early pregnant women, 2011-2015. For this study, all thyroid-stimulating hormone (TSH) analyses drawn as part of routine care, 2006-2022, were identified for each woman in the cohort. Elevated TSH before or after the pregnancy was defined by the non-pregnant upper reference limit (above 4.5 mIU/l) and the frequency was evaluated according to thyroid function and autoantibody status (thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies (Ab) using cohort- and method-specific cut-offs) in the early pregnancy biobank sample.

Results

Altogether 13,664 singleton pregnant women without clinically detected and treated thyroid disease were included and retrospective assessment of TSH, TPO-Ab, and Tg-Ab in the early pregnancy biobank sample revealed that 812 (5.9%) had unidentified TSH outside the range of 0.1-3.5 mIU/l, and 15.5% were antibody-positive (Table). Considering then all TSH results from routine care, altogether 7,207 women (52.7%) had had TSH assessed before the pregnancy under study (median 2.5 years before; median 3 times), and 10,250 (75.0%) after the pregnancy (5.1 years after; 6 times). The frequency of elevated TSH before or after the pregnancy was increased with increasing maternal TSH in the early pregnancy biobank sample and among thyroid autoantibody-positive women (Table).

Conclusions

Routine assessment of thyroid function in Danish women of fertile age is commonly performed. A substantial number of women with unidentified elevated TSH in early pregnancy previously had or later encountered an elevated TSH.

Assessment in the early pregnancy biobank sample	All women	TSH assessed before the pregnancy	TSH before elevated	TSH assessed after the pregnancy	TSH after elevated
Maternal TSH (mIU/l)	n	n	n (%)	n	n (%)
< 0.1	370	188	< 3 (NA)	285	9 (3.2)
0.1-2.5	12,080	6,398	151 (2.4)	9,048	318 (3.5)
2.6-3.5	772	392	69 (17.6)	576	115 (20.0)
3.6-6.0	357	191	56 (29.3)	276	136 (49.3)
> 6.0	85	38	16 (42.1)	65	50 (76.9)
Maternal TPO-/Tg-Ab	n	n	n (%)	n	n (%)
Positive	2,120	1,092	125 (11.4)	1,633	398 (24.4)

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PS3-23-02

B cells from anti-thyroid antibody positive, infertile women show hyper-reactivity to BCR stimulation

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Anti-thyroid antibody (ATA) positivity affects 1 out of 9 women in childbearing age and presents a significant risk for infertility. Emerging evidence indicates that alterations in the B cell receptor induced calcium (Ca2+) signaling could be key in the development of autoimmunity. We aimed to investigate the Ca2+ flux response of B lymphocyte subsets to BCR stimulation in Hashimoto's thyroiditis and related infertility. We collected peripheral blood samples from ATA+, infertile, euthyroid patients (HIE), hypothyroid, ATA+ patients before (H1) and after levothyroxine treatment (H2), and age-matched healthy controls (HC). All B cell subsets of ATA+, infertile, euthyroid patients showed elevated basal Ca2+ level and hyper-responsivity to BCR ligation compared to the other groups, which could reflect altered systemic immune function. The Ca2+ flux of hypothyroid patients was similar to healthy controls. The levothyroxine-treated patients had decreased prevalence of CD25+ B cells and lower basal Ca2+ level compared to pre-treatment. Our results support the role of altered Ca2+ flux of B cells in the early phase of thyroid autoimmunity and infertility.

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PS3-23-03

Prevalence of postpartum worsening of graves' orbitopathy in relation to thyroid dysfunction in patients with graves' disease in japan

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Background

Graves' hyperthyroidism is known to improve spontaneously during pregnancy due to immune tolerance, although postpartum worsening or relapse of hyperthyroidism is likely to occur.

Objective
To investigate the prevalence of postpartum worsening of Graves' orbitopathy (GO) in relation to thyroid dysfunction.
Methods
This was a retrospective cross-sectional study that included 8594 patients with Graves' disease (GD) with 12,322 live births, between January 2004 and August 2022. The patients in whom worsening of GO was suspected and were referred to ophthalmologists within 12 months after delivery were included in this study. Magnetic Resonence Imaging (MRI) was used for evaluating the activity of GO.
Results
A total of 75 patients were diagnosed with GO. The median age of the GO group was 32 (interquartile range 28-36) years, and the median time to worsening of GO was 7.0 (interquartile range 4.1-9.1) months. The values of TSH receptor (TSH-R) antibody and TSH-R stimulating antibody at the time of GO worsening were 9.0 IU/l and 1247%, respectively. Of the 75 patients, 65 developed postpartum exacerbation of thyroid dysfunction, 50 were not on medication, and 15 required antithyroid medication at delivery. In the postpartum thyroid dysfunction group, the median time to develop thyroid dysfunction was 6.3 months, though the median time to develop GO was 8.1 months. The detailed phases of GO were: active, 8 patients; recovery, 1 patient; inactive, 63 patients; and 3 patients who did not have MRI scans were not categorized. Eight patients in active phase received treatment for GO. Five patients received radiation therapy, and the remaining 3 patients received local steroid injection. Two of eight active GO patients were in the medication at delivery group, and the remaining 6 active GO patients were in the postpartum thyroid dysfunction group.
Conclusion
The prevalence of postpartum worsening of active phase GO was 0.064%. The results of the present study suggest that, active GO developed with postpartum thyroid dysfunction.

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PS3-23-04

Physical development, neuropsychological health and quality of life in a group of adult subjects with congenital hypothyroidism early treated with levothyroxine after newborn screening

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Background
The introduction of newborn screening for congenital hypothyroidism (CH) has led to prevent the most serious consequences of precocious deficit of thyroid hormone during child development, particularly neurological disability. However, little is known about long-term physical and psycho-social outcomes of CH after screening introduction.
Objective
To evaluate physical and neuropsychological development and Quality of Life (QoL) in adult subjects with primary CH early treated with levothyroxine (LT4).
Methods
We selected a patient group of 48 adult subjects with CH, who started LT4 therapy within the first months of life and continued it with an adequate control of disease, and a control group of 53 adult subjects without thyroid disorders, of homogeneous ethnicity and age compared to patients. We retrospectively collected clinical and biochemical data from infancy to adulthood, while QoL (including psychological health, social adaptation, and self-perception of health) was evaluated through a questionnaire.
Results
We didn't find differences between patients and controls in puberal and physical development and metabolic parameters. Educational attainment was worse in CH group, particularly in the subgroup with thyroid agenesis and in subjects who started LT4 therapy later. However, this result is strongly influenced by socio-cultural and environmental factors, as demonstrated by a positive correlation with mother instruction level. The same tendency, but without significative differences, has been found in concentration ability, which is self-judged better by control subjects, and, among CH patients, by the subgroup with thyroid gland in place and in patients treated earlier. Almost half of the patients refer to frequently feel in a depressed mood, and this result correlates to the timing of treatment initiation. Most patients don't think that disease has influenced their life, or that undergoing periodic visits is disabling. The only aspect of disease that seems to influence QoL is the necessity of a chronic medication intake; in fact, most patients fear to feel sick if they don't take their therapy.
Conclusions
CH newborn screening is effective in minimizing long-term consequences of disease. We only found small differences from controls regarding QoL and social adaption; socio-cultural and economic environment of families strongly influence this outcome, probably due to a better adherence to therapy and a greater exposure to cognitive stimuli during childhood. In conclusion, early and adequate treatment remains fundamental. In fact, it is possible to guarantee these patients a physical, puberal, neuropsychological and social development as close as possible to their genetic potential.

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PS3-23-05

Iodine nutritional status and related thyroid function in pregnancy: A results of a prospective study conducted in a large group of women

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Background and Objectives
During pregnancy normal thyroid activity undergoes significant changes, including an increase in the amount of iodine intake and maternal renal iodine excretion. Hence, dietary iodine requirements are higher in pregnant women than in non-pregnant ones. This study aimed to assess the nutritional iodine status in a large group of pregnant women and thyroid function according to different iodine intake and thyroid diseases.
Methods
A total of 1413 consecutive nonselected pregnant women were enrolled from 2012 to 2021 in the Endocrinology Unit of Pisa Hospital; 519 (36.7%) had no thyroid diseases (control group), 580 (41%) were diagnosed with autoimmune thyroiditis (AT), 66 (4.7%) with Graves disease (GD), 181 (12.8%) with nodular thyroid diseases (ND) and 67 (4,8 %) were affected by other thyroid disorders. We collected data about the use of iodized salt and/or a dietary supplement containing iodine and we measured urinary iodine concentration (UIC) in a single urine spot with mass spectrometry in each trimester of gestation. We defined the following categories of UIC in pregnancy: iodine deficiency if UIC was under 150 mg/l and adequate iodine intake if UIC was over 150 mg/l.
Results
The iodine status of our population is described in Table 1. During the first trimester, 20% of women did not assume any iodine supplementation (N), 29% utilized iodized salt (S), 19.9 % multivitamins containing iodine (M), and 30.8% both (B). Median UIC was 68, 73, 103, and 148 mg/l in groups N, S, M, and B, respectively, with statistically significant difference between group M and N ($P = 0.039$), group B and M ($P = 0.001$), B and S ($P = 0.000$), B and N ($P = 0.000$). These results were independent of thyroid diseases. In addition, we evaluated thyroid function according to iodine intake, excluding women under medication with L-thyroxine. When iodine deficiency was present, TSH concentration was significantly higher in AT women than in the control group in the first ($P = 0,000$), second ($P = 0,000$), and third ($P = 0,008$) trimesters of gestation. No differences were found when iodine intake was adequate.
Conclusions
Only women who assumed both iodized salt and multivitamins containing iodine reached the recommended iodine urinary levels in pregnancy. In AT women iodine deficiency was associated with a worse thyroid function than in the control group, thus confirming the importance of an iodine dietary supplementation from early pregnancy.

Table 1 Iodine status in our population with available IUC according to thyroid diseases Thyroid diseases

Thyroid diseases	Median UIC (IQR)	n
Control group	95 (157,5)	240
AT	94,5 (142,8)	198
GD	71 (85,5)	26
ND	80,5 (100,5)	72
Other thyroid diseases	84,5 (152)	37

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PS3-23-06

Iodine nutrition in italian pregnant women: preliminary results of a multicenter study

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Background and objectives
Recent data on median urinary iodine concentration (UIC) in schoolchildren showed that Italy has achieved iodine sufficiency. Nevertheless, no national data on iodine nutrition in pregnancy are available. Therefore, 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). The aim of the study was to evaluate iodine nutrition in pregnant women (n =500/region) and thyroid function in offspring. Here we present preliminary results on the use of iodized salt (IS) and/or iodine-containing supplements (ICS) during pregnancy, and UIC levels in the first 1,464 pregnant women recruited in the period 2022-2023.
Subjects and Methods
Pregnant women were recruited at the last visit before delivery (n =735 Northern, n =101 Central, n =628 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. Collection of data on neonatal TSH in the offspring is ongoing and therefore not analysed yet.
Results
We found that 71.3% of the recruited women used IS (77.7% Northern, 64.3% Central, 65% Southern Italy-Islands). Among the IS users, 89% were using IS since at least 2 years. Specifically, 25.0% of the recruited women used IS-only, 46.3% IS+ICS, 17.3% ICS-only, and 11.4% NO-IS/NO-ICS. Noteworthy, 13/1464 (0.9%) women were using IS+2 ICS with a consequent high daily iodine intake (range: 445-575 µg/day). Overall, a median UIC of 99 µg/l (IQR, 59-168) was found (110.4 µg/l Northern, 100.2 µg/l Central, 84 µg/l Southern Italy-Islands). As expected, the median UIC was significantly higher in women taking iodine during pregnancy (IS users and ICS users) than in NO-IS/NO-ICS women (101 µg/l *vs* 76 µg/l, $P < 0.001$).
Conclusions
These preliminary data show that in Italy iodine nutrition is still insufficient during pregnancy and that a North-South gradient is present. Furthermore, in the face of a non-negligible percentage of women who do not use IS or ICS during pregnancy, there is a certain number of women who take more iodine than recommended (250 µg/day). Although preliminary, these results confirm the importance of monitoring iodine nutrition in a phase of life during which an adequate iodine intake is extremely important for foetus growth and brain development.

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PS3-23-07

Effect of selenium supplementation on carbohydrate metabolism in hungarian patients with and without pregnancy

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In the last 20 years an increasing number of European patients with autoimmune thyroiditis are supplemented with selenium in case of elevated thyroid autoantibody levels. However, a multicenter research trial in the United States suggested that selenium supplementation might increase the incidence of type 2 diabetes. The aim of this small study was to assess whether selenium supplementation in patients with autoimmune thyroiditis has any effect on carbohydrate metabolism without and during pregnancy. Thirty patients with autoimmune thyroiditis and twenty pregnant women were treated with 2x100 µg selenium. Twenty control patients with autoimmune thyroiditis and 10 control pregnant women did not receive selenium. The following parameters were determined in all patients: fasting glucose and insulin concentration, TSH, fT4, thyroid autoantibody levels. After six months, the following parameters were determined: TSH, fT4, thyroid autoantibodies, fasting glucose, insulin, and an oral glucose tolerance test was performed. Serum selenium concentration was measured in order to confirm adherence to treatment. Statistical analysis was performed using the Microsoft Excel program. The thyroid autoantibody concentrations decreased varyingly. Insulin resistance measured as HOMA-index increased in patients whose serum selenium concentration exceeded the physiological range after six months of treatment with selenium. The oral glucose tolerance test, however, did not indicate type 2 diabetes in these patients. There was no difference regarding the frequency of gestational diabetes between the two groups of pregnant women (both 10%). Selenium supplementation with 200 µg has minimal effects on carbohydrate metabolism in this cohort of Hungarian patients with autoimmune thyroiditis.

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PS3-23-08

The thyroid status of patients with gestationnal diabetes

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Introduction
Pregnancy is a test for the thyroid, which has many physiological adaptation mechanisms to increased hormonal needs and iodine depletion. These changes expose the pregnant woman to dysthyroidism not devoid of maternal and fetal consequences. The prevalence of clinical and subclinical thyroid insufficiency in pregnant women are 0.3 to 0.7% and 2.2 to 2.5%, respectively. The objective of this study is to evaluate the thyroid status in a population of diabetic pregnant women.
Patients and methods
Cross-sectional, descriptive study, concerning 145 pregnant women followed in gynecology for gestational diabetes. They provided:
- an interrogation: research of the personal and family antecedents of dysthyroidism.
- a physical examination of the thyroid gland.
- a biological examination: FT4 and TSHus assay. The evaluation of the thyroid status had referred to the recommendations established by the American Association of Clinical Endocrinologists in cooperation with the American Thyroid Association

Results
- 98% of patients have type 2 diabetes No personal or family history of dysthyroidism
- Average age (years) = 32.6 ± 4.6
- The mean term of pregnancy (SA) = 25.69 ±7.52
- Distribution of parturients: 28% at T1, 47.7% at T2 and 49.5% at T3.
- Average FT4 (pmol/l): 11.35 ± 1.94 (6.16-15.74) (12.35pmol/l at T1, 10.72pmol/l at T2 and 11.9 pmol/l at T3.) Mean TSHus (uIU/ml) = 2.01 ± 0.96 (0.28-5.28) (1.52 uUI/ml at T1, 1.98 uUI/ml at T2 and 2.06 uUI/ml at T3.) Normal thyroid functio *n* =70% of cases; Hypothyroxinemia = 20.3% Mild hypothyroidism = 9% of cases; Patent hypothyroidism = 0.7%

Discussion
Dysthyroidism is common in our patients, they affected 30% of them. The most common thyroid disorder in our series is hypothyroxinemia, affecting 1 in 5 women. the prevalence of mild hypothyroidism is 9%. Hypothyroidism could have repercussions on the course of pregnancy, the fetal and intellectual development of the child. Currently, it is not recommended to screen for severe hypothyroidism associated with pregnancy, but our study showed a greatly increased prevalence in cases of gestational diabetes, which suggests a control on a larger scale.

Conclusion
Our results show an increased prevalence of unrecognized disorders in the case of gestational diabetes, thus underlining the interest of systematic screening in these women and raising the debate on the means of screening: TSH assay alone or combined with FT4.

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PS3-23-09

Clinical impact of the thyroid hormone measure and the reference intervals in critically ill pregnant women

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Thyroid hormones measure is inevitable in some critically ill patients and may help the management. Alternatively, the physiological changes in the thyroid imbalance during pregnancy also make establishing reference intervals for critical ill challenging.

Objectives
We aimed to compare reference intervals in an obstetric intensive care unit.

Methods
After excluding patients admitted after delivery or pregnant under thyroid disease treatment, we included 109 pregnant women admitted to the ICU between January 2018 and October 2023. We collected data from the mother (age, gestational age, previous diseases, body mass index, blood pressure, APACHE II and the critical events) and the newborn (weight, gestational age – Capurro, Apgar and critical events). Two reference intervals were compared (the assay reference range and the Hoffman-established reference interval). The Cobas Roche Elecsys immunoassay was used to measure the Thyroid Stimulate Hormone (TSH) and the Free Thyroxine (FT4) concentrations. TSH and FT4 were log-transformed before the analysis. Quantile-Quantile Plot and the Hoffman method were calculated using R statistical software. The chi-squared test, the Mann-Whitney and the logistic regression was performed in IBM SPSS Statistics for Windows.

Results
The Hoffman TSH calculated interval was 0.33 to 3.63 mUI/l and the FT4 was 0.79 to 1.29 ng/dL. Considering the participants, 56 (51.4%) on the assay reference and 65 (59,6%) on the Hoffman reference were classified as euthyroid. Conversely, the participants with TSH on the reference or below and a low FT4 reduced from 33 (30.3%) with the assay reference to 11 (10.1%) with Hoffman's. The assay reference was not able to predict any of the maternal or fetal critical events. On the contrary, Hoffman's interval predicts coagulation disorders with an odds ratio of 4.4 (*P*-value: 0.025, CI: 1.201 to 16.45).

Conclusions
Although this work had a selective blood collection for hormone dosages, Hoffman proposed intervals calculated for our pregnant population reduced the patients classified as abnormal and helped predict critical events.

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Thyroid Eye Disease

PS3-24-01

Simultaneous graves' orbitopathy and ocular myasthenia gravis in a patient with type 1 diabetes mellitus

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Introduction
Graves' orbitopathy and ocular myasthenia gravis are autoimmune disorders with overlapping clinical features that lead to difficulty in distinguishing both conditions. The simultaneous occurrence of both diseases is rare in frequency and occasionally followed by challenging management especially in pre-existing type 1 diabetes mellitus patient. We reported the case of ocular myasthenia gravis developed during the treatment in a patient with Graves' orbitopathy and type 1 diabetes mellitus.

Case report
A 23-year-old man presented with binocular double vision following bulging of his right eye and blurred vision since four months before admission. On examination, he was noted of having right eye proptosis and retro-orbital discomfort, with both eyes ophthalmoplegia related to partial oculomotor nerve palsies without pupillary involvement. Decreased visual acuity with dyschromatopsia were observed on both eyes. Paracentral scotomas were also revealed on Humphrey visual field examination. The diagnosis of dysthyroid optic neuropathy was made based on clinical signs and symptoms with laboratory findings concerning thyroid dysfunction. Corticosteroids as initial management was given under close observation along with insulin therapy considering the patient also suffered from type 1 diabetes mellitus. Clinical condition was worsened despite the treatment. Bilateral fatigable ptosis and general weakness were developed a month later. Diagnosis of ocular myasthenia gravis was confirmed based on clinical examinations and decremental response of repetitive nerve stimulation. Acetylcholinesterase inhibitor and plasmapheresis were added in the treatment. Ptosis and weakness were slightly improved but diplopia and visual function were moderately unchanged.

Conclusions
Detecting coexistence of Graves' orbitopathy and ocular myasthenia gravis is important in establishing comprehensive management of both diseases. Worsening condition in a patient with type1 diabetes mellitus as the risk factor may require specific treatment to obtain favourable outcome.

