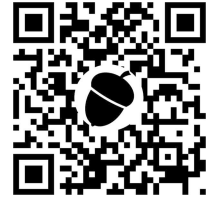


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## **Abstracts**

**American Thyroid Association Annual Meeting  
October 30–November 3, 2024  
Chicago, Illinois**



## Regular Call Oral Abstracts

### Oral 0001

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Oral*  
**Thyroid hormone promotes upper layer neuron specification in human cerebral organoids**

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Human nervous system development depends on normal thyroid hormone (TH) function. This is evident from the various neurological phenotypes in pediatric patients following TH deficiency or perturbed local TH signaling during early human brain development. However, scarcity and inaccessibility of human fetal brain tissue have been major roadblocks for experimental approaches to decipher mechanistic aspects of TH function during early stages of human brain development. In this study, we generated human cerebral organoids (hCOs) from induced pluripotent stem cell lines and assessed neuronal development in response to varying T3 media levels (0.002 – 20 nM). Immunofluorescence (IF) staining of hCOs cultured for up to 10 weeks verified successful differentiation of dorsal telencephalic tissue including a sequential appearance of deep and upper layer neurons consistent with the inside-out manner of fetal cortical layer emergence. However, quantitative image analyses of IF-stained organoid sections revealed a number of T3 concentration-dependent differences in cell type abundance including a strong stimulatory T3 effect on the abundance of SATB2+ upper layer neurons. Single cell RNA-seq of differentially treated hCOs confirmed an increased abundance of SATB2-expressing neurons in hCOs treated with increasing T3 concentrations. Notably, our single cell analyses also revealed a concurrent decrease in the abundance of TLE4-expressing deep layer neurons in hCOs treated with high T3 concentrations. We next exploited the conceptual power of single cell transcriptomics to impute T3 effects on gene-regulatory networks driving upper layer neuron generation. These analyses identified up-regulation of several key transcription factors implicated in upper layer neuron specification (*CUX2*, *POU3F2*, *POU3F3*, *ZBTB20*) already at early stages of neuronal differentiation whereas transcription factors regulating deep layer neuron programs (*FEZF2*) were down-regulated by T3. In conclusion, our organoid studies demonstrate that the molecular processes of upper layer neuron specification are very sensitive to changes in TH levels. In this respect, it is of note that the expansion of the upper layer neuron population is a key hallmark of human cortical evolution.

### Oral 0002

*Disorders of Thyroid Function, Basic, Oral*

**Hypothyroidism with Defective Thyroglobulin Co-opts the Machinery of Thyroid Hormone Synthesis to Drive Thyroid Cell Death**

Crystal Young<sup>1</sup>, Xiaohan Zhang<sup>\*1</sup>, Helmut Grasberger<sup>1</sup>, Xiao-Hui Liao<sup>2</sup>, Samuel Refetoff<sup>2</sup>, Aaron Kellogg<sup>1</sup>, Xiaofan Wang<sup>1</sup>, PETER ARVAN<sup>1</sup>, <sup>1</sup>University of Michigan, USA, <sup>2</sup>University of Chicago, USA

**Objective:** Recently it has been discovered that in the thyroid gland of patients and animal models expressing genetically-encoded misfolded mutant thyroglobulin (Tg, the secretory protein precursor for thyroid hormone synthesis), there is dramatic swelling of the thyrocyte endoplasmic reticulum (ER), with upregulation of ER stress markers, and thyrocyte cell death. This has been seen both in homozygotes (with severe hypothyroidism) and heterozygotes (with subclinical hypothyroidism). The thyrocyte death phenotype has been found to be inhibited in animals treated with exogenous thyroxine, suggesting that in the setting of hypothyroidism with defective Tg, thyroid cell death is either caused by ER stress from Tg protein misfolding, or might be influenced by one or more mechanisms independent of thyrocyte ER stress but perhaps secondary to thyrocyte stimulation by TSH.

**Methods:** Here we have engineered mice with the first reported complete thyroglobulin knockout (TgKO). TgKO animals rapidly develop severe goitrous hypothyroidism. TgKO animals can breed if supplemented with T<sub>4</sub>; maternal supplementation is continued until weaning.

**Results:** Histologically, the thyroid gland in Tg<sup>+/-</sup> heterozygotes exhibits no pathological phenotype and no thyroid cell death, but TgKO animals soon after weaning show smaller-than-normal follicles, and within a few months reveal mostly sheets of thyrocytes rather than a predominant follicular structure. In TgKO mice, TSH-driven thyrocyte proliferation is elevated at all ages tested, and the animals grow a large goiter. Essentially all indicators show that thyrocyte ER stress is not only lower in TgKO mice than in mice expressing defective Tg; it is actually lower than in the thyroid glands of wildtype mice. Nevertheless, in TgKO mice we find abundant thyroid cell death, and even in the absence of ER stress, we find elevation of the pro-apoptotic transcription factor, CHOP. Our preliminary evidence suggests that PTU treatment of TgKO mice, despite making hypothyroidism even worse, actually decreases the frequency of thyroid cell death.

**Conclusions:** These data suggest that in primary hypothyroidism with defective thyroglobulin, in addition to any effects on ER stress, the machinery of thyroid hormone synthesis itself, in conjunction with thyroid follicular cell overgrowth, contributes substantively to thyroid cell death.

### Oral 0003

*Disorders of Thyroid Function, Translational, Oral*

**Severe osteoporotic phenotype in Secisbp2 deficient mice**

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**Objective:** SECISBP2 deficient children manifest a consistent phenotype of severely delayed bone age and growth delay, and the long-term skeletal phenotype in this defect is unknown. The creER Secisbp2 inducible conditional knockout (*iCKO*) mice with Secisbp2 deficiency induced at postnatal day P35 manifest global deficiency in selenoprotein synthesis, replicate the characteristic serum thyroid

## A-2

function tests and other phenotypes reported in patients with *SECISBP2* defects. Both intracellular thyroid hormone (TH) availability and antioxidative protection are altered in *SECISBP2* deficiency. The skeleton is an exquisitely sensitive T3-target tissue, and increased levels of reactive oxygen species (ROS) in the bone are known to be deleterious to normal bone physiology.

**Methods:** Ten-weeks-old *Secisbp2* iCKO mice of both sexes and corresponding Wt littermates underwent static and dynamic histomorphometry studies of the bones.

**Results:** Body composition studies in *Secisbp2* iCKO mice reveal significant reduced bone mass, both at the femur and in the whole body. On X-ray microradiography, the femurs and vertebrae have significantly lower bone mineral content, and femurs but not vertebrae are significantly shorter in *Sbp2* iCKO mice compared to Wt littermates. Micro-CT analysis of trabecular bone shows reduced number and thickness of trabeculae with reduced trabecular volume, a more 'porous' trabecular bone overall, but normal mineral density in *Secisbp2* iCKO mice of both sexes compared to respective Wt littermates. In biomechanical testing, these findings translate as significantly reduced femur strength and stiffness for *Secisbp2* iCKO mice in the 3-point bend testing, with the cortical bone being thinner. Similarly, in vertebrae compression testing, the fewer and thinner trabeculae of *Secisbp2* iCKO mice are less able to sustain load in compression and demonstrate significantly reduced vertebral strength. Furthermore, plasma bone turnover marker PINP at 9-weeks was significantly decreased, while histomorphometry with osteoclast TRAP analysis performed at 16-weeks showed increased osteoclast number and surface in *Secisbp2* deficient mice of both sexes.

**Discussion:** *Secisbp2* deficient mice have a severe osteoporotic phenotype with evidence of decreased osteoblastic bone formation and increased osteoclastic bone resorption. These findings highlight important roles of selenoproteins in maintaining bone mass, with contributions from both the impaired TH metabolism as well as the increased ROS.

### Oral 0005

*Thyroid Cancer, Clinical, Oral*

#### ChatGPT-4's Accuracy in Estimating Thyroid Nodule Cancer Risk from Ultrasound Images

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**Objective:** Thyroid nodules (TNODs) are highly prevalent, and their detection rate has increased over the last decades. Artificial intelligence (AI) tools could improve the reliability and quality of TNODs assessment. This study aimed to assess the accuracy of ChatGPT-4 in predicting the risk of cancer from TNOD images.

**Methods:** This observational study was conducted from October 2023 to May 2024. Images of 223 TNODs were obtained from three open-access databases, 21 were excluded due to poor quality. Full images (unmodified) and their cropped version (focusing solely on the nodule) were assessed by expert radiologists and ChatGPT-4. A ground truth based on consensus was developed by two expert radiologists who independently assessed these nodules and estimated their American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) category. Subsequently, we developed a standardized prompt to generate a report from a given nodule image resembling a radiologist's assessment, including the ACR-TIRADS category. Each image and prompt were submitted to

ChatGPT-4's chat interface for evaluation. Accuracy was assessed by comparing the ground truth with the machine-generated responses for both the full and cropped images.

**Results:** Compared to gold standard, the accuracy of ChatGPT-4 when using full images was 93.4% (95% CI: 89.2-96.5) for TIRADS 1, 89.1% (95% CI: 83.9-97.0) for TIRADS 2, 76.4% (95% CI: 69.7-81.9) for TIRADS 3, 42.1% (95% CI: 35.2-49.2) for TIRADS 4, and 66.3% (95% CI: 59.4-72.8) for TIRADS 5. Similarly, when using cropped images the accuracy of ChatGPT-4 was 91.1% (95% CI: 86.3-94.96) for TIRADS 1, 90.6% (95% CI: 85.7-94.2) for TIRADS 2, 80.2% (95% CI: 74.0-85.5) for TIRADS 3, 46.0% (95% CI: 39.0-53.2) for TIRADS 4, and 62.3% (95% CI: 55.3-69.1) for TIRADS 5.

**Discussion:** ChatGPT-4 demonstrated higher accuracy in estimating cancer risk for TNODs categorized as TIRADS 1 to 3 compared to those categorized as TIRADS 4 and 5, with no major differences, regardless of the use of full or cropped images. This AI tool holds promise in facilitating cancer risk assessment of TNODs, yet further refinement and validation are needed before it can be used in clinical practice.

### Oral 0006

*Thyroid Imaging, Clinical, Oral*

#### Artificial Intelligence-Enhanced Infrared Thermography as a Diagnostic Tool for Thyroid Malignancy Detection

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**Objectives:** Thyroid nodules are common, and investigation is crucial for excluding malignancy. Increased intranodular vascularity is frequently observed in malignant tumors, which can be detected through increased skin surface temperatures using noninvasive infrared thermography. We aimed to develop a diagnostic tool for thyroid cancer using infrared thermal images combined with an artificial intelligence (AI) algorithm.

**Methods:** We conducted a prospective cross-sectional study involving participants with thyroid nodules undergoing thyroid surgery. Infrared thermal images were collected using a thermal camera on the day prior to surgery. In combination with the final thyroid pathological reports, we utilized a machine learning model based on the pre-trained ResNet50V2 model, a convolutional neural network, to evaluate diagnostic accuracy for malignancy diagnosis.

**Results:** The study included 98 participants, 58 with malignant thyroid nodules and 40 with benign thyroid nodules, as determined by pathological results. The AI-enhanced infrared thermal image analyses demonstrated good performance in distinguishing between benign and malignant thyroid nodules, achieving an accuracy of 75% and a sensitivity of 78%. Compared to the pre-surgery thyroid ultrasound findings and cytological results, the accuracy and the sensitivity of the AI-enhanced infrared thermal images were 81% and 84%, respectively.

**Conclusions:** The infrared thermal images, assisted by an artificial intelligence model, exhibit good performance in distinguishing thyroid malignancy from benign nodules. This imaging modality has great potential to be used as a noninvasive screening tool for adjunct evaluation of thyroid nodules.

### Oral 0009

*Thyroid Cancer, Clinical, Oral*

#### Efficacy, Safety, and Genomic Data in Patients With TRK Fusion Thyroid Carcinoma (TC) Treated With Larotrectinib

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Casanova<sup>8</sup>, Shivaani Kummar<sup>9</sup>, Se-Hoon Lee<sup>10</sup>, Serge Leyvraz<sup>11</sup>, Do-Youn Oh<sup>12</sup>, Lin Shen<sup>13</sup>, Natascha Neu<sup>14</sup>, Vadim Bernard-Gauthier<sup>15</sup>, Shalini Chaturvedi<sup>16</sup>, Hong Zheng<sup>15</sup>, Chiara Mussi<sup>17</sup>, David Hong<sup>1</sup>, Alexander Drilon<sup>18,19</sup>, Maria Cabanillas<sup>1</sup>,  
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**Objective:** Larotrectinib is the first-in-class, highly selective, central nervous system-active TRK inhibitor approved for tumor-agnostic use in TRK fusion cancer. We report updated efficacy, safety, and genomic data in larotrectinib-treated patients with TRK fusion TC.

**Methods:** Patients with TRK fusion TC enrolled in 3 larotrectinib trials (NCT02576431, NCT02122913, NCT02637687) were included. Responses were independent review committee (IRC)-assessed (RECIST v1.1).

**Results:** As of July 2023, 31 patients were included and eligible for IRC efficacy assessment. Overall response rate (ORR) was 65% (95% CI 45-81): 3 (10%) complete response, 17 (55%) partial response, 5 (16%) stable disease (4 [13%] for >30 months), 4 (13%) progressive disease, and 2 (6%) not evaluable. For patients with differentiated TC (DTC; n=24), ORR was 79% (95% CI 58-93). For patients with anaplastic TC (ATC; n=7), ORR was 14% (95% CI 0-58). Median duration of response, progression-free survival, and overall survival (OS) were 41 months (95% CI 19-not estimable [NE]), 44 months (95% CI 17-NE), and not reached at median follow-ups of 40, 39, and 58 months, respectively. The 6-year OS rate was 62% (95% CI 42-81). Treatment duration ranged from 1 to 76+ months. At data cutoff, 11 patients had progressed; 7 continued treatment post-progression for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 3 (10%) patients. No patients discontinued treatment due to TRAEs.

Baseline genomic data derived from circulating tumor DNA (ctDNA; n=17) and/or tissue DNA (n=23) were available for 27 patients. Baseline ctDNA analysis detected *NTRK* gene fusions in 5 patients. Additional baseline known/likely oncogenic variants were identified in 8 tumors (5 ATC). Six tumors had acquired potential larotrectinib-resistance mutations: 4 off-target and 2 with both on- and off-target pathogenic variants.

**Discussion/Conclusion:** In this updated dataset, larotrectinib continues to demonstrate rapid and durable responses, extended survival, and a favorable safety profile in patients with TRK fusion DTC, with limited activity in ATC. These results support the use of next-generation sequencing to detect *NTRK* gene fusions in patients with TC to identify those who may benefit from targeted treatment.

## Oral 0010

*Thyroid Cancer, Clinical, Oral*

### GLP-1RA Use and Thyroid Cancer Risk: Retrospective Emulation of a Target Trial

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**Objective:** With the increasing use of glucagon-like peptide 1 receptor agonists (GLP-1RA) in type 2 diabetes and obesity, and in the prevention of cardiovascular and kidney disease, a better estimate of their association with thyroid cancer is needed. This study aimed to estimate the risk of thyroid cancer in adults with type 2 diabetes starting treatment with GLP-1RA vs. other common glucose-lowering medications.

**Methods:** This was a secondary analysis of retrospective data, emulating an idealized comparative effectiveness target trial. It utilized claims data from commercial, Medicare Advantage, and Medicare fee-for-service plans across the U.S. Participants were adults with type 2 diabetes at moderate risk for cardiovascular disease and no prior history of thyroid cancer who had started prescriptions for GLP-1RA, sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i), or sulfonylurea between January 2014 and December 2021. Hazard ratios (HR) for thyroid cancer for GLP-1RA vs. the other three drug classes were estimated using inverse propensity-score weighted Cox proportional hazard models, both overall and within different times frames post-treatment initiation (Within one year, one to two years, and two or more years). Intention-to-treat (primary) and as-treated (secondary) analyses were performed.

**Results:** Of 351,913 included patients, 41,112 received a prescription for GLP-1RA, 76,093 for DPP-4i, 43,499 for SGLT2i, and 191,209 for sulfonylurea. Thyroid cancer incidence rates were 69 (0.17%) for GLP-1RA, 172 (0.23%) for DPP-4i, 72 (0.17%) for SGLT2i, and 381 (0.20%) for sulfonylurea users through the study period. In the intention-to-treat analysis, GLP-1RA initiation did not significantly increase the overall risk for thyroid cancer compared to other diabetes drugs (HR 1.24, 95% CI: 0.88, 1.76). However, the risk for thyroid cancer was significantly higher within the first year after GLP-1RA initiation (HR 1.85, 95% CI: 1.11, 3.08) and was amplified in the as-treated analysis that censored patients upon discontinuation of therapy or addition of another medication (HR 2.07, 95% CI: 1.10, 3.95) in the overall study period.

**Conclusion:** Although the absolute risk of thyroid cancer is low among patients starting GLP-1RA therapy, there is increased risk of new thyroid cancer diagnoses within the first of GLP-1RA initiation compared to other diabetes drugs, which may be due to enhanced early detection. Further research is necessary to understand the underlying causes of this association.

## Oral 0011

*Thyroid Cancer, Clinical, Oral*

### Efficacy of Selpercatinib by RET mutation in RET-mutant Medullary Thyroid Cancer: A combined analysis of LIBRETTO-001 and LIBRETTO-531 trials

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**Objective:** Selpercatinib is a highly selective and potent RET inhibitor approved for the treatment of advanced *RET*-mutant medullary thyroid cancer (MTC). Here, we report the results of an exploratory analysis to investigate the efficacy of selpercatinib by *RET* mutation in a combined cohort of patients with *RET*-mutant MTC from the phase I/II (LIBRETTO-001 [NCT03157128]) and phase III (LIBRETTO-531 [NCT04211337]) studies.

**Methods:** This pooled post-hoc analysis included 509 patients with *RET*-mutant MTC who received selpercatinib in the two LIBRETTO trials. The objectives were to evaluate response rate, duration of response and median progression-free survival according to the *RET* mutation group. A sub-analysis of patients from LIBRETTO-531 treated with selpercatinib (n=193) versus cabozantinib/vandetanib (control, n=98) was done. ORR and median PFS were assessed using RECIST 1.1 by an independent review committee.

**Results:** Of the 509 patients who received selpercatinib, 320 (62.9%) were treatment-naïve and 189 (37.1%) were previously treated for advanced disease. *RET* mutations were primarily identified by NGS (83.9%), in tissue (82.7%) and blood (9.4%). In total, 321 patients' cancers (63.1%) had the M918T mutation, 100 (19.6%) had Extracellular Cysteine mutation (EC) (mostly C634G/R/SW/Y [61/100]) and 88 (17.3%) had other mutations (most frequent being V804M/L [16/88]; A883F/S/Y [14/88]; D631\_L633delinsE [12/88]; E632\_L633del [12/88]). The ORR was 75.4% (95%CI, 70.3-80.0) for the M918T group, 67.0% (95%CI, 56.9-76.1) for EC, and 78.4% (95% CI, 68.4-86.5) for Other. In the M918T or EC groups, medians for PFS were not reached and could not be estimated (NE). For Others, median PFS was 51.4 months (95%CI, 41.3-NE). The median DoR was not reached for any *RET* mutation group.

Among LIBRETTO-531 patients, ORR was 71.9% (95%CI, 63.0-79.7) with selpercatinib versus 45.9% (95%CI, 33.1-59.2) with control for M918T; 62.5% (95%CI, 45.8-77.3) versus 30.0% (95%CI, 11.9-54.3) for EC; and 68.8% (95%CI, 50.0-83.9) versus 23.5% (95%CI, 6.8-49.9) for Other.

**Discussion/Conclusion:** This analysis constitutes the largest catalogue of *RET* mutations in MTC. Across mutation groups, selpercatinib demonstrated similar robust and durable responses, consistent with previously reported efficacy of selpercatinib for patients with *RET*-mutant MTC. In the LIBRETTO-531 analysis, the efficacy of selpercatinib was consistently better over control regardless of *RET* mutation.

#### Oral 0012

*Thyroid Nodules and Goiter, Clinical, Oral*

##### **Thyroid Nodules with Indeterminate Cytology and Negative Molecular Testing: Prevalence of Malignancy and Practice Paradigms for Surveillance**

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**Objective:** Management of molecular benign nodules is not currently defined. This institutional study evaluates the prevalence of malignancy (PoM) and practice paradigms for surveillance of cytologically indeterminate thyroid nodules that are classified as negative by ThyroSeq v3 (TSv3) molecular assay.

**Methods:** Thyroid nodules with indeterminate cytology (Bethesda categories III and IV) and negative (TSN), currently negative (TSCN), or negative but limited (TSNBL) TSv3 result from November 2017 to March 2022 were identified. PoM was calculated for all nodules (n=556, lowest estimate) and for surgically resected nodules (n=75, highest estimate). We also assessed follow-up practice patterns.

**Results:** Of 556 nodules in the study, TSv3 results were 443 TSN, 85 TSCN, and 28 TSNBL; 75 nodules underwent resection, where 15 were malignant (ATA risk of recurrence—Low 13, Intermediate 1, and 1 could not be categorized due to indeterminate angioinvasion) and 2 were NIFTP. The lowest estimated PoM was 3% (2%, 7%, 7% in TSN, TSCN, and TSNBL, respectively, p 0.02). The highest estimated PoM was 23% (18%, 30%, 33% in TSN, TSCN, and TSNBL, respectively, p 0.46).

Clinical management varied based on TSv3 negative subtype, with more nodules with TSCN (20%) and TSNBL (18%) undergoing immediate surgical resection as compared to TSN (7%) (p<0.001). Surveillance ultrasound was done for 319 (64%) nodules, of which 76 (24%) grew. Rates of subsequent surgical resection performed after ultrasound surveillance did not differ based on TSv3 results (p 0.65) or nodule growth (p 0.11). FNA was repeated for 23 nodules (16% of growing and 4.5% of stable nodules, p<0.01), with benign cytology in 6. Repeat TSv3 results remained a negative subtype in 15 nodules but became positive in 2 nodules (1 adenoma, 1 ATA low risk cancer).

**Discussion/Conclusion:** The true PoM in TSv3 negative subtype nodules is between 3-23%. The apparent higher PoM in TSCN and TSNBL nodules is likely due to higher rates of surgical resection. The variation in observed practice patterns precludes conclusions about optimal surveillance strategy for molecular benign nodules.

#### Oral 0013

*Health Disparities/Health Equity, Clinical, Oral*

##### **The Influence of Safety-Net Burden on Outcomes for High-Volume Thyroid Cancer Surgeons**

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**Objective:** Higher center and surgeon volume correspond with better outcomes for thyroid cancer patients. This study aims to investigate how a hospital's safety net burden (SNB) influences the outcomes of high-volume surgeons.

**Methods:** We performed a retrospective cohort study of all patients who underwent surgery for thyroid cancer in California from 1999 to 2017. We stratified treating facilities by the proportion of Medicaid-type and indigent payors into safety-net burden quartiles. We compared the perioperative and oncologic outcomes of high-volume (HV) surgeons (annual case volume ≥10) for patients undergoing total thyroidectomy across safety-net burden quartiles. A

multivariable regression model controlled for patient and tumor characteristics.

**Results:** Our sample comprised 42,347 patients (78% female, median age 50), of whom 13,848 (32%) were treated by HV surgeons (n=276). Compared to patients of lower-volume surgeons, patients of HV surgeons were more likely to be White, from the upper quartiles of socioeconomic status, and well-insured (all  $p < 0.001$ ). HV surgeons in each SNB quartile displayed similar case number distributions. Compared to patients treated by HV surgeons at first quartile (highest resourced) hospitals, those treated by HV surgeons at fourth quartile (lowest resourced) hospitals had higher absolute risks of endocrine complications (+7%,  $p = 0.007$ ), need for tracheostomy (+6%,  $p = 0.004$ ), disease-specific mortality (+1.3%,  $p = 0.046$ ) and all-cause mortality during the study period (+3%,  $p = 0.046$ ) in multivariable analysis.

#### Conclusion

The performance of high-volume thyroid cancer surgeons differs by a hospital's safety net burden, with patients treated at high SNB hospitals experiencing higher rates of operative complications, disease-specific mortality, and all-cause mortality. Having a HV surgeon alone may be insufficient to provide optimal short- and long-term outcomes for thyroid cancer patients.

#### Oral 0014

*Health Disparities/Health Equity, Clinical, Oral*

##### Multilevel Associations of Food Environment and Papillary Thyroid Cancer Outcomes in the United States

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**Background:** Papillary Thyroid Cancer (PTC) has massively increased in incidence over the past several decades, accompanied by increases in mortality and advanced staging. PTC has been previously associated with varying nutritional factors and traditional social determinants of health.

**Objective:** To examine associations between food environment, a CDC-derived measure combining food access and dietary health, and PTC outcomes in the United States.