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PS3-24-02

Long-Term outcome of moderate-to-severe, active graves' orbitopathy following treatment with sirolimus (Ramamycin): results in a case series

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Objectives
Sirolimus is an immunosuppressive drug with anti-fibrotic and anti-proliferative activities. In a recent study, sirolimus (given off-label as a second-line treatment) was found to be associated with a better outcome of Graves' orbitopathy (GO) at 6 months compared to the standard treatment (intravenous glucocorticoids). Here we investigated the effects of sirolimus over a longer period of time.

Methods
The study design entailed data analysis of 10 consecutive patients [2 men and 8 women, age: 60.7 (10) yr.] with moderate-to-severe and active GO, given sirolimus off-label as a second-line treatment at relatively low dosage (2 mg orally on first day, followed by 0.5 mg/day for 12 weeks). Primary outcome was the overall outcome (composite evaluation) of GO over time (12, 24 and 48 weeks). Secondary

outcomes were: 1) outcome of single eye features; 2) outcome of quality of life (GO-QoL); 3) TSH-receptor antibodies (TRAbs) across the observational period.
Results
The proportions of overall GO responders at 12, 24 and 48 weeks were 50%, 70% and 60%, respectively. Proptosis responders (reduction by at least 2 mm) were 50% at 12 and 24 weeks and 30% at 48 weeks. Clinical activity score responders (reduction by at least one point on a 5-point scale) were 40%, 50% and 60% (12, 24 and 48 weeks, respectively). An improvement of diplopia (disappearance or improvement in Gorman's score) was observed in 50% of patients at 12 weeks, 60% at 24 weeks, and 70% at 48 weeks. GO-QoL improved by at least 6% in 50% of patients at all time points. TRAb decreased over time, although not to a statistically significant extent. Ten mild adverse events were recorded in 6 patients, 4 of which possibly related to sirolimus.
Conclusions
Treatment with sirolimus is followed by a fairly good overall response of GO and of single eye features and the effect appears to be sustained over time. Thus, sirolimus may represent a valid and safe alternative treatment for moderate-to-severe and active GO. Further, randomized clinical trials are needed to confirm the efficacy and safety of sirolimus.

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PS3-24-03

Teprotumumab efficacy in european and us study sites participating in the phase 2, optic (Phase 3) and optic-x pivotal trials

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Background
Teprotumumab showed significant improvements vs placebo for the treatment of thyroid eye disease (TED) in clinical trials1,2 and is approved in the United States (US) but currently not in the EU. Differences exist in baseline patient demographics and characteristics between EU and US patients. Here we examine outcomes in these 2 cohorts.
Methods
Data from the EU and US sites for patients in the teprotumumab group ($n = 121$) from the integrated randomized, double-masked, placebo-controlled 24-week phase 2 and 3 trials and open label OPTIC-X trial (first time teprotumumab treated patients) were analyzed. The primary outcome was proptosis reduction of ≥ 2 mm from baseline (BL). Secondary outcomes were diplopia response (improvement from BL in diplopia of ≥ 1 grade [Gorman scale]), Clinical Activity Score (CAS) of 0 or 1, an Overall response (reduction of ≥ 2 in CAS plus reduction in proptosis of ≥ 2 mm), the least squares (LS) and mean BL change in proptosis (mm) and LS and mean change in Graves' ophthalmopathy-specific quality-of-life (GO-QOL) score. Tobacco exposure was controlled for using a mixed-model repeated-measures analysis with an unstructured covariance matrix.
Results
There were a total of 54 and 67 teprotumumab- treated patients in the EU and US, respectively. Tobacco use was 38.9% in EU vs 10.4% in US. More EU teprotumumab patients were white compared with US (96.3% vs 77.6%). Months since diagnosis of Graves' disease was longer in EU than US (43.8 vs 30.1). Fewer EU patients had constant diplopia (grade 3) at BL than US (18.5% vs 34.3%). At week 24, all the primary and secondary outcomes in EU teprotumumab-treated patients were not significantly different from US teprotumumab treated patients including proptosis response (83.3% [45/54] vs. 79.1% [53/67], $P = 0.591$), diplopia response (60.0% [24/40] vs. 73.5% [36/49], $P = 0.428$), CAS 0/1 (70.6% [36/51] vs. 56.9% [37/65], $P = 0.357$), overall response (78.4% [40/51] vs. 72.3% [47/65], $P = 0.447$), LS mean change in proptosis of -3.28 mm vs. -3.23 mm, $P = 0.876$, BL mean change in proptosis of -3.22 mm vs.-3.39 mm at Week 24; and LS mean change in GO-QOL overall score of 16.54 points vs. 16.65 points, $P = 0.974$ with BL mean change in GO-QOL of 15.9 vs. 18.32 at Week 24.
Conclusions
Despite some differences in patient characteristics at BL, EU teprotumumab treated patients had no significant difference in efficacy outcomes with respect to proptosis, CAS, diplopia, overall response, and quality of life as compared with US teprotumumab treated patients.

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PS3-24-04

Rituximab treatment in patients with graves' orbitopathy who are non-responsive to intravenous glucocorticoids is not better than IV glucocorticoids alone

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Background
Graves orbitopathy (GO) is the most frequent and feared complication of Graves' disease. In moderate-severe cases, intravenous (iv) glucocorticoids (GC) is the first-line treatment while Rituximab (RTX) is recommended as second-line treatment in patients non-responsive to GC. But data is scarce and contradictory.
Objective
To investigate if patients with GO and poor response to iv GC benefit from a switch to RTX early in the treatment course.
Method
This was a non-randomized controlled interventional study of GO patients treated with iv GC for 4 weeks. Patients with < 2 points improvement in clinical activity score (CAS) after 4 weeks were selected for RTX treatment (the non-responders (NR-RTX) group). They were compared to patients who had improved at least 2 in CAS at 4 weeks and who continued with a full treatment period of iv GC for 12 weeks (the responders (R-GC) group). A retrospective group of patients who were non-responders at 4 weeks and who were provided regular care with 12 weeks (w) of iv GC was used as control (the NR-GC group). Baseline data and CAS at baseline, 4w, 12w, 18w and 68w were collected in all groups. Quality of life (QoL) and safety data were collected from NR-RTX and R-GC groups at the same time points.
Results
Baseline characteristics of NR-RTX ($n = 10$) were similar to the other two groups, except for 1 point lower median CAS than NR-GC ($n = 12$) ($P = 0.03$). The NR-RTX group had twice as many men compared to the R-GC group($n = 13$) ($P = 0.03$). No group differences were observed in CAS, in QoL or in safety data at any timepoint with the exception of a higher CAS in NR-RTX group at 4w and 12w compared to R-GC ($P = 0.005$ and $P = 0.017$ respectively), as expected given that CAS at 4w was the factor that determined the group selection. Longitudinal analyses revealed no differences in CAS, except for an increase between 4w and 18w in the R-GC group and a decrease between 4w and 68w in the NR-RTX group.
Conclusions
We could not confirm the hypothesis that a switch to RTX in GO patients with a poor response to 4w of iv GC is more effective or safer than conventional GO treatment. This is of clinical importance, as RTX is recommended by international thyroid associations as second line treatment for GO and previous research has presented contradictory results.

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PS3-24-05

Teprotumumab for the treatment of recalcitrant thyroid eye disease

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Introduction
The initial clinical trials for teprotumumab excluded patients with previous orbital irradiation, surgery, glucocorticoid use (cumulative dose $>$ 1gm), or biologic treatment. Therefore, information on the use of teprotumumab for patients who failed prior therapy is limited. Our purpose is to characterize the efficacy of

teprotumumab for the treatment of recalcitrant TED.
Methods
This is a multicenter retrospective study of all patients treated with teprotumumab for moderate-to-severe TED after failing conventional therapy with corticosteroids, orbital radiation, surgical decompression, biologics, or other steroid sparing medications. Treatment failure was defined as an incomplete response to or reactivation after previous treatment. Only patients who received at least 4 infusions of teprotumumab were included in the analysis. Primary outcome measures comprised proptosis response ($\geq$ 2mm reduction in the study eye without a similar increase in the other eye), Clinical Activity Score (CAS) response ($\geq$2-point reduction in CAS), and diplopia response ($\geq$ 1 point improvement on the Gorman diplopia score (GDS)) following treatment. Adverse events and risk factors for recalcitrant disease were also evaluated.
Results
Sixty-seven patients were included in this study, 47 females and 20 males. Average age was 59.0 years (range 29-93). The mean duration of disease from TED diagnosis to first infusion was 57.8 months. The proptosis, CAS, and diplopia responses were 86.2%, 93.8%, and 60.9%, respectively. Patients experienced a mean reduction in proptosis of 3.2 $\pm$ 2.4 mm and mean improvement in CAS of 3.8 $\pm$ 1.6. Diplopia response was varied; patients who underwent prior decompression surgery experienced a statistically significant decrease in diplopia response (38.9% vs 69.6%, P =0.012) when compared with non-decompression patients. Acute patients also exhibited improved diplopia response (77.3% vs 51.2%, P = 0.022) after teprotumumab when compared to chronic patients. Otherwise, no other significant risk factors were found to be associated with proptosis, CAS, or diplopia responses. While most adverse events were mild to moderate, four patients reported serious adverse events related to persistent hearing loss.
Conclusions
Patients with recalcitrant TED demonstrated a significant improvement after teprotumumab in each of the primary study outcomes. Early treatment may result in improved diplopia outcomes, but further studies are needed to elucidate this relationship. These results indicate that TED recalcitrant to conventional therapies is responsive to teprotumumab and should be considered for the treatment of TED in patients who have failed prior therapies.

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PS3-24-06

Perceptions reported by graves' disease euthyroid patients with ophthalmopathy: A qualitative study

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Introduction
Knowing mental representations about the phenomenon of illness and medical care allows the clinical team to have better emotional handling of their patients, with gains in greater adherence to treatments. Graves' Ophthalmopathy is an inflammatory disease with primary involvement of the extraocular muscles and orbit, being the most frequent extrathyroidal manifestation of Graves' disease (GD). Many patients have psychological status changes even after successful treatment of hyperthyroidism, especially when the disfiguring signs of ophthalmopathy are predominant. An understanding of the symbolic aspects linked to this condition help endocrinologists to have a relationship more harmonious with them.
Aims
To interpret emotional meanings in reports of euthyroid GD patients with ophthalmopathy under follow-up, discussing contradictions perceived between a stigmatized body and clinical laboratory euthyroidism.
Method
Clinical-Qualitative design of Turato. Data was collected using semi-directed interviews with open-ended questions in-depth, carried out with patients at a tertiary outpatient service specialized in thyroid dysfunctions. The interview material was audio-recorded and fully transcribed. The interviews were treated by Clinical-Qualitative Content Analysis described by Seven Steps of Faria-Schützer. It is based on psychodynamic concepts from the Medical Psychology theoretical framework, whose main author is Michael Balint. The sample was closed by the Theoretical Saturation of Information studied by Fontanella *et al*. The finding validation has occurred by peers at the Laboratory of Clinical-Qualitative Research.
Results
The sample was composed by 10 patients. From the search of nuclei of meanings in the reports, four categories of analysis were constructed: 1) "No, this is not normal, I must have cancer": psychodynamics of the physician-patient relationship in Graves' Disease; 2) Types of illness according to their manifestations and auto-perception: silent illness and non-silent ones; 3) "The eyes are everything": the impacts of the disfiguring alterations of ophthalmopathy; 4) The contradiction perception between clinical and laboratory normality the stigmas of ophthalmopathy.
Conclusions
The patients with ophthalmopathy, maintained emotional distress despite being euthyroid, manifested by various emotional meanings reported in the interviews. The clinical-laboratory diagnosis of Graves' Disease alone was not sufficiently capable of responding to the psychological demands of the patients. Proper listening to emotional symbolic meanings attributed by patients could help endocrinologists in handling this setting.

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PS3-24-07

Incidence and risk factors for graves' orbitopathy in patients who underwent anti-inframmatory and immunosuppressive treatment during medical treatment for graves' disease

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Objective
Appropriate administration of anti-inflammatory and immunosuppressive treatment (AIIST) is still important for patients with Graves' orbitopathy (GO). This study aimed to clarify the incidence of and risk factors for GO treated with AIIST, among newly diagnosed Graves' disease (GD) patients in Japan.
Methods
A total of 1558 GD patients who were newly diagnosed at Ito Hospital during the year 2011 were investigated. AIIST included local administration and/or systemic glucocorticoid and retrobulbar irradiation. Local glucocorticoid administration included eyelid and/or sub-Tenon's injection. Using a multivariable Cox proportional hazards model, risk factors for GO that underwent AIIST during medical treatment, including at the diagnosis, of GD, were investigated. Baseline variables at the time of GD diagnosis [age, sex, smoking habit, FT3, FT4, TSH, TSH binding inhibitory immunoglobulin (TBII), thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), total cholesterol, white blood cells, neutrophils, lymphocytes, and the neutrophil to lymphocyte ratio] were analyzed.
Results
AIIST was administered to 97 patients (6.2%). The median interval between the first visit and AIIST was 5 (range 0.1-44) months. The severity of GO that underwent AIIST was mild in 29 patients (1.9%, 29/1558) and moderate to severe in 67 patients (4.3%, 67/1558), and most severe (sight-threatening) in only one case (0.1%, 1/1558). For AIIST, 93 subjects were administered glucocorticoids, and 19 patients received irradiation therapy. Of these patients, 39 received as combination therapy, and 58 patients received as monotherapy. Of the 72 patients who underwent eyelid injection, 29 were given as monotherapy despite moderate to severe GO. The reason for this was moderate to severe findings only in the eyelids (n =7) or moderate to severe proptosis, but with only active manifestations in the eyelids to be treated (n =22). The risk factors and associated hazard ratios for GO that underwent AIIST were: age (per 10 years) 1.23 (95% confidence interval: 1.07-1.42), P = 0.004; TSH binding inhibitory immunoglobulin (TBII) (per 10 IU/l) 1.35 (1.16-1.57), P = 0.0001; and thyroglobulin antibody (TgAb) negativity 2.98 (1.91-4.64), P < 0.0001.
Conclusions
AIIST was performed in patients with active manifestations of GO, accounting for 6.2% of newly diagnosed GD patients. The risk factors for GO that underwent AIIST were higher age, higher TBII, and TgAb negativity.

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PS3-24-08

Changes in therapeutic response, ocular manifestations of graves' orbitopathy and quality of life during the first year after orbital radiotherapy

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Objectives
Orbital radiotherapy (OR) is the most commonly used second-line treatment for the severe forms of Graves' orbitopathy (GO). The aim of our study was to assess the changes in the therapeutic response, ocular manifestations of GO and quality of life (QoL) during the first year after OR.
Methods
The study involved 26 consecutive patients with active moderate-to-severe GO indicated for OR, 18 females, mean age 57 ± 12.5. At baseline all patients underwent comprehensive ocular examination and thyroid hormone and antibody testing. Then, OR was performed with a total dose of 20 Gy, divided into 10 sessions of 2 Gy each, with concomitant intake of low-dose glucocorticoids. Therapeutic response and individual ocular manifestations were evaluated at the 1st, 3rd, 6th and 12th months after OR, and QoL – at the 3rd, 6th and 12th months by a disease-specific questionnaire.
Results
At month 1, therapeutic response (full or partial) was observed in 61.6% of the patients. During the follow-up the proportion of the full-responders gradually increased to 57.5% at the 12th month, while that of non-responders gradually decreased, reaching 11.5% at the 12th month. All individual ocular manifestations improved significantly 1-3 months after OR. At the 1st month, the proportion of patients with improvement in diplopia (34.6%) and proptosis (30.8%) was the highest, followed by visual acuity (26.9%). At 3rd and 6th month, most patients had improvement in visual acuity, subjective symptoms, diplopia and CAS. At the 12th month, the largest proportion of patients had an improvement in diplopia, followed by soft tissue involvement, subjective complaints and CAS. QoL related to visual functioning improved significantly at the 3rd month and at each subsequent time point of the follow-up, QoL related to appearance increased significantly at the 6th month with additional significant improvement at the 12th month.
Conclusions
OR is a highly effective treatment for active moderate-to-severe GO. The initial effect on the therapeutic response and individual ocular parameters was evident as soon as 1-3 months after the procedure. QoL improved gradually during the follow-up period.

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PS3-24-09

Clinical conditions related to the short, medium and long term clinical outcome of moderate/severe graves' ophthalmopathy to parenteral glucocorticoids: a retrospective study

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Introduction
Oxidative stress (OX) plays a role in the pathogenesis of moderate to severe Graves' ophthalmopathy (AMS-GO).
Aim
We evaluated the impact of clinical conditions related to OX on the outcome of parenteral glucocorticoids (PGLUC) therapy in AMS-GO.
Methods
We retrospectively evaluated patients with AMS-GO treated with PGLUC from January 2013 to May 2022. GO clinical evaluation was performed at baseline, at 6 (W6), at 12 (W12) and at 24 weeks (W24) after starting PGLUC. Patients were classified as Improved (I) or Not Improved (NI) by the EUGOGO overall clinical criteria. We then performed multiple univariate binomial logistic regression analyses including the following covariates as OX conditions: W6 outcome, total and calculated LDL cholesterol (LDLc), Body Mass Index (BMI), fasting glycemic values, history of hypertension (HoH), smoking, age and sex. Outcomes at W12 and W24 were set as dependent variables in different analyses. Some multivariate models were finally built with more representative variables by univariate analyses.
Results
139 patients, 40 males and 99 females, median age of 47 (36-55) years, with AMS-GO received a median PGLUC cumulative dose of 49 (36-65) milligrams/kg body weight. 56/122 (45.9%) patients were classified as I at W6, 60/139 (43.2%) at W12. 86 patients completed the follow-up at W24. Among them, 33/86 (38.4%) were I. When compared to NI, early I at W6 showed an 8 and 7 times greater chance of being classified as I at W12 and at W24, respectively (OR 8.1, 95% CI 2.8-23.0, $P < 0.001$ and OR 7.0, 95% CI 2.5-19.7, $P < 0.001$), I vs NI). At univariate regression analyses, total and LDLc cholesterol, HoH and age were predictive variables towards both W12 and W24 outcomes (Table 1). The multivariate model aimed at predicting W12 outcome was significant, $\chi^2(3) = 15.094$, $P = 0.002$. Among covariates, LDLc and HoH resulted significant ($P = 0.05$ and $P = 0.04$, respectively). The multivariate model aimed at predicting W24 outcome resulted significant, $\chi^2(2) = 9.458$, $P = 0.009$. LDLc and HoH almost reached significance ($P = 0.09$ and $P = 0.052$, respectively).
Conclusions
An early I (at 6W) to PGLUC is predictive of the medium and long term clinical response. HoH, total and LDL cholesterol are predictors of low clinical response to PGLU at W12. Although our data suggest the existence of a relationship with the long term outcome, further studies are needed to deepen it.

	W12 Outcome	W24 Outcome
W6 Outcome	$P < 0.001$	$P < 0.001$
Total cholesterol	$P = 0.037$	$P = 0.12$
LDLc	$P = 0.015$	$P = 0.042$
BMI	$P = 0.989$	$P = 0.319$
Fasting glycemia	$P = 0.356$	$P = 0.308$
History of hypertension	$P = 0.003$	$P = 0.031$
Smoking	$P = 0.941$	$P = 0.442$
Age	$P = 0.023$	$P = 0.017$
Sex	$P = 0.781$	$P = 0.046$

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Case Reports 2

PS3-25-01

Uncommon findings in a thyroid nodule: A case report of osseous metaplasia in a benign thyroid lesion

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Introduction
Although calcifications are a relatively common finding on a thyroid ultrasound, present in both benign and malign lesions, osseous metaplasia (OM) is a peculiar discovery, with only a few described cases in literature so far. Common pathophysiological explanations include abnormalities of bone morphogenetic protein family members and basic fibroblast growth factor. Most of the case reports are presenting OM in association with malign lesions, often with papillary thyroid carcinoma and even suggest this could be a sign of increased aggressivity. Other reports show OM accompanied by extramedullary hematopoiesis in patients with hematological disorders, but cases of bone formation in benign thyroid pathologies are extremely rare. We describe the case of a middle-aged female with histological findings of osseous metaplasia in a benign solitary nodule.
Case report
A 54-year-old female presented for endocrinologic evaluation, asymptomatic and with no prior thyroid pathology. Personal history included a meningioma and a breast hamartoma. A thyroid ultrasound revealed a 1.3/1.5 cm nodule in her right thyroid lobe, with micro and macrocalcifications and ill-defined borders (TIRADS 5). The remaining thyroid was homogenous, isoechoic and it had normal vascularization. Thyroid function tests and calcitonin levels were within

normal range and antithyroglobulin antibodies were negative. TPOAb were unfortunately not available. Serum calcium, phosphorus and 25 hydroxy-vitamin D3 levels were also normal and no parathyroid lesion was found. In addition, complete blood count and coagulation panel showed no abnormalities. Total thyroidectomy was performed. Histopathologic examination of the right lobe revealed a nodular area, markedly sclero-hyalinized, composed of a few follicular structures, alongside dystrophic calcifications, osseous metaplasia and small hemorrhagic foci. The rest of the thyroid parenchyma showed hyperactive follicles, with no signs of nuclear atypia nor hematopoietic cells, but with rare, small lymphoid aggregates. At follow-up, the patient had a benign evolution. Although personal history was indicative for a possible Cowden syndrome, the patient did not meet the diagnostic criteria and further genetic evaluation was not performed.

Conclusion

OM is an uncommon finding in thyroid tissue and its pathophysiology is yet to be completely understood. Here we reported a case of OM in a patient without signs of malignity, hematological or parathyroid abnormalities and with an unusual association of tumor growths. Apart from its rare occurrence, this could also lead to new pathophysiological explanations of this phenomenon, involving the PTEN gene mutations.

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PS3-25-02

A rare case of autoimmune polyglandular syndrome type 2

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A Rare Case of Autoimmune Polyglandular Syndrome Type 2 Autoimmune polyglandular syndromes (APS) are a group of immune-endocrine syndromes that cause autoimmune destruction of multiple endocrine organs. The most common in this group is APS type 2, which frequently presents with primary adrenal insufficiency with autoimmune thyroid disease and/ or type 1 diabetes mellitus. We present a case of 46 year old male, with no significant medical history who presented in our clinic with: weakness, fatigue and weight loss for the preceding last 3 months. On the examination he was found to have hypotension, tachycardia, hyper pigmentation of the skin and vitiligo. Based on the lab reports and physical exam findings diagnosis primary adrenal insufficiency, Graves Hyperthyroidism and vitiligo was made corresponding with the Autoimmune Polyglandular Syndrome type 2. Treatment with Hydrcortisone, Fludrocortisone and Thionamides was started in our patient resulting in significant improvement in patients symptoms. After achieving euthyroidism, the thionamide dose was gradually decreased and later discontinued after a year of treatment. Patient remains euthyroid to present day and continues only adrenal hormone replacement therapy with both glucocorticoid and mineralocorticoid. Patient is on regular follow up and is clinically well. He is given the instructions of "sick day rules" to change the hydrocortisone dose appropriately. Patient consent for publication is obtained. The Case report will be accompanied with the corresponding pictures depicting pre and post treatment appearance of the patient.

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PS3-25-03

Report of a case with new onset of thyroid eye disease following viral vector SARS-COV-2 Vaccine

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Introduction

The occurrence or worsening of thyroid eye disease (TED) after SARS-CoV-2 mRNA vaccines is extremely rare whereas has not been reported following viral vector vaccination. In the region of South-West Greece during the COVID-19 pandemic, a case of de novo appearance of TED referred to the Endocrinology Department of our hospital, following viral vector SARS-COV-2 vaccine.

Case report

The patient was a 62-year-old woman, heavy smoker (40 pack-years) with no known history of Graves' disease. Five days after vaccination for the 1st time with Vaxzevria (COVID-19 Vaccine (ChAdOx1-S[recombinant]- Previously known as COVID-19 Vaccine AstraZeneca), she presented with diplopia and at the same time she was diagnosed with hyperthyroidism due to Graves' disease. She was administered antithyroid drugs, selenium (100 mgx2/day) and intravenous glucocorticoid boosts (500 mg solumedrol/week for 6 weeks and then 250 mg solumedrol/week) by a private endocrinologist. She also stopped smoking. However, diplopia did not improve, and she was referred to our hospital. Upon presentation, she had active disease, exophthalmos, periocular edema and permanent diplopia. She received 2 doses of rituximab (1gr/week for 2 weeks). Two months later, permanent diplopia and strabismus remained with a slight remission of the activity of the disease and thus she was referred for surgical correction of her strabismus. The patient did not suffer from COVID-19 disease at the time of diagnosis.

Conclusion

We reported a case of de novo moderate-to-severe TED resistant to drug therapy, following viral vector vaccine, in a middle-aged heavy smoker woman. To the best of our knowledge, this is the first report of TED after this type of vaccine against SARS-COV-2.

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PS3-25-04

Dupilumab-related graves disease: A case report

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Introduction

Graves Disease (GD) is an autoimmune disease, in which CD4+ Th2 cells secrete interleucin-4 (IL-4) and IL-5 and activate antibody production. IL-4 has been considered a therapeutic target for treatment of immune-related diseases, by enhancing and redirecting T and B cell function. Dupilumab, a monoclonal antibody, inhibits IL-4 and IL-13 and is currently used for treatment of atopic dermatitis, nasal polyposis and asthma. There is a single case report of painless thyroiditis as an adverse effect of dupilumab.

Case Report

We report a case of a 47-year male with history of a severe nasal polyposis. He was treated with corticosteroids, with only mild improvement. In March 2022 he was started on dupilumab 600 mg followed by 300 mg every 2 weeks. At 6-8 weeks of treatment, he complained of irritability, weight loss and heat intolerance. In October 2022, laboratory studies revealed thyrotoxicosis, with TSH 0.01 μU/mL (0.27-4.2) and free T4 (FT4) 29.5 μg/dL (12-22). He was started on methimazole 15 mg/day in December 2022 by his family physician and was sent to the Endocrinology Department. At observation, he had no neck discomfort, compressive symptoms, or exophthalmos. Laboratory tests showed TSH <0.008 μU/ml, FT4 12.9 μg/dl, FT3 4.92 pg/ml (3.10-6.8), TRAb 3.17 U/l (<1.58 U/l), which confirmed the diagnosis of GD. Thyroid ultrasound revealed an enlarged thyroid gland, with heterogeneous echogenicity, but no nodules or cervical adenopathies. He currently maintains treatment with methimazole 10 mg/day and dupilumab 300 mg every 2 weeks.

Discussion

To the best of our knowledge, this is the first case ever reported of dupilumab-related GD. The suppression of Th2 cells through inhibition of IL-4 and IL-13 by dupilumab amplifies the Th1 pathway. In GD, the predominant patoghenic TSH receptor autoantibody is IgG1 isotype response, which is stimulate by Th1 cytokines. An increased Th1/Th2 ratio may promote the development of GD by dupilumab. More studies are needed to explain the underlying mechanism of this adverse effect. Thyroid function tests before treatment with dupilumab and during follow-up may be useful.

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PS3-25-05

A rare case of euthyroid gravès ophthalmopathy with negative trabs titers

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A Rare Case of Euthyroid Grave's Ophthalmopathy with Negative TRAbs titers

Introduction

Graves' ophthalmopathy (GO; also known as thyroid-associated ophthalmopathy or thyroid eye disease) is clinically evident in 25–50% of patients with Grave's disease. While the majority of patients experience only mild ocular symptoms,

3–5% of patients with GO suffer from severe disease (2). The spectrum of eye manifestations ranges from lid lag and retraction to proptosis, ophthalmoplegia, conjunctivitis, chemosis, and corneal ulceration, to loss of vision. TSH receptor antibodies (TRAbs) are the pathological hallmark of Graves' disease, present in nearly all patients with the disease. Euthyroid Graves' ophthalmopathy (EGO) is a well-recognized clinical entity, but its occurrence in patients with negative TRAbs is a potential source of diagnostic confusion.

Case

We present a case of a 55-year-old male presented to our clinic with 3-months history of impaired vision, left sided exophthalmus and diplopia in the absence of thyroid dysfunction. TRAbs were negative, as measured with a highly sensitive third(-)generation thyrotropin-binding inhibitory immunoglobulin (TBII) ELISA assay. MRI scans of the orbit showed asymmetrical thickening of the all recti muscles, especially inferior recti, with infiltration and no malignant orbital pathology. Graves' ophthalmopathy (GO) was diagnosed on the basis of the clinical and radiological features, and a good response to treatment with intravenous steroids. By this time, patient had developed positive TRAb as well as thyroid peroxidase antibodies. He responded to treatment with thionamides and remains euthyroid to this day.

Conclusions

This abstract demonstates the unique clinical case where GO developes while being in euthyroid state and seronegative for thyroid autoantibodies. Diagnosing GO is a complex process requiring meticulous review of signs, symptoms, and imaging results while excluding other causes of proptosis such as orbital mass/tumors. Clinicians should be aware of the variable temporal relationship between the clinical expression of thyroid dysfunction and orbital disease in the natural course of Graves' disease. This case emphasizes the fact that relying on thyroid hormone and autoantibody levels alone is not always adequate for the diagnosis of EGO. Timely diagnosis and initiating proper and adequate treatment would prevent the development of complications and requirement for interventions.

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PS3-25-06

DIfferent presentations of thyroid dermopathy

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Graves' disease (GD) is an autoimmune disease that can affect other tissues in addition to the thyroid gland. Depending on the intensity of the immune response, in addition to hyperthyroidism, orbitopathy, dermatopathy and acropachy can also occur. Extrathyroidal manifestations of GD are most often the result of a more pronounced immune response. Thyroid dermatopathy (TD) is a rare extrathyroidal manifestation of GD, almost always associated with Graves' orbitopathy (96%) and usually appears after ocular changing. About 0.5%–4.3% of patients with a history of thyrotoxicosis and 15% of patients with severe Graves' orbitopathy have this cutaneous manifestation. Presence of dermopathy and acropachy are indicators of severity of autoimmune process and a risk factor for severe orbitopathy. It is more common in older patients and women. TD represents diffuse mucinosis, with typical accumulation of glycosaminoglycans in the dermis and hypodermis. The most common form is diffuse non-pitting edema, followed by plaque and nodular forms and rarely the elephantiasic form. Clinically, TD presents as light-colored, sometimes yellowish-brown skin lesions, frequently with an orange peel texture, mostly in the pretibial region. Hyperpigmentation and hyperkeratosis may also occur. The appearance of dermopathy is related to the duration of the autoimmune disease and is seen less often today, since the diagnosis of GD is made earlier. We present four patients that came to our hospital in short period of time with different forms and different time of onset of TD. Two patients had severe form of dermopathy - elephatiasis, that appeared concurrently with hyperthyroidism and orbitopathy in one patients, and concurrently with hyperthyroidism, but before orbitopathy in second patient. In this patient, orbitopathy appeared one year after dermopathy. In the other two patients TD presented as the third manifestation of GD, after onset of hyperthyroidism and orbitopathy in one patient and after orbitopathy and hypothyroidism in second patient, as the plaque-type lesions, and elastic edema. In the last patient, GD started with Graves' orbitopathy, and after a year, hypothyroidism was diagnosed. TD appeared three years later in the form of pretibial plaque and swell of the toe. In all patients TD was associated with very high levels of TRAb >40 IU/l (Table1). TD is a rare manifestation of GD and is characteristic of long lasting disease and an intense autoimmune response. It is not often seen today, which makes the appearance of four patients with TD in a short period of time all the more interesting.

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PS3-25-07

A case report of graves' disease induced by IFN-β-1a therapy

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The risk of thyroid dysfunction induced by Interferon (IFN)-β1b therapy, in particular in patients having preexisting thyroid autoimmune disorders (AITD), is well known. We report a case of a 60-year-old female, with a 15-year history of euthyroid autoimmune thyroiditis and a 3-year history of Multiple Sclerosis (MS), in care for the evaluation of hyperthyroidism. The patient started a specific immunomodulant IFN-β1a therapy (30 μg/week) twenty months before the first visit, during which complained tachycardia, weight loss, blurry vision with swollen eyes and excessive lacrimation. The thyroid hormone profile showed hyperthyroidism with positive TSH-receptor-autoantibodies. An orbit Magnetic Resonance Imaging (MRI) was performed, revealing bilaterally mild enlargement of the extraocular muscles and supporting the suspect of Graves' ophthalmopathy (GO). To our knowledge, this is the first report of Graves' disease (GD) and GO associated with IFN-β1a treatment in a patient with MS. This case report could open new interesting insights behind the immunopathogenesis of GD.

Keywords: Graves' disease; Graves' ophthalmopathy; thyroid dysfunction; Interferon (IFN)-β1b therapy

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PS3-25-08

Resistance to thyroid hormone in the absence of thyroid hormone receptor mutation: A case report

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Introduction

Resistance to thyroid hormone beta is a genetic disease defined by impaired sensitivity of target tissue to thyroid hormone caused by mutation of thyroid hormone receptor beta gene, appearing with an incidence of 1/40,000. The characteristic biochemical profile of resistance to thyroid hormone is elevated serum thyroid hormone level and inappropriate serum level of thyrotropin (TSH) which is normal or elevated. Clinical picture is variable ranging from asymptomatic patients to patients with signs of overt hyperthyroidism or hypothyroidism. Diagnosis of resistance to thyroid hormone beta is confirmed by genetic testing. In 15% of patients with characteristic biochemical profile for resistance to thyroid hormone beta (after exclusion of other possible causes: laboratory interference, familial dysalbuminemic hyperthyroxinemia, TSH-secreting pituitary tumor) no mutation of thyroid hormone receptor beta gene is found. In such cases the disorder is called resistance to thyroid hormone in the absence of thyroid hormone receptor mutation.

Case report
A 55-year-old male was referred to the thyroid department because of imbalance between serum levels of TSH, free thyroxine (fT4) and free triiodothyronine (fT3): TSH 1.03 mIU/l (0.59-4.23 mIU/l), fT4 35.0 pmol/l (11.3-18.8 pmol/l), and fT3 9.98 pmol/l (3.79-6.05 pmol/l), respectively. Antibodies against thyroid peroxidase, thyroglobulin and TSH receptor were negative, level of thyroglobulin was normal, level of sex hormone binding globulin was normal 60 nmol/l (13-71 nmol/l). Ultrasound examination showed an enlarged (48 mL) thyroid gland with multiple small nodules, scintigraphy with Technetium-99m showed a nonhomogenous uptake in thyroid gland. Mutation of thyroid hormone receptor beta gene was excluded, as well as laboratory interferences, TSH-secreting pituitary tumor and familial dysalbuminemic hyperthyroxinemia as possible causes of imbalance between TSH and thyroid hormones. The patient reported palpitations and excessive sweating. Therefore, therapy with a beta blocker was initiated which partially improved the symptoms.
Conclusion
Resistance to thyroid hormone in the absence of thyroid hormone receptor mutation is a rare condition that can only be diagnosed by exclusion of other possible causes (resistance to thyroid hormone beta, laboratory interferences, TSH-secreting pituitary tumor, familial dysalbuminemic hyperthyroxinemia). Diagnosis can be further complicated by coexistent thyroid disease. Treatment, if needed, is individually tailored (beta blockers, radioiodine therapy, thyroidectomy).

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PS3-25-09

Autoimmune hypothyroidism associated with pseudohypoparathyroidism

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Introduction
Hashimoto thyroiditis is an autoimmune disorder affecting the thyroid gland leading to chronic inflammation and gradual decline of the thyroid gland function eventually requiring hormone replacement. Patients present with classic symptoms and signs of hypothyroidism. The term pseudohypoparathryoidism (PHP) refers to a group of rare genetic and epigenetic disorders characterized by resistance to the action of parathyroid hormone (PTH) that activates cAMP signaling in target cells. In most cases this genotypically diverse group of syndromes are caused by mutations and/or epigenetic changes at the complex GNAS locus on chromosome 20q13.3. Patients with PTHT clinically manifest with tetany seizures, soft tissue calcifications and many congenital malformations. Association of PHP with autoimmune disorders is rare and seldom reported in the literature.
Case
We describe a case of sporadic pseudohypoparathyroidism, confirmed hashimoto thyroiditis, iron deficiency anemia, chronic erosive gastritis. 28 year old Caucasian female visited our clinic with complaints of frequent hospitalizations due to seizures and tetany since December 11, 2021. Patient was hospitalized at least 4 times and required Ca infusions. Patient complained of mild, intermittent and self-limited paresthesias, persistent asthenia, tachycardia, arrhythmia since early years. She had been diagnosed at the age of 6 with hypocalcemia and possible pseudohypaparathyroidism, but diagnosis was not verified by genetic test. Initial lab investigation revealed TSH in the upper ranges of normal, normal FT4, FT3 and positive anti TPO titers, elevated PTH, hypocalcemia, hyperphosphatemia, hypocalciuria, decreased bone mineral density on Dexa Scan. Combined calcium and calcitriol supplementation was commenced, with symptomatic and laboratory improvement. Couple days after initiating Ca supplements and calcitriol, we achieved laboratory and clinical improvement.
Conclusion
To confirm this presumptive diagnosis, patient's genomic DNA has to be analyzed. In case of confirmed diagnosis, patients should be monitored annually for calcium, phosphate, PTH and urinary calcium levels, TSH, FT4 and gonadotropin levels. With initiated treatment, we hope for complete resolution of patient's complaints and attaining symptomatic remission. There are only few cases and at least one study describing possible association of autoimmune thyroiditis and pseudohypoparathyroidism, further studies and research are still required to confirm the link between these gland dysfunctions. A careful follow-up is needed to avoid complications and recurrence. Replacement of deficient gland function should follow.

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Thyroid hormone diagnostics 2

PS3-26-01

Predictors of bethesda i category in thyroid fine needle aspiration cytology

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Introduction
Fine needle aspiration cytology(FNAC) is the mainstay for evaluation of nodular thyroid disease. Internationally reported prevalence for Bethesda I(unsatisfactory sample) category is 5-60%. Several factors may determine this result, including patient and nodules' features as well as both FNAC performer and pathologists' skills. Few studies have evaluated pre-procedure factors associated with unsatisfactory cytology results. If present, recognizing these factors, before performing FNAC, could help to adapt technique performance and sampling.
Objectives
Our aim was to determine clinical predictors of FNAC Bethesda I category.
Materials and Methods
Retrospective study of nodules submitted to FNAC, between January 2016 and December 2021. Clinical data from patients with FNAC Bethesda I category was retrieved and compared to Bethesda II to VI categories regarding gender, age, history of cervical radiation and malignancy, family history of thyroid disease, multinodular goitre, nodule's side, location and largest diameter, EU-TIRADS ultrasound classification, TSH and anti-thyroid peroxidase and anti-thyroglobulin antibodies. A multivariate logistic regression was used to evaluate putative predictors of unsatisfactory results, including variables with different distribution between groups.
Results e conclusions
Included 1617 nodules in 1525 patients, 625(38.6%) with Bethesda I results after FNAC. Among these, in 140(22.4%) nodules, patients were male, their median age was 60(50-69) years old, previous cervical radiation and family history of benign thyroid disease's prevalence was 27(4.3%) and 217(34.7%), respectively; most nodules[296(47.4%)] were located on the right lobe and in the middle third of the lobe[299(47.8%)]. Median TSH was 1.30(0.80-2.06)mUI/l. Nodules were classified, on ultrasound, as EU-TIRADS 2, 3, 4 and 5 in 62(9.9%),211(33.8%),265(42.4%) and 87(13.9%), respectively. The median largest diameter was 21.0(16.00-29.25)mm. Male gender, older age, nodule location and EU-TIRADS were significantly associated with unsatisfactory results in the univariate analysis. Variables included in the multivariate logistic regression were male gender, age, EU-TIRADS and nodule location. Male gender(OR 1.53 CI 95% 1.17-1.99, $P = 0.002$), age(OR 1.01 CI 95% 1.00-1.02, $P = 0.008$, per year), EU-TIRADS 3 to 5(OR 1.66 CI 95% 1.19-2.34, $P = 0.003$, OR 2.69 CI 95% 1.92-3.78, $P < 0.001$ and OR 2.37 CI 95% 1.56-3.59, $P < 0.001$, respectively), in comparison with 2, and location in the lower and upper thirds of the lobe(OR 1.409 CI 95% 1.098-1.809, $P = 0.007$ and OR 1.718 CI 95% 1.131-2.610, $P = 0.011$, respectively), in comparison with the middle third, were independently associated with unsatisfactory results. In this highly Bethesda I prevalent cohort, older age, male gender, EU-TIRADS 3 to 5 nodules located at upper/lower thyroid poles were associated with higher risk of unsatisfactory FNAC.