**Methods:** Patients diagnosed with PTC between 2000 and 2017 were identified using the SEER database. Food Environment Atlas-vulnerability scores (FEA) were based on 282 county-level variables of food security, store-restaurant availability, SNAP/WIC enrollment, pricing, taxes, and producer vicinity while adjusting for traditional social determinant factors of socioeconomic status, race-ethnicity, transportation access, and comorbidities. Relative FEA rankings across US counties were averaged into a composite score and assigned to patients by county-of-residence. Associations of FEA with overall mortality, early mortality (3-years), and number of primary tumors on preliminary diagnosis were analyzed by multivariate cox-proportional hazards and logistic regression models. Stratified analyses were also performed based on race/ethnicity (non-Hispanic White vs. non-White) and age (younger/<45yrs, older/45+yrs).

**Results:** Among 148,296 patients (77% white, 38% <45yrs), increased FEA-vulnerability was associated with decreased overall survival (HR 1.06, 95% CI 1.04-1.07). These FEA effects were exacerbated among non-White patients (1.08, 1.05-1.11) compared to White patients (1.05, 1.04-1.07). Increased FEA-vulnerability was also associated with increased 3-year mortality (OR 1.05, 95% CI 1.03-1.07). These effects were exacerbated among non-White (1.06, 1.02-1.10) and older patients (1.05, 1.02-1.07). Increased FEA-

vulnerability was additionally associated with increased odds of having more than one primary tumor (OR 1.02, 95% CI 1.01-1.03,  $p < 0.001$ ). When stratified separately for race and for age, worse food environment was associated with non-White patients (OR 1.03, 95% CI 1.01-1.06,  $p < 0.01$ ) and patients aged 45 years and older (OR 1.02, 95% CI 1.01-1.03,  $p < 0.01$ ).

**Discussion/Conclusion:** Food environment vulnerability was associated with poorer prognosis after adjusting for traditional social determinant vulnerabilities, with worsened effects experienced by those who are older and of non-White race/ethnicity. Given PTC's massive rise in incidence and severity, the impact of food environment should be considered when informing future investigation and policy.

#### Oral 0015

*Health Disparities/Health Equity, Clinical, Oral*

##### Factors Influencing the Time Interval to Thyroid Biopsy and Cancer Diagnosis Post-Thyroid Ultrasound

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**Objective:** delays in diagnosis and procedures impact patient outcomes and exacerbate disparities. We aim to study the timeline from ultrasound-identified nodules to biopsy and to subsequent thyroid cancer diagnosis, and to identify patient and healthcare system level predictors affecting these intervals.

**Methods:** we conducted a retrospective cohort study of adult patients in the OneFlorida+ Data Trust (2015–2021) who underwent their thyroid ultrasound and found with nodules. We excluded patients with prior thyroid nodules or thyroid cancer. We used separate general linear models to identify factors associated with time intervals 1) between ultrasound and biopsy, and 2) between biopsy and cancer diagnosis.

**Results:** we identified 67,238 patients with thyroid nodules on ultrasound. At 18-month follow up, 12,582 (18%) underwent biopsy and 1,275 (10%) had a thyroid cancer diagnosis post-biopsy. The median (interquartile range) to undergo biopsy post-ultrasound was 50.0 days (21.0-126), and 30.0 days (6.00-78.3) to cancer diagnosis post-biopsy. There was an average delay in thyroid biopsy of 26 days [mean(CI): 26.2 (7.73-44.7)] and 23 days [mean(CI) 23.6 (3.37-43.8)] among patients and clinics with higher social vulnerability indices, respectively (SVI; higher levels indicate more vulnerability). An average delay of 16 days between ultrasound and biopsy [mean(CI): 16.4 (10.8-22.1)] was observed in those who identified as Black (versus White) and of 11 days [mean (CI): 11.4 (5.41-17.5)] in those who identified as Hispanic (versus Non-Hispanic). Charlson Comorbidity Index (CCI) scores were associated with delays of 6, 15, and 18 days among patients with mild, moderate, or severe CCI, respectively. Compared to patients with Medicaid, those with Medicare and private insurance underwent biopsies on average 25 and 29 days sooner, respectively. Regarding cancer diagnosis, none of the predictors appeared to exert significant influence on the time between biopsy and cancer diagnosis. However, lower SVI scores at the facility level were associated with a 60-day earlier detection of cancer [(mean(CI): 60.1 (-113,-7.07)].

**Discussion/Conclusion:** Social vulnerability indices, race, ethnicity, Charlson Comorbidity Index and insurance coverage significantly impacted the timeline between ultrasound and subsequent biopsy. These findings suggest disparities in the care of patients with thyroid nodules.

## Oral 0017

Autoimmunity, Clinical, Oral

**Reduced Proptosis and Muscle/Fat Volume by MRI/CT in a Proof-of-Concept Study in TED Shows Potential for Disease-Modifying Effects of VRDN-001, a Targeted TED Therapy**

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**Objective:** VRDN-001 is full antagonist monoclonal antibody targeting the IGF-1 receptor in development for thyroid eye disease (TED). Clinical outcomes from a small phase 2 proof-of-concept study of VRDN-001 in active TED have been previously presented. This MRI/CT analysis explores the potential disease-modifying effects on key components of TED pathophysiology (enlarged orbital muscle and fat) in patients from the phase 2 study.

**Methods:** Patients with active TED treated with 2 IV infusions of 10 mg/kg VRDN-001 or placebo at Weeks 0 and 3 in a phase 2 proof-of-concept study were included. Preliminary MRI/CT mean changes from baseline in proptosis, extraocular muscle volume (EOM), and orbital fat volume (OF) were assessed at Weeks 6 and 12 for all eyes.

**Results:** VRDN-001 was generally well tolerated with no severe or serious adverse events. A total of 4/6 VRDN-001-treated patients (8 eyes) and 5/5 placebo patients (10 eyes at Week 6, 8 eyes at Week 12) had evaluable MRI/CT scans; the 2 unevaluable scans had poor image quality. Mean changes from baseline at 6 weeks for VRDN-001 vs placebo were -4.6 mm vs -0.2 mm (proptosis), -31% vs -10% (EOM), and -19% vs -2% (OF); changes at 12 weeks were -5.9 mm vs -0.1 mm (proptosis), -37% vs -17% (EOM), and -37% vs 0% (OF).

**Discussion/Conclusion:** In this small number of patients with active TED, MRI/CT analysis shows potential for a disease-modifying effect of VRDN-001, with reductions of EOM and OF associated with improvements in proptosis at 6 weeks that continued through 12 weeks (9 weeks beyond last treatment).

## Oral 0018

Disorders of Thyroid Function, Translational, Oral

**Severe Neurodevelopmental Phenotype, Diagnostic and Treatment Challenges in Patients with SECISBP2 (SBP2) Deficiency**

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**Objective:** Defects in the gene encoding selenocysteine insertion sequence binding protein 2, *SECISBP2*, produce global but variable deficiency in selenoproteins, with multisystem manifestations and characteristic serum thyroid function with impaired thyroid hormone (TH) metabolism. Its identification brought into focus the roles of selenoproteins in humans through the observed consequences of their deficiency. Being a rare and often missed condition, only twelve families have been reported so far and knowledge about this condition remains limited. With the participation of several medical centers, we investigated six new families with *SECISBP2* deficiency representing one third of the families known worldwide.

**Methods:** Genetical, clinical and biochemical evaluations of families with inherited TH metabolism defect.

**Results:** A complex neurodevelopmental phenotype emerges as a prominent feature in four of the six families, with impaired communication, absent speech, autistic features, fine and gross motor developmental delay, and seizures. Serum TT3/TT4 ratio proves to be more informative than serum glutathione-peroxidase activity to distinguish biallelic affected from *SECISBP2* heterozygous and unaffected individuals. Thyroid hormone treatment improved motor development, while speech and intellectual impairments persisted. Pediatric neurological evaluation in two cases prompted genetic investigations leading to the identification of *SECISBP2* variants before diagnosing their characteristic thyroid tests. This defect poses great diagnostic and treatment challenges for clinicians, as illustrated by a case that escaped detection for twenty years, as *SECISBP2* was not included in the neurodevelopmental genetic panel and his complex thyroid status prompted anti-thyroid treatment instead.

**Discussion:** This syndrome uncovers the role of selenoproteins in humans. The severe neurodevelopmental disabilities manifested in several patients with *SECISBP2* deficiency highlight an additional phenotype in this multisystem disorder. In severe cases early diagnosis is needed to prevent mismanagement, and initiation of treatment is necessary to rescue some of the consequences of *SECISBP2* deficiency. Long-term evaluation will determine the full spectrum of manifestations and the impact of therapy. We highlight the requirement of a more comprehensive thyroid testing in neonatal screening and the need to include the *SECISBP2* gene in neurodevelopmental new generation sequencing panels. The identification and characterization of these patients will help uncover the natural history of this syndrome as well as the roles and relevance of selenoprotein biology for human health and disease.

## Oral 0021

Autoimmunity, Clinical, Oral

**Glandly EXO: A Deep Learning Approach for Proptosis Measurement in Thyroid Eye Disease**

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**Objective:** Thyroid eye disease (TED) can cause proptosis which can significantly impair the quality of life of patients. The Hertel

exophthalmometer, a longstanding clinical standard for assessing proptosis, is prone to errors and requires a skilled examiner for accurate measurements. We developed and validated Glandy EXO which is a deep learning-based proptosis measurement system using high-resolution photography and depth map technology.

**Methods:** A total of 839 patients aged 20 or older, receiving treatment for thyroid eye disease, were enrolled in the study. Each patient underwent proptosis measurement using the standard Hertel exophthalmometer during their medical visits. Additionally, high-resolution digital cameras were utilized to capture facial images, resulting in a total of 1,136 images across an average of 1.35 hospital visits per patient. To predict the degree of exophthalmos, we developed a dual-stream neural network-based deep learning model that integrates captured images and depth maps.

**Results:** The deep learning model exhibited a mean absolute error in proptosis measurement of 1.34mm (95% CI, 1.28-1.41) for the left eye and 1.31mm (95% CI, 1.25-1.38) for the right eye. A strong correlation was observed between the model's predictions and the actual proptosis measurements (Pearson rho=0.8, P<0.001).

**Conclusion:** The Glandy EXO system employs advanced deep learning techniques alongside high-resolution facial photography and depth mapping technology to accurately measure proptosis. This system is expected to overcome the limitations of traditional methods for measuring proptosis, aiding in the precise monitoring of ocular changes during the diagnosis and treatment of thyroid eye disease. Additionally, it demonstrates the potential for self-monitoring of proptosis through smart devices.

## Oral 0022

*Thyroid Nodules and Goiter, Clinical, Oral*

### Enhanced performance of the new optimized version (v2) of the microRNA and DNA-based molecular classifier test: Insights from a Latin American Multicenter Study

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**Objective:** The aim of this study was to assess the diagnostic performance of the new v2 algorithm of mir-THYpe full molecular classifier test for preoperative diagnosis of cytologically indeterminate thyroid nodules, optimized by employing novel machine learning techniques, a larger sample cohort, multicentricity, and incorporation of DNA mutation analysis.

**Methods:** A multicenter validation study was conducted on a cohort of 2,372 thyroid nodules with Bethesda 3 and 4 cytology from 15 academic, community, and private centers in Brazil, Argentina, and Peru. Eligibility criteria were met in 510 nodules. FNA smear slides were used to acquire and analyze microRNA expression and DNA mutations (BRAF V600E and pTERT C228/250T) by qPCR. Molecular data from 306 nodules (150 benign/156 cancer+NIFTP) were utilized to retrain and optimize the mir-THYpe v2 algorithm, employing random forest, SVM, and neural networks machine learning techniques. For final validation, molecular data from 204 nodules (151 benign/53 cancer+NIFTP) were used to measure diagnostic performance, with anatomopathological data serving as the gold standard for blinded comparison.

**Results:** In the validation set, 61.8% of the samples were categorized as Bethesda 3 (126), while 38.2% were Bethesda 4 (78). The v2 algorithm had a specificity of 94%, a sensitivity of 89%, and an accuracy of 91%. With a cancer prevalence of 26%, the negative predictive value was 98%, and the positive predictive value was 76%, with a benign call rate of 68%. The v2 algorithm was able not only to classify, but also to identify medullary thyroid carcinoma (MTC) in all the positive MTC samples.

**Discussion/Conclusion:** The optimized classifier demonstrated robust diagnostic performance in identifying benign nodules, potentially avoiding diagnostic surgeries in 68% of patients with indeterminate nodules, and up to 89% of all benign nodules. Integration of BRAF and pTERT status analysis, along with the capability to confirm cancerous samples, help guide prognostic decisions, including the extension of surgical procedures and personalized treatment approaches.

## Oral 0023

*Autoimmunity, Clinical, Oral*

### Validation of Glandy CAS™ Software as Medical Device for Thyroid Eye Disease Activity Assessment: A Confirmatory Clinical Trial for Ministry of Food and Drug Safety Approval

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**Objective:** We previously developed a machine learning (ML)-assisted system, Glandy CAS, to assess the clinical activity score (CAS) in thyroid eye disease (TED) using digital facial images. In this study, we externally validated the performance of Glandy CAS for detecting active TED (CAS ≥ 3) using digital facial images. This study was designed as a confirmatory clinical trial to obtain approval from Korea Ministry of Food and Drug Safety for a software as medical device.

**Methods:** In this retrospective study, we utilized Glandy CAS to classify 756 photos of TED patients exhibiting various levels of inflammatory activity into active or inactive TED. The diagnostic performance of Glandy CAS for active TED was compared with the accuracy of three general ophthalmologists with less than 5 years of clinical experience in diagnosing active TED using facial

photographs, with diagnostic accuracy expressed as the F1 score. The reference CAS was based on the CAS recorded in medical records, evaluated by an oculoplastic specialist through assessing actual patients at the time of capturing facial photographs.

**Results:** Active TAO (CAS  $\geq 3$ ) was identified in 207 out of 756 patients. Glandly CAS demonstrated a sensitivity of 87.9% (95% CI, 82.7–92.0), specificity of 95.8% (95% CI, 92.9–96.7), and an F1 score of 0.88 (95% CI, 0.84–0.90). For general ophthalmologists, these values were 60.4% (95% CI, 56.5–64.3), 83.0% (95% CI, 81.3–84.8), and 0.57 (95% CI, 0.53–0.61) respectively. Glandly CAS predicted CAS within 1 point of the reference CAS in 82.3% of cases using facial images, with a mean absolute error between predicted and reference CAS of 0.83.

**Conclusions:** Glandly CAS, a ML-assisted system to detect active TED using facial images showed reasonable accuracy and outperformed compared with general ophthalmologists. This system can consistently and accurately assess disease activity, facilitating early detection and timely treatment of active TED. Based on the results of this clinical trial, this software as a medical device has obtained approval from Korea Ministry of Food and Drug Safety (Product License No. 24-93).

## Oral 0024

*Surgery, Clinical, Oral*

### Factors Increasing the Likelihood of Postoperative Hematomas Following Thyroid Surgery

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**Objective:** Neck hematoma, following thyroid surgery, is a life-threatening complication. In the context of resource constraints of public healthcare systems, investigating the viability of outpatient surgery as a measure to improve patient care and comfort in the postoperative setting while helping to alleviate hospital resource burden is a sensible goal. As a result, identifying patients at higher risk of hematoma following thyroid surgery is of paramount importance when determining which patients require overnight hospital admission. This study aims to discern patient and surgical characteristics of post-thyroidectomy hematomas while investigating contextual features, such as the timing of hematoma development and the extent of surgery.

**Methods:** A single-institution retrospective study reviewed cases of neck hematomas requiring surgical intervention following thyroid surgery from 2009 to 2024 using surgeon databases, operating room archives and the National Surgical Quality Improvement Program (NSQIP) database. Patient demographics, surgical indication, thyroid pathology and peri-operative hemodynamics were analyzed using descriptive statistics, one-way ANOVA and chi-squared test.

**Results:** Over the 15 years, among 5502 thyroid surgeries performed, the incidence of hematomas requiring a return to the operating room was 0.55% (n = 30). The mean time of onset was 2.8 hours postoperatively, with 60% (18/30) in the post-anesthesia care unit.

The mean age of patients was 53.6 years old, 70% (21/30) were women, average body mass index was 26.86, 16.7% (5/30) were smokers, 43.3% (13/30) had hypertension and 13.3% (4/30) had type II diabetes mellitus. All patients with type II diabetes mellitus had comorbid hypertension. Four patients (13.3%) had Graves' disease, 53.3% (16/30) had a central neck dissection and 40% (12/30) had a total thyroidectomy. Systolic blood pressure measurements exceeded 160 mm Hg in 44.8% (13/29), 31% (9/29), and 34.5% (10/29) of patients in the preoperative, intraoperative and postoperative periods, respectively. Late hematomas (6 hours or more) were associated with a prolonged hospitalization (p=0.024). Total thyroidectomies complicated by hematomas were associated with longer surgical time (p=0.029), unintended parathyroidectomy (p=0.001) and thyroid hyperplasia on final pathology (p=0.046).

**Conclusion:** Patients with comorbid hypertension, diabetes, Graves', uncontrolled perioperative blood pressure, or those requiring total thyroidectomy or neck dissection may not be appropriate candidates for outpatient thyroid surgery.

## Oral 0025

*Surgery, Clinical, Oral*

### Prospective Implementation of Thyroid Lobectomy Guidelines and Preoperative ThyroSPEC Molecular Testing: Impact on Rates of Lobectomy and Completion Thyroidectomy

Caitlin Yeo<sup>\*</sup>, Jiahui Wu, Paul Stewardson, Markus Eszlinger, Sana Ghaznavi, Ralf Paschke, University of Calgary, Canada

**Objective:** Guideline and evidence-based criteria for appropriate patient selection for lobectomy and completion thyroidectomy were implemented at our institution in July 2017. Reflexive ThyroSPEC molecular testing was introduced in August 2020 for Bethesda III and IV indeterminate thyroid nodule cytology. The study objective was to evaluate the real-world impact of implementation of lobectomy criteria and ThyroSPEC molecular testing on lobectomy and completion thyroidectomy rates in a tertiary referral setting.

**Methods:** The study population included adult well-differentiated thyroid cancer patients that underwent surgery at our institution between July 2017 to October 2023. Patients were categorized into the following groups: total thyroidectomy (TTx), diagnostic lobectomy (DxL), therapeutic lobectomy (TxL), and completion thyroidectomy (CTx). Patients were reviewed to assess adherence to institutional lobectomy criteria and the impact of ThyroSPEC molecular testing on CTx rates. Post-operative surgical complications and need for thyroid hormone replacement (THR) were also examined.

**Results:** Of 799 well-differentiated thyroid cancer patients, 231 (29%) underwent lobectomy as initial surgery (TxL n=99, DxL n=131). The CTx rate was 26% among TxL patients and 44% among DxL patients. The CTx rate remained stable in the TxL group pre- and post-implementation of ThyroSPEC. The CTx rate for DxL patients decreased significantly from 57% to 38% post-implementation of ThyroSPEC (p=0.027), accompanied by a significant increase in upfront TTx from 33% to 46% (p=0.015). Approximately one-third of indeterminate nodules underwent upfront TTx due to malignant molecular markers or high-risk mutations. Surgical complications were less frequent with lobectomy (6%) compared to CTx (12%). Additionally, 44% of lobectomy patients required THR, with 77% requiring THR if preoperative TSH exceeded 2mIU/L.

**Conclusions:** Our findings demonstrate a direct benefit of molecular testing in guiding appropriate surgical selection. Implementation of institutional criteria for appropriate patient selection for lobectomy and addition of ThyroSPEC testing resulted in an increase in upfront TTx rates and a decrease in the need for CTx after initial

lobectomy. The net result was a greater proportion of patients receiving appropriate upfront diagnostic or therapeutic surgeries, minimizing the need for subsequent operations, and thereby reducing patient anxiety, time off work, and healthcare system costs.

### Oral 0026

*Surgery, Clinical, Oral*

#### **Patient-Reported Outcomes after Thyroid Surgery for Differentiated Thyroid Cancer: A Crucial Consideration for Personalized Treatment Decisions**

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**Objective:** Surgical treatment for differentiated thyroid cancer (DTC) includes thyroid lobectomy (TL) or total thyroidectomy (TT). While numerous studies suggest that both options offer comparable survival, there is a scarcity of data on how quality of life and patient-reported outcomes (PROs) are impacted by the extent of thyroid surgery, particularly in North American populations. The purpose of this study was to determine changes in PROs by extent of thyroid surgery.

**Methods:** This single institution prospective cohort study included adults undergoing thyroidectomy for DTC from 2015-23. PROs for 25 items related to quality of life, thyroid-specific symptoms, and core cancer-related symptoms were obtained using the M.D. Anderson Symptom Inventory for Thyroid cancer (MDASI-Thy) preoperatively and postoperatively in the short-term (<30 days) and long-term (<sup>3</sup>30 days). Higher numbers indicate worse symptom severity or interference in daily life. Data were analyzed to compare differences in PROs for TL versus TT before and after surgery.

**Results:** Of the 623 eligible patients, 148 (24%) underwent TL and 475 (76%) TT. There were no differences in overall or subset MDASI-Thy scores comparing TL to TT. For individual thyroid-specific symptoms, hoarseness was not statistically different between TT and TL preoperatively (1.43 vs 0.65;  $p=0.12$ ), or short-term post-surgery (1.71 vs 1.50;  $p=0.44$ ), but was worse for TT versus TL long-term (1.19 vs 0.58;  $p=0.04$ ). However, for both TL and TT, hoarseness was improved long-term after surgery as compared to before surgery (both  $p<0.05$ ).

Among core symptoms, distress and sadness were similar for the TL and TT cohorts at all time points. However, both distress and sadness were improved after surgery in the short-term and long-term after TT (both  $p<0.01$ ). No differences in distress or sadness were observed following TL ( $p=0.74$  &  $0.96$ , respectively).

**Discussion/Conclusion:** Overall PROs were not significantly different for DTC patients treated with TL as compared to TT. Although hoarseness was worse long-term for TT versus TL patients, both groups reported improvement after surgery. Improvements to distress and sadness were only observed following TT. These findings are useful to guide personalized treatment decisions for low-risk DTC, particularly for patients experiencing a high level of distress regarding their disease.

### Oral 0028

*Thyroid Cancer, Basic, Oral*

#### **Characterization and targeting of synthetic lethal vulnerabilities uncovered by inhibition of one carbon metabolism in anaplastic thyroid cancer**

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Anaplastic thyroid cancer (ATC) has a median survival of less than 9 months when patients are treated with multimodal therapy. Cytotoxic

chemotherapy and external beam radiation are ineffective in prolonging survival of ATC patients. The recent approval of a BRAF/MEK inhibitors combination for BRAF<sup>V600E</sup>-positive ATC has improved the progression-free survival of eligible patients. However, this therapy only benefits a subset of patients, and only for a short period of time. Thus, ATC remains a paradigmatic model for those aggressive tumors that need novel, rationally designed therapeutic approaches that overcome or bypass critical roadblocks to cell death and effectively induce rapid demise of tumor cells.

We have found that ATCs display a significant upregulation of genes involved in the one-carbon metabolic pathway (1CM), and have shown that inhibition of *SHMT2*, a key enzyme of the mitochondrial arm of the 1CM, leads to significant reduction of ATC cell proliferation in the short term, and a dramatic impairment of colony forming ability, both primarily caused by depletion of the purine pool and cell cycle arrest.

The nucleotide shortage induced by inhibition of 1CM is predicted to induce replicative stress and activation of the ATM/Chk2/TP53 (G1/S phase) and ATR/Chk1 (S-phase) checkpoints. Due to the very frequent loss or mutation of *TP53*, we posited that ATC cells are primarily dependent on the ATR/Chk1 S-phase checkpoint to cope with replication stress, and that inhibition of this checkpoint in G1/S checkpoint-deficient ATC cells would result in improper progression of 1CM-impaired ATC cells through the cell cycle, with mitotic catastrophe and cell death as the endpoint.

We show that non-cytotoxic concentrations of ATR and Chk1 inhibitors, combined with either tool compounds or clinic-ready inhibitors of 1CM, induce massive death of *TP53* mutant ATC cells, but have no combinatorial effect in *TP53* wt cells. Exogenous hypoxanthine rescues the lethal effect of these combinations, supporting the critical role of purine depletion in this synthetic lethal relationship.

Thus, inhibition of one-carbon metabolism generates metabolic and functional vulnerabilities that can be harnessed in synthetic lethal strategies that represent a compelling foundation for the clinical development of novel, rationally designed therapeutic approaches.

### Oral 0029

*Thyroid Cancer, Translational, Oral*

#### **Integrated Genomic Analysis Identifies Tumor Differentiation Status as a Crucial Determinant of Immune Infiltration and Potential Combinatorial Therapeutic Targets with Immunotherapy in Papillary Thyroid Carcinoma Patients**

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**Objective:** The thyroid differentiation score (TDS) has been identified as associated with reduced tumor differentiation, decreased likelihood of RAI sensitivity, and a more aggressive disease course for Papillary thyroid cancers (PTCs). Recent studies have also highlighted that less differentiated PTCs in cases with lower TDS are associated with increased enrichment of immune cells and immunosuppressive markers. However, investigations into potential combinatorial therapeutic targets with immune checkpoint inhibitors (ICIs) in PTCs are lacking.

**Methods:** We conducted comprehensive genomic and transcriptomic analyses of two independent cohorts: 111 patient specimens from MD Anderson (MDA) and 409 samples from TCGA to explore potential targets.

**Results:** We first utilized a rank-based approach to mitigate batch effects and calculate single sample TDS (ssTDS) score across our

## A-10

MDA and TCGA PTC cohorts, establishing a consistent ssTDS cut-off for stratifying samples into TDS.H (High) and TDS.L (Low) groups based on progression-free survival data. Subsequent transcriptome analyses revealed that while many TDS.L tumors may exhibit higher immune infiltrates compared to TDS.H tumors, a significant portion of TDS.L specimens may still lack sufficient immune infiltrate to elicit meaningful responses to ICI alone. Multiple factor regression analysis identified our ssTDS as the most significant factor associated with the immune score, surpassing other genetic factors like mutation burden. Network guilt-by-association analysis uncovered that a substantial portion of top TDS-related genes and pathways are immune-related, indicating their pivotal role in immune regulation in PTC and the potential to identify therapeutic targets from these genes for combinational therapy with ICIs in TDS.L PTCs. Finally, our integration analysis of top genes in the network association, up-regulated genes in TDS-low groups, and drug target data prioritized certain targets for therapeutic combinations with immunotherapy, such as AURKB and MMPs.

**Conclusion:** In summary, TDS is the most significant factor associated with immune microenvironment composition in PTC, surpassing mutation burden. The identification of TDS-related genes as potential immune regulators in PTC suggests promising avenues for combinational therapy with ICI. Moreover, our integration analysis highlights potential targets whose inhibitors could enhance the anti-cancer effects of ICI for poorly differentiated PTC.

## Oral 0030

*Thyroid Cancer, Translational, Oral*

**Metabolic pathways associated with timing to thyroid cancer diagnosis**

*Maaike van Gerwen<sup>\*1</sup>, Haibin Guan<sup>1</sup>, Elena Colicino<sup>1</sup>, Georgia Dolios<sup>1</sup>, Mathilda Monaghan<sup>1</sup>, Girish Nadkarni<sup>1</sup>, Roel Vermeulen<sup>2</sup>, Eric Genden<sup>1</sup>, Lauren Petrick<sup>1,3</sup>, <sup>1</sup>Icahn School of Medicine at Mount Sinai, USA, <sup>2</sup>Utrecht University, Netherlands, <sup>3</sup>Sheba Medical Center, Israel*

**Introduction:** Multiple environmental pollutants and endocrine disrupting chemicals persist and bioaccumulate in the environment as sources of exposure to humans through several routes. Several pollutants are linked to thyroid disruption and/or thyroid cancer. However, potential carcinogenic pathways are still poorly understood. This nested case-control study investigated metabolomic pathways associated with a thyroid cancer diagnosis.

**Methods:** 88 Patients with thyroid cancer and 88 healthy (non-cancer) pair-matched controls were identified in BioMe, a medical record-linked biobank at Mount Sinai Hospital. The cohort was stratified in a longitudinal group (cases diagnosed at least 1 year after plasma sample collection; n=62) and a cross-sectional group (cases diagnosed within 1 year following plasma sample collection; n=114) with their matched controls. Metabolites were measured using untargeted analysis with liquid chromatography-high resolution mass spectrometry and suspect screening. Associations between individual metabolites and thyroid cancer were evaluated using unconditional logistic regression models to estimate adjusted odds ratios (OR<sub>adj</sub>) and 95% confidence intervals (CI).

**Results:** Metabolites in the endocrine and inflammation pathways were associated with pre-clinical diagnosis of thyroid cancer (i.e., longitudinal group). Cortisone (OR<sub>adj</sub>: 0.34 (95% CI: 0.20; 0.55)) and cortisol (OR<sub>adj</sub>: 0.60 (95% CI: 0.40; 0.88)) were negatively associated while epipregnanolone sulphate/epiallopregnanolone sulfate (OR<sub>adj</sub>: 3.45 (95% CI: 1.94; 6.44)) and 5beta-pregnane-3alpha,20alpha-diol glucuronide (OR<sub>adj</sub>: 2.39 (95% CI: 1.58; 3.76)) were positively associated with a thyroid cancer diagnosis. For the inflammatory

pathway, Alpha/gamma-linolenic acid (OR<sub>adj</sub>: 1.94 (95% CI: 1.34; 2.95)) was positively associated with a thyroid cancer diagnosis in the longitudinal group. In the cross-sectional group, thyroxine (OR<sub>adj</sub>: 2.14 (95% CI: 1.51; 3.15)), a biomarker of thyroid dysfunction, was positively associated thyroid cancer diagnosis.

**Conclusion:** Endocrine disrupting and inflammatory pathways are associated with a thyroid cancer diagnosis in the longitudinal group while the thyroid pathway is associated with a thyroid cancer diagnosis in the cross-sectional group. This indicates that dysregulated metabolomic pathways are dependent on the time prior to diagnosis and provides insights into potential carcinogenic pathways. Future longitudinal studies with repeated sample collection are important to explore this further.

## Oral 0032

*Thyroid Nodules and Goiter, Basic, Oral*

**Development of a nomogram—a visually intuitive tool—that illustrates the contribution of molecular testing in addition to all diagnostic components in an optimized integrated interdisciplinary thyroid nodule diagnostic pathway facilitating integrated malignancy risk assessment and clinical decision-making for indeterminate thyroid nodules**

*Jiahui Wu, Paul Stewardson, Markus Eszlinger, Moosa Khalil, Sana Ghaznavi, Erik Nohr, Adrian Box, Ralf Paschke\*, University of Calgary, Canada*

**Objectives:** Molecular testing (MT) of cytologically indeterminate thyroid nodules (ITNs) did not impact thyroidectomy rates in the USA. We therefore evaluated MT as an adjunct to an optimized integrated interdisciplinary thyroid nodule diagnostic pathway.

**Methods:** A total of 1024 consecutive ITNs underwent reflexive ThyroSPEC MT between July 30, 2020, and October 30, 2023 were included. A multivariate regression model was built to assess the odds ratios for rates of malignancy (ROM) for ThyroSPEC MT categories, maximum nodule size, Bethesda atypia feature, ultrasound categories, palpation discovery, and Bethesda category. Based on the regression analysis a nomogram was generated as a graphical tool for computation of the overall ROM.

**Results:** The multivariate model achieved a cross-validated AUC of 0.831. Patients who tested positive for high-risk mutations or malignant molecular markers had 152.79 times higher odds of malignancy histology compared to those with mutation-negative or benign molecular marker results. For the most prevalent intermediate-risk (5.67 odds) patient the nomogram attributes 35 points, with a maximum nodule size greater than 5 cm 30 pts), BIII cytology 0 points, presence of nuclear atypia in the cytology report 30 points, along with ATA high risk or ACR-TIRADS 5 US classification 21 points, palpation nodule discovery 12 points, with an overall score of 128 points corresponding to a malignancy probability of over 90%. Despite positive mutation results, 40% of patients opted against surgery due to patient preference based on informed shared decision-making, including 64 with intermediate-risk mutation (60 RAS positive with 53% malignancy risk in our setting), 3 with malignant molecular marker, and 1 with high-risk mutation. The ThyroSPEC test showed a negative predictive value (NPV) of 92% [CI 84–97%] for ATA low suspicion or ACR-TIRADS 3 category nodules, and 89% [CI 83–94%] for ATA intermediate suspicion or ACR-TIRADS 4 category nodules.

**Conclusions:** Our results highlight the importance of appropriately positioning and interpreting MT as an adjunct to an optimized integrated interdisciplinary thyroid nodule diagnostic pathway to further improve diagnostic impact. For the most frequent intermediate-risk mutation nodules, integrating the ROM of the MT results with the ROM for additional clinical variables facilitates clinical decision-making.

## Thursday, October 31, 2024

## Poster 0100

*Autoimmunity, Case Study, Poster***Subacute Thyroiditis Secondary to Chikungunya Virus:  
A Case Report***Laila Daibes Rachid<sup>\*1</sup>, Marianna Daibes<sup>2</sup>, Monica Thimoteo<sup>1</sup>,  
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**Introduction:** Subacute thyroiditis (SAT) is an inflammatory disease of the thyroid gland, typically triggered by viral infections and manifesting 2–6 weeks post-exposure. Common viral triggers include influenza, adenovirus, coxsackievirus, and Epstein-Barr virus. Recent reports also associate SAT with SARS-CoV-2 and dengue virus infections. However, no cases of SAT induced by the chikungunya virus have yet been documented in the literature.

**Case Description:** A 67-year-old male, previously in good health, presented with a 30-day history of persistent low-grade fever, night sweats, and a weight loss of 4.4 pounds, accompanied by notable weakness and fatigue. Physical examination of the thyroid revealed no palpable abnormalities. Initial laboratory investigations highlighted hyperthyroidism, characterized by suppressed TSH and elevated T4 levels with negative anti-thyroglobulin, anti-TPO, and TRAb antibodies. Serological assays confirmed Chikungunya IgM antibodies, while other infectious screens returned negative. Ultrasound findings included an increased gland volume with a hypoechoic echotexture. Radionuclide thyroid scans showed diminished tracer uptake, leading to the diagnosis of subacute thyroiditis. The patient was managed with prednisolone and propranolol, resulting in clinical improvement. Follow-up ultrasound at 42 days post-treatment showed a hypoechoic thyroid gland with a significant reduction in thyroid volume from 21 cm<sup>3</sup> to 10 cm<sup>3</sup> and a normalized systolic velocity of the inferior thyroid artery, indicating a positive response to the therapeutic regimen.

**Discussion:** Subacute thyroiditis is a rare and often overlooked consequence of Chikungunya, characterized by high T4 and low TSH levels, with generally absent antithyroid antibodies. Radionuclide thyroid scans often show diminished or absent tracer uptake. In the acute phase, ultrasound often reveals bilaterally diffusely heterogeneous and hypoechoic regions with increased vascularization and velocity of the inferior thyroid arteries. In remission, vascularization, velocity, volume, and echogenicity normalize. Unlike other cases of SAT, this patient lacked neck pain. Thyroiditis due to Chikungunya should be included in the differential diagnosis for fever of unknown origin, in regions with a high incidence of mosquito-borne diseases, particularly since early corticosteroid use for SAT may improve clinical outcomes. Further investigation is required to determine the prevalence and outcomes of SAT in patients with Chikungunya.

## Poster 0101

WITHDRAWN

WITHDRAWN

## Poster 0102

*Disorders of Thyroid Function, Case Study, Poster***Recurrent Cardiac Tamponade: A Rare And Critical  
Manifestation Of Untreated Hypothyroidism Leading  
To Myxedema Coma***Adriana Luzuriaga<sup>\*1</sup>, Patricia Guia<sup>2</sup>, Hery Mejia<sup>3</sup>, Susana  
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Jackson Health System Program, USA*

Myxedema coma, a rare but potentially life-threatening complication of hypothyroidism, is characterized by severe hypothyroidism leading to altered mental status and multiorgan dysfunction. Despite its name, patients may present with varying degrees of consciousness alongside severe systemic manifestations. Cardiovascular emergencies, including large volume pleural effusions, significantly contribute to the mortality rate associated with this condition.

A 49-year-old male with a history of untreated hypothyroidism presented to the emergency department after a syncopal episode and one week of progressive weakness. The patient reported no additional symptoms and was able to participate in the medical interview. Upon evaluation, chest X-ray revealed cardiomegaly, prompting further investigation with echocardiography, which revealed a large pericardial effusion causing cardiac tamponade. Concurrently, thyroid function tests demonstrated a markedly elevated thyroid-stimulating hormone (TSH) level of 500 mIU/L and undetectable free thyroxine (T4). Prompt recognition of the association between hypothyroidism and cardiac tamponade led to an emergent pericardial window, along

with the initiation of high-dose corticosteroids and intravenous levothyroxine and liothyronine. Following thyroid hormone replacement therapy and pericardial intervention, the patient exhibited significant clinical improvement, with normalization of TSH levels within one week.

Myxedema coma is seen in 0.1% of patients with hypothyroidism. The magnitude of the clinical impact depends on the severity of hormone deficiency. Widespread and early use of thyroid-stimulating hormone assays has led to a progressive reduction in the complications associated with hypothyroidism. However, if myxedema is present, mortality despite treatment ranges between 20 to 40%.

Our case highlights the clinical variability of myxedema coma, as patients may present with minor alterations in mental status despite experiencing life-threatening complications such as pericardial effusion and cardiac tamponade. Timely diagnosis and intervention, including aggressive thyroid hormone replacement and pericardial decompression, are crucial in decreasing mortality associated with this rare but critical illness. Clinicians should have a high index of suspicion for hypothyroidism-related complications, even in patients with preserved consciousness, as it can be the determinant factor in avoiding fatal outcomes.

### Poster 0103

*Disorders of Thyroid Function, Case Study, Poster*

#### **Roller Coaster Ride: Thyroid Function Rises and Dives; A Case of Competing Autoantibodies and Medication-Induced Thyroid Dysfunction**

*Nicole Chan<sup>\*</sup>, Grace Kim, Albany Medical Center, USA*

Thyroid function varies depending on the patient's underlying risk factors. Medications and underlying autoimmunity have been well documented to cause dysfunction due to numerous mechanisms. We present a case in which a patient's fluctuating thyroid function due to different etiologies contributing to this interesting circumstance.

This is a 60-year-old female with a history of Graves' disease (GD) during teenage years with spontaneous remission in one year and a longstanding history of multiple sclerosis (MS). For her MS, she was treated with alemtuzumab and carbamazepine. Her thyroid function was, therefore, monitored during her therapy. She was referred to the endocrine clinic for TSH 0.16 uIU/mL (nl. 0.27-4.2) and free T4 0.55 ng/dL (nl. 0.93-1.7), suggestive of central hypothyroidism. She started thyroid hormone replacement therapy. Repeat TSH in 2 months showed elevated TSH of 21.76, at which time TPO antibody and TSI were checked, and both were strongly positive. Levothyroxine dose was increased. Subsequently, she was noted to have thyrotoxicosis requiring a decrease in her levothyroxine dose. Despite a significant decrease in levothyroxine dose, she remained biochemically hyperthyroid with eventual discontinuation of the medication. During thyrotoxic state, both thyrotropin receptor stimulating antibody and inhibiting antibody were elevated at 14.8 (nl. 0-1.75 IU/L) and 12.9 (nl. 0-1.75 IU/L), respectively. She had been off levothyroxine for 2 years with periodic monitoring of thyroid function tests. After 2 years, TSH was again low at 0.008 and low free T4 0.89, suggestive of central hypothyroidism. She started low dose levothyroxine (25 mcg) daily with subsequent free T4 normalization.

Carbamazepine, an antiepileptic drug, has been well-known to cause central hypothyroidism. Alemtuzumab, a monoclonal antibody that targets CD52 used in treating relapsing MS, is also known to increase the risk of autoimmune pathologies such as GD or Hashimoto's thyroiditis in up to 30% of patients. This patient had fluctuating thyroid function due to her underlying autoimmunity and medication regimen. This case presents a unique situation in which careful follow up of thyroid function is necessary as the thyroid function depends on the balance between these autoantibodies.

### Poster 0104

*Thyroid Cancer, Clinical, Poster*

#### **"Metastatic Odyssey: Renal Cell Carcinoma's Journey to the Thyroid – A Case Study"**

*Bhavika Agrawal<sup>\*</sup>, Vidhi Mehta, Feruze Cavdar, Edward Ruby, Mercy Fitzgerald hospital, USA*

**Introduction:** Renal cell carcinoma (RCC) metastasis to the thyroid gland is a rare phenomenon, representing less than 1% of all thyroid malignancies. RCC is known for its ability to metastasize to various organs, but its occurrence in the thyroid is uncommon and often poses diagnostic challenges.

**Case:** A case of a 61-year-old female on Synthroid with a history of right nephrectomy in 1998 for stage 1 clear cell carcinoma of the kidney was found on pelvic ultrasound as an incidental renal mass. She was in complete remission with regular follow-ups and imaging. On a routine follow-up, she was found to have a palpable nodule in the left thyroid. Ultrasound findings showed high vascularity suspicious of cancer followed by Fine needle aspiration which revealed clusters of epithelial cells with vacuolated cytoplasm and blood suspicious of metastatic RCC. She was also found to have enlarged left paratracheal and Delphian lymph nodes which were negative for cancer. The patient underwent total thyroidectomy with pathology consistent with metastatic RCC. MRI brain and bone scan were negative for any metastatic findings and the patient is currently in remission with close monitoring.

**Discussion:** The metastatic spread of RCC to the thyroid typically occurs via hematogenous dissemination, as RCC is highly vascularized and also by direct extension from adjacent structures in cases of locally advanced RCC. The mean lag time to diagnosis of thyroid metastases was 8.7 years which is 12 years in our case. Clinically, metastatic RCC to the thyroid gland can present as a palpable neck mass, dysphagia, hoarseness, or compressive symptoms. Imaging studies may be employed to evaluate thyroid nodules and assess the extent of metastatic disease. Fine-needle aspiration biopsy (FNAB) is pivotal to confirm the diagnosis by obtaining cytological samples for analysis, which may reveal characteristic features of RCC, such as clear cell morphology. A weak correlation has been found between lag time and the size of metastases. Management depends on the extent of metastatic disease, the patient's overall health status, and the presence of concurrent metastases which include surgical resection, radiotherapy, targeted therapy, and immunotherapy. At 1 year follow-up, 55.6% of patients operated were alive versus 35.3% who did not have surgery. We need to consider yearly thyroid studies followed by ultrasound of thyroid every 5 years in patients of RCC due to increased prevalence of metastatic to thyroid.

### Poster 0105

*Disorders of Thyroid Function, Case Study, Poster*

#### **"Hoffman Syndrome: Thyroid dysfunction silent impact on Neuromuscular health"**

*Bhavika Agrawal<sup>\*1</sup>, Piyush Agrawal<sup>2</sup>, Vidhi Mehta<sup>1</sup>, Feruze Cavdar<sup>1</sup>, Rabia Naseem<sup>1</sup>, <sup>1</sup>Mercy Fitzgerald hospital, USA, <sup>2</sup>Sri Aurobindo Institute of Medical Science, India*

**Introduction:** Hoffman syndrome is a rare neurological condition seen in patients of uncontrolled hypothyroidism causing progressive muscle weakness, first documented by Johann Hoffman in 1897. It is one of the forms of myopathy that is completely reversal with treatment.

**Case:** A 38-year-old lady with no significant medical history presents in outpatient clinic with 2 years of worsening weight gain

despite low appetite and excessive hair loss. She endorsed having menorrhagia followed by oligomenorrhea, excessive fatigue, constipation and hoarseness of voice. She noticed slowing of her movements and swelling of limbs which prompted her to come to clinic. Physical examination shows thin brittle skin, hair loss in occipital region, puffy eyes, enlarged nose, bilateral galactorrhea and diffusely enlarged calf muscles with pretibial non pitting edema along with delayed deep tendon reflexes. Pertinent lab work showed macrocytic anemia with low hemoglobin of 6.4. Thyroid studies show TSH>100 IU/ml, T4 2.12 mcg/dl, T3 0.46ng/ml, anti-thyroid peroxidase level >1300 IU/ml and prolactin of 42 ng/ml. CT head showed widened pituitary fossa and MRI brain reveal pituitary hyperplasia. Patient was started on levothyroxine up titrated to maximum dose with resolution of muscle hypertrophy in 6 months.

**Discussion:** Hoffman syndrome is a hypothyroid myopathy causing progressive muscle weakness due to selective atrophy of type 2 fibers which are dependent on glycolysis for energy. Thyroid dysfunction causes decrease in muscle carnitine leading to myopathic symptoms. It is commonly seen in woman in both adult and congenital hypothyroidism causing pseudohypertrophy, painful spasm and proximal muscle weakness and stiffness. Hormone replacement therapy has favorable prognosis and hypertrophic muscles results to normal in 3 months. Few cases are also caused by hyperprolactinemia hypothyroidism presenting with hypothyroid features along with visual defects and galactorrhea seen in case above. Pituitary hyperplasia occurs due to lack of negative feedback by hypothalamus causing elevated TRH. Pituitary hyperplasia can be seen on imaging and treatment leads to regression of thyro-lactotroph hyperplasia in 12 months. Failure to regress symptoms after optimal therapy requires further investigation for pituitary adenoma.

### Poster 0106

*Autoimmunity, Case Study, Poster*

**Nivolumab's Thyroid Tale: Immunotherapy induced thyroiditis**  
bhavika agrawal<sup>1</sup>, hardik Jain<sup>2</sup>, Feruze Cavdar<sup>1</sup>, Vidhi Mehta<sup>1</sup>, Rabia Naseem<sup>1</sup>, <sup>1</sup>Mercy Fitzgerald hospital, USA, <sup>2</sup>allegheny general hospital, USA

**Introduction:** Nivolumab is an immunotherapy that works by blocking a protein called programmed cell death protein 1 (PD-1) thereby boosting immune response against cancer cells. Thyroiditis caused by checkpoint inhibitors is associated with T lymphocytes with the predominance of intra-thyroidal CD8 and CD4 T lymphocytes.

**Case:** A 58-year-old female with past medical history of hypertension on amlodipine, hyperlipidemia on a statin, smoking-induced stage 3 squamous cell carcinoma of head and neck (HNSCC) treated with Nivolumab for the past 3 months. She came to the outpatient clinic with complaints of progressive fatigue, weight gain, and neck discomfort on palpation worsening in the past 1 month. The patient had stable vitals and physical examination revealed mild tenderness over the thyroid gland but no palpable nodules or lymphadenopathy were observed. Thyroid studies showed elevated Thyroid stimulating hormone to 15 mIU/L, normal Free T4 of 1 ng/dl, and positive thyroid peroxidase antibodies. Thyroid ultrasound revealed diffuse heterogeneous echogenicity consistent with thyroiditis. Nivolumab was discontinued and the patient was symptomatically treated with non-steroidal anti-inflammatory drugs. In addition, she was advised to follow up with oncology to treat with alternative immunotherapy such as Ipilimumab, and the patient's thyroid function was closely monitored and normalized within 2 months of discontinuing Nivolumab.

**Discussion:** Thyroiditis induced by Nivolumab can present as hypothyroidism or hyperthyroidism depending on the immune response triggered by the therapy. Diagnosis is made by thyroid function studies and the presence of thyroid peroxidase and anti-thyroglobulin antibodies. In studies done on PD-1 inhibitors, autoimmune thyroiditis is significantly observed in patients treated with Nivolumab and Pembrolizumab. Several meta-analyses revealed CTLA-1 inhibitors had a significantly lower rate of hypothyroidism as compared to PD-1 and PD-L1 inhibitors which in our case was an alternative treatment for the patient. Studies have revealed thyroid function assessment before each cycle of medications for up to 6 months. Additionally, it has also been found that the tumor type is not associated with the incidence of hypothyroidism with PD-1 inhibitors.

### Poster 0107

*Thyroid Cancer, Case Study, Poster*

**“When worlds collide: Diffuse large B cell lymphoma in patient of hypothyroidism”**

Feruze Cavdar, Bhavika Agrawal<sup>\*</sup>, Vidhi Mehta, Edward Ruby, Mercy Fitzgerald hospital, USA

**Introduction:** Primary thyroid lymphomas are very rare tumors, typically presenting as a rapidly enlarging, painless thyroid mass, which may cause pressure symptoms of the aerodigestive tract. This case highlights the importance of considering lymphoma in the differential diagnosis of thyroid nodules, particularly in elderly patients with a history of primary hypothyroidism.

**Case:** A 82-year-old female with past medical history of primary hypothyroidism on 75 mcg levothyroxine for 3 decades, hypercholesterolemia, hypertension, and prediabetes who presented after noticing a lump on the left neck side of her neck which becomes more noticeable on swallowing for the last 3-4 weeks. Physical examination revealed palpable left and right thyroid nodules more prominent on swallowing. Additionally, her deep tendon reflexes were slightly increased in the relaxation phase. Thyroid stimulating hormone levels was 5.9 and a free T4 level was 1.9 ng/ml. Ultrasound of the thyroid reported a solid hyper vascular nodule occupying almost the entire right lobe, measuring 3.8 x 1.5 x 2.6 cm and the left lobe nodule, measuring 6.3 x 2.9 x 3.5 cm. Both nodules were categorized as Thyroid Imaging Reporting and Data System (TI-RADS) 4. Fine needle aspiration of both thyroid nodules revealed Diffuse Large B-cell Lymphoma. Given the unexpected diagnosis, the patient was referred for multidisciplinary management and the management plan was considered based on the patient's age, comorbidities, and the extent of lymphoma extent. She is started on R mini-CHOP therapy for up to 6 cycles if tolerated with close follow-up and regular monitoring to assess for treatment response and to ensure comprehensive care.