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PS3-26-02

Diverse clinical and laboratory phenotypes associated with heterozygous PAX8 mutations

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Introduction
Paired box gene 8 (PAX8) is a key transcription factor required both for normal fetal thyroid development and maintenance of the differentiated thyroid phenotype, mediating transcriptional activation of SLC5A5, TG, and TPO, and synergizing with NKX2-1 at the TG promoter. Heterozygous PAX8 mutations are a rare but well-recognized cause of congenital hypothyroidism (CH) due to thyroid dysgenesis (TD), and are classically associated with thyroid hypoplasia. However, a spectrum of thyroidal morphologies and biochemical severities have been reported, with infrequent association of urogenital tract malformations. We report diverse clinical phenotypes in

4 kindreds harbouring different heterozygous PAX8 mutations, with supporting laboratory functional characterization of the mutant PAX8.
Case Reports
P1 harbours a novel PAX8 missense mutation (p.I34F) associated with severe CH, thyroid hypoplasia and hypospasias. P2 is a female child harbouring a truncating mutation (p.R207*) previously reported in the context of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. Here, p.R207* is newly associated with mild CH, and absent Tc-99m uptake in an ultrasonographically normal sized thyroid gland-in-situ (GIS) without associated urogenital tract defects. P3 exhibits severe CH with a dysplastic thyroid associated with PAX8 c.162C > A, p.S54R; the same amino acid mutation due to a different nucleotide change (c.162C > G) has previously been reported in individuals with TD. P4a and P4b are sisters harbouring PAX8 p.S59R associated either with permanent GIS CH or mild CH with hemiagenesis. This contrasts with previously reported cases in whom p.S59R is associated with severe GIS CH and partial iodide organification defect, or goitrous CH with cryptorchidism and hydrocele.
Laboratory Data
p.S54R has previously been characterized in detail (1). Here, functional evaluation of PAX8 p.S59R, p.R207* and p.I34F demonstrated that the mutant proteins were expressed, but exhibited impaired transactivation of both TPO and TG promoters in luciferase reporter assays, compared to wild-type PAX8. Co-transfection studies with NKX2-1 achieved at least partial rescue of TG promoter transactivation with both missense mutations but not p.R207*, supporting a role for the PAX8 carboxyterminus in this interaction. Homology modelling suggests steric hindrance due to the p.S59R and p.I34F mutations may indirectly affect PAX8-DNA interactions.
Conclusion
Our studies characterize a novel PAX8 mutation (p.I34F) associated with both thyroid and urogenital tract pathology, and yield further insights into PAX8-NKX2-1 synergism. Additionally, we expand the clinical phenotypes associated with reported PAX8 mutations, demonstrating isolated CH with possible impaired SLC5A5 function in MRKH-associated p.R207*, and thyroid hemiagenesis with p. S59R. 1. Hermanns *et al* (2013) Thyroid 23, 791

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PS3-26-03

Association between ultrasonographic findings and thyroid function in autoimmune diffuse thyroid disease in children and adolescents

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Purpose
To evaluate the association between ultrasonography (US) feature of thyroid gland and thyroid function in pediatric and adolescent populations with autoimmune diffuse thyroid diseases (AITD).
Methods
From 2000 to 2020, we reviewed thyroid ultrasound (US) images and thyroid function statuses in 133 children and adolescent AITD patients. Our review of the images focused on decreased echogenicity and heterogeneity, which were classified into four grades.
Results
Among patients with overt hypothyroidism or overt hyperthyroidism, 94.2% (65/69) showed a US grade of 3 or 4. In patients with subclinical hyper/hypothyroidism or euthyroidism, 45.3% (29/64) showed grades 1 or 2. There were no overt hyper/hypothyroidism patients with US grade 1. When we compared US grades according to thyroid status, more severe thyroid dysfunction was significantly associated with higher US grade ($P = 0.047$). Thyroid stimulating hormone (TSH) level differed significantly according to US grades when we evaluated hyperthyroid ($P = 0.035$) and hypothyroid ($P = 0.027$) states independently. 11 patients showed both US grade and thyroid function status changes on follow-up US.
Conclusions
In children and adolescent AITD patients, there was an association between decreased echogenicity and heterogeneity on US and thyroid dysfunction.
Key words: ultrasonography, autoimmune thyroid disease, children, adolescents

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PS3-26-04

Diagnostic performance of 18F-choline PET/CT for detection of hyperfunctioning parathyroid glands in patients with primary hyperparathyroidism: a single-center experience

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Objectives
^{18}F-choline PET/CT is a recently introduced imaging modality to localize hyperfunctioning parathyroid glands in patient with hyperparathyroidism. But there has been no study according the diagnostic power of ^{18}F-choline PET/CT in Korea so far owing to its limited distribution. Therefore, we evaluated the diagnostic performance of ^{18}F-choline PET/CT in detection of hyperfunctioning parathyroid gland in patients with primary hyperparathyroidism.
Methods
Fifty patients with primary hyperthyroidism who underwent ^{18}F-choline PET/CT before parathyroidectomy between July 2020 and October 2022 at Samsung Medical Center were included. Lesion-based analysis was performed. The diagnostic performance of ^{18}F-choline PET/CT in all patients and in patient with inconclusive results of ultrasonography and ^{99m}Tc-MIBI SPECT/CT were evaluated comprehensively. Data included demographics, laboratory findings, image findings and pathologic reports.
Results
The sensitivity, specificity, positive predictive value, negative predictive value and accuracy ^{18}F-choline PET/CT in all patients included were 100%, 99.3%, 98%, 100% and 99.5%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{18}F-choline PET/CT in 12 patients with inconclusive ultrasonography and ^{99m}Tc-MIBI SPECT/CT results were 100%, 97.2%, 92.3%, 100% and 97.9% respectively.
Conclusion
^{18}F-choline PET/CT showed superior diagnostic performance to conventional modalities in both main analyses and subgroup analyses of inconclusive ultrasonography and ^{99m}Tc-MIBI SPECT/CT. False-positive result was observed only in a patient. ^{18}F-choline PET/CT could be considered as a first-line modality in localizing hyperfunctioning parathyroid glands in primary hyperparathyroidism.

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PS3-26-05

Radiomics analysis of thyroid ultrasound in relation to the radioactive iodine therapy-related sialadenitis

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Objective
Patients with thyroiditis often have sialadenitis. Radioactive iodine therapy (RAIT) sialadenitis could lower the patient's quality of life. However, it had not been investigated about the occurrence of RAIT sialadenitis and the presence of underlying thyroiditis. Therefore, we analyzed the preoperative thyroid ultrasound (US) with radiomics to figure out the occurrence of the RAIT sialadenitis.
Materials and Methods
In this retrospective single-centered study, patients who underwent the preoperative thyroid US for thyroid cancer, subsequent total thyroidectomy, and RAIT were identified between January 2012 and December 2020. A neuroradiologist qualitatively rated the echogenicity and echotexture of the thyroid. Moreover, radiomics analysis was performed for the region of interest in the thyroid using PyRadiomics
Results
Twenty-five patients with sialadenitis and 56 patients with sialadenitis were enrolled in this study. Both groups with or without sialadenitis show no difference in the statistical significance in terms of age, sex, TNM stage by AJCC 8th Ed., the total dose, and numbers of the RAIT. In the qualitative analysis, there were no significant statistical differences in the echogenicity and echotexture of the thyroid of both groups. In the LASSO regression for the radiomics analysis, the max probability from the gray-level co-occurrence matrix (GLCM) was only selected (coefficient -0.042).
Conclusion
It is difficult to directly correlate thyroiditis itself with the future occurrence of RAIT sialadenitis only with clinical factors or qualitative analysis of thyroid US. The role of radiomics could help the access between thyroiditis and RAIT sialadenitis.
Keywords: Radioactive iodine therapy (RAIT); Sialadenitis; Thyroid cancer; Thyroiditis

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PS3-26-06

Does hypoechogenicity, as a single variable in decision of FNA, offer similar sensitivity and specificity as the elaborate tirads in the 10-20 mm range of thyroid nodules for cancer detection?

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Background
Widespread use of imaging has led to the detection of an increasing number of thyroid nodules. Thyroid societies have recommended the use of Thyroid Imaging, Reporting and Data System (TIRADS). However, there is a multitude of such risk stratification systems (RSS) for selecting thyroid nodules for FNA. They may be time consuming and consensus on thyroid nodule descriptors lacks. Also studies have suggested that operators' experience may not be inferior to using a formal RSS evaluation in this context.
Objective
During nodule selection for FNA, <10 mm nodules may be left unsampled, while most nodules >20 mm require FNA irrespective of TIRADS score. We hypothesized that in the 10 to 20 mm thyroid nodule diameter range, where TIRADS score almost exclusively matters, nodule echogenicity, as a stand-alone descriptor, might provide comparable performance to the more complex approaches.
Patients and Methods
Seven highly experienced investigators from four countries evaluated, online, the ultrasound video-recordings of 123 histologically verified thyroid nodules by answering 17 thyroid nodule characteristics-related questions. The diagnostic performances of the most used five TIRADS (AACE/ACE/AME, ACR, ATA, European, Korean) were compared to decision making based solely on echogenicity, for indicating FNA in 110 nodules with a diameter of ≥ 10 mm.
Results
In nodules >20 mm, the sensitivities of the 5 TIRADS were significantly higher (from 92.9 to 100%) than the solely echogenicity-based decision (77.8%, $P < 0.05$). In nodules 10 to 20 mm, the sensitivities and specificities of the TIRADS' in identifying malignant nodules ranged between 80.5% and 91.0%, and between 31.4 and 50.9%, respectively. Had FNA been suggested in all hypoechoic nodules irrespective of other ultrasound characteristics, comparable sensitivity and specificity, 87.2% and 43.4%, respectively, were obtained. Compared to nodules >20 mm, a higher proportion of cancers were hypoechoic in the 10 to 20 mm size range (87.2% vs. 77.8%, $P = 0.04$). In those 10 to 20 mm, significantly lower proportion of isoechoic than hypoechoic nodules showed suspicious findings (30.0% vs. 70.7%, $P = 0.008$).
Conclusion
In nodules 10 to 20 mm, in contrast to larger nodules, the decision to offer FNA may rely on a single US feature, echogenicity. Using well-defined criteria for thyroid nodule descriptors, based on a lexicon, our data need to be challenged and confirmed in large-scale studies before accepting a simplified RSS for thyroid nodules in the 10 to 20 mm range.

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PS3-26-07

Ultrasound and cytological evaluation of PET-CT positive incidental thyroid lesions

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Introduction
Positron emission tomography - computed tomography (PET-CT) is a highly sensitive imaging modality for evaluating a variety of conditions, including detection of cancer and potential metastases. PET-CT positive thyroid lesions are found incidentally in about 2.5 % of the scans. They can be focal or diffuse and as they pose a considerably high risk of malignancy further diagnostic tests such as neck ultrasound and fine-needle aspiration biopsy (FNAB) are recommended.
Objective
To assess the sonographic and cytological characteristics of PET-CT positive thyroid lesions in a single university endocrine center between 2019-2022.
Patients and Methods
The study included 42 patients (35 women and 7 men) who underwent PET-CT for suspected or confirmed non-thyroid malignancy. The patients were referred for further diagnostic evaluation to the endocrinology department of Kaspela University Hospital, Plovdiv, Bulgaria. All patients had clinical examination, neck ultrasound and FNAB with subsequent cytological examination when indicated. The ultrasound findings were described according to EUTIRADS reporting system and the cytological report was consistent with BETHESDA system. Surgically removed thyroid lesions were further evaluated by pathologist.
Results
The ultrasound examination revealed focal lesions determined as nodules in 35 of the studied patients. In the remaining 7 cases no distinct thyroid lesion was identified (EUTIRADS 1) and the presence of autoimmune thyroiditis was confirmed. After FNAB 12 nodules (34.3 %) were determined malignant or suspicious for malignancy and 91.7 % were confirmed histologically as thyroid carcinomas ($n = 11$). All of the malignant nodules had at least one risk ultrasound characteristic (EUTIRADS 5). The distribution of the remaining nodules with regards to the US fundings was as follows: EUTIRADS 4 – 4; EUTIRADS 3 – 13, EUTIRADS 2 – 6. The overall incidence of malignancy among PET-CT positive thyroid nodular lesions in our center was 31.4 %.
Conclusion
The results from the present sample confirm the high frequency of thyroid neoplasms among all the incidental findings in the thyroid gland detected on PET-CT. Careful ultrasound examination followed by FNAB is justified in all patients to avoid overdiagnosis and unnecessary interventions

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PS3-26-08

Assessment of thyroid stiffness in beta thalassemia patients by using shear-wave ultrasound elastography

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Objective
Beta thalassemia is associated with a number of endocrinopathies. Iron overload is thought to be at the root of thalassemia-related endocrinopathies, including hypothyroidism; however, morphologic changes that could be attributable to iron deposition in the thyroid gland have been under investigated. This study aims to evaluate thyroid gland volumes and stiffness in thalassemia patients using shear-wave ultrasound elastography (SWE), and to analyze if there is any relationship between thyroid stiffness and thyroid functions.
Methods
A total of 43 thalassemia patients were examined. Three patients were excluded because thyroid volume measurements were missing, and five were excluded because they were on levothyroxine treatment. The final analysis included thirty-five patients (19 male, 16 female). Regarding the significant difference between left and right thyroid lobe volumes, SWE measurements were corrected according to ipsilateral thyroid volume (cSWE = SWE:ipsilateral thyroid volume).

Results
The median age at the time of study enrollment was 33 years (range: 19-46). Most patients had thalassemia major (29, 83%), whereas the remaining six had thalassemia intermedia. Twenty-six (74%) of the patients had at least one thalassemia-related endocrinopathy. All patients were euthyroid except the two with subclinical hypothyroidism, and all were negative for thyroid autoantibodies. None of the patients were receiving levothyroxine. The median serum TSH, fT4, and fT3 levels and serum ferritin values were presented in the Table. Mean volumes for the right and left thyroid lobes were 3.24 ± 1.49 cm^3 and 4.19 ± 1.85 cm^3, respectively. Mean SWE measurements in the right and left thyroid lobes were 10.25 ± 4.51 kPa and 10.32 ± 4.62 kPa, respectively. Thyroid volume was negatively associated with serum TSH ($P = 0.03$, $r = -0.37$ for left lobe, $P = 0.017$, , $r = -0.40$ for right lobe). cSWE was also negatively correlated with serum TSH ($P = 0.03$, $r = 0.37$ for left lobe, $P = 0.01$, $r = 0.43$ for right lobe). In addition, cSWE showed negative significant correlations with patients' height ($P = 0.006$, $r = -0.46$ for left lobe, $P = 0.002$, $r = -0.53$ for right lobe), and positive correlations with age ($P < 0.001$, $r = 0.56$ for left lobe, $P = 0.01$, $r = 0.44$ for right lobe). No correlations were found between cSWE and ferritin, cardiac or hepatic magnetic resonance T2 star values.
Conclusions
SWE has been successful in making the differential diagnosis of thyroid nodules and diffuse thyroid diseases. To date, no studies have investigated thyroid gland stiffness and its relationship with thyroid function tests in thalassemia patients. Our findings indicate that thyroid gland volume decreases and thyroid stiffness increases in thalassemia patients as they age, in correlation with an increase in TSH.

	Value	Range	Laboratory normal range
Median TSH (mIU/mL)	2.83	1.10-7.40	0.38-5.33
Median fT4 (pmol/L)	10.34	8.44-13.97	7.86-14.41
Median fT3 (pmol/L)	5.29	2.22-6.40	3.8-6.0
Median ferritin (µg/L)			
Most recent	720.4	52.9-6070.0	11-307
Last 1 year	836.6	239.0-6672.7	
Last 5 years	885.1	343.8-5531.5	

Ferritin values for the 'last 1 year' and 'last 5 years' were calculated by taking the arithmetic average of ferritin values for the previous 1 year and 5 years, **respectively.**

TSH: Thyroid stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine.

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PS3-26-09

Thyroid antibodies and early response to treatment in graves' disease
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Objective
Some patients with Graves' disease (GD) respond faster to antithyroid drugs (ATD) than others. Our aim was to study if levels of autoantibodies to the TSH-receptor (TRAb), thyroid-stimulating immunoglobulin (TSI), thyroid peroxidase antibodies (anti-TPO) and/or clinical factors influence the early response to anti thyroid drugs (ATD) in women with GD.
Methods
This was a longitudinal cohort study of 65 women with GD and fT4 ≥ 50 pmol/l (reference range 12-22 pmol/l), and/or total T3 ≥ 6 nmol/l (reference range 1.3-3.1 nmol/l). All started with tiamazol 5 mg 3 x 2 and decrease of fT3 and fT4 was evaluated after median 8 days. Groups were created for patients with antibody levels over and under the median for TRAb and TSI and patients positive or negative for TPO. Decrease in fT4/T3/day of ATD was compared between groups. We also assessed duration of symptoms, goitre, age and smoking. Variables were correlated to the decrease of fT3/fT4/day of ATD.
Results
Patients with high TRAb decreased more in fT3 (median 2.1 and 1.0 $P < .01$ and fT4 (median 4.0 and 2.1 $P < .001$) per day of ATD compared to those with low TRAb. The same was true for TSI for fT3 (median 2.3 and 1.0, $P < .001$) and fT4 (median 4.0 and 2.0, $P < .0001$). The decrease of hormones correlated with levels of TRAb (fT3 $\rho = 0.45$, $P < 01$, fT4 $\rho = 0.48$, $P < .001$) and of TSI (fT3 $\rho = 0.52$, $P < .001$, fT4 $\rho = 0.51$, $P < .0001$). In those positive for anti-TPO the decrease in fT3 (median 1,8 and 0.9, $P < .01$) and fT4 (median 4.1 and 1.9, $P < .01$) per day of ATD was greater compared to TPO negative patients but initial hormone levels did not differ. Levels of anti-TPO correlated with the decrease of fT3 ($\rho = 0.50$, $P < .01$) and fT4 ($\rho = 0.48$, $P < .01$) but not with initial hormone levels, TRAb or TSI. No difference could be found between those with none or mild goiter compared to those with moderate to significant goiter or between smokers ($n = 8$) and non-smokers. No correlation was found between the decrease of hormones and age.
Conclusion
That GD patients with high TRAb, TSI and thyroid hormones respond more promptly to ATD compared to those with lower levels is not surprising. However, the greater response in those positive for anti-TPO cannot be explained by this and poses questions to the mechanism of action of the drugs and a possible influence of anti-TPO in GD.

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Thyroid Cancer Clinical 3

PS3-27-01

Clinicopathological features of intrathyroidal thymic carcinoma: A single center experiences
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Intrathyroidal thymic carcinoma (ITTC) is a rare thyroid malignancy. Its histology resembles that of squamous cell carcinoma (SCC) of the thyroid. However, ITTC shows a much more favorable prognosis than SCC. We analyzed the backgrounds and clinicopathological features of 10 patients who treated with ITTC in our medical center. Five patients was male, and another five was female. The average tumor size was 4mm, and it ranged from maximum 68mm to minimum 13mm. In pre-operative ultrasonography, 100% patients' findings were malignant (8 cases). In five patients, there was a clinical node metastasis, and six patients had a pathological node metastasis. Total thyroidectomy was done for six patients, and 4 patients had less than total thyroidectomy. In four patients, additional lateral neck dissection was done. There was an extrathyroidcal extension in 8 patients. It is important todifferentiate it from other more aggressive thyroid malignancy. Although it is difficult to diagnose CASTLE preoperatively, radical surgery should be regarded as the first choice of treatment for CASTLE. Radiotherapy and chemotherapy should be considered to the stage of the disease as effective treatment modalities.