**Discussion:** A rapidly growing neck mass mobile while swallowing is the most common clinical presentation of severe thyroid malignancy which was the presentation in our case. DLBCL is the most common lymphoma and features of Mucosal associated T cell lymphoma (MALT) can be seen in over one-third of cases. As a group, High-Grade MALT-type lymphomas had a worse outcome than DLBCL, primarily due to higher clinical stage at diagnosis. Statistically, stages greater than IE, presence of DLBCL, rapid clinical growth, abundant apoptosis, presence of vascular invasion, high mitotic rate, and infiltration of the perithyroidal soft tissue are significantly associated with mortality. Timely diagnosis through fine needle aspiration and interdisciplinary collaboration are vital for optimal management and outcomes in such cases. Therapeutic strategies distinct from other thyroid malignancies include local therapy alone (surgery, radiotherapy, surgery plus radiotherapy) or combined multimodality treatment (mainly chemoradiation therapy).

**Poster 0108***Thyroid Nodules and Goiter, Case Study, Poster***The Great Imitator: A thyroid nodule mimicking Medullary thyroid carcinoma**Hardik Jain<sup>1</sup>, Bhavika Agrawal<sup>\*2</sup>, Joshika Agarwal<sup>2</sup>, Harshil Patel<sup>2</sup>,  
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**Introduction:** Thyroid nodules are a common clinical entity, and the evaluation of such nodules poses a diagnostic challenge, especially when they exhibit cytological features reminiscent of medullary carcinoma thyroid (MTC). While its diagnosis typically relies on histopathological examination, the presence of calcitonin secreting nodules can mimic MTC, leading to diagnostic dilemmas.

**Case Presentation:** A 47-year-old female presented with a six-month history of a palpable neck mass associated with worsening dysphagia, and hoarseness of voice. Physical examination revealed a firm, non-tender mass in the left side of the neck. Thyroid ultrasound showed a well-defined, hypoechoic nodule with irregular margins and increased vascularity, raising suspicion for malignancy. Fine needle aspiration (FNA) biopsy revealed abundant amyloid-like material and spindle-shaped cells arranged in nests, consistent with findings of Medullary thyroid carcinoma (MTC). However, serum calcitonin levels were within normal limits. The discordance between cytological features suggestive of MTC and normal serum calcitonin levels prompted a re-evaluation of the diagnosis. Repeat imaging with ultrasound and computed topography helped to reassess characteristics of nodule. The immunohistochemical analysis was negative for calcitonin staining which prompted reconsideration of thyroid nodule. Histopathological correlation with thyroid function studies were vitals in confirming the benign nature of the nodule. The patient was managed conservatively with close observation and regular follow-ups.

**Discussion:** Medullary carcinoma thyroid (MTC) is a rare neuroendocrine tumor arising from the parafollicular C cells of the thyroid gland, accounting for 5-10% of all thyroid malignancies. It typically presents as a solitary thyroid nodule and is associated with elevated serum calcitonin levels. Thyroid nodules mimicking MTC present a diagnostic dilemma, necessitating a comprehensive approach for diagnosis and management. The differential diagnosis of thyroid nodules resembling MTC includes C cell hyperplasia, adenomatous nodules, and other neuroendocrine tumors. Accurate diagnosis often requires ancillary studies such as immunohistochemistry for calcitonin and genetic testing for RET proto-oncogene mutations. This case underscores the importance of integrating clinical, radiological, cytological, and biochemical findings to avoid unnecessary interventions in benign thyroid nodules.

**Poster 0109***Thyroid Hormone Action, Metabolism and Regulation, Case Study, Poster***Demystifying Hashitoxicosis- Autoimmune assault on thyroid function**Bhavika Agrawal<sup>\*1</sup>, Hardik Jain<sup>2</sup>, Rabia Naseem<sup>1</sup>, Vidhi Mehta<sup>1</sup>,  
Feruze Cadvar<sup>1</sup>, <sup>1</sup>Mercy Fitzgerald hospital, USA, <sup>2</sup>Allegheny Hospital, USA

**Introduction:** Hashitoxicosis is a transient thyrotoxicosis caused by destructive inflammation due to Hashimoto's thyroiditis damaging the thyroid follicles resulting in excess release of thyroid hormone.

**Case:** A 45-year-old female with a medical history of controlled hypertension presented with complaints of fatigue, chest discomfort, muscle weakness, recurrent headaches, and mood swings for 3

months that started affecting her daily activities. The patient endorsed an active lifestyle and initially attributed her symptoms to stress. The patient has a family history of diabetes and hypertension. Vitals were normal and physical examination revealed a diffusely enlarged thyroid gland but no nodules were palpable. The patient was also noted to have fine tremors at rest. Thyroid stimulating hormone was low 0.01mIU/L, and free T3 and T4 were elevated with positive thyroid peroxidase antibodies and thyroglobulin antibodies. Thyroid ultrasound showed increased vascularity consistent with autoimmune thyroiditis. The patient was started on beta blockers and methimazole which improved symptoms and thyroid hormone levels in 6 months. The patient's thyroid hormone levels and antibody titer gradually regressed which coincided with symptom resolution.

**Discussion:** Hashitoxicosis is caused by an insult-provoking Th-1 immune reaction and CD4 lymphocyte activation causing releasing of interleukin 2, interferon-gamma, and tumor necrosis factor resulting in an autoimmune attack. Symptoms of mild to moderate hyperthyroidism may coexist with a diffuse, firm, painless goiter. Thyroid scintigraphy shows normal to slightly increased uptake which helps to distinguish it from Grave's disease. Anti-thyroid peroxidase antibodies are positive in 45-80% of Grave's disease patients and TSH-receptor antibodies are positive in 6% patients of with Hashimoto thyroiditis which is not helpful in diagnosing Hashitoxicosis. The most crucial test is the Ultrasound of the thyroid which is based on vascularity. Grave's disease shows a highly vascular picture whereas Hashitoxicosis shows normal/slightly increased vascularity. Most patients are initially treated with beta-blockers and in the thyrotoxic state started on anti-thyroid drugs for a short course and close monitoring. The outcome is variable with most patients recovering from the thyrotoxic phase and a small proportion remaining in persistent thyroid dysfunction.

**Poster 0110***Disorders of Thyroid Function, Case Study, Poster***Recurrent Thyrotoxic Periodic Paralysis – A Rare Complication of Uncontrolled Graves' Disease**Brihant Sharma<sup>\*</sup>, Mariya Khan, Ajaykumar Rao, Temple University Hospital, USA

**Introduction:** Thyrotoxic Periodic Paralysis (TPP) is a rare complication of hyperthyroidism presenting with reversible acute paralysis. We present a patient with uncontrolled Graves' disease who presented with recurrent episodes of TPP.

**Case Description:** Patient is a 28-year-old, African American male, presenting for sudden numbness and weakness in lower extremities. He woke up in the morning with distal weakness which progressed proximally. He recently has been fasting for Ramadan and doing frequent gym sessions. Before the current admission, the patient has had two similar presentations. He was diagnosed with Graves' disease during the first hospitalization for weakness one year ago. TSI was 541 (normal < 140% baseline). Thyroid ultrasound imaging showed a moderately enlarged thyroid and increased vascularity. He presents now for a third admission for weakness and admits he has not taken his medications for around 2 months. The physical exam was significant for mild tachycardia, thyromegaly and mild proptosis. Neurological exam was significant for 2/5 strength in lower extremities, 4/5 strength in upper extremities and decreased deep tendon reflexes. Labs were pertinent for potassium level 1.3 mmol/L, TSH <0.005 µIU/L (normal 0.55-4.78), Free T4 3.46 (normal 0.89-1.76 ng/dL) and Free T3 15.0 (normal 2.3-4.2 pg/mL). He was given multiple doses of intravenous and oral potassium until resolution of hypokalemia. He was re-started on Methimazole 20 mg BID

and Propranolol 40 mg BID. Patient had resolution of his lower extremity weakness and was discharged 2 days later.

**Discussion:** TPP is very rare in African American populations, it is mostly seen in Asian men. In patients with TPP, it has been found that there is increased activity of  $\text{Na}^+/\text{K}^+$ -ATPase pumps in skeletal muscles. Studies suggest that the condition is precipitated by a combination of thyrotoxicosis, environmental factors such as a high carbohydrate load or intense exercise. Treatment of acute TPP is quickly reducing thyroid hormone levels in addition to potassium supplementation. Non-selective  $\beta$ -blockers could terminate neuromuscular symptoms rapidly while reducing an intracellular shift of potassium and phosphate. Good medication compliance and maintenance of euthyroid status is paramount to prevent recurrent episodes.

### Poster 0111

*Disorders of Thyroid Function, Case Study, Poster*

#### Thyrotoxicosis in a Post Heart Transplant Patient - A Diagnostic Dilemma

*Brihant Sharma\*, Mariya Khan, Ajaykumar Rao, Paul Guido, Temple University Hospital, USA*

**Introduction:** This case describes a patient with thyrotoxicosis post orthotopic heart transplant (OHT) with difficulty in diagnosing the underlying cause due to a set of broad differentials and no prior thyroid history.

**Case Description:** A 40-year-old female was seen after an OHT for peripartum cardiomyopathy. During the transplant operation, the patient received intravenous (IV) Levothyroxine 83 mcg. Post-operatively, she developed complications of distributive shock, requiring vasopressors and inotropic support. Post-operative Day 1 labs showed TSH < 0.005, Free T4 8.04 (normal 0.89 - 1.76 ng/dL) and Total T3 147.70 (normal 60.00 - 181.00 ng/dL). Quantitative Thyroglobulin (TG) levels 106.9 (normal 0.1 - 36.8 ng/mL). A bedside point of care Ultrasound did not show an enlarged or hyper vascular thyroid or any discrete nodules. TSI antibodies were normal. Three months prior to the OHT, TSH was normal and Free T4 was elevated (2.29). The patient was on Amiodarone at the time. She was started on glucocorticoids for immunosuppression and for treatment of Amiodarone induced thyrotoxicosis (AIT) Type 2. Free T4 normalized after four weeks of steroids use, therefore the dose was tapered. Four weeks later, labs showed TSH 0.021 and Free T4 3.00, suggesting recurrence of thyrotoxicosis. The steroid dose was again increased and labs one week later showed Free T4 down trending to 1.30. The patient expired two weeks later from non-thyroid related complications.

**Conclusion:** There was initially suspicion for thyrotoxicosis from exogenous IV Levothyroxine, which is primarily given perioperatively to improve outcomes in recipients of heart transplant patients. However, the elevated quantitative TG and prolonged duration of elevated Free T4 levels were support against this diagnosis. The half-life elimination of Levothyroxine is approximately 9-10 days, meanwhile the thyrotoxicosis in our patient took approximately 4 weeks to resolve. Graves' disease and AIT Type I was less likely from the negative antibody testing and Ultrasound findings. The incidence of post-OHT thyroiditis has been strongly associated with pre-transplant Amiodarone use. The present case makes a strong argument that thyroid labs should be followed closely before and during the post-transplant period, especially when the patient is exposed to Amiodarone or IV Levothyroxine.

### Poster 0112

*Disorders of Thyroid Function, Case Study, Poster*

#### Thyrotoxic Cardiomyopathy Leading to Acute Heart Failure: A Case Report

*Harshita Marasandra Ramesh\*, Rashmi Subramani, Ferrol Lee, Guthrie Robert Packer Hospital, USA*

**Introduction:** Thyrotoxicosis often presents with various cardiovascular symptoms, including palpitations, dyspnea, atrial fibrillation, and heart failure (1,2). The incidence of heart failure in thyrotoxicosis is approximately 6%. We present a compelling case of thyrotoxic cardiomyopathy resulting in heart failure due to medication non-compliance.

**Case Description:** A 34-year-old woman, previously diagnosed with Grave's disease during pregnancy at 26, presented with worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and pedal edema. She had been non-compliant with methimazole and lost to follow-up due to personal and insurance issues. Physical examination revealed periorbital edema, lid lag, thyroid swelling, bilateral pedal edema, rales, and hand tremors. Lab tests showed elevated T3 of 229 ng/dL, T4 of 4.1 ng/dL, TSH of <0.02 uIU/ml, elevated TSH receptor antibody of 7.96 IU/L, positive thyroid stimulating immunoglobulins and elevated NT proBNP of 1134. EKG showed sinus tachycardia. ECHO revealed a left ventricular ejection fraction of 60%, concentric left ventricular hypertrophy, biatrial enlargement, and mild mitral regurgitation. Ultrasound thyroid showed heterogeneous echotexture. She was diagnosed with heart failure with preserved ejection fraction exacerbated by thyrotoxicosis-induced cardiomyopathy and was treated with furosemide. The patient returned a year later exhibiting signs and symptoms indicative of both heart failure and thyrotoxicosis, attributable to non-compliance with medication. Her methimazole dosage was escalated to 20 mg thrice daily, alongside an increase in furosemide to 40 mg daily. Comprehensive treatment discussions ensued, encompassing definitive options such as total thyroidectomy or radioactive iodine therapy, followed by thyroid hormone replacement therapy and adherence to medication protocols.

**Discussion:** Untreated thyrotoxicosis can lead to cardiac complications, including heart failure. Therefore, early diagnosis and treatment are crucial. Treatment aims to restore euthyroid state and manage heart failure collaboratively (1,2). Prompt therapy often resolves heart failure symptoms (1).

### Poster 0113

*Disorders of Thyroid Function, Case Study, Poster*

#### Painful Thyroiditis: Subacute Thyroiditis or Painful Hashimoto's Thyroiditis

*Harshita Marasandra Ramesh\*<sup>1</sup>, FNU Manas<sup>1</sup>, Sundas Zahra<sup>2</sup>, Sneha Singh<sup>2</sup>, Ferrol Lee<sup>2</sup>, <sup>1</sup>Guthrie Robert Packer Hospital, USA, <sup>2</sup>GuthrieRobert Packer Hospital, USA*

Subacute thyroiditis is the most common cause of painful thyroiditis. It is usually preceded by upper respiratory tract infection and associated with fever, leukocytosis, elevated inflammatory markers and transient hyperthyroidism. The thyroid gland can be of normal size or enlarged with diffuse or focal hypoechoogenicity on ultrasonography. The treatment is pain control with NSAIDs or steroids and symptoms management of hyperthyroidism. Rarely Hashimoto's can present as painful thyroiditis which can be challenging to differentiate from subacute thyroiditis without histopathological evidence. Less than half of the patients with painful Hashimoto's thyroiditis can have fever with elevated inflammatory markers. The

thyroid function can vary from hypothyroid, euthyroid or hyperthyroid state but the thyroid auto-antibodies (anti-thyroid peroxidase and anti-thyroglobulin) are always positive. Ultrasonography shows diffuse heterogeneous hypoechoic thyroid gland. Patients usually do not respond well to NSAIDs or steroids and thyroidectomy is recommended in patients with recurrent painful episodes.

**CASE PRESENTATION:** A 39 year old female with no significant prior medical history presented for evaluation of thyroid problem. Two months ago, the patient had right anterior neck pain, swelling and tenderness. She was treated with antibiotics and NSAIDs without any improvement in the symptoms. Her symptoms eventually improved over the next 3-4 weeks. Two weeks later, she had an episode of pain, swelling and tenderness of the left anterior neck. She had no history of trauma, fever or preceding upper respiratory tract infection. She denied any history of thyroid disorder, head or neck irradiation, hoarseness or dysphagia. Examination revealed scant thyroid tissue palpable and minimal tenderness on palpation of left anterior neck. Laboratory testing showed no leukocytosis, elevated ESR at 30mm/hr (normal:0-20 mm/hr) and low TSH level at <0.02 uIU/ml (normal:0.27-4.2 uIU/ml). Free T3 and free T4 were normal at 2.65 pg/ml and 1.0 ng/dl respectively. Thyroglobulin antibody was positive at 5 IU/ml (normal:less than 1 IU/ml). Thyroid peroxidase antibody was positive at 97 IU/ml (normal:less than 9 IU/ml). Thyroglobulin level and thyroid stimulating immunoglobulin was normal. Ultrasound revealed asymmetrically heterogeneous hypoechoic right hemithyroid. It was unclear whether the patient had a subacute thyroiditis or a painful Hashimoto's thyroiditis as there was no pathological testing done.

**CONCLUSION:** It is challenging to differentiate between subacute thyroiditis and painful Hashimoto's thyroiditis in the absence of histopathological evidence. Physicians should be aware of this rare variant especially if the symptoms fail to improve as anticipated.

#### Poster 0114

*Disorders of Thyroid Function, Case Study, Poster*

##### **Myxedema Coma With Dangerously Elevated TSH: A rare presentation of an even rarer disease**

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**Introduction:** Myxedema coma is a rare presentation of uncontrolled hypothyroidism. The first case was reported in St Thomas Hospital in 1879. Patients today especially in the USA have much higher screening for hypothyroidism with the availability of assays. The incidence of myxedema coma in the Western world is approximately 0.22 per 100,000 in a European study [1]. Herein we present an interesting case of myxedema coma in a 56 year old, non-compliant patient.

**Description:** A 56 y/o homeless gentleman with PMH of hypothyroidism induced multiple myxedema crises' presented in the ED with complaint of hypotension, bradycardia and altered mental status. In ED vitals were: Temp 95, Pulse 52, BP 87/65. Labs were: Hgb 11.4, PLT 341, Na 132, K 3.2, Cl 102, HCO3 22, TSH 93, T4 0.2 Total T3 0.17. Of note, the previous TSH two months ago during a crisis was 350. Patient was started on Levothyroxine 200 microgram bolus and 100 micrograms daily, hydrocortisone 100mg Q8Hrs and admitted to ICU. Patient improved in a couple of days and was discharged with outpatient follow-up with our medical and endocrinology clinic.

**Discussion:** Myxedema coma presents with three major symptoms: Altered mental status, defective thermoregulation and a precipitating event [2]. This patient was presenting in the winter time with TSH levels in the hundreds found comatose in different locations likely with poor follow-up and diet. The treatment remains

thyroid hormone, steroids and supportive measures (blankets for hypothermia, dextrose for hypoglycemia etc.) [3]. Guidelines published by ATA recommend thyroxine dose adjustments by age, weight and cardiac status [4]. There still remains controversy regarding use of lithium given cardiac side effects [5]. Mortality remains high at 30 percent in one Japanese study with cardiac comorbidities at 40 percent [6]. The most significant risk factor which was not present in our patient is macroglossia requiring intubation which may improve the hypercarbia induced mental status changes but worsen outcomes. GCS and APACHE II scores have been used to stratify. In our patient a strong social framework and regular labs would be necessary for follow-up to prevent these repetitive crises'.

#### Poster 0115

*Disorders of Thyroid Function, Case Study, Poster*

##### **Prolonged sub-acute thyroiditis - A perfect storm**

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**Introduction:** Iodine is an essential nutrient that is used by the thyroid gland for the production and regulation of thyroid hormones triiodothyronine (T3) and thyroxine (T4) to maintain bodily homeostasis. The thyroid gland has auto regulatory mechanisms to modulate iodine uptake and the synthesis of these hormones.

**Description:** A 29-year-old female seen by PCP for acute pharyngitis and was prescribed antibiotics, following which, she experienced a rapid increase in pain in her anterior neck accompanied by swelling in the area prompting an ED visit. In the ED, she was found to have swelling in the neck/thyroid. Labs revealed a TSH of 0.220 (0.5-4.7) mIU/L. CT soft tissue of neck with iodinated contrast showed heterogenous appearance of thyroid parenchyma, possibly goiter. She was referred to endocrine as outpatient and a detailed history revealed that patient had been taking supplements, Alpha Greens (AG1) for one-month prior containing iodine. Ultrasound thyroid revealed heterogenous appearing thyroid gland, with increased vascularity. Right thyroid nodule 1.2x1.1x1cm, left nodule 1.4x1.2x1.1cm, hypoechoic. Repeat TSH showed a downward trend, 0.125 (0.5-4.7) mIU/L, FT4 of 2.05(0.82-1.77 ng/dl) followed by TSH of 0.01, FT4 of 3.5. Serum iodine level was elevated at 149 mcg/L (52-109 mcg/L). I131 uptake scan revealed 4 hr uptake of 2.5% and 24 hr uptake less than 1% (10 to 30%). Subacute thyroiditis suspected, no evidence of toxic adenoma. A final diagnosis of painful De Quervain's subacute thyroiditis was determined. Patient was advised to discontinue all supplements. Patient had prolonged pain in her neck, requiring multiple courses of steroids and NSAID's lasting greater than 6 months. Patient labs were monitored until TSH, and iodine levels returned to normal range.

**Discussion:** Here we present a case of prolonged subacute thyroiditis. Although at first glance this appears to be viral, it is indeed a perfect storm of viral thyroiditis compounded by iodine containing supplements and administration of iodinated contrast. Iodine induced hyperthyroidism develops in patients with underlying autonomy of the thyroid, in which the iodine load acts as a substrate for the thyroid to produce excess amounts of thyroid hormones. (Jod-Basedow phenomenon).

#### Poster 0116

*Disorders of Thyroid Function, Case Study, Poster*

##### **A Rare Case of Central Hypothyroidism and Secondary Adrenal Insufficiency in Moyamoya Disease**

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**Introduction:** Moyamoya disease (MMD) is a rare, progressive cerebrovascular disorder characterized by stenosis and occlusion of carotid arteries, leading to a compensatory collateral vessel network. It presents with symptoms of cerebral ischemia or hemorrhage. Emerging evidence suggests a potential link between MMD and hypothalamic-pituitary dysfunction due to chronic ischemia.

**Case Description:** 53-year-old male with a history of Moyamoya disease, diagnosed following a left intracranial hemorrhage at age 46. Despite undergoing an extracranial-intracranial bypass in 2017, the patient had recurrent episodes of symptomatic hyponatremia which led to multiple hospitalizations. During the most recent episode, he tested positive for COVID-19. During hospitalization, low cortisol level of  $<3.0 \mu\text{g/dL}$ , serum TSH of  $0.95 \text{ mIU/mL}$ , free T4 of  $0.5 \text{ ng/dL}$  and an atrophic thyroid gland identified incidentally via CT imaging. The tests were repeated 2 weeks following recovery with TSH level  $1.06 \text{ mIU/L}$ , free T4 of  $0.5 \text{ ng/dL}$ , total T3 of  $0.67 \text{ ng/mL}$  with negative thyroid peroxidase and thyroglobulin antibodies suggesting central hypothyroidism. Low serum cortisol  $<3.0 \mu\text{g/dL}$  and non-elevated ACTH  $16 \text{ pg/mL}$  suggested secondary adrenal insufficiency. Plasma renin activity (PRA) was  $0.38 \text{ ng/mL/hour}$  and plasma aldosterone concentration were  $5 \text{ ng/dL}$ . PAC/PRA ratio was 13.2. Patient underwent a cosyntropin stimulation test that showed cortisol at  $9.2 \mu\text{g/dL}$  and  $10.1 \mu\text{g/dL}$ . Brain MRI was unremarkable for pituitary abnormalities. He was started on levothyroxine  $50 \text{ mcg}$  daily. Given that he was asymptomatic in his daily life and showed no symptoms of adrenal insufficiency unless he was stressed or ill, it was decided to manage the condition with stress dosing of prednisone  $5 \text{ mg}$  as needed during acute illnesses to prevent adrenal insufficiency during stressful events.

**Discussion:** This highlights a rare association of MMD with central hypothyroidism and secondary adrenal insufficiency, suggesting a spectrum of endocrinopathies potentially linked to the vascular pathology of MMD. The vascular insufficiency characteristic of MMD may affect the hypothalamic-pituitary axis, leading to hormonal dysfunctions. Surgical revascularization aims to reduce ischemic risks and improve cerebral perfusion. However, as evidenced in our patient, such interventions may not fully reverse the endocrinological impact of the disease. This underline the importance of long-term endocrinological monitoring in patients with MMD, even after successful surgical intervention, to manage potential delayed or progressive endocrine complications.

### Poster 0117

*Disorders of Thyroid Function, Case Study, Poster*

#### **A Rare Case of Graves' Disease Induced Cardiomyopathy**

*Christina Marchese<sup>\*</sup>, David Felske, Matthew Gilbert, University of Vermont Medical Center, USA*

**Introduction:** Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder that is classically associated with thyroid, ophthalmic, and dermatologic involvement. Graves' cardiomyopathy is a rare ( $<1\%$ ) extra-thyroidal complication and is an underestimated cause of heart failure with reduced ejection fraction<sup>1</sup>. We present a case of a young adult male without previous cardiac history who developed an acute, severe cardiomyopathy in the setting of uncontrolled Graves' disease.

**Case Description:** A 43 year-old male with a past medical history of Graves' disease on methimazole and beta-blockade, anxiety, depression, and alcohol and tobacco use disorder presented after cardiac arrest secondary to ventricular fibrillation. Five days prior to presentation thyroid labs were TSH  $<0.02 \text{ mIU/L}$ , Free T4  $2.7 \text{ ng/dL}$ , Total T3  $304 \text{ ng/dL}$ . He was found to have a mildly dilated left ventricle ejection fraction of  $10\%$  that improved to  $60\%$  with appropriate

control of thyroid hormone level within one week. Left heart catheterization revealed normal coronary arteries. His course was complicated by shock liver, ileus, acute kidney injury requiring hemodialysis, and sepsis secondary to aspiration pneumonia. After two months, he was discharged with close follow-up. The patient represented on multiple occasions for abdominal pain and severe malnutrition (BMI  $13.8 \text{ kg/m}^2$ ) with uncontrolled hyperthyroidism. Imaging revealed complex enterocolonic post-ischemic changes related to prior cardiac arrest, including a developing large bowel obstruction treated with left hemi-colectomy. He was referred for total thyroidectomy; however, multidisciplinary conference recommended he be medically optimized as much as possible before proceeding. After nine months and improvement of his body weight (BMI  $25.6 \text{ kg/m}^2$ ), he started Lugol's solution to achieve euthyroidism prior to total thyroidectomy.

**Discussion:** Throughout this patient's protracted hospital course, thyroid function remained difficult to control despite high doses of methimazole. This case illustrates the intricate management of hyperthyroidism while navigating the optimal timing for surgical intervention. It also highlights an uncommon cause of heart failure as Graves' cardiomyopathy can be easily overlooked. Other cases of cardiac complications associated with Graves' disease similarly demonstrated improved cardiac function with appropriate treatment<sup>2</sup>. Clinicians should remain aware of severe cardiac manifestations in uncontrolled Graves' disease.

### Poster 0118

*Disorders of Thyroid Function, Case Study, Poster*

#### **Silent Storm - Apathetic hyperthyroidism: case report**

*Claudia Guillen<sup>1</sup>, Sarah Lahud<sup>1</sup>, Aesha Patel<sup>\*1</sup>, Mounika Allam<sup>1</sup>, Chloe Arima<sup>1</sup>, Shweta Mahesh<sup>1</sup>, Daisy Buenaventura-Collazos<sup>2</sup>, <sup>1</sup>Loyola Medicine MacNeal Hospital, USA, <sup>2</sup>Hospital Universitario del Valle, Colombia*

Apathetic hyperthyroidism (AH), initially described by Dr. Frank H. Lahey in 1931, presents a challenge due to its subtle or absent symptoms, especially in older patients. Unlike classic hyperthyroidism with prominent adrenergic symptoms, AH often manifests as fatigue, weakness, weight loss, insomnia, depression, and apathy. The deficiency or unresponsiveness to brain catecholamines contributes to these symptoms, sometimes leading to bilateral ptosis. However, conditions like atrial fibrillation and congestive heart failure can hint at underlying hyperthyroidism. The etiology of AH remains unclear but is associated with factors like age-related changes in adrenergic tone, tissue resistance to thyroid hormone, comorbidities, immune response variations, or hypomagnesemia. Despite its subtle presentation, AH can lead to complications such as cardiovascular and bone diseases and even thyroid eye disease. AH has been related to malignancy, mainly lung cancer, where symptoms could be masked by either one. The importance of the unique presentation of AH is that it may lead to underdiagnosis and delayed treatment.

A 77-year-old male with a medical history of hypertension, type 1 diabetes mellitus, and Graves' disease experienced symptom exacerbation after discontinuing methimazole due to elevated TSH levels. He presented with swallowing difficulties, weakness, sadness, weight loss, bilateral ptosis, and skin lesions. TSH was  $0.02 \text{ mIU/mL}$ , FT3  $>2000 \text{ pg/dl}$ , and FT4  $>5.0 \text{ ng/dl}$ . CT neck and chest showed thyromegaly and para mediastinal left upper lobe mass with pleural contact with the superior mediastinum, suggesting mild invasion. Skin biopsy showed basal cell carcinoma. However, lung biopsy results were negative for malignancy, necessitating continued surveillance. Treatment with methimazole led to symptom improvement and

normalization of thyroid function tests. The patient denies dysphagia, dysphonia, neck pain, or dyspnea.

In older patients with thyrotoxicosis, atypical symptoms or their absence complicate the identification of this condition. Understanding demographic patterns and risk factors associated with AH is crucial for targeted screening and prompt diagnosis. This case highlights the potential for both benign and malignant conditions to coexist in elderly patients with AH-like symptoms. Early diagnosis of AH is essential for effective treatment and reducing morbidity and mortality. However, the overlap of symptoms with malignancies underscores the importance of considering a broad range of differential diagnoses, particularly in elderly patients with nonspecific clinical presentations.

### Poster 0119

*Disorders of Thyroid Function, Case Study, Poster*

#### **The Mind Behind The Thyroid: Exploring Psychiatric Manifestations Of Hypothyroidism**

*Dania Kaur\*, Abhinav Vyas, Mina Iskander, Bhargavi Nagendra, Sunpil Hwang, Rachna Valvani, North Alabama Medical Center, USA*

**Introduction:** Myxedema psychosis, a manifestation of untreated or suboptimally treated hypothyroidism, presents with gradual onset psychiatric symptoms, including delusions and hallucinations. Here, we illustrate a case where suboptimal treatment of hypothyroidism resulted in the manifestation of psychotic symptoms.

**Case Presentation:** A 72-year-old female with a history of hypothyroidism on levothyroxine 88 mcg and major depressive disorder was brought to the hospital after being found unresponsive at home and soiled in fecal matter. On arrival, her vital signs were notable for a blood pressure of 134/78 mmHg, heart rate of 42 beats per minute, and temperature of 91.4 degrees Fahrenheit. Laboratory investigations revealed leucocytosis (27000/uL), creatinine (7.4 mg/dL), blood urea nitrogen (176 mg/dL), CK (998 U/L), hypernatremia (167 mmol/L), with metabolic acidosis with bicarbonate (17 mmol/L) and anion gap (22). Her TSH was markedly elevated at 91.4 uIU/mL, with low free T4 (0.73 ng/dL) and free T3 (2.26 pg/mL). Further, her urine culture was positive for E.Coli, and the cough aspirate revealed MSSA. She underwent fluid resuscitation per sepsis protocol and was started on broad-spectrum antibiotics, which were tapered down. Further investigation unveiled a history of delusions, hallucinations, and mania-like episodes over the past several months, accompanied by social isolation and questionable medication adherence. She was diagnosed with myxedema psychosis and was treated in the ICU with 200 µg of levothyroxine and 100mg of IV hydrocortisone every 8 hours. After a few days, she was switched to oral 100 µg levothyroxine daily. Her symptoms improved significantly, which was reflected clinically and in subsequent TSH readings.

**Discussion:** Untreated hypothyroidism often presents with hypothermia, bradycardia, and cold intolerance. However, it can escalate into a severe condition known as myxedema coma. Myxedema psychosis, characterized by psychiatric symptoms, is a rare but potentially severe complication of hypothyroidism. Myxedema coma is managed in the ICU, and the ATA guidelines recommend the management with intravenous loading doses of 200-400 µg of levothyroxine. Clinical improvement is typically seen with continued thyroid hormone replacement medication within seven days. Antipsychotics should only be prescribed to patients who have received thyroid replacement therapy, achieved a euthyroid state, and have not had improvement in their psychosis. Despite its potential reversibility, myxedema psychosis is often overlooked as a cause of acute psychosis, highlighting the importance of considering thyroid dysfunction in psychiatric evaluations.

### Poster 0120

*Disorders of Thyroid Function, Case Study, Poster*

#### **Thyroid Function Test Dilemma: A Case of Misleading Pattern**

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Discordant thyroid function test results highlight the need to heed caution interpreting such tests. Atypical patterns such as hyperthyroxinemia with non-suppressed TSH warrant considering a broad differential diagnosis including assay interference, TSH secreting adenoma and resistance to thyroid hormone. Here we present a patient with hypothyroidism who was taken off thyroid hormone treatment due to unusual thyroid function pattern requiring an extensive work-up.

This report discusses a 40-year-old man with history of hypothyroidism treated with levothyroxine presenting with mixed symptoms including fatigue, insomnia, anxiety, weight loss, and constipation. He was recently taken off levothyroxine due to abnormal thyroid labs: TSH 5.97 uIU/mL (0.456-4.68), free T4 1.94 ng/dL (0.78-2.19), and free T3 >22.8 pg/mL (2.8-5.3). Thyroid function tests repeated several times showed similar findings. Physical exam showed no overt signs of hypo- or hyperthyroidism. TSI and TPO were negative while thyroglobulin antibody was positive. Thyroid ultrasound and uptake/scan were normal. SHBG was 64 nmol/L (16-55), alpha-subunit:TSH ratio <1. Other pituitary labs were unremarkable. MRI showed no evidence of pituitary adenoma. The patient denied any family history of abnormal thyroid function tests. Human anti-mouse antibodies were negative. However, thyroid function tests repeated with equilibrium dialysis showed TSH of 20.4 uIU/mL, free T4 0.7 ng/dL (0.9-2.2), and free T3 of 3.0 (1.81-4.06) pg/mL, consistent with hypothyroidism. Further evaluation showed positive heterophile antibody falsely elevating free T3 and T4. The patient was restarted on levothyroxine with plans to monitor TSH and avoid checking T4 and T3 by direct immunoassays.

Heterophile antibodies illustrate an example of how assay interference produces unusual thyroid function test results. Atypical thyroid function patterns can result from various forms of assay interference and from less common thyroid-related conditions. This patient's heterophile antibodies, or antibodies not specific to distinct antigens, affected T4 and T3 levels unless corrected for. Since diseases like thyroid hormone resistance and TSH-producing pituitary adenomas are rare, considering the assay's methodology provides essential context in interpreting atypical patterns. Identifying the etiology of discordant results helps optimize management of patients' thyroid function, including limiting unnecessary diagnostics and improper therapeutic intervention.

### Poster 0121

*Disorders of Thyroid Function, Case Study, Poster*

#### **Severe Thyrotoxicosis as a Precipitant for Diabetic Ketoacidosis**

*Leslie Ha\*, Prasanth Surampudi, Joaquin Lado, UC Davis Medical Center, USA*

**Introduction:** Concurrent presentation of severe thyrotoxicosis and diabetic ketoacidosis (DKA) is rare and early detection is challenging given overlap in symptoms. We present a case of severe thyrotoxicosis in a patient with type 1 diabetes (T1DM), precipitating DKA.

**Description of the Case:** A 53-year-old woman with T1DM and Graves' disease (last treated in 1993 with methimazole) presented with abdominal pain, vomiting and diarrhea. Initial labs revealed glucose 350 mg/dl, bicarbonate (HCO<sub>3</sub>) 20 mEq/L, anion gap (AG)

16 mmol/L with normal beta-hydroxybutyrate (BHB) and venous blood gas (VBG) pH. She was observed and continued on basal-bolus therapy. After several hours, she developed somnolence, agitation, tachycardia and hypertension. Initial investigation identified no clear etiology. However, labs did note undetectable TSH (<0.01 mIU/L), free T4 6.19 ng/dl (n 0.93-1.70) and total T3 9.2 pg/ml (n 1.6-3.9 pg/ml) with thyroid stimulating-immunoglobulin 4.07 IU/L (n <=0.54 IU/L) and thyroid peroxidase antibodies >1000 IU/ml (n <35 IU/ml). A Burch-Wartofsky score of 40 points suggested severe thyrotoxicosis versus possible thyroid storm. She was found to be in DKA nine hours later with glucose 618 mg/dl, HCO<sub>3</sub> 10, AG 32, VBG pH 7.16, and BHB 7.90 mmol/L. In the ICU, the patient was treated concomitantly for DKA and severe thyrotoxicosis. Her DKA resolved and thyroid function improved over several days with propylthiouracil (PTU), iodine supplementation, propranolol, dexamethasone, an insulin drip, and intravenous fluids. Upon resolution of symptoms, she was transitioned from PTU to methimazole on discharge.

**Discussion:** Concurrent presentation of severe thyrotoxicosis and diabetic ketoacidosis (DKA) is rare but potentially fatal, with fewer than 35 published cases and an estimated mortality rate of 15%. Unlike previously reported cases in which patients were found with simultaneous thyrotoxicosis and DKA, our patient presented in thyrotoxicosis without initial ketoacidosis and subsequently developed DKA.

In individuals with Graves and T1DM, one should evaluate for DKA in cases of thyrotoxicosis and vice-versa as excessive thyroid hormone can cause imbalances in glucose homeostasis through synergistic effects on carbohydrate and fatty acid metabolism. In rare cases of concomitant presentation, we recommend early initiation of anti-thyroid therapy and empiric DKA treatment due to risk of rapid decompensation and high associated mortality rates.

### Poster 0122

*Disorders of Thyroid Function, Case Study, Poster*

#### **Case Report: A Rare Presentation of Complete Molar Pregnancy Complicated by Concurring Severe Hyperthyroidism and Preeclampsia with Severe Features in a Perimenopausal Woman**

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**Introduction:** In the United States, hydatidiform moles are observed in approximately 1 in 600 therapeutic abortions and 1 in 1,000–1,200 pregnancies(1,2) and the prevalence of hyperthyroidism and pre-eclampsia in complete hydatiform moles is nearly 7%(3) and 3.5%(4). Within perimenopausal women, complete hydatiform mole is rare(5) and our case highlights prompt recognition and treatment of both severe hyperthyroidism and preeclampsia in complete molar pregnancy in perimenopausal women.

**Case Presentation:** A 51-year-old female G6P4024 presented with a 6-week history of progressively worsening shortness of breath, lower extremity edema, abdominal discomfort, and abnormal vaginal bleeding. Physical examination revealed hypertensive urgency with BP of 188/84mmHg and HR of 105/min, without thyromegaly. Her uterine fundus was palpable at the level of umbilicus and she had +2 bilateral pedal edema. Her workup revealed a positive urine pregnancy test, elevated initial beta-hCG (1167mIU/mL), low TSH (<0.01uIU/mL), elevated free T4 (4 ng/dl), free T3 (1007pg/dl), elevated urine protein creatinine ratio (0.48). CT Abdomen and pelvis with IV contrast and transabdominal ultrasound demonstrated an enlarged uterus with central heterogeneously and enhancing mass concerning for molar pregnancy and subsequent

beta hCG further elevated (270,000mIU/mL). Burch- Wartofsky score was <25 implying low concerns for thyroid storm. Patient was started on Methimazole, Propranolol, and Nifedipine. She was also started on IV MgSO<sub>4</sub> for seizure prophylaxis, due to overall features being consistent with preeclampsia with severe features. Definitive management with a total abdominal hysterectomy and bilateral salpingectomy was performed, and the biopsy confirmed the diagnosis of complete molar pregnancy. She was discharged with oral methimazole and closely followed in outpatient clinic. Over the course her BP normalized, had down trending beta hCG (27mIU/mL), normal TSH (0.599uIU/mL), and low T4 (0.75ng/dL) as she was still on methimazole.

**Discussion:** Hyperthyroidism in molar pregnancy is due to the alpha subunit of human chorionic gonadotropin (hCG) being structurally similar to thyroid stimulating hormone (TSH) causing hyperthyroidism (6,7). While preeclampsia before 20 weeks of gestation is rare, it can present in complete hydatiform moles. To date, very few cases of severe hyperthyroidism in GTD, especially in perimenopausal were reported and only one case of concurring severe hyperthyroidism and preeclampsia in perimenopausal woman has been reported (8). Our case highlights the importance of prompt evaluation with beta-hCG, TSH, T4 and Urine Protein Creatinine ratio to identify the cause of hypertensive urgency in perimenopausal woman and providing appropriate treatment leading to positive outcome.

### Poster 0123

*Disorders of Thyroid Function, Case Study, Poster*

#### **Navigating the Intersection of Graves' Disease and Severe Thrombocytopenia: A Case Report and Management Approach**

Paola Reyes-Torres<sup>\*</sup>, Neshma Román-Velez, San Juan City Hospital, USA

**INTRODUCTION:** Graves' disease is an autoimmune disorder causing hyperthyroidism, which manifests with palpitations, exophthalmos, weight loss, and goiter. Few cases describe the acute diagnosis of Graves' disease in patients with a history of long-term ITP treatment. We describe a 42-year-old female with refractory ITP, initially managed with steroids and IV immunoglobulins, who presented acutely with symptoms suggestive of thyrotoxicosis. Diagnosis of Graves' was confirmed afterward. Methimazole treatment and I-131 radioiodine ablation resolved hyperthyroidism and improved thrombocytopenia with stable platelet levels on follow-up.

**DESCRIPTION OF THE CASE:** We present a 42 y/o female with PMHx of refractory ITP who presented to the ER complaining of palpitations, elevated blood pressure, palpitations, irritability, and gastrointestinal hyperfunction over 2 weeks. Examination revealed facial flushing, rapid speech, tachycardia, exophthalmos (CAS score 1), a WHO grade 2 goiter without bruits or thrills, and a palpable nodule at the left lobe. Laboratories findings showed thrombocytopenia (52K), suppressed TSH (0.007uIU/mL), elevated freeT4 (>5.0ng/dL), elevated TotalT3 (7.5ng/mL), elevated TotalT4 (29uG/DL), ThyroglobulinAb: 11UI/mL and TSI: 273 confirming thyrotoxicosis due to Graves' Disease. Hepatic transaminase, bilirubin, renal function, and electrolytes were all normal. Thyroid ultrasound revealed a heterogeneous thyroid gland with a solid hypoechoic nodule in the left lobe. Management included acute control of thyrotoxicosis with Propranolol 60mg and subsequent treatment with Atenolol 25mg and Methimazole 10mg. Thyroid Scan showed diffuse goiter with increased tracer uptake (79%) and the patient underwent I-131 radioiodine ablation. Follow-up revealed clinically euthyroid with expected post-iodine hypothyroidism (low FT4: 0.15ng/dL, TSH: 2.84uIU/mL), resolution of symptoms, goiter, and platelet levels (146K). Levothyroxine was initiated at 125 mcg based on lean weight, achieving euthyroidism six weeks later.

**DISCUSSION:** Graves' stands as the predominant cause of autoimmune hyperthyroidism, commonly linked with hematologic abnormalities. Despite extensive treatment, the patient experienced recurrent thrombocytopenia and thyrotoxicosis. Our case highlights the effectiveness of radioiodine ablation in achieving euthyroidism, as it concurrently improves platelet levels. Moreover, we advocate for thyroid function test screening in individuals with ITP, particularly in the absence of goiter and exophthalmos. Additionally, it emphasizes the need for a multidisciplinary approach in managing complex cases involving endocrine and hematological disorders.

### Poster 0124

*Disorders of Thyroid Function, Case Study, Poster*

#### **Sexual Dysfunction, Hypertestosteronemia, and Surprising Thyrotoxicosis!**

*Sarah Makadsi, Ranim Chamseddin\*, Julie Samantray, Wayne State University, USA*

The relation of sex hormone binding globulin (SHBG) and thyroid hormone is well documented in the literature. The serum concentration of SHBG is elevated in hyperthyroid state and has been used in the past as a marker of thyroid hormone effect at the peripheral tissue. Sexual dysfunction has been reported in males with thyroid dysfunction. Here we highlight a case of thyrotoxicosis presenting with hypertestosteronemia.

A 64-year-old man with history of well controlled type 2 diabetes presented to his primary care physician with multiple complaints. He reported a 6 month history of poor energy, weight loss and erectile dysfunction. He attributed the weight loss to lifestyle changes for diabetes and obesity.

He was found to have a resting HR of 120/min and was in atrial fibrillation at that visit. Laboratory results revealed Total Testosterone 1,115 (350-720 NG/dL), FSH 30.1 mIU/mL and LH 46.3 mIU/mL. Calculated free testosterone level was low normal. Prolactin, IGF1, Cortisol levels were normal. CT of the pituitary, abdomen and pelvis were normal. Due to persistent symptoms, he was referred to endocrinology. Thyroid function testing was done and showed TSH <0.005 (0.45-4.5 uIU/mL) and Free T4 of >7.7 (0.82-1.77 NG/dL) with a total T3 of 587 (71-180 NG/dL). Methimazole and a beta blocker were started. SHBG level was 239 (19.3-76.4 nmol/L). 12 weeks after starting methimazole he reported improved energy, weight gain, and resolution of erectile dysfunction. Labs showed normalization of Free T4, SHBG, gonadotropins and total testosterone levels.

Thyroid hormones act indirectly to increase the hepatic synthesis of SHBG. SHBG binds testosterone with high affinity and positively correlates with testosterone levels. The testosterone bound to SHBG is biologically inactive and therefore, not a true reflection of androgen status. Elevated LH and FSH with high total testosterone but normal free testosterone levels can be explained by age related dysregulation of feedback. Elevated SHBG should prompt an evaluation for hyperthyroidism. In this case, early diagnosis and treatment would have prevented unnecessary laboratory and imaging studies.

### Poster 0125

*Disorders of Thyroid Function, Case Study, Poster*

#### **Battling the Perfect Storm – A Case Report of Unyielding Treatment Challenges in Refractory Thyroid Storm**

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**Introduction:** Thyroid storm is a rare, life-threatening event that can lead to multiorgan failure and death. Treatment involves a multidisciplinary approach including supportive care in an intensive care unit (ICU) (1,2). Patients who fail medical therapy require adjunct therapy such as therapeutic plasma exchange (TPE). This case highlights a patient with severe thyrotoxicosis who failed multiple treatment modalities including medical therapy, TPE, VA-ECMO, and thyroid artery embolization.

**Description of the Case:** A 49-year-old male with a past medical history of Graves' disease noncompliant with methimazole, diabetes mellitus, and methamphetamine abuse presented to the emergency department with shortness of breath. The vital signs were temperature of 37.7 C, pulse 155 and irregular, blood pressure 95/73, respiratory rate 26, and requiring FiO<sub>2</sub> of 30%. He was found to be in atrial fibrillation with rapid ventricular rate. Pertinent labs included TSH <0.01 ng/dL, free T4 6.41 ng/dL, total T3 410 ng/dL, and left ventricular ejection fraction (LVEF) of 15-20%. He required cardioversion for unstable atrial fibrillation with admission to the ICU for cardiogenic shock and thyroid storm. In the ICU, he required intubation then was started on propylthiouracil, potassium iodide, stress dose corticosteroids, esmolol and cholestyramine. He continued to decline, leading to placement of Veno-Arterial Extracorporeal Membrane Oxygenation Support (VA-ECMO). He later underwent 5 TPE sessions without improvement. He eventually underwent a right inferior thyroid artery embolization, given that he was deemed high risk for total thyroidectomy. Before benefits of therapy could be assessed, the patient died from cardiac arrest.

**Discussion:** Thyroid storm is a sequela of severe thyrotoxicosis with mortality rates as high as 10-30%. (4). Patients who do not respond to standard therapy will require interventions such as TPE, VA-ECMO, and thyroid artery embolization before definitive surgical management. Current guidelines for treatment of refractory thyroid storm are based primarily on case reports and retrospective studies. This patient had persistent thyrotoxicosis despite standard medical therapy, TPE, thyroid artery embolization, and VA-ECMO (7,8). Conducting interventional clinical trials for testing the safety and clinical effectiveness of TPE treatment and thyroid embolization is essential to improve clinical outcomes in refractory thyroid storm.

### Poster 0126

*Disorders of Thyroid Function, Case Study, Poster*

#### **A Rare Case of Acute Infectious Thyroiditis Masquerading As Subacute Thyroiditis - A Diagnostic Dilemma**

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**Introduction:** While subacute thyroiditis (SAT) is commonly encountered in outpatient settings, acute infectious thyroiditis (AIT) is very rare. In AIT, the patient presents with acute neck pain and abnormal thyroid function tests (TFTs) which may be difficult to differentiate from SAT.

**Case Description:** 45 year old female with no significant medical history presented with neck pain, fevers, palpitations, and weight loss for one month. After week one she was seen by an endocrinologist and found to be hyperthyroid. Prednisone and atenolol were commenced for presumed SAT. There was an initial improvement in symptoms, but she later worsened clinically and eventually presented to another endocrinologist tachycardic, febrile and was hospitalized. Lab investigations were significant for leukocytosis (14.9), elevated ESR and fT4 and low TSH. Thyroid ultrasound showed an enlarged heterogenous and hypervascular gland. Patient was treated for AIT with empiric intravenous ampicillin/sulbactam and

prednisone. She clinically improved and was discharged in four days. Two weeks post-hospital discharge her TFTs normalized and at week 3 became hypothyroid and commenced on levothyroxine.