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PS3-27-02

Central (N1A) and latero-cervical (N1B) lymph nodes metastases in sporadic medullary thyroid carcinoma patients: clinical impact on disease specific and recurrence free survival
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Background
Distant metastases at diagnosis is the worst prognostic factor for disease specific survival (DSS) in sporadic medullary thyroid carcinoma (MTC). Also, lymph node metastases are negative prognostic factors both for DSS and recurrence free survival (RFS). The question whether central (N1a) and latero-cervical compartment lymph nodes metastasis (N1b), separately evaluated, can have a different impact on DSS and RFS remains to be clarified.
Patients and methods
We evaluated 674 sporadic MTC patients (2000-2020), all of them followed at the Unit of Endocrinology of the Pisa University Hospital. We excluded all patients with distant metastases at diagnosis (60/674 – 8.9%). From the remaining ($n = 614$) we excluded those in whom central and/or latero-cervical compartment lymph nodes dissection was not performed (Nx) (57/614 – 9.3%) and patients lost to follow-up (11/614 – 1.8%). Then, according to histology, we defined 3 groups:

1) N0 (310/546 – 56.8%) without lymph nodes metastases, 2) N1a (105/546 – 19.2%) with metastatic lymph nodes of the central compartment alone, 3) N1b (131/546 – 24%) with metastatic lymph nodes of the latero-cervical ± central compartment.
Results
In a median time of 110 months (IQR 60-164.25) we observed 37 (6.8%) cancer related death (CRD): 5/310 (1.6%) in N0 and 32/131 (24.4%) in N1b group; no CRD were observed in N1a. Indeed, Kaplan Meier (KM) analysis showed a DSS of 100% at 5 and 10 years in N0 and N1a, while 83% and 78% in N1b group ($P < 0.01$). After excluding patients with structural disease at first post-operative evaluation (67/546 – 12.3%) we observed 69/479 (14.4%) structural recurrences in a median follow-up time of 75 (IQR 32.75-130) months. Of these, 14/308 (4.5%) in N0, 17/99 (17.2%) in N1a and 38/72 (52.8%) in N1b group. KM showed a RFS of 99% and 97% in N0, 87% and 82% in N1a and 58% and 48% in N1b group, at 5 and 10 years respectively ($P < 0.01$). When directly comparing N0 and N1a ($P < 0.01$) and N1a and N1b ($P < 0.01$) a RFS was significantly different.
Conclusions
In our series of sporadic MTC patients without known distant metastases at diagnosis, regardless of other potential risk factors, the presence of N1b at diagnosis was confirmed as a negative prognostic factor both for DSS and RFS. Conversely, the presence of N1a alone, regardless of number and dimension of the metastatic lymph nodes, has no impact on DSS and is comparable to N0 patients. However, in N1a patients the occurrence of recurrence over time cannot be overlooked, since they showed a risk significantly higher than N0, but lower than N1b, of having a structural recurrence over time.

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PS3-27-03

A large series of patients with anaplastic thyroid cancer managed in a tertiary referral center

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Objectives
Anaplastic thyroid cancer (ATC) is one of the deadliest cancers, with a median overall survival (OS) of 4 months and a disease-specific mortality of ~100%. Although to date no effective treatment can cure the disease, some anecdotal cases achieved longer survival and very rarely the cure of the disease. Multimodal treatment with surgery, radiotherapy, multikinase inhibitors (MKI) could improve survival in ATC, particularly when surgery is not feasible.
Methods
We retrospectively evaluated 145 consecutive patients followed at the Endocrine Unit of the University Hospital of Pisa, with pathologically confirmed ATC having complete follow-up data, from 1972 to 2023. The aim was to characterize the clinical features of ATC and investigate the possible role of MKI in prolonging survival.
Results
Females (58.1%) and males (41.9%) were equally represented. The median age was 67 years (IQR 57-75; min-max 33-92). Stage at diagnosis was IVa in 17 (11.7%) patients, IVb in 23 (15.9%) and IVc in 105 (73.4%). The median OS was 4.02 months (IQR 1.97-7.16; min-max 0.13-240). Surgical treatment was feasible in 92 (63.4%) cases: total thyroidectomy with apparently R0 resection in 46 (50%) cases and only debulking in the other 50% of cases. At diagnosis, 69 (48.9%) patients had tracheal invasion, 40 (28.6%) had esophageal invasion and 7 (7.1%) had neck cutaneous infiltration. Some patients received also radiotherapy ($n = 66$, 47.5%) and chemotherapy ($n = 53$, 37.9%). MKI were administered in 35 (25.2%) patients: sorafenib in 18 (51.4%) and lenvatinib in 15 (42.9%). In 2 cases (5.7%) dabrafenib and trametinib were also used. Analyzing the potential utility of MKI treatments compared to conventional chemotherapies, an improvement in OS was observed with MKI in the first 2 years after diagnosis [HR 0.538; 95% CI 1.201-2.876; $P = 0.005$]. Unfortunately, this association was later lost. Three patients were considered long survivors (median follow-up: 56.77 months; min-max 22.08-131.52) and today are still alive. Two patients are in remission after surgery, chemotherapy, radiotherapy and in one of these also sorafenib treatment. The third patient underwent radiotherapy and is now on dabrafenib-trametinib, showing a partial response at the last evaluation.
Conclusions
In this large single-center series we confirmed that survival of ATC has not changed over the years, despite new and emerging treatments. However, MKI may be helpful in controlling disease progression, especially in the first 2 years after diagnosis. Although very rarely, some cases of ATC benefited from the treatments performed, up to having a longer survival.

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PS3-27-04

Comparison of patient-reported outcomes between active surveillance and immediate surgery for low-risk papillary thyroid carcinoma: A longitudinal study with one-year follow-up

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Objectives
Active surveillance (AS) for low-risk papillary thyroid carcinoma (PTC) has been adopted as a reasonable approach to management worldwide. In our previous cross-sectional study, patients who chose AS had better mental patient-reported outcomes (PRO) compared to those who underwent immediate surgery. This prospective, longitudinal study aimed to compare PROs between patients who chose AS and those who underwent surgery, during a one-year follow-up from the time of decision-making.
Methods
Among 78 patients with low-risk PTC (T < 15 mm, no extrathyroidal extension or metastasis), 58 chose AS and 20 chose immediate surgery, including conventional surgery ($n = 11$) and video-assisted neck surgery ($n = 9$). The SF-36v2 questionnaire was used to measure physical, mental, and role-social PRO. The survey was conducted at the next decision-making consultation and the one-year follow-up visit.
Results
In the entire cohort, mean age was 52.6 ± 12.4 years and 62 patients (79.4%) were women. Patients in the AS group were significantly older compared to the surgery group (58.8 ± 11.4 years vs. 46.0 ± 13.0 years, $P = 0.011$). In the initial survey, the surgery group had better scores for physical functioning (PF) and physical component summary (PCS) compared to the AS group. At one year after decision-making, the surgery group had better PF scores, but worse vitality (VT) and mental component summary (MCS) scores compared to the AS group. During the one-year follow-up, the AS group showed an improvement in general health (GH) but had a worsening in social functioning (SF) scores and role-social component summary (RCS). However, no significant changes were seen in other subscales in either group. In comparing the component summary scores of each management type with Japanese norm-based scores, the surgery group had better PCS, whereas the AS group had better MCS and RCS than the Japanese population norms. No subscale showed significantly worse outcomes compared to Japanese norm-based scores in either group during the survey.
Conclusions
This prospective, longitudinal study showed no inferiority in PROs compared to the Japanese norm-based scores, regardless of whether patients chose AS or immediate surgery, and some subscales had better scores. At one year after decision-making, patients who chose AS felt better mentally than those who underwent surgery; however, their role-social PRO deteriorated during follow-up. Longer follow-up is necessary to elucidate optimal management for individual patients with low-risk PTC in terms of aspects of PRO.

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PS3-27-05

Changes in clinical presentation of paediatric differentiated thyroid cancer (DTC) treated in one centre over 40 years

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Background
Differentiated thyroid carcinoma (DTC) in children is a rare cancer, occurring in 1/100,000 children/year. In the adults a steady increase in the incidence and change in presentation of DTC has been observed over the past 30 years.
Purpose
Evaluation of changes in the clinical presentation of paediatric DTC on the example of children treated in Institute of Oncology in Gliwice between 1970 and 2015.
Material and methods
Retrospective analysis of 475 patients with DTC diagnosed $\leq$18 years of age.
Results
Half of the children were $>$15 years, 9.9% were under 10 years of age at the time of diagnosis. The girls: boys ratio was 2.7. Median follow-up time was 11 years (0.1- 47.8 years), 2% of patients were lost to follow-up. PTC was diagnosed in 88%, FTC in 11%, and poorly-differentiated carcinoma in 1%. Primary tumor size could be determined in 70% of children. 56% of tumors were less than 2 cm, 12.3% $>$4 cm. Multifocality was found in 34%, extrathyroidal invasion in 20%. Lymph node metastasis occurred in 59% of patients. Distant metastases were found in 76 patients (16%). Analysis revealed increasing DTC incidence among adolescents ($>$15 years of age) and decreasing incidence of FTC compared to PTC. There was an increase of small tumors $\leq$2 cm and a decrease of multifocality, particularly for tumors $\leq$1 cm. Extrathyroidal invasion was stable over time and correlated with tumor size. There was a significant increase in the rate of central neck node metastases. The percentage of distant metastases decreased significantly. Prognostic factors for distant metastasis were tumor size, multifocality, and lateral neck node metastasis.
Conclusions
We can expect an increasing incidence of pediatric DTC, diagnosed at an earlier stage than in years when USG were not widely available. Despite the increasing number of small, monofocal papillary carcinomas in children, the frequency of carcinomas $>$3-4 cm is not decreasing, multifocal carcinomas still affect every fourth patient and extrathyroidal invasion every fifth. The increased frequency of metastases to the central neck lymph nodes probably results from their increased detectability and does not increase the risk of distant metastases. The incidence of distant metastases in the study group was highest between 1996 and 2000 (30%), which may be due to a selection bias, and then gradually decreased to about 10%. Risk factors for distant metastasis were larger tumor, multifocality and lateral neck nodes metastases.

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PS3-27-06

Skeletal related events in differentiated thyroid carcinoma with bone metastasis: A bicentric study

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Purpose
Bone metastases (BM) are frequent in differentiated thyroid cancer (DTC). These patients may present skeletal-related events (SRE), the leading cause of DTC-related morbidity. We aimed to evaluate the clinical features, treatment approaches, and outcomes including overall survival (OS) of DTC patients with BM complicated by SRE and their evolution over time.
Methods
178 consecutive DTC patients harbouring BM were enrolled in this retrospective study conducted in two tertiary referral centres of the French ENDOCAN-TUTHYREF network between 1989 and 2015. SRE were defined as the need for any bone irradiation or surgery, spinal cord compression, pathologic fractures or hypercalcemia.
Results
A hundred and twenty-seven patients (71.3%) had SREs associated with BM including the 75 cases (42.1%) with SRE occurring at diagnosis. The median time to first SRE was 13 months [0-67.5]. Seventy-six patients (66%) had multiple SRE (median: 2 (1-3) . The most frequent SRE was the need for radiotherapy (75.6%) following by bone surgery (58.3%) and pathologic fractures (52%). In patients with SRE, before 2005 (n =54), the number of locoregional treatment (LTR) performed was respectively 94 in 55 patients before 2005 and 155 in 78 patients after 2005. Bone resorption inhibitors (BRI) were used in 34% of the patients with SRE being prescribed for osteolytic BM only (29.6% of the cohort before 2005 and 38.7% after 2005). Pathological fracture occurred respectively in 34 patients (63%) and 40 patients (51.2%) before and after 2005. In the multivariate analysis, only osteolysis and aggressive variants or poorly DTC (PDTC) were able to predict SRE (OR, 6.7; 95% CI, 1.4-34.9, P = 0.02; OR, 7.7; 95% CI, 1.2-50, P = 0.03 respectively); no association was found with an age $>$ 55 years (P = 0.3), synchronous BM (P =0.3), number of BM (P = 0.055), BM FDG-PET/CT uptake (P = 0.129) and the RAI refractory status (P = 0.6). Among the patient with BM FDG-PET/CT uptake, 92% patients had a SRE. The median OS from BM diagnosis for patients with SRE was 45 months (24–81.7) vs 72 months (33.7-101) for patients without SRE. The occurrence of SRE (HR, 0.6; 95% CI, 0.2-1.4, P = 0.246) was not independently associated with increased overall mortality in multivariate analysis.
Discussion
Almost two thirds of DTC patients with BM experience a SRE. Osteolysis and aggressive variants or PDTC were associated to higher risk of SRE. We observed an increased in LTR and BRI prescription after 2005 with a decrease of pathological fracture. Among these patients, SRE occurrence did not impact OS.

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PS3-27-07

Clinical significance of de novo appearance of anti-thyroglobulin antibodies in patients of differentiated thyroid cancer with radioiodine therapy

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Objectives
This study analyzed the prevalence of newly discovered anti-thyroglobulin antibody (TgAb) and its clinical significance during the follow-up period of patients with differentiated thyroid cancer.
Methods
Among patients who underwent total thyroidectomy and radioactive iodine treatment between 2008 and 2022 in a single center, 184 patients (23 male, 161 female) with Tg $<$ 1ng/ml and TgAb positive ($>$ 60 IU/mL) at least once were targeted. Six hundred twenty patients with consistently normal TgAb were used as controls.
Results
An analysis was conducted on 38 patients of de novo detection of TgAb at least two consecutive follow-up tests during a mean follow-up of 7.2 years. Among them, 20 patients had a temporary increase, and 4 patients had a sustained or increased increase. Fourteen patients performed only two tests, so the temporary and continuous increase could not be identified. None of the patients with a transient increase had not confirmed structural recurrence pathologically, however two of the patients with maintained or increased TgAb levels had recurrence and subsequently underwent surgery. There was no significant association between de novo TgAb-positive patients and structural recurrence compared to normal patients.
Conclusions
Although there was no significant relationship between de novo TgAb detection and structural recurrence of DTC, additional studies are needed because patients with consistently high or increasing TgAb following de novo appearance are predicted to have an association with structural recurrence.

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PS3-27-08

Lymph nodes metastases from papillary thyroid microcarcinoma negatively impact on outcome

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Background
Papillary thyroid microcarcinoma (microPTC), defined as PTC measuring 10 mm or less in greatest diameter, is the most common type of thyroid cancer. MicroPTC generally has an indolent clinical course, with slow and exclusivelly intrathyroidal growth, without any significant impact on patient morbidity and mortality of patients. Sometimes, even microPTC can show lymph nodes (LNs) involvement, ranging from incidental histological findings to preoperative evidence of palpable or ultrasonographic lymphadenopaties. In this specific setting, the real impact of LN metastases on the patients response to therapy is not clear.
Objectives
To determine the difference in clinicopathological features and outcomes between patients with microPTC and LNs metastases (N1) and patients with larger (> 10 mm) PTC associated with LNs or distant metastases (N1/M1).
Methods
We performed a retrospective observational study on patients diagnosed with PTC in follow-up at the Endocrinology Unit of our Institution. Clinical data of 364 patients were retrived, selecting only those who underwent total thyroidectomy, followed or not by radioiodine (RAI) therapy, belonging to one of these groups: patients with microPTC N1, patients with microPTC without histological evidence of involved LNs (microPTC N0) and patients with large PTC N1/M1.
Results
The study population included 239 patients, with no significant differences of age and sex among the three groups (Table). Among all cases of microPTC ($n = 155$), LNs involvement was observed in 25.8% and was significantly associated with primary tumor size, extrathyroidal extension (ETE) and angioinvasion. MicroPTC N1 ($n = 40$) was mainly diagnosed by fine needle aspiration on suspected LNs metastases respect to large PTC N1/M1 ($n = 84$; 32.5% vs. 11.9%, $P = 0.006$) but did not show any differences in term of histological subtypes, multifocality, angionvasion and number of involved LNs. ETE of the primary tumor was more frequent in large PTC N1/M1 than microPTC N1 group (46.4 vs. 25%, $P = 0.02$) but lateral cervical LNs was observed more in the latter (50% vs. 31%, $P = 0.04$). Patients with microPTC N1 were more likely to have biochemical or structural incomplete response to therapy compared with microPTC N0 (25% vs. 0, $P < 0.001$) but as likely as large PTC N1/M1 patients (25% vs. 23.8%, $P =$ ns). Between the two metastatic groups, patients were similar regarding the use of RAI therapy, median cumulative RAI exposure and median lenght of follow-up.
Conclusions
LNs metastases from microPTC are not uncommon and can lead to an overall treatment and a probability of disease persistence comparable to that of large PTC N1/M1.

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PS3-27-09

Finding the right balance in optimizing post-operative suppression therapy after papillary thyroid carcinoma - a case report

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Introduction
Papillary thyroid carcinoma (PTC) is a common thyroid gland malignancy. Postoperative suppression therapy with levothyroxine (LT4) is commonly used to prevent recurrence or progression of the disease. The optimal duration and dose of LT4 suppression therapy remain a matter of debate. The optimal duration and dose of LT4 suppression therapy remain a matter of debate, with recommendations varying based on the patient's age, sex, tumor characteristics, and risk of recurrence. Therefore, it is important to balance the potential benefits of LT4 suppression therapy against the risks of adverse effects when deciding on the duration and dose of therapy for each patient.
Case Report
We present a case of a 32-year-old male patient who underwent total thyroidectomy after detecting PTC. The patient was evaluated as a low-risk patient by the ATA risk stratification system to estimate the risk of recurrent thyroid tumor. He had been on LT4 suppression therapy with a stable dose of 250 mg daily after the surgery. Physical examination revealed a body mass index (BMI) of 40.56 kg/m^2, blood pressure of 140/90mmHg, and a heart rate of 98bpm. Laboratory investigations showed elevated levels of serum TSH (9.2mIU/l) and undetectable levels of Thyroglobulin (TG) and Anti-thyroid peroxidase (anti-TPO) antibodies. The patient was administered an increased LT4 dose (275 mg), after which he experienced more severe tachycardia (105-110bpm) despite taking the prescribed beta-blocker medicine. We implemented a weight loss plan for the patient, involving modifications to his diet and an exercise regimen. At 6 months follow-up, the patient had lost 18 kg of weight, and his BMI had decreased to 34.47 kg/m2. His blood pressure and heart rate had also improved. Lab tests showed normal serum levels of TSH (1.5mIU/l) and undetectable TG, anti-TPO levels. The patient was encouraged to continue the weight loss plan and advised to reduce his LT4 dose to 175/200 mg daily, with close monitoring of TSH, TG, anti-TPO.
Conclusion
The use of TSH suppressive therapy should merit careful consideration since it carries an increased risk of complications. Individualized treatment should be based on patient characteristics and risk stratification. While LT4 suppression therapy can be effective in preventing the growth of residual or recurrent thyroid tissue, it can lead to adverse effects, particularly in patients with pre-existing obesity. Thus, we should consider whether the patient benefits more from TSH suppression therapy or an individualized approach to reach even subclinical hypothyroid status, taking into account the low risk of disease recurrence and comorbidities. Lifestyle modifications, including dietary changes and physical activity, should also be implemented as part of the management of obesity and hypothyroidism.