**Discussion:** AIT is most commonly due to gram positive bacteria in immunocompromised patients but 28% of cases are without an identifiable cause. 80% of cases present with fever and tenderness of the anterior neck (1). SAT presents similarly, and this may lead to misdiagnosis as seen here. Therefore, it should be noted that in the reported cases of bacterial thyroiditis, in addition to fevers, there is usually an elevated white cell count and ESR (1). In comparison with SAT, fever and leukocytosis are less common (only in 30% of cases) and usually preceded by upper respiratory tract infections (2). Additionally, transient thyrotoxicosis at presentation is usually seen in SAT. This is less common in AIT, but when present more than 1/3 of cases has  $ft4 > 2x$  ULN (1). Prednisone use in thyroiditis can result in initial improvement clinically, but subsequent worsening of symptoms should raise a red flag for AIT (3). Finally, clinicians should be aware of the progression of AIT as 25% of cases result in long-term hypothyroidism (1), as early as week 3 post-infection as in our case.

### Poster 0127

*Iodine Uptake and Metabolism, Case Study, Poster*

#### **A rude awakening: Atrial Fibrillation because of IV Contrast Administration**

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**Introduction:** Jod-Basedow phenomenon (JBP) is a rare, usually self-limiting condition in which exposure to massive amounts of exogenous iodine or iodinated compounds results in the development of a hyperthyroid state. In a small number of the population, this can result in life threatening thyrotoxic complications like arrhythmias, heart failure and cardiomyopathy. We present an interesting case of a 67-year-old-female who developed JBP after receiving intravenous iodinated contrast for computed tomography angiogram (CTA) chest to rule out pulmonary embolism.

**Case Presentation:** A 67-year-old female with history of ESRD on dialysis, hypertension and type 2 diabetes presented to the hospital with shortness of breath in setting of missed dialysis resulting in volume overload. She was admitted to the hospital and underwent dialysis without any complications. However, she was persistently hypoxic and tachycardic, rising concern for pulmonary embolism. CTA chest was obtained and ruled out pulmonary embolism but did show asymmetric enlargement of the left thyroid lobe containing small, calcified nodules. The following day, she developed new onset atrial fibrillation with rapid ventricular response. Further workup revealed a TSH level of less than 0.01uIU/mL (normal: 0.45-5.33 uIU/mL) with elevated free thyroxine of 1.83 ng/dL (normal: 0.60-1.31 ng/dl). A review of past records revealed low TSH levels, consistent with subclinical hyperthyroidism. Her new atrial fibrillation was attributed to her abnormal thyroid function. She underwent NM scan of the thyroid gland, which revealed no uptake. TRAB, TSI and anti-TPO antibodies were negative. Endocrinology deemed that her sudden overt thyrotoxic state during this admission was possibly due to the administration of iodinated contrast, when CTA chest was obtained, likely leading to JBP, exacerbated due to contrast administration on her non-dialysis day. Her atrial fibrillation was controlled on a beta blocker, and she was advised to follow up with endocrinology outpatient to check for resolution.

**Discussion:** JBP is usually self-limiting, with return to euthyroid state gradually, once the contrast is eliminated from the body. Patients with underlying clinical or subclinical hyperthyroid disorder

are at a predisposed risk for development of JBP. Physicians should be cautious while ordering iodine-based studies in patients with underlying thyroid conditions and keep this mind with new onset symptoms of hyperthyroidism in the clinical course.

### Poster 0128

*Pediatrics, Case Study, Poster*

#### **Metastatic Oncocytic Thyroid Carcinoma Presenting as Back Pain: An Autobiographical Case Report**

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**INTRODUCTION:** This case report is an autobiographical summary of a 17-year-old teenager's journey with metastatic oncocytic thyroid carcinoma (OCC).

**DESCRIPTION:** As a 17 year old high school senior, I began experiencing severe back pain and underwent MRI spine which incidentally visualized a 4.1 cm right thyroid nodule. FNA demonstrated Bethesda IV cytology, and molecular testing estimated a 50% chance of malignancy. After diagnostic right thyroid lobectomy, surgical pathology showed a 3.1 cm OCC with possible vascular invasion. There was no evidence of cervical lymph node metastases by ultrasound. I underwent completion thyroidectomy, which was complicated by permanent hypoparathyroidism. Postoperatively, my Tg was noted to be still very high at 675.4 ng/mL. I was referred for dosimetric RAI treatment. During dosimetry, ten metastatic sites were discovered in my bilateral humeri, thoracic spine, ribs, sacrum and pelvis. I received 346 mCi I-131, which has led to long-term xerostomia. One year after RAI therapy, I-131 whole body scan showed no iodine avid disease, but MRI still showed bony metastases. Therefore, we have continued to monitor my disease with MRIs, as well as neck ultrasounds and upper extremity x-rays every 6 months. My Tg trend has also been reassuring: over the past two years, my Tg level has decreased from 675.4 ng/mL to 1.8 ng/mL. I am currently in college, swimming at the NCAA Division III level and pursuing a degree in chemistry. I also have had the opportunity to educate others and raise awareness about thyroid cancer, through my Instagram account @kathleenscancerchronicles, podcasting, and local newspaper interviews.

**DISCUSSION:** Pediatric differentiated thyroid cancer is rare, and OCC is even less common, accounting for less than 10% of pediatric differentiated thyroid cancer cases. A 5-patient case series of pediatric OCC suggests that OCC is no more invasive than other pediatric differentiated thyroid cancer histotypes. As my case highlights, vascular invasion with distant metastasis may occur in pediatric OCC. Additional cases and research are needed to understand the incidence, behavior and response to therapy of pediatric OCC, in order to optimize care and provide more accurate anticipatory guidance to individual patients like myself.

### Poster 0129

*Pediatrics, Case Study, Poster*

#### **The Effectiveness of Teprotumumab in Treating Graves' Dermopathy in an Adolescent**

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**Introduction:** Graves' dermopathy, an autoimmune complication of Graves' disease, is typically managed with steroids and sometimes intravenous immunoglobulins (IVIG) or rituximab for progressive cases. Teprotumumab, a monoclonal antibody targeting the insulin-like growth factor 1 receptor, has demonstrated efficacy in refractory adult cases of Graves' dermopathy, but little is described in pediatric cases. Here, we present a case of an adolescent male with refractory Graves' disease-associated pretibial myxedema successfully treated with teprotumumab, shedding light on its potential in pediatric patients.

**Case Presentation:** A 17-year-old male, diagnosed with Graves' disease three years prior to presentation was mostly euthyroid after initiating methimazole. Following diagnosis, he developed thyroid eye disease, and a year later, progressive severe bilateral lower extremity swelling and small joint acropachy emerged. At presentation, his free T4 was 1.4 ng/dl (reference range 1-1.6 ng/dl), total T3 of 166 ng/dl (reference range 91-218 ng/dl), and TSH was suppressed at <0.01. An incisional skin biopsy demonstrated significant mucin deposition indicative of Graves' myxedema. Initial management with topical steroids followed by three doses of IVIG resulted in no symptom alleviation. Due to his persistent and severe clinical course, teprotumumab therapy was initiated. After three infusions (initial dose of 10 mg/kg followed by 20 mg/kg every three weeks), notable reduction in skin induration, lower extremity girth, and swelling was observed. The affected surface areas on the shins bilaterally have decreased in size, with midfoot circumferences measuring 27.5 cm on the right and 27 cm on the left (improved from 29 cm bilaterally). Additionally, measurements just above the right ankle decreased to 26 cm (from 27.5 cm). Complete resolution of prior acropachy was noted, with no further soft tissue enlargement between his finger interphalangeal joints. Given the favorable response, teprotumumab infusion has been continued without any side effects.

**Discussion:** This case highlights the potential efficacy of teprotumumab in managing refractory Graves' dermopathy in pediatric patients as a promising therapeutic option in cases resistant to conventional treatments. Further studies are warranted to assess its efficacy and safety profile in pediatric populations.

### Poster 0130

*Surgery, Case Study, Poster*

#### **Metastatic Lower Extremity Leiomyosarcoma with Thyroid Metastasis**

*Amy Li<sup>\*</sup>, Dong Ren, Kiarash Mashayekhi, Warren Chow, Beverly Wang, Melissa Mao, University of California, Irvine, USA*

**Introduction:** The thyroid is an extremely rare site of metastatic disease, occurring in approximately 1.4-3% of all thyroid tumors. The most common malignancies that metastasize to the thyroid include renal cell carcinoma, colorectal, and lung cancers. Approximately 4% of thyroid metastases result from sarcoma. While there have been upwards of >20 cases of thyroid metastases originating from uterine/vaginal leiomyosarcoma, lower extremity leiomyosarcoma is an even rarer source of metastasis to the thyroid.

**Description of the Case:** A 53-year-old gentleman presented with an 11cm left thigh leiomyosarcoma. Staging workup revealed synchronous contralateral thigh, lung, and bony metastases. He underwent resection of a large 25cm left thigh primary tumor due to rapid growth with debilitating pain. Lung biopsy was also performed. Pathology was consistent with metastatic poorly differentiated leiomyosarcoma. Postoperatively, he completed adjuvant chemotherapy and targeted therapy, with progression of disease, followed by development of liver metastases and rapid growth of

multiple thyroid nodules. Ultrasound of one large thyroid nodule showed a solid, hypoechoic, taller-than-wide lesion with macrocalcifications and ill-defined margins. The isthmus nodule was solid, hyperechoic, wider-than-tall with lobulated/irregular margins. Biopsy of both lesions showed atypical spindle cells concerning for metastasis. There was rapid growth of the goiter with worsening neck pressure/discomfort, though without dysphagia or dyspnea. The patient underwent subtotal thyroidectomy due to concern for impending aerodigestive compromise. Intraoperatively, there was encasement of the left recurrent laryngeal nerve. Palliative debulking was performed while preserving the left recurrent laryngeal nerve. Pathology was consistent with metastatic leiomyosarcoma with extensive tumor necrosis, Ki 67 >50%. He tolerated the procedure well and was since started on pembrolizumab.

**Discussion:** To our knowledge, this is the third case in the literature of a lower extremity sarcoma that has metastasized to the thyroid, and only the second case reported in the United States. Consistent with the prior case reports, leiomyosarcoma metastasis to the thyroid is characterized by rapid growth. Ultrasound findings can vary even between nodules. Thyroid metastasis reflects the aggressive nature of the primary disease process and treatment options appear to be limited. Pathologic diagnosis is necessary to determine diagnosis and dictate management.

### Poster 0131

*Surgery, Case Study, Poster*

#### **Delayed, Recurrent Post Thyroidectomy Seroma: Case Report and Literature Review**

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**Introduction:** Seroma is defined as a collection of fluid within the surgical site during the postoperative period that can cause several complications, including pain, anxiety, and increased hospital visits, leading to higher costs of care. The reported incidence of seroma from conventional thyroid surgery varies from 1.3% to 7%.

**Description of the Case:** A 46-year-old woman underwent a total thyroidectomy on 11/16/23 due to multinodular thyroid hyperplasia with compressive symptoms, including dysphagia, odynophagia, and globus. Postoperative labs showed an intact PTH of 14 and calcium of 9.2. She had an uncomplicated 23-hour observation and was discharged the next morning. The final pathology was consistent with multinodular hyperplasia. At the outpatient follow-up two weeks later (11/29/23), she reported improved compressive symptoms. On 1/9/24 (54 days after the operation), she presented to the ER (emergency room) complaining of neck swelling and tenderness, and dysphagia. She mentioned she was recovering from a recent upper respiratory infection. Blood tests showed a WBC of 10, and Tmax was 101.4. 3 mL of serous fluid was aspirated and sent for culture; no growth was reported. She was discharged 24 hours later with a 7-day course of Flagyl (Pfizer Inc., New York, USA). She returned to the ER on 1/21/24 (66 days after the operation and 12 days after the previous evaluation) with a cough, sore throat, neck swelling, shortness of breath, headache, and dysphagia. Blood tests showed a WBC of 13, and she was afebrile. Incision and drainage of the infected seroma were performed, and the culture grew Haemophilus influenzae. She was discharged with a course of Levaquin (Janssen Pharm., Beerse, Belgium) once the Jackson-Pratt drainage was removed.

**Discussion:** This case illustrates the potential for delayed, recurrent post-thyroidectomy seroma, although patients often present 7 to 10 days following wound closure or wound drain removal with a

fluctuant collection near the operative site. Possible contributing factors include the involvement of residents/trainees leading to increased operative time (138 minutes compared to 200 minutes), continued tobacco use by the patient, and the older age of 46.

### Poster 0132

*Thyroid Hormone Action, Metabolism and Regulation, Case Study, Poster*

#### **Thyroid Associated Ophthalmopathy; A Rare Presentation of Hypothyroidism**

*Marcos Chacon<sup>\*</sup>, Jorge Soto, Mayaguez Medical Center, Puerto Rico*

Thyroid-associated ophthalmopathy (TAO) is an ocular condition that frequently manifests with thyroid dysfunction, and is the most common extrathyroidal manifestation of Graves' disease. A systematic review of prevalence of thyroid function in patients already diagnosed with thyroid-associated ophthalmopathy, found 86.2% prevalence with hyperthyroidism; 10.36% prevalence with hypothyroidism; and 7.9% with euthyroid states. Thyroid associated ophthalmopathy is rare in patients with Hashimoto's thyroiditis, and only few cases have been reported.

Case of 90 y/o female patient with Past medical history of diabetes mellitus type 2, hypertension, atrial fibrillation, hypothyroidism and osteopenia who was brought to ER after suffering a fall from her bed, earlier today over her left side; since then, she reifers Left hip pain associated with limited active and passive range of motion. Orthopedic surgeon consulted who performed a Left hip hemiarthroplasty w/o complication. Upon evaluation, patient was found with exophthalmos bilaterally. The patient received 4/7 points in the Clinical Activity Scale (CAS) due to the eyelid edema, redness, conjunctival injection, and inflammation of left caruncle. Laboratory work up revealed TSH in 7.14 uIU/mL, FT4 0.79 ng/dl, Thyroid peroxidase antibody <9 IU/mL, Thyroglobulin <0.1 IU/mL, Thyroid Stimulating Immunoglobulin <0.10. Also, orbital CT was performed and found with bilateral orbital proptosis of up to 28 mm. Imaging findings correlate with clinical presentation of exophthalmus.

This case illustrates a rare presentation of Hypothyroidism, due to Thyroid ophthalmopathy prevalence with hypothyroidism is 10.36% and is more described in a patient with Graves Disease. As a Doctor, no matter what medical specialty we have, a good clinical history and physical examination is always an essential part of making a correct diagnosis. This Thyroid associated ophthalmopathy can sometimes occur in Hashimoto's thyroiditis and awareness of this atypical form is important. Prompt recognition and treatment can prevent corneal involvement and blindness due to optic nerve compression. Patient was discharged home with home care and endocrinologist follow up.

### Poster 0133

*Thyroid Nodules and Goiter, Case Study, Poster*

#### **Not So Benign: A Case of Thyroid Nodule Regrowth**

*Karen Jong<sup>\*1</sup>, Muddasir Fariduddin<sup>2</sup>, Daniel Toft<sup>1</sup>, <sup>1</sup>University of Illinois Chicago, USA, <sup>2</sup>Ayaan Institute of Medical Sciences, India*

A benign thyroid fine needle biopsy result is almost always great news. It becomes concerning when these benign nodules behave unexpectedly and aggressively. We present a case of recurrent thyroid tissue regrowth and discuss the role of genetic testing.

A 33 year-old female with history of multinodular goiter status-post total thyroidectomy with benign pathology in 2006 presented to clinic in 2019 with recurrent bilateral thyroid nodules causing compressive

symptoms. Fine-needle aspiration revealed two Bethesda II and one Bethesda III nodule. In 2020, CT neck showed increasing size of the nodules now extending into the superior mediastinum. She underwent revision thyroidectomy requiring partial sternotomy in July 2021 to remove recurrent thyroid tissue in the right and left thyroid bed, a suprasternal nodule, and a level 5 thyroid mass. Some residual left thyroid bed tissue remained due to proximity to the recurrent laryngeal nerve. Pathology of the suprasternal nodule was follicular adenoma and the rest was thyroid follicular nodular disease. Ultrasound in May 2022 showed tissue regrowth in the right and left thyroid beds, 4.9cm and 5.7cm, respectively. Her levothyroxine was increased for TSH suppression. Ultrasound in March 2024 showed slightly increased growth in both thyroid bed masses. GeneAssure testing showed no BRAF or RAS mutations, but Tier III variants BRCA1 p.K619E and MYC p.V185I, copy number variant gain in NF1, RAD51D CDK12, BRCA1, and RNF43, and hemizygous loss of TP53.

Follicular thyroid adenomas (FTA) and follicular thyroid carcinomas (FTC) may constitute a continuum of disease, given similarities in their genetic backgrounds. TP53 mutations have been found in both follicular thyroid adenoma and carcinoma, and some even suggest that TP53-mutant FTA is a precursor to FTC and anaplastic thyroid carcinoma. We suspect that hemizygous loss of TP53 may have conveyed aggressive growth potential in this patient's tumor. There are also several other mutations present which are of uncertain clinical significance. We are not aware of any reported case series regarding somatic mutations in "benign," but aggressive, follicular adenomas. There is also no expert consensus on treatment of these entities, causing a clinical challenge for the clinician and the patient.

### Poster 0134

*Thyroid Nodules and Goiter, Clinical, Poster*

#### **Training Programs for Thyroid Biopsy and Ablation: A Systematic Review and Meta-Analysis**

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**Objective:** The care of patients with thyroid nodules often involves the consideration of thyroid biopsy (FNA) and, more recently, ablative techniques. This study aimed to summarize the key components of training programs for these procedures, and their outcomes.

**Methods:** A systematic review was conducted on training programs for FNA or ablative procedures. Studies from 2000 to October 2023 were identified from five databases. Data extraction by two reviewers encompassed study design, training program components, and outcomes, categorized using the Kirkpatrick classification and risk of bias assessment. A narrative synthesis of findings is presented due to limited and heterogeneous data, with the exception of the rate of non-diagnostic results for which meta-analysis was performed.

**Results:** Eleven studies, encompassing 131 participants, were included. Risk of bias was moderate to high as most studies were single cohorts with before and after training outcome assessment. The majority (9/11, 82%) of training programs employed a multimodal approach, incorporating didactics and practical sessions using various thyroid training models. Additional training strategies included direct clinical supervision, debriefing exercises, and communication scenarios. Among the 10 studies assessing FNA training using the Kirkpatrick classification, 4 evaluated learners' reaction to the training, 6 measured learning outcomes, and 3 examined clinical outcomes. A single study focusing on ablative techniques demonstrated a volume reduction rate of 82% in procedures performed

by those who completed the training. Of the studies assessing learners' reactions, all demonstrated consistent enhancements in confidence, comfort, and overall satisfaction with the training. Among the studies focusing on learning outcomes, one assessed conceptual knowledge and reported post-training testing improvements, while the remaining five evaluated technical skills. Of these, two studies reported statistically significant improvements in at least one technical skill, such as nodule identification and/or aspiration time. Two studies conducted before-and-after training evaluations of non-diagnostic rates, with an average reduction in non-diagnostic rate of -8.6% (95% CI -8.94, -8.28,  $I^2=99$ ).

**Conclusions:** This comprehensive review of training programs for FNA and ablative procedures revealed a predominant use of multi-modal approaches, including didactics and practical sessions. Improvements were observed in learners' confidence and technical skills and decreases in non-diagnostic rates post-training.

### Poster 0135

*Thyroid Cancer, Case Study, Poster*

#### **Cytologically Indeterminate Thyroid Nodules with 3 or More High-Grade Genetic Mutations Have Poor Outcomes**

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While thyroid carcinomas with multiple genetic alterations have been shown to have poor prognosis, there is limited data on cytologically indeterminate tumors with 3 or more mutations. We present a series of 6 such cases with outcomes.

Of 6 thyroid tumors at our institution identified between 2016 and 2023 with 3 or more potent oncogenic driver mutations, 5 were malignant and 1 was benign, with sizes ranging from 1.7 to 7.2 cm. The average age at diagnosis was 63 years, and 5 cases were female. Despite the genetically high-grade profiles, all cases had benign or indeterminate cytology.

The primary driver mutation was an isoform of *RAS* in all 6 cases. All cases had *TERT* mutations. Additional mutations included *EIF1AX*, *DICER1*, and *PIK3CA*. Based on initial surgical pathology, 3 patients were ATA high-risk, including a follicular thyroid carcinoma (FTC) with extensive angioinvasion, poorly differentiated thyroid carcinoma with extensive angioinvasion, and a follicular variant of papillary thyroid carcinoma (PTC) with extensive angioinvasion. An FTC with minimal capsular invasion was ATA low-risk; however, follow-up to date has only been 12 months. The remaining 2 cases were benign follicular adenomas (FA) on initial surgical pathology. However, one of these "benign" FAs developed sternal metastases 7 years later. Genomic analyses of the metastasis and retrospective analysis of the original benign FA confirmed that both had an identical high-grade genetic profile suggesting that the "benign" FA was in fact a metastatic carcinoma.

Although this series includes only 6 patients, it is the largest to date reporting cytologically indeterminate thyroid tumors with 3 or more potent genetic driver mutations, of which 4 demonstrated aggressive clinical features. The majority of these tumors presented with benign or indeterminate cytology, likely because primarily *RAS*-driven tumors have histologically follicular architecture and lack nuclear changes typical of PTC, whereas *BRAF*-driven tumors generally have overtly malignant cytology for which genetic testing is typically not done. Given the clinically aggressive behavior of these tumors with indeterminate cytology and 3 or more potent oncogenic driver mutations, primary surgical management with total thyroidectomy should be considered, even though the initial cytology is not highly suspicious.

### Poster 0136

*Pregnancy and Development, Case Study, Poster*

#### **Transient Hypoparathyroidism in Pregnancy**

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Hypoparathyroidism in pregnancy can be difficult to diagnose given the changes in calcium homeostasis. Complications include seizures, miscarriage, preterm delivery, and *in utero* fractures. We present a case of a pregnant woman who developed transient hypoparathyroidism resulting in seizures.

A 44-year-old G2P1 woman with a history of hypothyroidism presented with numbness and tingling during her second pregnancy. During her first pregnancy she developed mild asymptomatic hypocalcemia in the 3rd trimester. Between her first and second pregnancy she had normal calcium levels. Initially in her second pregnancy, her corrected calcium was normal and PTH levels decreased, as is expected in pregnancy. At 24 weeks of gestation, she presented again with numbness and tingling. Labs were notable for an ionized calcium of 5.0 mg/dL (range 4.8-5.6), PTH 13.1 ng/mL (range 10-65), 25-OH vitamin D 39 ng/mL, and an undetectable 1,25-OH vitamin D. Although started on calcitriol 0.5 mcg daily, she experienced a focal seizure. Labs showed ionized calcium of 4.4 mg/dL (range 4.8-5.6), Mg 1.8 mg/dL (range 1.5-2.5), PTH of 3.3 ng/mL (range 10-65), PTHrP 15 pg/mL (range 14-27). She had no prior history of neck surgery or radiation. Her calcium and calcitriol supplements were increased and she remained stable. Delivery was complicated by a pneumothorax in the baby, but was otherwise unremarkable. She was followed for 3 years postpartum with normal calcium, vitamin D, and PTH levels without supplementation.

During pregnancy, the placenta and breast tissue produce PTHrP, leading the maternal kidneys and placenta to increase calcitriol production. The PTH level correspondingly decreases, so that the corrected calcium and ionized calcium levels remain normal throughout. The patient presented here developed symptomatic hypocalcemia in the 3rd trimester and was found to have a low PTH, but the PTHrP did not rise as would be expected. The etiology of this patient's transient and clinically significant hypoparathyroidism remains unclear, but it is hypothesized that she may have failed to manifest the appropriate PTHrP elevation of pregnancy or perhaps she developed calcium sensing receptor (CaSR) antibodies leading to decreased PTH release. Fortunately, her infant was not affected.