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Translational 2

PS3-28-01

Study on the role of podoplanin in papillary thyroid carcinoma using rna sequencing

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Introduction
Podoplanin (PDPN) is a transmembrane protein linked with metastases of various cancers, including papillary thyroid carcinoma (PTC). PDPN is significantly upregulated in PTC specimens and PTC- derived cell lines: TPC1 and BCPAP, harboring RET/PTC and BRAF V600E alterations, respectively. We observed that depletion of PDPN impairs migration of TPC1 cells, but surprisingly, augments metastases of BCPAP cells. To elucidate this phenomenon we aimed to further investigate the role of PDPN in the biology of PTC cells using NGS-based RNA sequencing (RNAseq).
Material and Methods
BCPAP (BRAF V600E) and TPC1 (RET/PTC) cell lines were used in the study. siRNA was used for knockdown of PDPN expression. Cells transfected with negative siRNA served as controls. Total RNA extracted from the cells was sequenced using the RNAseq technique. The expressional profile of the cells and GO terms were assessed. Statistical significance was considered at $P < 0.05$.
Results
Depletion of PDPN was found to have a significant, but disparate effect on the tested PTC cells. In TPC1/siPDPN cells, GO terms of negative regulation of transcription, regulation of mitotic nuclear division and cell cycle regulation were the most abundant. In contrast, in BCPAP/siPDPN cells, the assigned GO terms referred to positive regulation of transcription, protein phosphorylation and migration. Also, depletion of PDPN resulted in decreased levels of NF-κB and cIAP2 in TPC1 cells, but increased levels of IRAK1 and STAT2 in BCPAP cells.
Conclusion
We conclude that the role of PDPN in PTCs likely depends on the mutational status of the cells. Silencing of PDPN in TPC1 cells leads to promotion of signaling pathways related to the control of cell stability and adhesion processes, while in BCPAP cells – paths involved in cell proliferation and migration. This research was supported by: National Science Centre (No. 2018/29/B/NZ3/02642) Centre of Postgraduate Medical Education (No. 501-1-26-02-22)

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PS3-28-02

Hypothesizing a role of ret hyperactivation on weight control in patients with type 2A multiple endocrine neoplasia (MEN2A)

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Introduction
RET gene is responsible for various human cancers and is mutated and hyperactivated in nearly 100% of familial (germline mutation) and in about 60%

of sporadic (somatic mutation) MTC cases. Moreover, RET gene play a role in several physiologic and pathologic conditions. Very recently, the hyperfunction of RET was found to be a key process in weight loss. The hypothesis is that in a peculiar population in which RET gene is mutated and constitutively activated from birth, RET hyperfunction could be a factor in weight loss.
Objectives
To evaluate potential differences in weight at the diagnosis in RET germline positive (gRET+) vs RET germline negative (gRET-) MTC cases.
Methods
98 gRET+ MTC patients, all index cases of different families, were matched one-to-one according to gender and age at diagnosis, with 98 gRET-. Anthropometric data were collected for all patients.
Results
Each group had 39 males and 59 females. Median age at diagnosis was 47 years old in both groups. In all population median weight was 69 Kg (IQR 60-80) and BMI 24.7 Kg/m^2 (IQR 22.1-27.7). Therefore, 2.0% of patients were underweight (BMI $\leq$ 18.4), 51.6% normal weight (18.5-24.9), 30.6% overweight (25-29.9) and 15.8% obese ($\geq$ 30). No difference in obesity prevalence was observed in patients with or without RET germline mutations (17.3% vs 14.3%, $p > 0.05$), as well as in BMI and weight ($p > 0.05$ for both). Moreover, analysing the distribution of BMI according to the different types of RET mutation, again no difference was observed. When dividing patients according to gender, in females, we confirmed that BMI and weight did not differ between gRET+ and gRET-. Conversely, in males, gRET+ patients showed higher BMI values (median 26.9 vs 24.6), more frequently > 30 (30.7% vs 12.3%) and weight (median 83 vs 77 Kg) than gRET- ($P < 0.05$ for all).
Conclusions
No differences in weight and BMI were highlighted in our matched cohort population of gRET+ and gRET- patients. Differently from the initial hypothesis and animal models, although only in males, gRET+ patients showed higher weight and BMI than gRET-. Further studies with larger number of patients are needed to unveil the potential effect of RET hyperactivation on human weight control.

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PS3-28-03

Molecular analysis of multiple foci of sporadic medullary thyroid carcinoma suggests that they are intrathyroidal metastases from the same primary tumor

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Sporadic medullary thyroid cancer (sMTC) presents mutations of the *RET* proto-oncogene in about 50% of the cases and of the *RAS* proto-oncogene in about 20% of the cases. In about 15% of cases, sMTC is multifocal and it is not known whether multiple foci can be considered as intrathyroidal metastases of the main tumor focus or if they can be considered as independent tumors. To clarify this issue, we examined the mutation profile of multiple intrathyroidal tumor foci to verify if they share the same somatic mutations present in the main focus. We analyzed 34 cases of sMTC that had at least 1 tumor focus in addition to the main tumor. There were 13 cases that harbored 1 additional focus, 16 with two other foci, 4 with three foci and 1 with four other foci. DNA was extracted from paraffin-embedded (FFPE) tumor tissue or by fresh frozen tissues. For FFPE samples, DNA was specifically recovered from the tumor focus as indicated by the pathologist. Primary tumors were analyzed by Next-Generation Sequencing (NGS) using a custom panel in the IONS5 platform. Mutations were then validated by Sanger Sequencing and/or droplet-digital-PCR (ddPCR); the mutation observed in the main tumor focus was tracked in secondary tumor foci by ddPCR and/or by Sanger Sequencing. Five out of 34 sMTC cases (15%) included in this study had no detectable mutation in the main focus, 28 (82%) had one single mutation, and 1 (3%) had three different somatic mutations. Among the 28 cases with a single mutation: 26 (93%) harbored a somatic *RET* mutation, 1 (3.5%) had a *HRAS* mutation and 1 (3.5%) had *KRAS*. We demonstrated that in 33/34 investigated cases, the mutation profile of the main tumor focus was the same in all foci of the same patient. The mutation profile was not confirmed in 1/4 tumor foci of the only patient harboring 3 different somatic mutations in the main tumor focus. In conclusion, we show that virtually all tumor foci of the same patient had the same mutation; these data support the hypothesis that different tumor foci of the same patient are likely intrathyroidal metastases from the same primary tumor and not independent foci.

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PS3-28-04

Effect of pazopanib in anaplastic thyroid cancer in primary culture

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Anaplastic thyroid cancer (ATC) is usually treated with surgery, external hyperfractionated radiation therapy, and chemotherapy. However, because of the aggressiveness of this type of cancer, these treatments allow about 6-10 months of median survival. Therefore, it is challenging to predict the ATC patient clinical therapy responsiveness. Pazopanib is a multitarget tyrosine kinase inhibitor of VEGF receptors, PDGF, and c-Kit, and its effect in primary human ATC cells (pATC) has not been reported in the literature. We aim to evaluate the antineoplastic effect of pazopanib in pATC *in vitro*. We collected surgical thyroidal tissues from five patients with ATC, from thyroid biopsy at the moment of first surgical operation, and we tested the effect of pazopanib. We showed an inhibition of proliferation, migration, and invasion, and an increase in apoptosis upon treating pATC cells with pazopanib ($P < 0.05$). Moreover, the VEGF expression in pATC cells decreased in a significantly manner ($P < 0.05$) with pazopanib. To sum up we demonstrate the antineoplastic activity of the antiangiogenic inhibitor, pazopanib, in human pATC *in vitro*.
Keywords: anaplastic thyroid cancer; tyrosine kinase inhibitor; primary culture
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PS3-28-05

Pediatric thyroid nodules with germline and somatic DICER1 variants

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Objectives
Pathogenic variants in the *DICER1* gene can be found in both benign and malignant thyroid nodules, more often in pediatric patients. Somatic pathogenic variants in "hotspot" regions can coexist with germline variants in other regions of the *DICER1* gene, which are associated with DICER1 syndrome, an autosomal

dominantly inherited disease that predisposes to the development of various tumors from childhood. In addition to thyroid tumors, pleuropulmonary blastoma, pediatric cystic nephroma and other tumors can develop. The aim of the work was to detect variants in the *DICER1* gene in a large group of pediatric patients with thyroid nodules.

Methods

The study consisted of two cohorts - fresh frozen thyroid tissue samples from 239 patients and samples collected by fine needle aspiration biopsy (FNAB) from 78 patients; both aged 2-20 years. In case of positive findings, peripheral blood was determined. Extracted DNA was used for next-generation sequencing on MiSeq sequencer (Illumina) using the Nextera XT DNA Library Prep Kit (Illumina). Mutations in the *DICER1* gene were visualized in Integrative Genomics Viewer (Broad Institute) and evaluated by the VarSome platform (Saphetor SA).

Results

Pathogenic *DICER1* hotspot mutations were detected in 13 of 239 (5.4%) fresh frozen pediatric thyroid tissues including 6 papillary thyroid carcinomas (PTCs), 1 low-risk tumor, 6 benign nodules. Additional mutation in the *DICER1* gene was found in 8 of them. There were 4 patients with tumor-specific biallelic *DICER1* mutation, who, according to available studies, are risk-free of other tumors associated with DICER1 syndrome. Four patients with germline variants were classified as individuals with DICER1 syndrome. Patients with PTCs had no lymph metastasis and had excellent response to the treatment. In the cohort of FNAB samples, 6 (7.7%) *DICER1*- positive samples were detected (cytologically evaluated as 3x Bethesda II, 2x Bethesda IV, 1x Bethesda VI). Two patients had second germline pathogenic *DICER1* variant and one had another somatic variant. A total of 4/6 patients had already undergone surgery - samples were histologically evaluated as nodular goiters and one as follicular carcinoma.

Conclusions

In summary, *DICER1* variants are important molecular markers in pediatric thyroid nodules. In the case of positive finding, it is also necessary to exclude germinal origin of detected variants. Although the penetrance of DICER1 syndrome is incomplete, regular follow-up of these individuals and their relatives according to surveillance recommendations is very important for earlier detection of additional tumors.

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PS3-28-06

Next-generation-sequencing on fine needle aspirates in neck recurrence of thyroid cancers

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Objectives

Tumor molecular genotyping plays a key role in improving the management of advanced thyroid cancers. Molecular tests are classically performed on Formalin-Fixed Paraffin-Embedded (FFPE) carcinoma tissue. However alternative molecular testing strategies are needed when FFPE tumoral tissue is unavailable. The objective of our study was to retrospectively assess the performance of targeted DNA and RNA-based Next Generation Sequencing (NGS) on the fine needle aspirate from thyroid cancer cervical recurrences to determine if this strategy is efficient in clinical practice.

Design/Methods

A retrospective study of 33 patients who had had DNA and/or RNA-based NGS on neck ultrasound (US)-guided fine needle aspirates of cervical thyroid cancer recurrences in our Department from July 2019 to September 2022.

Results

In total, 34 DNA and 32 RNA-based NGS analyses were performed. Out of the 34 DNA-based NGS performed, 27 (79%) were conclusive allowing the identification of an oncogenic driver for 18 patients (53%). The most common mutation ($n = 13$) was *BRAF* c.1799T>A. Out of the 32 RNA-based NGS performed, 26 were interpretable (81%) and no gene fusion was found. The identification of a BRAFV600E mutation was decisive for one patient in our series, who was prescribed dabrafenib and trametinib.

Conclusions

NGS performed on fine needle aspirates of neck lymph node metastases enabled the identification of an oncogenic driver alteration in 53% of the cases in our series of advanced thyroid cancer patients and could significantly alter patient management.

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PS3-28-07

Expression of focal adhesion kinase microrna regulators is related to dedifferentiation in thyroid neoplasia spectrum

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Objectives

The specter of malignant thyroid lesions comprises tumors with different degrees of differentiation, rendering the differential diagnosis and prognosis of these tumors challenging. Focal adhesion kinase (FAK) is a tyrosine kinase involved in cellular communication and locomotion, functioning as a hub in the interactome of focal adhesions. Its upregulation has been demonstrated in a number of tumor types including thyroid cancer. FAK is regulated on several levels, one of which includes posttranscriptional inhibition by microRNAs among which are miR-7-5p, miR-135a-5p, and miR-138-5p. Changes in the regulation of FAK can disturb its activation and indirectly influence malignant transformation and cancer progression. We aimed to investigate how the levels of microRNA regulators of FAK correlate with histologic aggressiveness, clinicopathological factors and assess their usefullness in differential diagnostics.

Methods

We collected the samples of postoperative thyroid tumor tissues along with the adjacent normal thyroid gland tissue from 82 patients. We classified the cases into 5 groups with increasing aggressiveness: healthy tissue, follicular and classical variant of papillary thyroid carcinoma (PTC), rare forms of PTC and anaplastic carcinoma. Three microRNAs (miR-7-5p, miR-135a-5p, and miR-138-5p) were selected by literature review and bioinformatic analysis for miR target prediction via miRDB software tool. MiRNA levels were determined via quantitative RT-PCR. TCGA database was queried via UCSC Xena tool, developed by University of California Santa Cruz.

Results

In our sample cohort all three miRs were upregulated in healthy tissue compared to malignant. MiR-135a-5p was negatively correlated with tumor aggressiveness showing a decreasing trend in expression in more aggressive tumor types. The expression of miR-135a-5p and miR-138-5p significantly discriminated follicular from the classical variant of PTC. Neither miR correlated with clinicopathological parameters. The results of TCGA analysis corroborated these findings, and showed that miR135a and miR138 are negatively correlated to the miRNA expression levels of FAK gene.

Conclusions

The selected miRs undergo downregulation during thyroid neoplastic transformation, and could present thyroid tumor suppressors whose effect is exerted through FAK regulation. MiR-135-5p although correlated to histological aggressiveness, does not show prognostic usefulness. MiR-135a-5p, and miR-138-5p are beneficial in thyroid differential diagnostics, while pinpointing the different developmental paths for the different PTC subtypes.

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PS3-28-08

Understanding the putative role OF ACE2, TMPRSS2 and furin proteins on thyroid neoplastic transformation

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Angiotensin-converting enzyme 2 (ACE2), Transmembrane serine protease 2 (TMPRSS2) and Furin were known to be key players for the SARS-CoV-2 infection. Thyroid gland was shown to be one of the relevant targets for SARS-CoV-2 infection allegedly due to the higher expression levels of these molecules in follicular cells. However, it remains to be fully determined the expression of ACE2, TMPRSS2 and Furin in normal follicular cell. In addition, the putative role of these molecules in the neoplastic transformation of the thyrocytes has never been explored. We aimed to characterize the expression of ACE2, TMPRSS2 and Furin in a series of thyroid lesions in comparison to adjacent thyroid. To attain this objective, we quantified the mRNA expression of these molecules by RT-qPCR in 191 samples that included, adjacent thyroid tissue (AT), and benign and malignant neoplasms. We also performed IHQ on 68 samples of FFPE thyroid tissues to understand the expression pattern of these proteins *in situ*. The results were correlated with the clinicopathological and molecular data available (https://doi.org/10.3390/cancers12071846). Our results revealed a significant decrease of ACE2 mRNA in all thyroid lesions when compared with ATs. On the other hand, Furin showed a significant increase in the mRNA levels, particularly in adenomas, but also in carcinomas, when compared with ATs. Interestingly, within carcinomas, follicular carcinomas seemed to have a decreased expression of Furin when compared with papillary carcinomas. Regarding the clinicopathological and molecular data, ACE2 expression was significantly increased in smaller adenomas ($P < 0.05$), with the presence of lymphocytic infiltrate ($P < 0.005$), specifically thyroiditis ($P < 0.01$), and positive expression of TERT mRNA. Furin mRNA expression was significantly increased in tumours from male patients ($P = 0.005$) and in cases that presented lymph node metastasis ($P < 0.05$). On the other hand, Furin expression was significantly decreased in tumours with NRAS mutations ($P < 0.05$). No significant differences were found concerning TMPRSS2. Regarding protein expression in the tissue samples, the pattern of expression observed for ACE2 was membranous, limited to the cells in small vessels. The expression was increased in benign lesions when compared to ATs and papillary carcinomas ($P < 0.05$). Cytoplasmic expression of TMPRSS2 was decreased in malignant lesions when compared to AT and Furin nuclear staining was significantly increased in adenomas when compared to thyroid carcinomas and ATs. Our study shows that the expression of these three molecules is altered in thyroid neoplastic lesions but further studies are needed to understand their putative role in tumorigenesis of the thyroid gland.

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PS3-28-09

Detection of ras mutations leads to non-aggressive treatment of thyroid tumors

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Introduction
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or well-defined, not invasive neoplasm with a follicular growth pattern and core features of papillary thyroid carcinoma (PTC). This is considered to be a 'pre-malignant' lesion of the RAS-like group. The RAS oncogene plays a huge role in human tumorigenesis. RAS gene mutations occur, in an average of 30–45% of follicular thyroid cancers (FTC). Among other molecular markers for thyroid cancer, there has been considerable interest in the potential clinical utility of RAS mutations as diagnostic and prognostic molecular markers. The role of RAS mutations in the clinical behavior of thyroid tumors is also unknown. How to properly manage these nodules is also controversial.
Objective
We present a case of a patient who was planning pregnancy when thyroid cancer was found with regular check up.
Case Report
Our patient was planning pregnancy, when a nodule with irregular margins was found in the thyroid gland during check up (TIRADs 4A - 0.7x0.9 cm). This nodule had no indication of fine needle aspiration (FNA), but as an enlarged lymph node with a lesion was also found, decision was made to perform FNA. FNA of nodule and lymph nodes revealed Bethesda VI-grade malignancy (follicular thyroid cancer - FTC). Total thyroidectomy and lymph node dissection was performed. Usually, after total thyroidectomy guidelines also recommend radioiodine therapy (RAI). But after the results of FNA, NIFTP was suspected and molecular testing was also performed, which typically involves TERT, BRAF, PAX8/PPARγ, RAS, and RET/PTC. In this patient RAS mutation was found and decision was made that RAI therapy may not be beneficial in this case, as RAS mutation is typical for NIFTP, and the likelihood of NIFTP recurrence is very low (<1%).
Conclusions
Studies over the past few years have illuminated the role of RAS mutations in the clinical behavior of thyroid tumors and the value of RAS mutations in advancing the management of thyroid nodules and thyroid cancer. We recommend considering diagnostic and prognostic molecular markers. RAS mutation-positive, differentiated thyroid cancer has a good prognosis and can be treated with less aggressive measures. *RAS* mutation-positive but cytologically benign thyroid nodules can be managed without radioactive iodine therapy.

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Treatment 2

PS3-29-01

Impact of local treatments in progressive, advanced, radioiodine-refractory thyroid cancer

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Introduction
The majority of patients with radioiodine-refractory thyroid carcinoma (RAIR-TC) have an indolent disease and require active surveillance (AS) only, while those with progression of the disease (PD) may benefit from local treatment (LT) or systemic therapy with tyrosine-kinase inhibitors (TKI). In the literature, no data about the real impact of LTs in avoiding/delaying systemic treatment in RAIR-TC patients are present.
Objective
This study describes the impact of LTs in patients with RAIR-TC in progression not treated with TKI.
Patients and Methods
We retrospectively evaluated 279 patients RAIR-TC, referred to our institution from January 2016 to December 2021. Clinical examination, serum markers measurements and neck ultrasound were performed every 6-12 months. Disease staging was assessed by Total Body Computed Tomography and/or other imaging exams (Magnetic Resonance Imaging, Positron Emission Tomography/Computed Tomography and Bone Scintigraphy). PD was defined according to RECIST 1.1. Definition criteria of RAIR-TC and the indication to start a LT or systemic therapy with TKI were determined according to 2016 ATA guidelines.
Results
After the diagnosis of radioiodine-refractoriness (RR), 176/279 (63.1%) patients presented a PD. Of this group, 33/176 (18.7%) patients were assigned to AS, 44/176 (25.0 %) to LTs and 99/176 (56.3%) to TKI. Regarding the 44/176 (25.0%) patients that receiving LTs, the mean time from the initial diagnosis to the end of the follow-up was 12.8 years (interval 1.5-33.7 years). A total of 74 LTs were performed in the 44 patients. In particular, the following LTs were performed: 31/74 (42.0%) surgical treatment of local recurrence or lymphadenectomy, 19/74 (25.7%) external beam radiation therapy on the neck, 9/74 (12.2%) external beam radiation therapy on the bone metastases, 4/74 (5.4%) radiofrequency thermal ablation of local disease/lymph node metastases, 2/74 (2.7%) surgical excision of bone metastases, 2/74 (2.7%) surgical excision of lung metastases, 2/74 (2.7%) endoscopic laser unblocking and tracheal recanalization, 2/74 (2.7%) trans-arterial chemoembolization or radioembolization of liver metastases, 1/74 (1.3%) surgical excision of pancreatic metastases, 1/74 (1.3%) external beam radiation therapy on pulmonary metastases and 1/74 (1.3%)

stereotaxic radiosurgery on brain metastases. The mean time from the first LTs to the end of the follow-up was 2.6 years (interval 0.6-20.4 years). During the follow-up after LTs, no patient started TKI and no patient deceased.
Conclusions
This study showed that 25.0% of RAIR-TC patients had a PD of either single lesions or single organs that can be treated with LTs. These LTs allowed to avoid or delay the systemic therapy with TKI that, as known, has a rather relevant impact on the quality of life of these patients.