### Poster 0137

*Thyroid Cancer, Case Study, Poster*

#### **Follow-up of radiofrequency ablation for papillary thyroid microcarcinoma: is the fine needle aspiration biopsy a good strategy?**

Cristhian Garcia<sup>\*1</sup>, Andrea Solis<sup>2</sup>, Michelle Ojeda<sup>1</sup>, Ana Perez<sup>1</sup>, Kevin Carrillo<sup>1</sup>, Eduardo Pilatuna<sup>3</sup>, <sup>1</sup>Instituto de Tiroides y Enfermedades de Cabeza y Cuello, Ecuador, <sup>2</sup>Santa Casa de Misericordia, Brazil, <sup>3</sup>Universidad San Francisco de Quito, Ecuador

**Introduction:** Ultrasound is currently the most reliable tool in the follow-up post-radiofrequency ablation (RFA) in thyroid nodules. However, thyroid fine needle aspiration biopsy (FNA) is an accurate test for determining malignancy in a nodule.

**Objectives:** This study aimed to evaluate the safety and efficacy of RFA in papillary thyroid microcarcinoma (PTMC) using FNA in the follow-up.

**Methods:** Single-center, retrospective study at ITECC. We included adults undergoing RFA for PTMC between May 2021 and

May 2023. In the follow-up, all patients who underwent FNA cytology were classified according to the Bethesda scoring system. The primary endpoints were local tumor progression (LTP) and disease-free survival (DFS).

**Results:** Among the 18 patients (median age, 46 [21- 63 years]; 15 women), nobody had LTP during a median follow-up of 1.5 years. The pre-RFA median volume in the PTMC group was 0.22 ml (IQR 0.05- 1). After ablation, the 1-month, 3-month, and 6-month mean volumes were 0.24 (range 0.02- 1.39;  $p=0.002$ ) mL, 0.02 (IQR 0.00-0.4;  $p=0.001$ ), and 0.00 (IQR 0.00-0.26;  $p= 0.03$ ), respectively. The volume reduction (VR) was increased in the first month post RFA 63.09 (-64.06; 1615.28). Then those decreased to -76.85 (-99.43; - 483.33), -95.1 (-100; 100), and -100 (-100; -98) at 3, 6, and 12 months after RFA. No local recurrence, new tumors, lymph node metastasis, distant metastasis, or deaths caused by recurrent/metastatic PTMC were found at the last follow-up. All patients underwent FNA at 9 months after RFA. All FNA cytology results were reported as benign (Bethesda II), except one patient who had positive FNA (Bethesda III) and underwent an additional RFA.

**Conclusion:** FNA stands as a practical and efficient evaluation tool for PTMC post-RFA, enabling the early detection of residual cancer cells and helping in the decision of additional treatments.

### Poster 0138

*Thyroid Nodules and Goiter, Case Study, Poster*

#### **Outcomes of patients who underwent hemithyroidectomy: A first retrospective cohort study in Ecuador**

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**Introduction:** Thyroid cancer incidence is building up. Over the last two decades, the guidelines recommend less invasive therapies for the treatment of low-grade thyroid nodules like hemi thyroidectomy (HT). It is a less aggressive and more personalized therapy for the patient, avoiding hypothyroidism secondary to surgery, and reducing the risk of hypoparathyroidism. This article presents a group of patients who underwent hemithyroidectomy following the guidelines of the ATA and NCCN, as well as their postoperative follow-up to demonstrate the guarantee of this surgical procedure in patients with low-risk nodules.

**Methods:** Single center, retrospective study at ITECC. We include adults undergoing an HT from 2019 to December 2022. In the follow up we collected thyroid cancer markers measured after the HT, histopathological features (size, type, invasion, and focalization), and complications (hypocalcemia, recurrent laryngeal nerve injury). All the surgeries were performed by the same surgeon.

**Results:** Among of 23 patients (18 female, 78,3%) the mean age was 45 years. 52% were benign thyroid nodules (BTN) and 48% were papillary thyroid microcarcinoma (PTMC). In the BTN the mean tumor size was  $3.8 \pm 1.6$  cm, whereas in the PTMC was  $6.6 \pm 3$  mm. All patients had stage I disease according to the AJCC staging system. In the follow-up, most of the patients (83%) had normal thyroid hormones (TSH 2.95  $\mu$ IU/ml). Four patients developed hypothyroidism in the postoperative. In the PTMC group, the mean thyroglobulin was 9.65 and most of them kept a descending or flat TG trend. There was no local tumor progression or lymph node metastasis

**Conclusions:** Hemithyroidectomy for benign thyroid nodules and low-risk thyroid cancers is safe to perform in an outpatient setting for a selected patient. It is associated with less extensive surgery and lower rates of surgical complications.

### Poster 0139

*Thyroid Cancer, Case Study, Poster*

#### **Diffuse Parenchymal Micro-calcifications in the Thyroid Gland with or without Thyroid Nodule: Clinical Significance**

*FNU Manas<sup>\*</sup>, Sharon Lahiri, Henry Ford Hospital, USA*

**Introduction:** Microcalcifications are sub-centimetric punctate echogenic foci without posterior acoustic shadowing seen in ultrasonography (US). They may represent dystrophic calcification, intravascular tumor thrombi calcifications, or malignant papillae infarction. Fine needle aspiration (FNA) biopsy is warranted if microcalcifications are seen in thyroid nodules, especially in solid hypoechoic nodules. Microcalcifications without nodules can be seen in up to 2% of patients with papillary thyroid cancer (PTC) and have been reported in diffuse sclerosing variant PTC and classical PTC. They are a predictor of thyroid malignancy, even without a clear nodule, and are associated with multifocality, intrathyroidal lymphatic spread, and cervical lymph node metastasis.

**Description of the Case:** A 30-year-old female presented with diffusely enlarged thyroid and finding of snowstorm appearance on US of the thyroid. She has a family history of Graves' disease. Her TSH was 2.49 (0.45-5.33uIU/mL) and thyroid peroxidase antibody was 21 (<9IU/mL). US of the neck revealed a heterogeneous non-enlarged thyroid gland with diffuse hyperemia and numerous punctate echoes. A discrete nodule was not visualized. Several lymph nodes with punctate echoes were seen around the right thyroid lobe. CT neck showed a 1.8 x 1.1 cm heterogeneous nodule with a large dystrophic calcification in the right thyroid lobe and several abnormal-appearing right level 2 to 4 lymph nodes. FNA of the dominant right neck lymph node was positive for PTC. Thyroglobulin in the washout from the lymph node FNA was 63,843 ng/mL. She underwent total thyroidectomy with central and right lateral neck dissection. Pathology revealed 1.8 cm conventional type PTC in the right thyroid lobe, papillary thyroid microcarcinomas diffusely involving both thyroid lobes (greater than 20 foci), all well-differentiated with papillary and follicular growth patterns, and 26 out of 74 regional lymph nodes with PTC (largest 1.8 cm). Chronic lymphocytic thyroiditis was also seen.

**Discussion:** Diffuse microcalcifications in the thyroid gland, even without a clearly delineated thyroid nodule is an indicator of thyroid malignancy and can predict cervical lymph node metastasis. Current guidelines do not specifically address how to manage this sonographic finding. Further evaluation to assess cervical lymph nodes is warranted if diffuse parenchymal microcalcifications are seen on ultrasound.

### Poster 0140

*Thyroid Nodules and Goiter, Case Study, Poster*

#### **Concurrent Thyroid and Lung Nodules: Unveiling Rare Pathways in Malignancy**

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**Introduction:** Thyroid cancer (TC) is the most common endocrine malignancy. Despite its frequency, distant metastases are seen in only 1% to 4% of patients. However, such metastatic events often carry a grim prognosis, becoming the primary driver of TC-related fatalities. Conversely, metastasis to the thyroid gland is rare, with breast, renal cell and lung being the most common primary sites. While instances of patients having two distinct primary malignancies exist, most cases involving multiple organs originate from a single

primary source. This case series highlights patients with co-existing lung and thyroid nodules each exhibiting unique outcomes.

**Case series:** We present three cases involving concurrent thyroid and lung masses. The first case involved bilateral lung nodules seen on CT ordered for evaluation of cough. A thyroid nodule was detected concurrently and an FNA showed atypical cells of undetermined origin. Further molecular testing showed a TERT mutation and concurrently a lung biopsy showed metastatic melanoma with an identical TERT mutation. The second case involved incidentally discovered lung nodules with lymphadenopathy in a non-smoker. Biopsy revealed adenocarcinoma with BRAF V 600 E mutation. PET-CT showed cervical lymphadenopathy and further evaluation revealed multiple thyroid nodules in the US. FNA biopsy of thyroid nodules showed papillary TC without BRAF V 600 E mutation. The third case had thyroid nodules and was diagnosed with papillary thyroid cancer after FNA biopsy. Her CT chest noted multiple bilateral pulmonary nodules with the largest in the left lower lobe. FNA of lung nodules confirmed metastatic PTC.

**Conclusions:** A thorough review of existing literature revealed no consensus regarding the incidence of synchronous lung and thyroid nodules. Instances of TC metastases and a separate primary cancer spreading to the thyroid are both rare phenomena. Moreover, the presence of two distinct primary malignancies is uncommon. Our case series underscores the importance of obtaining proper tissue samples of both lung and thyroid masses identified concurrently to facilitate accurate diagnosis and treatment.

#### Poster 0141

*Thyroid Cancer, Case Study, Poster*

#### **SNOWGLOBE APPEARANCE ON CECT NECK AS A PREDICTOR OF LOCALLY ADVANCED PAILLARY THYROID CARCINOMA WITH PHARYNGEAL INFILTRATION-A CASE STUDY AND SERIES FROM A TERTIARY HOSPITAL IN SOUTH INDIA**

*KARTHIKEYAN MURALIDHARAN\*, PAUL JACOB, CHRISTIAN MEDICAL COLLEGE, India*

**Introduction:** Locally Advanced Papillary thyroid carcinoma (LATC), occasionally presents as cases that can be picked up earlier using imaging modalities. This includes locally advanced PTCs that extend beyond the thyroid capsule, invading nearby tissues and trachea, increasing morbidity and mortality. We put forward an unique 'SNOWGLOBE APPEAREACE' on pre-operative CECT which could often be overlooked as benign or missed, leading to poor intra operative decision making and postoperative management. Over 15 years, our case series of 35 patients aims to highlight the diverse manifestations and management strategies.

**Description of the Case:** One such case among the 35 other cases discussed in the case series involves a 27 year old gentleman who experienced a noticeable increase in neck swelling over a five-year period, which was accompanied by dysphagia and respiratory difficulties. Clinically a very large neck swelling extending into the thoracic inlet, consistent with the thyroid's right lobe, exhibited restricted mobility with no palpable carotid pulsation on the right side. CECT revealed a large "Snowglobe appearance" due to its uniquely large 16\*14 cms exophytic cystic lesion arising from a small 3cms thyroid tissue base abutting the trachea with probable right cervical lymph node metastasis. The treatment strategy involved a total thyroidectomy with right selective lymph node dissection with tracheal resection and anastomosis. Intra operatively, large cystic nodule originating from a stout thyroid base exhibiting the Snowglobe appearance and tracheal involvement were encountered necessitating a tracheal resection and anastomoses.

**Discussion:** LATC's, particularly those with pharyngeal involvement and distinctive cystic features like the Snowglobe appearance, pose significant challenges intra-op and post operatively due to the potential for recurrence and severe complications from tumor infiltration into adjacent structures. This case, along with 35 others in our 15-year series, underscores the critical role of a multidisciplinary approach and meticulous look by the operating surgeon and team into advanced imaging modalities like CECT is vital to precisely delineate the extent of the disease and guide comprehensive surgical planning. These cases emphasize the constant look out for a SNOW-GLOBE APPEAREANCE of large cystic masses arising from a narrow thyroid base of high suspicion of LATC and meticulous preoperative evaluation.

#### Poster 0142

*Thyroid Nodules and Goiter, Case Study, Poster*

#### **MALIGNANCY VEILING IN AUTONOMOUSLY FUNCTIONING THYROID NODULES(AFTN)-IS ROUTINE CYTOLOGY REPORTING OF HOT NODULES NECESSARY?-RETROSPECTIVE CASE STUDY AND LITERATURE REVIEW FROM A TERTIARY HOSPITAL IN SOUTH INDIA**

*KARTHIKEYAN MURALIDHARAN\*, PAUL JACOB, Christian Medical College, India*

**Objective:** The primary objective of this comprehensive study over 15 years in a tertiary care thyroid hospital in South India was to evaluate the incidence of malignancy within hyperfunctioning thyroid nodules, colloquially known as "hot" nodules, while hot nodules are predominantly benign, the possibility of malignancy cannot be dismissed out of hand and cytology is indicated for such cases controversial to the current guidelines.

**Methods:** Our retrospective case study, focusing on surgeries done on solitary hyperfunctioning thyroid nodules in our department over the past 15 years. We had a thorough understanding of our patient demographics, clinical presentation, biochemical markers, imaging characteristics, and histopathological findings. Special attention was given to the characteristics of nodules that underwent surgical resection and that turned out malignant, providing a direct insight into the histological nature of these lesions.

**Results:** 56 patients with autonomously functioning thyroid nodules underwent total thyroidectomy in view of suspected malignancy, with a median age of 47 years, and a gender distribution of 34 females and 22 males showed, prevalence of malignancy of 8 (14.2%) were found to have malignant nodules upon histological examination post-thyroidectomy. Female: Male ratio was 2:1. It was also noted that certain clinical features were more frequently associated with malignant hot nodules, including rapid nodule growth and suspicious sonographic findings such as microcalcifications and taller than wider hot nodules with irregular borders.

**Discussion/Conclusion:** Our study over 15 years provides critical insights into the management of hyperfunctioning thyroid nodules. Although the overall prevalence of malignancy in these nodules is relatively low, the potential for malignancy is non-negligible and warrants careful consideration in clinical practice. The study advocates for a more nuanced approach to the evaluation of hot nodules potentially including fine-needle aspiration biopsy or surgical exploration. Our study underscores the necessity for a balance between vigilant assessment and avoiding overtreatment, especially considering the benign nature of most hot nodules. Future research should aim to refine predictive models for malignancy in hyperfunctioning thyroid nodules by integrating

advanced imaging techniques, molecular markers, and perhaps genetic profiling, which could lead to more personalized and precise management of these patients.

### Poster 0143

*Thyroid Cancer, Case Study, Poster*

#### **Elevation of Thyroglobulin Antibodies Induced by IVIG in a Lung Transplant Recipient with Papillary Thyroid Cancer: A Case Report**

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**Introduction:** American Thyroid Association guidelines recommend monitoring differentiated thyroid cancer patients with serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb) measurements post-thyroidectomy. Rising Tg or TgAb levels prompt further investigations and potential additional therapies.

Intravenous immunoglobulin (IVIG), which is a pooled human serum product, contains TgAb. Commercially available TgAb assays may detect the TgAbs contained within the administered intravenous immunoglobulin, leading to alarm and further imaging to exclude progressive malignancy. We present a unique case with differentiated micropapillary thyroid cancer (MPTC) who received lung transplant and was treated with IVIG.

**Description of the case:** A 75-year-old woman with interstitial lung disease was incidentally diagnosed with thyroid cancer during a lung transplant evaluation. Imaging revealed a 0.8 x 0.6 cm thyroid nodule and biopsy confirmed papillary thyroid carcinoma (PTC), follicular variant, infiltrative. Although staging the cancer without surgery was not feasible, though without any clinical evidence of metastatic disease and favourable prognosis of MPTC decision was made to support proceeding with the transplant. The patient underwent a thyroidectomy 18 days post bilateral lung transplantation. Surgical pathologist confirmed TNM Stage: T1aN0M0. Tumour markers including TgAbs were negative 8 weeks post surgery. Three months post-transplant, she began monthly IVIG infusions for hypogammaglobulinemia and recurrent infections. A week post IVIG Elevated TgAb levels (21.4 Int Unit/mL) raised concerns about metastatic thyroid cancer, but variations correlated with the initiation of IVIG. Follow-up imaging showed no evidence of structural recurrence. Ultimately, discontinuation of IVIG led to normalization of TgAb levels, confirming the absence of metastatic or recurrence of thyroid cancer.

**Discussion:** This case underscores the difficulties in interpreting tumor markers in transplant patients, given the potential interference from IVIG therapy. Encountering such a situation is uncommon because patients with active malignancy are typically not candidates for organ transplants. However, our patient's favorable response till date encourages a reassessment of the broad exclusion of all cancer patients from transplant eligibility, emphasizing the need for a more individualized evaluation approach.

The absence of established sensitivity and specificity parameters for TgAb as a tumor marker in patients receiving IVIG might result in unnecessary diagnostic procedures. It's crucial to increase awareness of this issue and approach evaluations with caution in such cases, taking into account additional clinical and imaging data. Alternative diagnostic techniques, such as mass spectrometry-based assays unaffected by TgAb interference, are suggested to improve diagnostic precision in these scenarios.

### Poster 0144

*Disorders of Thyroid Function, Case Study, Poster*

#### **METHAMPHETAMINE ABUSE AS A TRIGGER FOR MYXEDEMA COMA IN A PATIENT WITH AN UNKNOWN DIAGNOSIS OF HASHIMOTO'S THYROIDITIS: A CASE REPORT**

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 David Wisinger<sup>3</sup>, <sup>1</sup>Creighton University, USA, <sup>2</sup>Anahuac University, Mexico, <sup>3</sup>Valleywise, USA*

**Introduction:** Myxedema Coma is a rare and life-threatening clinical condition that typically occurs in patients with long-standing, severe untreated hypothyroidism. While methamphetamine use has been associated with dysregulation of the hypothalamic-pituitary-thyroid axis, it is more commonly linked to thyroid storm as an outcome.

**Description of the case:** 66-year-old adult male with a history of polysubstance abuse, who presented to the hospital for altered mental status. Upon arrival, he exhibited hypothermia and hypertension. Notably, his blood work demonstrated a high creatine kinase levels exceeding 16,000 U/L and a urine drug screen returned positive for amphetamine and methamphetamine. The patient was admitted for methamphetamine intoxication with associated rhabdomyolysis and toxic acute encephalopathy. The night following admission, the patient's mental status further deteriorated. Laboratory results revealed significant hypothyroidism with a thyroid-stimulating hormone level of 88 mIU/L and a free thyroxine level less than 0.07 ng/dL. Subsequently, thyroid hormone replacement therapy was initiated with levothyroxine and a single dose of triiodothyronine was given. Patient was intubated for airway protection. A thyroid ultrasound was performed and showed a heterogeneously thyroid parenchyma without discernible nodules. Patient's condition gradually improved with adequate treatment. Positive results for thyroglobulin antibody and thyroid peroxidase antibodies oriented the diagnosis towards myxedema due to Hashimoto's thyroiditis.

**Discussion:** Initially, the patient's history of methamphetamine abuse led to an assumption of drug-induced symptoms, but his deterioration and response to thyroid hormone therapy shifted suspicion towards myxedema coma. Methamphetamines, which affect central nervous system function and can dysregulate the hypothalamic-pituitary-thyroid axis, typically increase thyroid hormones, contrasting with the hypothyroidism observed in this patient. Chronic methamphetamine use may mask underlying hypothyroidism, and cessation could exacerbate hypothyroid symptoms, potentially leading to myxedema coma. Additionally, thyroid hormones have been shown to mitigate methamphetamine-induced cognitive deficits in animal models, suggesting that thyroid hormone therapy could address both the hypothyroidism and the neurologic damage from methamphetamine use, illustrating a complex interaction between drug abuse and thyroid dysfunction in this patient's presentation. It's possible that the thyroid deficiency in our patient was amplifying the neurological damage caused by methamphetamine, potentially making him more susceptible to complications like myxedematous coma.

### Poster 0145

*Thyroid Cancer, Case Study, Poster*

#### **NTRK Fusion Genes in Thyroid Cancer and Implications for Treatment – A Case Report**

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**Introduction:** Thyroid cancer is the most common endocrine malignancy, and its prognosis and clinical outcome can be associated

with the type of mutation in thyroid cancer. Neurotrophic-tropomyosin receptor kinase (NTRK) fusion genes, detected in thyroid cancer, may alter treatment strategies for the disease.

**Description of the Case:** A 20-year-old woman with a recent discovery of a thyroid nodule during a routine checkup visited our endocrinology clinic. Her thyroid ultrasound revealed a small, solid, hypoechoic nodule with smooth margins and punctate echogenic foci. Her medical history was otherwise uneventful, and thyroid function tests came back normal. A fine needle aspiration (FNA) was indeterminate and suggestive of follicular neoplasm, Bethesda IV, prompting genomic sequencing which confirmed an EML4/NTRK 3 fusion.

Due to the increased risk of more aggressive thyroid cancer and multifocality linked with NTRK fusion-positive tumors, a total thyroidectomy was performed. This involved removing the entire thyroid gland and conducting bilateral central neck dissection.

Pathology revealed a multifocal classic subtype papillary thyroid carcinoma with a predominant follicular growth pattern affecting both lobes and the isthmus, with the largest focus measuring 0.7 cm. Two lymph nodes in the bilateral central neck dissection showed signs of metastatic papillary carcinoma, with one exhibiting extracapsular extension. The patient also underwent radioactive iodine (RAI) treatment as part of her management.

**Discussion:** EML4/NTRK3 is a type of NTRK fusion. NTRK positive thyroid cancers have been reported to be associated with lymph node metastases, chronic lymphocytic thyroiditis, and follicular growth pattern. While NTRK fusions in thyroid cancer are rare, they have been reported in various types and can impact prognosis.

If a thyroid nodule contains the NTRK fusion gene, it may be recommended to undergo a total thyroidectomy because of the heightened probability of multifocality and malignancy, potentially necessitating subsequent treatment with RAI. For NTRK fusion-positive tumors resistant to RAI, larotrectinib, a tyrosine receptor kinase inhibitor, can be utilized in treatment.

Our case emphasizes the role of molecular testing in guiding treatment decisions in thyroid cancer. However, additional research is required to fully comprehend and assess the broader effects of molecular testing and genomic profiling in thyroid cancer.

## Poster 0146

*Disorders of Thyroid Function, Case Study, Poster*

### **Ashwagandha Induced Hyperthyroidism**

*Mona Vahidi Rad\*, Samir Ahmed, Joseph Arguinchona, Aditi Kumar, Mayo Clinic, USA*

**Introduction:** Ashwagandha, also known as *Withania somnifera*, is an herb commonly used in traditional Ayurvedic medicine. It is believed to have various health benefits, including stress reduction, improved cognitive function, and increased energy levels. While it has been promoted for various health benefits, its impact on thyroid function remains controversial. We report a case of hyperthyroidism from Ashwagandha use.

**Description of the case:** A 34-year-old male presented with tremors, sweating and palpitations and was diagnosed with hyperthyroidism. He had no prior history of thyroid disease and prior thyroid function tests were normal. He reported taking Ashwagandha for nine months before the symptoms appeared. His thyroid-stimulating hormone (TSH) was <0.01 mIU/L, free thyroxine was 3.1 ng/dl (nl-0.9-1.7 ng/dL) and total T3 was 267 ng/dL (nl-80-200 ng/dL). Thyroid Stimulating Immunoglobulin (TSI), thyrotropin receptor antibody and thyroperoxidase antibody were negative. Thyroid ultrasound revealed no abnormalities. He was advised to discontinue Ashwagandha and beta blockers were initiated for symptom control.

His symptoms gradually improved and repeat thyroid function tests in 12 weeks after stopping Ashwagandha were normal.

**Discussion:** Ashwagandha contains bioactive compounds which have been suggested to have thyroid-stimulating properties. Several studies have explored the relationship between Ashwagandha and thyroid function in humans. In one study, Ashwagandha increased free T3 and free T4 with no change in TSH. A double-blind, randomized placebo-controlled trial of Ashwagandha for hypothyroidism showed that Ashwagandha improved serum TSH, T3, and T4 levels significantly compared to placebo. Several cases of Ashwagandha induced thyrotoxicosis have also been reported in the literature. The variability in responses may be attributed to differences in individual susceptibility, dosage, and duration of supplementation.

This case highlights the potential risk of Ashwagandha-induced hyperthyroidism, emphasizing the importance of awareness among healthcare providers and patients regarding the potential adverse effects of herbal supplements. It underscores the need for cautious use and monitoring of Ashwagandha, especially in individuals with underlying thyroid conditions. Further research is warranted to understand the exact mechanism of Ashwagandha's effect on thyroid function and to establish safe dosing guidelines.

## Poster 0147

*Thyroid Cancer, Case Study, Poster*

### **Oncocytic Carcinoma of the Thyroid with Extensive Tumor Thrombus in the Innominate Vein: A Case Report**

*Suedeh Ranjbar\*, Helen Liu<sup>1</sup>, Rajam Raghunathan<sup>2</sup>, Yesha Maniar<sup>1</sup>, Matthew Krell<sup>1</sup>, Alec Vaezi<sup>1</sup>, Scott Schubach<sup>1</sup>, Reese Wain<sup>1</sup>, Mala Gupta<sup>1</sup>, John Allendorff<sup>1</sup>, <sup>1</sup>NYU, USA, <sup>2</sup>NYU, USA*

**Introduction:** We present a case of oncocytic (Hürthle cell) carcinoma with occlusive tumor thrombus to the left internal jugular, innominate vein to the level of the SVC and its surgical management.