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PS3-29-02

Efficacy of ethanol ablation in the long-term local control of recurrent neck nodal metastases occurring after bilateral thyroidectomy, extensive nodal resection and postoperative radioiodine therapy in adult patients presenting with node-positive UICC/AJCC ptnm stage i papillary thyroid carcinoma.

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Introduction
Ethanol ablation (EA) of "persistent or recurrent" neck nodal metastases (NNM) in adult papillary thyroid carcinoma (APTC) patients was first introduced in 1993 to clinical endocrine oncologic practice (JCEM 2011;96: 2717). At Mayo Clinic we have been impressed by the efficacy of EA in controlling postoperative NNM in stage I APTC patients. We now describe the long-term outcome results of EA in controlling recurrent NNM in 41 patients consecutively managed in one endocrinologist's practice during 2001-2017.
Methods
For study inclusion all 41 node-positive stage I APTC patients (mean MACIS score 4.1) were treated with bilateral thyroidectomy (BT), extensive nodal resection and radioactive iodine therapy (RIT) and were followed at Mayo Rochester with neck ultrasound (US) exams for >48 months after EA. Each received a median cumulative RIT dose of 5.55 GBq (range 1.11-20.35); pre-EA 28 patients (68%) had 41 additional neck surgeries with postoperative unilateral cord paresis (UCP) in four. The cytologic diagnosis of PTC in 71 NNM (volume range 12-1404 mm^3; median 150) selected for EA was confirmed by US-guided biopsy. The techniques of EA (AJR 2002;178:699) and follow-up protocol details were as previously described (JES 2020;4:bvaa095).
Results
The 41 patients (26 women, 15 men; median age 36 yr) were followed by Mayo US for 4.1-20.6 yr; mean 10.5 yr); each had 1-4 NNM (median 1). 67/71 NNM (94%) received 2-4 (median 2) ethanol injections (total volume ranged 0.2-3.0 mL; median 0.8). Post-EA all 71 ablated NNM (46% at levels 6/7) shrank (mean volume reduction of 93%) and nodal hypervascularity was eliminated. 39 NNM (55%) with initial volumes of 12-1404 mm^3 (median 164) disappeared on neck sonography.32 hypovascular foci from ablated NNM (pre-EA volume range 31-636 mm^3; median 147) were identifiable with volume reductions of 13-98% observed (median 81%). There were no complications and no post-procedure hoarseness. EA was successfully performed in 3 patients with known UCP on 5 NNM (3 central; 2 lateral) situated on the side with the intact RLN function and 4 (80%) disappeared. Latest median post-EA serum thyroglobulin (range <0.1 – 1.4 ng/mL) on TSH-suppressive treatment in 39 patients was 0.2 ng/mL.
Conclusions
EA of NNM in stage I APTC is effective and safe. Our present results demonstrate that for patients with stage I APTC, who do not wish further surgery or RIT and are uncomfortable with active surveillance, EA represents a well-tolerated and minimally invasive outpatient management option for the control of recurrent NNM.

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PS3-29-03

TKIS for advanced thyroid cancer increase tsh levels in thyroidectomized patients: A meta-analysis

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Background
Tyrosine kinase inhibitors (TKIs) are modern antineoplastic molecules widely used in the medical treatment of many cancers including iodine refractory differentiated thyroid carcer (DTC) and advanced medullary thyroid cancer (MTC). In patients with thyroid gland, TKIs frequently cause a destructive and/or autoimmune thyroiditis with consequent hypothyroidism. However, authors have reported unexpected TSH increase or hypothyroidism even in patients with total thyroidectomy on levothyroxine replacement therapy during treatment with TKIs. There is still no agreement in the literature on the real frequency and mechanisms underlying this phenomenon.
Objectives
Aim of this meta-analysis is to evaluate the risk of TSH increase in thyroidectomized patients treated with TKI and identify potential influencing factors.
Methods
The study was conducted according to MOOSE. The search was performed on online databases Medline and ClinicalTrials.gov. No language or time restriction were used. Article type restriction was applied with filters "Clinical Trial" and "Randomized Controlled Trial". Molecules considered in the search were those proposed by the last update of ESMO guidelines on the use of systemic therapy in advanced thyroid cancer (July 2022). The last search was performed on December 17th, 2022. Quality assessment was performed, when appropriate. Proportion meta-analyses were performed using random-effect model. Statistical analyses were performed using StataSE 17.
Results
The online search retrieved 2037 studies and 19 of which with total 1747 patients were finally included for quantitative analysis. The risk of bias was generally low. The pooled absolute risk of TSH increase was 32% (95%CI: 22–42%; I^2= 95.44%). The heterogeneity was explored according to several covariates, including sample size, kind of drug and mean time of drug treatment, and was solved by severity of TSH increase reported (increase within normal range vs hypothyroidism) (P = 0.04). Drugs used for MTC showed a pooled risk of TSH increase of 43% (95%CI: 26–60%; I^2=97.2%) and those used for DTC 25% (95%CI: 13–37%; I^2=93.9%). This difference almost reaches statistical significance (P = 0.08). Lenvatinib 24 mg/die (pooled risk 29%; 95%CI: 8-50%; I^2=96.6%) and Cabozantinib 140 mg/die (pooled risk 65%; 95%CI: 40-89%; I^2=86.21%) are respectively the drugs with higher risk of TSH increase in DTC drug subgroup and in MTC ones. There are no statistically significant differences between the various drugs of each subgroup.
Conclusions
This is the first meta-analysis to estimate the risk of TSH increase in thyroidectomized patients during treatment with TKIs for advanced thyroid cancer. The absolute risk seems to be very important, especially for patients treated with drugs used for MCT. Therefore, physicians and in particular endocrinologists must pay attention to this insidious side effect.

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PS3-29-04

Effectiveness of lenvatinib in progressive metastatic radioiodine refractory well differentiated and poorly differentiated thyroid carcinoma

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Introduction and objectives
Lenvatinib is the first line treatment for advanced radioiodine refractory (RAIR) differentiated thyroid carcinoma (DTC). Poorly differentiated thyroid carcinoma (PDTC) outcomes with Lenvatinib have only been subjected to sub analysis in one PHASE III study (SELECT), which might limit its real-world use in PDTC. We intend to compare the effectiveness of Lenvatinib in metastatic RAIR DTC and PDTC patients.
Methods
Retrospective study of all progressive metastatic RAIR DTC and PDTC patients followed at a single tertiary center from January of 2016 to September of 2022. Exclusion criteria included the presence of areas of PDTC in DTC cases, high grade thyroid carcinomas and absence of progression in the last 12 months. Response criteria were assessed on computed tomography studies, performed every 3 months and reviewed by an expert radiologist. Kaplan-Meier curves were used to calculate Progression-free survival (PFS) and Overall survival (OS).
Results
A total of 27 metastatic patients treated with Lenvatinib (20 with DTC and 7 with PDTC) were included. No statistical significance (NS) was found between PTC and PDTC baseline prognostic parameters: 70% vs 71% had at least T3 disease; 65% vs 57% had neck nodal metastasis, and distant metastases in 2 or more sites were present in 75% vs 57%. Also, NS was found on previous therapies: surgery was performed in 95% vs 86%; RAI therapy in 95% vs 71%; neck radiotherapy in 48 vs 57% and previous tyrosine kinase inhibitors (TKI) in 24% vs 43%. The median daily dose of Lenvatinib was 15.3 mg vs 19.0 mg and the mean duration of treatment was 16.3 vs 16.8 months. Partial responses were observed in 40% vs 29% and stable disease in 45% vs 71%. The PFS at 6,12 and 18 months, was 74%, 62% and 62% in PTC and 86%, 54% and 36% in PDTC, respectively (NS). The OS at 6 and 12 /18 months, was 74% and 69% in PTC and 100% and 67% in PDTC, respectively (NS).
Conclusion
Our results in two real world populations of progressive metastatic PTC and PDTC showed a statistically similar efficacy of Lenvatinib, as seen in the OS and PFS during the first 18 months of therapy. Nevertheless, a non-significant decrease in PFS was observed in the PDTC group which could be related to a higher exposure to previous TKI in this group of patients. This study confirms the usefulness of Lenvatinib in patients with metastatic PDTC.

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PS3-29-05

Tailored mortality risk in stage I-II DTC patients by integrating ata stratification and response to initial therapy

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Objectives
AJCC/TNM staging system provides an estimate of mortality risk in differentiated thyroid cancer (DTC) patients and recent evidence showed that ATA risk stratification may improve the definition of this risk. We speculated that the integration of the response to the initial therapy (RIT) could better define the mortality risk.
Methods
We retrospectively evaluated 891 consecutive DTC patients followed at the Section of Endocrinology, University of Siena, Italy from January 2006 to December 2020. Patients were classified according to the eighth edition of AJCC/TNM, ATA risk classes and response to RIT.
Results
The mortality rate in the whole cohort was 3.5%, decreased to 1% in Stage I and raised up to 21.6% in Stage II patients ($P < 0.0001$). After dividing by ATA risk stratification, the mortality rate in Stage I was 0.3% in low risk and 2.9% in intermediate-high risk patients ($P = 0.005$). Finally, considering the RIT, Stage I-low risk patients with excellent response (ER) showed a lower mortality rate than Stage I-low risk patients with persistent disease (PD) after initial therapy (0% vs 4.4%, $P = 0.0058$). Similar trend was observed in Stage I patients with intermediate-high risk class ($P = 0.0013$). In Stage II-intermediate-high risk patients, the mortality rate was 6.4% and 50% in patients with ER and PD, respectively ($P < 0.001$). The corresponding Kaplan–Meier curves showed six subgroups of patients with increasing disease specific mortality ($P < 0.001$).
Conclusion
Mortality risk estimated by AJCC/TNM staging system could be improved by integrating ATA risk classes and RIT and that the patient management could be tailored accordingly.

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PS3-29-06

Dabrafenib and trametinib treatment in patients with braf-mutated advanced thyroid cancer

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Introduction
The combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) was approved by the Food and Drug Administration in USA as first line treatment for BRAF-positive anaplastic thyroid cancer. Moreover, it was also available as second line treatment in BRAF-positive advanced thyroid cancers, previously treated with other systemic treatments.
Purpose
We evaluated the efficacy and safety of the combination therapy with dabrafenib and trametinib (D+T) in BRAF-mutated iodorefractory thyroid cancers (TC/BRAF+) and anaplastic thyroid cancers (ATC/BRAF+), followed at the Unit of Endocrinology of Pisa University Hospital.
Patients and Methods
We assessed the Best Overall Response (BOR) and the clinical outcome of 5 TC/BRAF+ patients and 2 ATC/BRAF+ patients, treated with D+T. All patients with TC/BRAF+ had an advanced, metastatic and progressive disease: 4 of them were already treated with total thyroidectomy and radioiodine, and all performed at least one MKI (lenvatinib=3, sorafenib+lenvatinib=1, Lenvatinib+cabozantinib=1). Patients with ATC/BRAF+ were inoperable: both received prior radiation therapy and one of them also MKI (lenvatinib).
Results
Mean follow-up time was 5.6 months. Total body CT scan with i.v. contrast was used for the imaging assessment over time. Six patients performed at least one imaging evaluation after the beginning of D+T, while 1 patient died before the first imaging evaluation. One patient with ATC/BRAF+, showed a partial response during D+T, without relevant adverse events over time, and is still alive after 18 months of treatment. The other patient with ATC/BRAF+, showed a significant shrinkage of the neck mass but at the same time a progression on the metastatic lung lesions, and died because of disease progression. Four TC/BRAF+ patients showed progression of the disease on D+T and only one of them experienced a stable disease, but all of them died.
Conclusions
In our clinical experience, the combination therapy with D+T showed poor efficacy in controlling the disease of TC/BRAF+ patients. Conversely, better results were obtained in patients with ATC/BRAF+, particularly in the control of the disease in the neck. Larger studies are needed to better clarify the real efficacy of this treatment.

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PS3-29-07

Hypocalcemia occurrence in patients with advanced thyroid cancer during tyrosine-kinase inhibitor treatment

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Background
Several adverse events are recorded during treatment with tyrosine-kinase inhibitors (TKIs). Hypocalcemia was reported during phase III clinical trials with both Lenvatinib and Vandetanib, but scanty data are available in a real-life setting. Aim of our study was to evaluate hypocalcemia occurrence and its characteristics in a cohort of patients treated with these drugs for advanced thyroid cancer. Moreover, in patients treated with Lenvatinib, we examined a possible correlation between hypocalcemia occurrence and TKI efficacy.

Methods
We retrospectively evaluated all patients treated with Lenvatinib and Vandetanib in our centre from June 2008 and March 2023. We included patients with a follow-up of more than 3 months and with available data about calcium levels. Lenvatinib efficacy was evaluated as progression free survival (PFS) and overall survival (OS).
Results
We included 34 patients: 28 patients treated with Lenvatinib for differentiated thyroid cancer and 6 patients treated with Vandetanib for medullary thyroid cancer. In the Lenvatinib group, after a median follow-up of 33 months (range 4-78 months), 6 patients (21.4%) recorded hypocalcemia and in two of them (7.1%) it was of grade $\geq$ 3. The average time of the first hypocalcemia occurrence was 3 months (range 0.5-13 months); two patients with hypocalcemia had a secondary hyperparathyroidism, while four patients had low or inappropriately normal PTH levels. No differences were found in terms of gender, age at diagnosis, presence of post-surgical hypoparathyroidism, length of treatment, dose at start and mean dose of Lenvatinib. Median PFS was 22.8 and 28.3 months and median OS was 32.2 and 33.5 months in hypocalcemic and eucalcemic groups, respectively (P = NS). Only 1/6 patients (16.7%) on Vandetanib recorded hypocalcemia, after a median follow of 88 months (range 20-176 months). Hypocalcemia occurred after 48 months of treatment. It was of grade 1 and associated to secondary hyperparathyroidism.
Conclusions
Hypocalcemia was reported in more than 20% of patients treated with Lenvatinib and it was milder and less frequent during Vandetanib treatment. During Lenvatinib, hypocalcemia was an early adverse event, usually occurring during the first 3 months of treatment. Both PTH-dependent and PTH-independent mechanisms are involved in the development of this adverse event. The occurrence of hypocalcemia was not associated to drug efficacy during Lenvatinib treatment. Since hypocalcemia can be severe, a periodic assessment of phosphocalcic metabolism is recommended to prevent the possible severe consequences of this TKI side effect.

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PS3-29-08

Efficacy of tyrosine-kinase-inhibition in thyroid cancer – A retrospective, single-centre, real-world evaluation

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Therapeutic strategy for the management of radioiodine-refractory differentiated thyroid cancer (rrDTC) and advanced medullary thyroid cancer (MTC) had changed with the introduction of the multityrosine-kinase-inhibitors (MKI) sorafenib&lenvatinib and vandetanib&cabozantinib respectively. Only recently, the market approval of pralsetinib (FDA) and selpercatinib (FDA and EMA) as first highly selective RET(*rearranged during transfection)*- inhibitors have expanded the therapeutic landscape of thyroid cancer treatment. Here, we evaluated clinical characteristics, therapy regimes and efficacy of 77 rr(P)DTC (18 PTC, 22 FTC, 38 PDTC) and 59 advanced MTC patients upon TKI treatment (in total: 136 pts.) in a single tertiary reference centre. In the subset of (P)DTC patients the median age at diagnosis was 59 years (DTC: 59 years (29-79 years); PDTC 58 (29-79 years)). The median age at initialisation of the first TKI was 63 years. 75 patients were treated with lenvatinib and 48 patients were treated with sorafenib. Lenvatinib was first line option in 63 patients and sorafenib in 11 patients. One patient received pazopanib (PFS: 14 months) as first line therapy. The median PFS for lenvatinib was 18 months and three months for sorafenib. Upon responders, median PFS was 23 and eight months respectively, and 22 and 14 months when applied as first line option. To date, a total of four patients received cabozantinib as third line treatment. The median PFS for this subsets was not calculated. The subgroup of MTC patients included 51 sporadic patients and four with multiple endocrine neoplasia (MEN2a: two patients; MEN2b: two patients). The median age at diagnosis was 50 (15-90) years. The median age at initialisation of the first TKI was 56 years (22-90 years). Fifty patients were treated with vandetanib and 14 were treated with cabozantinib. Eleven patients received pralsetinib and selpercatinib was administered in 8 patients during their course of disease. Pazopanib and sunitinib were applied in two patients as an individualised treatment concept. Vandetanib was first line treatment option in 47 patients and cabozantinib only in two patients. Median PFS in vandetanib was 30 months and 12 in cabozantib respectively. To date, therapy with pralsetinib (5/11) and selpercatinib (5/8) is ongoing in five patients respectively. In conclusion, TKI therapy in advanced thyroid cancer appears to be effective in a real-world scenario.

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PS3-29-09

Effects of neoadjuvant chemoradiotherapy on unresectable anaplastic thyroid carcinoma

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Background
Anaplastic thyroid carcinoma (ATC) is associated with the highest mortality risk of any thyroid-arising tumor; however, there is currently no effective therapy for ATC, and multimodal therapy is associated with a relatively high mortality risk. Here, we investigated the effects of neoadjuvant chemoradiotherapy on patients with ATC treated with paclitaxel and intensity-modulated radiation therapy (IMRT).
Methods
The medical records of 157 patients with ATC at Gangnam Severance Hospital were reviewed between January 2016 and November 2022. Only nine patients were eligible for surgery after neoadjuvant chemoradiotherapy according to the Gangnam Severance Hospital protocol for ATC.
Results
Seven patients were female, and two were male. The median age of the patients was 62 years (range: 53–76 years). The median tumor size of the patients was 3.94 cm (range: 2.1–5.6 cm). All the patients were treated with neoadjuvant paclitaxel and concomitant IMRT. The median number of cycles of neoadjuvant paclitaxel was 5 (range: 2–6 cycles) and the median IMRT dose was 5680 cGy (range: 5250–6600 cGy). Six patients showed a reduction in tumor size after neoadjuvant chemoradiotherapy. Three patients showed no significant differences or increases in tumor size after neoadjuvant chemoradiotherapy, but did display eminent tumor necrosis. Of the six patients with initial regional node metastasis, four showed a decrease in the size of metastatic nodes and internal necrosis. One patient had initial distant metastasis in the lung, and another showed newly diagnosed lung metastasis after neoadjuvant therapy. The mean interval from neoadjuvant radiation therapy to surgery was 93 days (range: 14–170 days). The median survival of patients with ATC who received neoadjuvant chemoradiotherapy was 358 days (range: 123–2,023 days).
Conclusion
Effective neoadjuvant chemoradiotherapy followed by complete surgical resection could result in good prognosis in terms of median survival, with safe local progression control.

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Thyroid Physiology in Periphery & Development Basic

PS3-30-01

Developing an animal-free testing battery for thyroid hormone related developmental neurotoxicity

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Background
Over the last few decades, *in vivo* animal experiments have been the gold standard for the assessment of safety of chemicals and pharmaceuticals for human health. However, *in vivo* animal data has limited relevance for toxicity prediction in humans, especially considering species-specific issues of age, sex and exposure in different life-stages. Within the Virtual Human Platform for Safety Assessment (VHP4Safety) project we aim to develop an animal-free testing strategy to assess the safety of compounds for developmental neurotoxicity mediated by disruption of thyroid hormone signaling.
Method
We developed an Adverse Outcome Pathway (AOP) network on brain development based on available data of existing thyroid related AOPs and human physiology. By combining these data, critical molecular initiating events and key events have been identified and used as a basis for selecting parameters for an *in vitro* testing battery. The first part of the testing battery consists of human cell models representing neurons (SHSY-5Y and SK-N-AS), oligodendrocytes (MO3.13) and astrocytes (H4). Thyroid hormone uptake and metabolism by the cell lines was tested using radiolabeled thyroid hormone.
Results
The first critical events shown in the AOP are related to thyroid hormone availability in the brain via transport and metabolism. Time-dependent uptake of T3 and T4 was observed in all cell models, which was partially reduced by the MCT8 inhibitor silychristin. *In vitro* metabolism assays showed conversion of T4 into T3 by H4 cells, and conversion of T3 into T2 by MO3.13, SHSY-5Y and SK-N-AS cells. SHSY-5Y showed higher rates of T3 conversion than SK-N-AS cells.
Conclusion
The selected cell lines are suitable models to test the effect of compounds on uptake of thyroid hormones. Furthermore, deiodinase activity was as expected for the different cell types, with H4 cells showing D2 activity, and MO3.13, SHSY-5Y and SK-N-AS D3 activity. Future experiments will include testing (reference) compounds on uptake and *in vivo* metabolism to further validate the models. Furthermore, the cell models will be used to study whether developmental neurotoxic compounds disrupt the thyroid hormone balance in the developing brain. The VHP4Safety project NWA 1292.19.272 is part of the NWA research program 'Research along Routes by Consortia (ORC)' and is funded by the Netherlands Organization for Scientific Research (NWO).

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PS3-30-02

Combined triiodothyronine and preconditioning improves cardiac diastolic dysfunction in ex vivo rat hearts subjected to normothermic perfusion: a new method for donor heart preservation

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Objectives
Machine perfusion may become a platform for cardioprotective approaches, enabling repair and reconditioning of donor hearts. Ischemic preconditioning (PC) is a powerful means of cardioprotection. Triiodothyronine (T3) is shown to repair the injured myocardium and recently this cardioprotective action was demonstrated in an ex vivo rat heart normothermic perfusion model. This study investigated potential effects of low-flow PC with and without T3 administration in an ex vivo rat heart model.
Methods
Rat hearts were perfused in Langendorff apparatus with constant flow. Control isolated hearts were subjected to normothermic perfusion (NP) with Krebs-Henseleit for 6h (NP, $n = 9$). Another group of hearts, after stabilization for 30min, was perfused with normal flow for 30 min followed by 5 cycles of preconditioning (40 min of low flow perfusion and 20 min normal flow perfusion) with either vehicle (PC, $n = 11$) or 60nM T3 (PC + T3, $n = 10$) in the perfusate. T3 or vehicle administration started at the end of stabilization period (30min). Left ventricular end-diastolic pressure (LVEDP), left ventricular developed pressure (LVDP), perfusion pressure (PP), as an indirect index of microvascular function and % change of these parameters from baseline values were measured.
Results
Changes in LVEDP and PP are shown in table as Mean (SD). LVEDP at the end of perfusion was significantly increased from the baseline in both NP and PC groups. The magnitude of this change was significantly less in PC hearts vs NP. In PC + T3 hearts, LVEDP at the end of perfusion was similar to baseline. PP at the end of perfusion was significantly increased from the baseline in all groups, however this increase was significantly less in both PC and PC + T3 hearts vs NP. LVDP at the end of perfusion was significantly reduced from baseline in all groups and no difference between the groups was observed.
Conclusion
PC limits cardiac and microvascular dysfunction and T3 added to PC prevents the increase in LVEDP after prolonged perfusion. These data may have important therapeutic implications for normothermic perfusion of marginal human donor hearts.

	LVEDP (mmHg)			PP (mmHg)		
	End of stabiliz-ation (30 min)	End of per-fusion (360min)	% Change	End of stabiliz-ation (30 min)	End of perfusion (360min)	% Change
NP	7.6 (0.3)	21.8 (7.0)*	188 (94)%	69 (5)	153 (47)	120 (63)%
PC	7.7 (0.4)	13.4 (7.8)* #	73 (98)% #	68 (6)	105 (22)* #	58 (35)% #
PC + T3	7.6 (0.3)	8.3 (4.6) #	8 (58)% #	66 (4)	90 (19)* #	39 (27)% #

* $P < 0.05$ vs Baseline, paired samples t-test, # $P < 0.05$ vs NP, OneWay ANOVA

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PS3-30-03

The human thyroid-derived cl-huthyrecs cell line expresses the thyrotropin (TSH) receptor and thyroglobulin but lacks other essential characteristics of thyroid follicular cells

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Background
Thyroid hormones are essential for normal development and metabolism. Their synthesis requires a normal function of thyroid follicular cells and adequate nutritional intake of iodine. Immortalized thyroid cell lines are widely used to study thyroid physiology and pathology. The best characterized and most widely used ones include the FRTL5 rat thyroid cell line and a derivative thereof, the PCCL3 cell line. A permanent human thyroid cell line is currently lacking. A recent report described a cell line obtained from human thyroid cells designated as Cl-huThyrEC.
Materials and Methods
Four clones of Cl-huThyrEC cells were obtained and cultured in the presence of thyroid stimulating hormone (TSH). The expression of key genes defining the thyroid follicular cell phenotype was determined by reverse-transcription PCR (RT-PCR) in FRTL5, PCCL3 and Cl-huThyrEC cells. The latter were cultured as monolayers and as organoids in Matrigel. Iodide uptake, which is essential for thyroid hormone synthesis, was measured and compared among cell lines.
Results
Gene expression analysis reveals that Cl-huThyrEC cells express the thyroid-restricted transcription factors (*PAX8, NKX2.1, FOXE1*), the TSH receptor (*TSHR*), and thyroglobulin (*TG*), but not other genes that are essential for thyroid follicular cell function such as the sodium-iodide symporter (*NIS*), thyroid peroxidase (*TPO*), and pendrin (*SLC26A4*). Importantly, Cl-huThyrEC cells are unable to concentrate iodine, a result that is in line with the absence of *NIS* gene expression.
Conclusion
Despite expression of certain key genes limited or restricted to thyroid follicular cells, Cl-huThyrEC cells lack some of the essential characteristics of thyroid follicular cells, in particular *NIS*. This limits their value for studies focusing on thyroid cell function.

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PS3-30-04

Thyroid hormone treatment counteracts pathological alterations in diabetic nephropathy and diabetic cardiomyopathy

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Diabetic nephropathy (DN) and cardiomyopathy (DC) are two major complications of diabetes that account for over two thirds of deaths among diabetic patients. Our previous studies have shown that thyroid hormone (TH) signalling – in addition to its critical role in physiological growth and organ development – plays similar roles in pathological conditions that encompass cellular dedifferentiation, cyto-architectural reorganization and compensatory growth. Though the role of TH signalling in cell differentiation and growth is well-known, it remains unclear whether its alterations contribute to the pathobiology of diabetic cells and/or in the adaptive repair of diabetic organs. Here we aim to investigate whether triiodothyronine (T3) administration can prevent diabetes-induced alterations of TH signalling and the associated cellular pathological remodelling in kidney and heart of Zucker diabetic fatty (ZDF) rats, an experimental model of type II diabetes. Immunofluorescence and western blot analyses showed that T3 administration reversed the diabetes-induced adoption of TH foetal profile and prevented the reactivation of foetal markers both in kidney and heart of ZDF rats. Moreover, T3 provision strongly reduced glomerular damage as well as glomerular and cardiac fibrosis. Electron microscopy analysis showed that T3 provision preserved glomerular and podocyte's ultrastructure, and reversed cardiomyocyte damage (i.e., mitochondrial swelling, cristae fragmentation, myofibril disruption and Z line disappearance). Also, T3 treatment counteracted polyploidisation-induced hypertrophy of podocytes and cardiomyocytes in ZDF rats, normalising DNA content and restoring the physiological size and shape of cardiomyocytes, as assessed by DNA content evaluation and morphometric studies. To evaluate whether TH signalling could exert these effects also in humans, we optimised and used *in vitro* glucose-induced injury models for cell culture and hiPSC-derived cardiac and kidney organoids. Treatment with T3 reversed the marked increase in cell area of glucose-stressed podocyte and cardiomyocyte and normalised the altered long to short axis ratio in cardiomyocytes. Moreover, T3 administration strongly decreased fibrosis and alteration of Connexin-43 expression in cardiac spheroids as well as podocyte injury in kidney organoids. Our data highlight the key role that TH signalling plays in the dedifferentiation, morpho-phenotypical alterations and pathological growth of podocytes and cardiomyocytes in both animal and human models of diabetes and suggest that its activation, through T3 administration, can substantially counteract cellular pathological remodelling.

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PS3-30-05

Acute T3 administration reduces myocardial infarct size

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As thyroid hormones (TH) are essential for the normal heart function, a low TH state in ischemic cardiovascular events is often correlated to a poor prognosis. While clinical and experimental data suggests that TH intervention in acute myocardial infarction might be beneficial, a detailed insight in the mechanisms on TH action in IR injury or post infarct recovery of the heart is still lacking. In this study, we examined the effect of thyroid hormone pre- and postconditioning on infarct size and post-ischemic cardiac function in an isolated mouse heart ischemia/reperfusion setting and assessed classical cardioprotective pathways. We showed that T3 administration reduces infarct size in a dose dependent manner, but is equally effective when administered at baseline before ischemia or after ischemia at reperfusion. Additionally TH were beneficial for the recovery of left ventricular function after ischemia, with an increase in left ventricular developed pressure and a constant increase in coronary flow at reperfusion upon T3 administration. To contribute to the clarification of mechanisms underlying the cardioprotective effect of TH we also analyzed classical cardioprotective signaling pathways as well as eNOS phosphorylation at different time points at reperfusion. Here we could show that the enzyme activating phosphorylation of eNOS-Ser_{1177} did not differ upon T3 administration. However, increased phosphorylation of eNOS-$Thr_{495,}$ which is reducing NO production, could be observed. Co-administration of eNOS cofactor BH_4 reversed the cardioprotective T3 effect, suggesting that T3 is reducing excessive NO levels in the myocardium.

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PS3-30-06

Development and characterization of a simple human thyroid organoid *in vitro* model for thyroid metabolism investigation

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Please Development and preliminary characterization of a simple human thyroid organoid *in vitro* model for thyroid metabolism investigation For decades, *in vitro* studies of the thyroid have relied on thyroid-derived tumor cell lines, which are limited by their undifferentiated phenotype, lack of response to TSH, and chromosomal abnormalities. A viable alternative are monolayer (2D) cultures of primary thyrocytes isolated from histologically normal thyroid glands. However, these cultures are short-lived and tend to lose thyroid differentiation status. Furthermore, they cannot recapitulate the structural architecture on which follicular units are dependent for thyroid hormone biosynthesis. Thyrocytes are arranged in a single layer around the colloid. To overcome 2D culture limitations, we developed and characterized a three-dimensional (3D) thyroid culture, comparing it to 2D cultures. Non-tumorous thyroid samples were obtained from healthy donors (University Hospital of Pisa, Italy). The fragmented tissues were digested through collagenase IV (1 mg/ mL)-$CaCl_2$ at 37°C and 5% CO_2 for 2 hours. The cells were seeded into T-25 flasks in Humanized 7 homeostatic additives (h7H) medium. Then, 80 % confluent primary thyrocytes (P0) were collected and sed in Nunclon Sphera™ 96-well Microplates (10000 cells/cm^2) in h7H and 3% Geltrex™. Cell aggregates were collected after 7 to 10 days. Morphology was characterized by transmission electron microscopy (TEM). The expression of functional thyroid markers TPO (Thyroperoxidase), TSHR (Thyroid-Stimulating Receptor), PAX8 (Paired Box-8), TTF-1 (Thyroid Transcription Factor-1), NIS (Sodium/iodide symporter), IYD (Iodotyrosine deiodinase) and TG (Thyroglobulin) was examined by quantitative RT-PCR, immunocytofluorescent staining, western blotting and ELISA. Confocal and TEM analyses revealed a follicle-like 3D structure with the colloid compartment. TPO, TSHR, PAX8, NIS, and TG ($P < 0.05$) gene expression was significantly higher as compared to 2D cultures. In addition, ELISA test also revealed a higher production of TG protein. In conclusion, our findings revealed that the developed 3D thyroid cultures possessed the morphological traits and peculiarities of the real tissue, both in functionality and marker expression and may therefore be a suitable tool to investigate thyroid metabolism and physiology.

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PS3-30-07

Combined effect of a perinatal exposure to a thyroid hormone signaling disrupting chemical (TBBPA) and western diet on hypothalamic transcriptome

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Obesity rate keeps growing worldwide and weighs heavily on the healthcare system because of the related metabolic disorders like diabetes. In addition to calorie-rich diet and sedentary lifestyle, environmental exposure to obesogens, endocrine disrupting chemicals (EDC) targeting adipose tissue and its function as well as central pathways regulating food intake and energy expenditure, could add to the raising obesity incidence. The flame-retardant tetrabromobisphenol A (TBBPA) is an obesogen known to target thyroid hormone signaling, which has important roles in metabolic control. TBBPA is widely used and it is detected in human samples including mother's milk and cord blood. Thereby, babies are

exposed to this EDC during the vulnerable perinatal period. We wanted to study the combined effect of perinatal TBBPA exposure and adult life Western diet (high in fat and sucrose, HFHS) to metabolic health in adulthood using C57BL/6J mice. Hypothalamus, the central regulator of many bodily functions including thyroid axis and metabolism, consists of various nuclei, each having a unique role in the central control of metabolism. In particular, two nuclei are deeply involved in metabolic regulations, the arcuate nucleus (AN) and the paraventricular nucleus (PVN). Pregnant dams received 10 mg/kg/d TBBPA or vehicle for 4 weeks (last week of gestation through end of lactation). Pups followed a HFHS diet from 2 to 6 months of age. We measured several metabolic parameters, including food intake and weight gain in the four study groups of male mice: vehicle + control diet, vehicle + HFHS diet, TBBPA + control diet and TBBPA + HFHS diet. We also compared the transcriptomes of each group to discover how the hypothalamic nuclei respond to the treatments: we used the cutting-edge technology of spatial transcriptomics (10X Genomics) adding a spatial localization to differential gene expression studies. We measured the whole transcriptome activity, mapped to the relevant hypothalamic regions, focusing more precisely the PVN (controlling thyroid axis) and the AN, to identify the specific transcriptional pathways regulated in each hypothalamic nucleus. The results allow us to determine the molecular pathways specifically affected by the different treatments in each hypothalamic nucleus involved in the central control of 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 a metabolic challenge.

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PS3-30-08

Identification of FOXE1 promoter variants in families with cleft palate, struma ovarii and thyroid lesions

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Introduction

Forkhead box E1 (*FOXE1*) gene encodes a transcription factor crucial for thyroid morphogenesis, differentiation, and function. We previously found evidence of the involvement of a rare germline *FOXE1* variant in familial non-medullary thyroid carcinoma (FNMTC) etiology. FNMTC most common subtype is papillary thyroid carcinoma (PTC), and family members frequently present thyroid follicular nodular disease (FND). Germline *FOXE1* mutations have also been associated to congenital hypothyroidism due to thyroid dysgenesis, thyroid ectopy, and cleft palate (CP). Struma ovarii is a teratoma, containing mostly ectopic thyroid tissue. Among malignant struma ovarii (MSO), the PTC type is the most common. Due to its rarity, the genetic basis of MSO remains poorly understood, although its somatic alterations resemble those arising in eutopic thyroid cancer (TC). Several polymorphisms in the *FOXE1* gene regulatory regions, affecting expression levels, have been associated with increased susceptibility to CP, PTC and TC aggressiveness. In this study, two families were identified: F1) proband with MSO (PTC) and FND, mother asymptomatic, and maternal grandmother with FND; and F2) proband with follicular variant PTC (fvPTC) and septate uterus, sister, mother and maternal uncle with CP, and maternal grandmother with hypothyroidism.

Aim

To clarify the role of *FOXE1* in CP, MSO and TC in these families.

Methods

The *FOXE1* gene, including the promoter region, was analysed through Sanger sequencing, in probands' leucocyte DNAs. Immunohistochemistry (IHC) and qRT-PCR analyses of patients' tumours and adjacent normal tissues were undertaken. MSO's somatic alterations were assessed by next-generation sequencing (NGS). Luciferase assays using plasmids with wild-type *FOXE1* promoter or variants were performed in cervix uteri carcinoma (SiHa) and normal thyroid (PCCL3) cells.

Results

We identified two unreported germline heterozygous variants in the *FOXE1* promoter: F1: c.-522G>C, detected in the proband and her mother; F2: c.9C>T, segregating in the proband, her sister and mother. Remaining relatives were not assessed yet. Both variants are described with very low frequency in population databases and were absent in healthy Portuguese population controls. IHC and qRT-PCR analyses of probands' tumours revealed lower FOXE1 expression levels than in normal adjacent thyroid tissues. Luciferase assays showed significantly higher gene expression of the c.-522G>C *FOXE1* variant, compared to wild-type, in SiHa ($P<0.001$) and PCCL3 ($P < 0.05$) cell models. MSO NGS analysis unveiled a likely pathogenic somatic variant in *BRAF* p.(Gly469Ala). Studies for c.9C>T are ongoing.

Conclusions

The present data suggest that germline promotor variants, particularly c.-522G>C, may account for deregulation of FOXE1 expression, influencing thyroid precursor cells migration, and initiation/progression of neoplasms; *BRAF* somatic activation may then lead to MSO development, as commonly observed in TC.

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PS3-30-09

Desiccated thyroid powder: old-new therapy of hypothyroidism and quantitative analysis of triiodothyronine and thyroxine in the pharmceutical preparation

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Personalized medicine is a crucial part of modern medicine. As a result, other therapeutic options apart from levothyroxine are considered when treating hypothyroidism. Desiccated thyroid pharmaceuticals, that in addition to thyroxine (T4), contain triiodothyronine (T3), are one of them. ETA recognized the rapid use of desiccated thyroid pharmaceuticals and described specific guidelines for its utilization. The biggest problem of their use is unresolved issues of content that differ between manufacturers, but also between individual series of the same manufacturer Nevertheless, an increasing number of patients are resorting to desiccated thyroid powder in the last two decades. Very few studies that focus on the quantification of T3 and T4 content in desiccated thyroid powder have been done so far. For therapy monitoring and stability studies of described pharmaceuticals, new methods of quantification are necessary. Correspondingly, our goal was to develop a specific, fast, and accurate method for the quantification of T3 and T4 in a desiccated thyroid powder that is applicable in most laboratories. The RP-High-Performance Liquid Chromatography with UV-Vis detection and LC/MS/MS methods were applied for the quantification of T3 and T4 in Pronase® hydrolysates of desiccated thyroid samples. Their analytical yields in samples were high, T4: 98.74% and T3:99.72%obtained by HPLC; T4:99.50 % and T3: 100% by LC/MS/MS. High concordance was shown in analytical yields for T3 and T4 obtained by the methods used. Although LC/MS/MS is a more sensitive method, the fully validated RP-HPLC has been confirmed as a suitable method for the quantitative analysis of total T3/T4 content. The developed method had been improved regarding sample pretreatment by using a commercially available mixture of proteolytic enzymes Pronase® in incubation buffer Tris(hydroxymethyl) -aminomethane and 2-mercapto-1-methylimidazole) which showed high utilization. In conclusion, the methodology used for the pre-analytical processing of thyroid powder and validated HPLC UV-Vis method shows potential for the analytical analysis of thyroxine and triiodothyronine in commercially available thyroid preparations and monitoring the stability of such preparations.

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