**Description of the Case:** A 69-year-old male presented with a rapidly enlarging left neck mass, dysphagia and dysphonia. Thyroid ultrasound revealed a 10.6cm hypoechoic nodule replacing the left lobe and enlarged left Level III lymph nodes. Thyroid function tests were normal. A fine-needle aspiration biopsy of the thyroid nodule and a Level III node showed oncocytic/follicular cell cytopathology (Bethesda IV); molecular testing identified high-level copy number alterations and PTEN mutation, with 80-90% risk of malignancy. CTA showed tumor occlusive thrombus within the jugular vein extending into the innominate vein to the level of the SC. There was marked tracheal and esophageal deviation without laryngeal invasion.

The patient underwent a left thyroid lobectomy, isthmusectomy, central and modified left radical neck dissections. Thrombectomy and innominate vein repair with pericardial bovine patch required median sternotomy and resection of the clavicular head for safe access.

Surgical pathology confirmed differentiated high-grade thyroid carcinoma, oncocytic type, Stage IVA T4bN1bMX. Tumor profiling showed microsatellite-stability, with *ATM*, *NF1* (5727 and Q97) and *PTEN* (517DR and D24V) biomarkers. Recovery was uneventful and there was no evidence of metastases at two-month follow-up. Patient will continue close observational surveillance with no planned adjuvant therapy.

**Discussion:** We highlight a surgically complex procedure. A multidisciplinary approach achieved optimal management of this case of widely invasive oncocytic carcinoma.

**Poster 0148***Thyroid Cancer, Case Study, Poster***Poorly Differentiated Thyroid Carcinoma in the Second Trimester of Pregnancy: A Diagnostic and Clinical Challenge**Suedeh Ranjbar<sup>\*1</sup>, Rajam Raghunathan<sup>2</sup>, Michael Weintraub<sup>2</sup>, Steven Hodak<sup>2</sup>, Cheng Liu<sup>2</sup>, Bruce Wenig<sup>3</sup>, Kepal Patel<sup>2</sup>, Insoo Suh<sup>2</sup>, John Allendorf<sup>1</sup>, <sup>1</sup>NYU, USA, <sup>2</sup>NYU, USA, <sup>3</sup>Moffitt Cancer Center, USA

**Introduction:** We describe a rare tumor with confounding pathology on the spectrum between poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC) in a second trimester pregnant patient.

**Case Description:** A 40-year-old G1P0 female at 20 weeks' gestation presented with presyncope. A carotid ultrasound revealed a 4 cm right thyroid nodule without suspicious lymph nodes. There were no compressive symptoms, nor family history of thyroid cancer. An FNA biopsy showed Bethesda V cytopathology. Molecular testing revealed *NRAS* and gene expression profile abnormalities, with 70-80% risk of malignancy. She was counseled on appropriate surgical timing and underwent a second trimester right thyroid lobectomy. Surgical pathology showed a 4.3 cm giant cell-type ATC arising in an infiltrative follicular thyroid carcinoma, negative margins (R0), extensive angioinvasion, and one negative lymph node, with TTF1, PAX8, CD31 positive on immunohistochemistry. Molecular pathology identified *NRAS* c.182A>G, *FGFR2* c.1967A>G, and TP53 mutations. Outside pathology review reclassified the specimen as PDTC on the spectrum with ATC. After significant discussion of pregnancy termination to initiate systemic therapy, a shared multidisciplinary decision was made for postpartum completion thyroidectomy with concurrent radioiodine (RAI) treatment and chemotherapy. One month postpartum, she underwent completion thyroidectomy, with benign left lobe pathology. A post-RAI scan showed focal uptake in the midline neck, consistent with treated residual thyroid tissue without evidence of abnormal uptake in the lateral neck or body. Thyroglobulin remained low post-operatively.

**Discussion:** PDTC and ATC are rare thyroid cancer subtypes portending poor outcomes. Knowledge of their genetic aberrations can aid appropriate management. Pathology revealed 40% ATC with mixed PDTC, favoring PDTC given retained TTF-1 expression and thyroglobulin. Bizarre nuclei and atypical mitoses were concerning for ATC, though pregnancy may have hormonally perpetuated nuclear atypia. Consistent with PDTC, thyroglobulin remained low; high frequencies of RAS with TP53 mutations are also characteristic. First-line treatment of PDTC includes total thyroidectomy with possible central lymph node dissection, followed by radioiodine for locoregional control. Molecular-targeted therapy is appropriate in RAI-refractory disease.

**Conclusion:** This diagnostically and clinically challenging case highlights the importance of understanding the relationship of tumor genotype to phenotype, and multidisciplinary care of the pregnant patient.

**Poster 0149***Thyroid Cancer, Clinical, Poster***Age but not tumor size modifies the association between extrathyroidal extension and long-term outcomes in patients with follicular cell-derived thyroid carcinoma**Saad Samargandy<sup>\*1</sup>, Shaza Samargandy<sup>1</sup>, Hani Marzouki<sup>1</sup>, Raghda Alotaibi<sup>1</sup>, Rahaf Alotaibi<sup>1</sup>, Hanan Faruqi<sup>2</sup>, Ahad Alsawat<sup>3</sup>, Marwan Alhajeili<sup>1</sup>, Asala Baharoon<sup>1</sup>, <sup>1</sup>King Abdulaziz University, Saudi Arabia, <sup>2</sup>Dr.Soliman Fakeeh Medical Center, Saudi Arabia, <sup>3</sup>King Faisal specialist hospital & Research center, Saudi Arabia

**Objectives:** Extrathyroidal extension (ETE) increases the risk of incomplete response to therapy in patients with follicular cell-derived thyroid carcinoma (FCTC). Recently, age and tumor size have been recognized to influence response to therapy in FCTC. We aim to determine whether age and tumor size modify the association between ETE and long-term outcomes in FCTC patients.

**Methods:** This was a retrospective chart review study at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. We included patients 13 years and older with papillary, follicular, Hurthle cell, or poorly differentiated thyroid cancer from 2017-2021 who underwent thyroidectomy. Clinical outcomes were based on the 2015 ATA response to therapy classification, with the study outcome defined as the risk of biochemical or structural incomplete response. Minimal and gross ETE were grouped for the analysis. We separately tested the effect modification of age and tumor size on the association between ETE and risk of incomplete response using logistic regression. Models adjusted for age, tumor size, vascular invasion, lymph node involvement, and radioactive iodine use.

**Results:** There were 255 patients included, mean age (SD) was 41.6 (14.3) years; 74% were females. Patients were followed for a median of 4 years. There were 20(8%) patients with minimal and 18(7%) patients with gross ETE. There were 58% and 17% with incomplete response in patients with and without ETE, respectively (p-value=0.0001). Age modified the association between ETE and incomplete response such that the OR (95% CI) for ETE in patients <55 years was 2.5 (0.9, 7.1), while in patients ≥55 years was 26.5 (5.2, 134.9), p-value for interaction=0.05. Size of the tumor did not modify the association between ETE and incomplete response (p-value for interaction=0.25); OR (95% CI) for ETE in tumor size ≤4 cm was 4.3 (1.6, 11.6), and for size >4 cm was 5.6 (1.1, 27.6).

**Conclusion:** The risk of incomplete response to therapy in patients with FCTC with ETE is modified by age but not tumor size. Older FCTC patients with ETE, regardless of the tumor size, have worse long-term outcomes and should be managed and monitored more judiciously.

**Poster 0150***Thyroid Cancer, Clinical, Poster***PD-L1 Expression Varies Across Thyroid Cancer Types and Histological Subtypes**Deema Al-Sour<sup>\*1</sup>, Illiam Kuenstner<sup>1</sup>, Jennifer Rosen<sup>1</sup>, Gretchen Hubbard<sup>2</sup>, Leonard Wartofsky<sup>1</sup>, Vasy Vasko<sup>3</sup>, Kenneth Burman<sup>1</sup>, Leila Shobab<sup>1</sup>, <sup>1</sup>MedStar Washington Hospital Center, USA, <sup>2</sup>CARIS Molecular Intelligence, USA, <sup>3</sup>Uniformed Services University of the Health Sciences, USA

**Background:** Thyroid cancer (TC) remains a significant clinical challenge worldwide, with a subset of patients facing aggressive disease progression and therapeutic resistance. Immune checkpoint inhibitors targeting programmed death-ligand 1 (PD-L1) have emerged as promising therapeutic avenues in various malignancies, yet their efficacy in TC remains uncertain. The objective of this study was to investigate PD-L1 expression in aggressive TC and its association with histological subtypes and molecular mutation.

**Methods:** This is a retrospective study of patients with advanced TC seen in our institutions. Patients with advanced TC (Stage II in age <55 and Stage 3 and 4 in age >55) with recurrence or progression on therapy were included in this study for whom tumor molecular profiling and PD-L1 status were available. Charts were reviewed and detailed clinical, pathological and response to therapy were collected. Descriptive analysis using Fisher's exact test and the chi-squared test was performed to evaluate the association of PD-L1 with histological subtypes and TC types.

**Results:** 175 patients with advanced thyroid cancer were included (48.9% female, 51% male). Twelve patients had Anaplastic TC(ATC), 11 Medullary TC(MTC), 76 Papillary TC (PTC), 20 Follicular TC(FTC), 8 Oncocytic TC(OTC), 10 Poorly Differentiated TC(PDTC), 30 Papillary TC Follicular Variant (PTCFV) and 5 Papillary TC Tall Cell Variant (PTCTC). BRAF mutation was present in 73(41%), TERT in 52(30%), RAS in 34(19%), TP53 in 18(10%), and RET in 15(8.6%) patients. PD-L1 positivity was significantly different across different TC types and histological subtypes: Patients with ATC had the highest frequency of PD-L1 positivity (75%), followed by HTC(71%), PTCTC(60%), PTC(26%) and FTC(11%). Patient with MTC and PTCFV did not exhibit any PD-L1 positivity. TP53 mutation was positively associated with PD-L1 expression (21.6% vs 7.5%,  $p=0.03$ ), and RAS mutation was negatively associated with PD-L1 expression (8.1% vs 24.2%  $p=0.04$ ).

**Conclusions:** PD-L1 expression varies across different TC types and histological subtypes and may be modulated by mutational landscape. Follow up studies are warranted to elucidate the molecular mechanism driving the observed differences in immune pathways, paving the way for the development of more effective and personalized immune therapies for patients with aggressive TC resistant to standard therapy.

### Poster 0151

*Thyroid Cancer, Case Study, Poster*

#### **Deleterious Co-Mutation: A Case of Co-existent BRAF and TERT Mutations in a Patient with Metastatic PTC**

Aastha Sehgal<sup>\*1</sup>, Dmitriy Stasishin<sup>1</sup>, Ruben Alberto Hiraldo<sup>1</sup>, Jacqueline Jonklaas<sup>2</sup>, <sup>1</sup>MedStar Washington Hospital center, USA, <sup>2</sup>Georgetown University Hospital, USA

**Introduction:** This case highlights the influence of co-existent BRAF and TERT mutations on disease progression and prognosis in a patient with PTC.

**Case Description:** This is the case of a 64-year-old male who presented with hoarseness. Imaging showed a RUP nodule of 1.9 cm and RLP nodule of 8 cm, resulting in deviation of the trachea. Pathology confirmed RUP as Bethesda 3, AUS and RLP as Bethesda 4 with suspicion for follicular neoplasm. He underwent thyroidectomy, and pathology revealed a follicular variant of PTC with no spread, categorized as pT3a. Mutation testing showed BRAF, K601E, and TERT mutations. Dosimetry scan demonstrated thyroid bed activity without evidence of metastasis. He underwent RAI ablation, and a post-ablation PET had no evidence of metastasis. Post-ablation labs showed thyroglobulin levels of 0.7-0.8, so he was scheduled for follow-up. Labs after one year showed elevated TSH(22) and thyroglobulin(7.1), however chest and neck imaging showed no metastasis. His levothyroxine was increased, and subsequent thyroglobulin levels were 1.8-2.1, so he was scheduled for follow-up. Next visit's results revealed significantly elevated levels of thyroglobulin(152). A PET scan revealed hypermetabolic lytic lesions in the L3 vertebral body, indicating distant metastasis, but no hypermetabolic activity inside the thyroidectomy bed to suggest local recurrence. MRI Lumbar spine showed a L3 vertebral body lesion suspicious for metastasis, but fluoroscopy-guided L3 vertebral body biopsy did not show evidence of carcinoma. He underwent CT-guided radiation therapy of the lumbar region. Post-radiotherapy, his labs improved, and a PET/CT confirmed resolution of previously seen lesions in the L3 vertebra. He was then scheduled for follow-up.

**Discussion:** This case highlights the importance of risk stratification in thyroid cancer. DTC generally has good long-term survival rates; therefore, it is important to distinguish patients who need aggressive treatment and surveillance from those who do not. Our

patient, while having no cancer spread to begin with, developed metastatic disease later on due to the high-risk nature of his tumor. The co-occurrence of these mutations is associated with poor prognosis and loss of RAI avidity in PTC cases. Therefore, surveillance is of paramount importance in such cases.

### Poster 0152

*Thyroid Cancer, Case Study, Poster*

#### **Medullary Thyroid Carcinoma Associated with a Rare RET Proto-Oncogene Mutation: p.K666N**

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**Introduction:** Although medullary thyroid carcinoma (MTC) accounts for less than 5% of thyroid cancer cases, it is responsible for up to 13% of thyroid cancer deaths. Therefore, early detection and treatment are paramount. For individuals at risk of harboring a mutation associated with multiple endocrine neoplasia type 2, genetic screening may provide insight into the risk of current or future MTC and pheochromocytoma or primary hyperparathyroidism (PHPT). We present a case of MTC associated with a rare RET proto-oncogene mutation.

**Case:** Patient is a 41-year-old male with past medical history of hypercholesterolemia who presented to establish care for abnormal genetic testing. His 72-year-old mother had breast cancer and therefore had genetic testing performed revealing a RET proto-oncogene mutation. His mother has no history of thyroid cancer, PHPT, or pheochromocytoma. The patient has a brother and two daughters who have not had genetic testing. The patient had genetic testing showing a RET proto-oncogene mutation: p.K666N. Calcitonin and CEA levels were <5.0pg/mL and 0.55ng/mL, respectively. Ultrasound neck was performed and showed no thyroid nodules. Biochemical screening for pheochromocytoma and PHPT was negative. Prophylactic total thyroidectomy was performed. On surgical pathology, a solitary 0.2cm focus of medullary thyroid carcinoma involving the right lobe of the thyroid was identified. There was no evidence of angioinvasion, lymphatic invasion, or extrathyroidal extension. Ki-67 labeling index was 1%. Margins were negative for carcinoma. One level VI lymph node was removed and negative for carcinoma. This was consistent with AJCC stage T1aN0aMx.

**Discussion:** Codon 666 is within exon 11 of the RET receptor tyrosine kinase, which is in the intracellular juxtamembrane region, downstream from the transmembrane domain. Approximately 12 cases of MTC in patients with p.K666N have been previously reported with variable disease courses. One case of pheochromocytoma was reported in a patient with p.K666N, but this patient was homozygous for the mutation. The patient had MTC and bilateral pheochromocytoma however had no evidence of PHPT. Primary hyperparathyroidism is uncommon in patients with p.K666N with only one case being reported. Our case highlights the importance of early genetic screening in at-risk patients.

### Poster 0153

*Thyroid Cancer, Case Study, Poster*

#### **Not so Minimally Invasive, Minimally Invasive Follicular Thyroid Carcinoma: A Case without Capsular Breakthrough Presenting with Multiple Metastases**

Diego Moreno Watashi<sup>\*</sup>, Kenneth Burman, MedStar Washington Hospital Center/Georgetown University, USA

**Introduction:** Minimally invasive follicular thyroid carcinoma (MIFTC) represents a distinct subset of differentiated thyroid cancers with generally favorable prognosis and low propensity for metastasis. This case presents a patient with MIFTC, minimal stratification risk and no capsular breakthrough complicated with multiple metastases.

**Description of Case:** A 58-year-old woman with a history of breast cancer in remission presented to our clinic with a right femur lesion identified on a CT scan. Biopsy of the lesion confirmed adenocarcinoma with positive stains for TTF1, PAX8, CK7, and thyroglobulin, indicative of a differentiated thyroid carcinoma of follicular pattern.

The patient was asymptomatic from a thyroid standpoint, with normal thyroid function tests TSH 3.5 uIU/ml, T4 8.6ng/dL, elevated thyroglobulin levels 44.6 ng/mL but no thyroglobulin antibodies.

Thyroid ultrasound identified an isoechoic solid nodule, taller than wide, located at the mid lobe measuring 1.1 x 0.7 x 1.3 cm (TI-RADS 4) without local pathologic adenopathy, and fine needle aspiration yielded an undiagnostic result.

Total thyroidectomy was performed, revealing a microfollicular lesions with singular focal capsular invasion without loss of capsular continuity, consistent with minimally invasive follicular carcinoma.

Post-thyroidectomy, the patient received radioactive iodine therapy with 303 mCi of I-131. Tg decreased to 0.4, and antibodies continued negative. Molecular profiling revealed TERT and HRAS Q61K mutations. Subsequent scans demonstrating iodine uptake in the right scapular area indicative of additional metastatic disease.

**Discussion:** MIFTC is characterized by capsular invasion with no or minimal vascular invasion, contrasting with widely invasive follicular thyroid carcinoma which displays more extensive infiltration.

Management is based on the likelihood of metastasis, through risk stratification after thyroid lobectomy or thyroidectomy. Most guidelines do not routinely recommend radioactive iodine ablation in patients with low-risk disease, but to consider in the setting of a primary tumor size  $\geq 4$  cm, multiple vascular invasion sites or distant metastasis.

The existence of severe metastatic disease with deemed "low-risk" primary cancer can point that the nomenclature of minimally invasive may not mirror the tumor's behavior.

## Poster 0154

*Thyroid Cancer, Case Study, Poster*

### **Unusual Metastatic Journey: Benign Thyroid Nodule to Lung Metastasis**

*Eman Allhussain\*, Julie Samanthy, Wayne state university, USA*

**Introduction:** Thyroid nodules are common, detecting a broad spectrum of histopathological features from benign to malignant. The incidence of metastatic thyroid carcinoma to the lung without gross pathological evidence of primary thyroid cancer is very unusual. This case shows the diagnostic challenges and management options in a patient who had an initially benign hyperplastic thyroid nodule in gross thyroid pathology and was later found to have metastatic thyroid cancer to the lung.

**Description of the Case:** A 63-year-old African American male underwent regular follow-up for a right thyroid nodule. Thyroid ultrasonography (US) revealed a 6 x 5.6 x 3 cm right thyroid gland with internal cystic degeneration. Over five years, the nodule increased to 8.8 x 5.0 x 7.3 cm. Fine-needle aspiration (FNA) biopsy indicated a Follicular lesion of undetermined significance. Computed tomography (CT) of the neck and thorax demonstrated a large heterogeneous cystic nodule in the right thyroid lobe, causing leftward tracheal deviation and multiple subcentimeter lung nodules. Given the patient's concurrent treatment for prostate cancer, a

positron emission tomography (PET) scan was performed to rule out distant metastasis. FDG PET revealed an SUV of 8.1 for the thyroid nodule, indicating FDG avidity and non-FDG avid subcentimeter pulmonary nodules.

The patient underwent a total thyroidectomy. Post-surgical pathology revealed a benign hyperplastic nodule with extensive cystic degeneration. Approximately two years following total thyroidectomy, a biopsy of a growing right lung nodule revealed metastatic thyroid cancer, confirmed by immunohistochemical staining for TTF-1 (positive), PAP (negative), NKX3.1 (negative), PAX8 (positive), and thyroglobulin (positive). Thyroglobulin was more than 450. The initial thyroid pathology was reviewed again; no evidence of capsular or vascular invasion was found. A nuclear medicine thyroid scan showed residual post-operative thyroid tissue in the thyroid bed and increased uptake of functioning lung metastases. Consequently, the patient underwent radioactive iodine therapy. Repeated thyroglobulin went down from 450 to 5.

**Discussion:** Thyroid nodule is a very common finding in adults. Benign Hyperplastic thyroid nodule can cause compression symptoms when it enlarges but usually does not metastasize. In this case, an unexpected benign thyroid nodule ended up metastasizing to the lung.

## Poster 0155

*Thyroid Cancer, Case Study, Poster*

### **An Unresectable Papillary Thyroid Cancer Presenting with Extensive Cervical Lymphadenopathy and Miliary Pulmonary Metastasis Treated Successfully with Both Neoadjuvant and Adjuvant Tyrosine Kinase Inhibitors (TKI)**

*Haley Niu<sup>\*1</sup>, Shriya Kundranda<sup>2</sup>, Amanda Edmond<sup>3</sup>, Chafeek Tomeh<sup>3</sup>, Iram Ahmad<sup>4</sup>, Jiabin Niu<sup>3</sup>, <sup>1</sup>Basis Scottsdale, USA, <sup>2</sup>Desert Mountain High School, USA, <sup>3</sup>Banner MD Anderson Cancer Center, USA, <sup>4</sup>Virginia Mason Franciscan Health, USA*

**Introduction:** The standard therapy for newly diagnosed advanced well-differentiated thyroid cancer includes surgery followed by radioactive iodine ablation (RAI). The role of tyrosine kinase inhibitors (TKIs) in neoadjuvant and adjuvant settings has not been well studied.

**Description of the Case:** A 19-year-old Native American male initially presented to the ER with progressively worsening neck swelling, non-productive cough, and shortness of breath for 4 months. He required 6 L/minute O2 for hypoxia and had enlarged cervical lymphadenopathy encasing the left carotid artery as well as innumerable miliary lung nodules. A biopsy of the left cervical mass and a lung nodule revealed papillary thyroid cancer.

The case was discussed on a multidisciplinary tumor board; he was deemed medically inoperable due to severe hypoxia. Lenvatinib 24 mg daily was started to reduce tumor burden and oxygen requirement. He responded rapidly and underwent total thyroidectomy with bilateral and central neck dissection. NGS disclosed NCOA4-RET fusion. He received RAI ablation, TSH suppression, and was able to discontinue Lenvatinib 2 months later.

The patient was doing well for 2 years before he started to experience dyspnea on exertion, his thyroglobulin level was also rising. Given his significant disease burden in the lung and concerns for long-term toxicity of high-dose RAI, the decision was made to treat him with a specific RET inhibitor, pralsetinib, first to cytoreduce the lung metastases before the second RAI ablation optimally. He had a remarkable response in 6 months and underwent the second RAI ablation. Clinically he responded well to both Pralsetinib and RAI. His dyspnea on exertion resolved quickly and he has been progression-free for 3 years with declining thyroglobulin level over time (5436 to 62) despite the discontinuation of pralsetinib after RAI.

**Discussion:** We present a rare case of papillary thyroid cancer where surgical resection could not be performed due to extensive cervical lymphadenopathy encasing the carotid artery as well as hypoxia secondary to miliary lung metastases. The patient was successfully treated with lenvatinib allowing total thyroidectomy and RAI. He was treated with Pralsetinib against RET allowing a more effective second dose of RAI. This case highlights the unique role of RAI in this challenging clinical scenario.

### Poster 0156

*Thyroid Cancer, Case Study, Poster*

#### **Somatic BRAF V600E Mutation Found in Sporadic Medullary Thyroid Carcinoma**

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**Introduction:** The majority of sporadic medullary thyroid cancer (MTC) arise from RET and RAS alterations. Interestingly, BRAF V600E, commonly observed in other forms of follicular-cell thyroid neoplasms, is rarely seen in MTC.

**Description of the case:** We present the case of a 63-year-old female with a left thyroid nodule measuring 2.7cm and cytology consistent with MTC. Initial calcitonin level was elevated (188 pg/mL), while carcinoembryonic antigen (CEA) level was normal (1.7 ug/L). Testing for RET germline mutations in exon 8, 10, 11, 13-16 showed no mutations. Initial staging with computed tomography (CT) revealed no locoregional or distant metastases.

The patient underwent total thyroidectomy with central and ipsilateral lateral neck dissection. Histology revealed a low-grade MTC, with an infiltrative growth pattern, focal positive margins, microscopic extrathyroidal extension into skeletal muscle and only one of the four positive (2.3mm) lymph nodes. Notably, a BRAF V600E mutation was identified by immunohistochemistry and later by next-generation sequencing (NGS). Furthermore, one of the blocks was retested using real-time PCR-based biocartis Idylla, yielding the same result of a BRAF V600E mutation. Histological review of tumor blocks did not reveal any incidental admixed papillary carcinoma. MTC cells stained diffusely, as expected, with calcitonin, CEA, and INSM-1, confirming the diagnosis.

**Discussion:** Several studies have shown that RET (~50%) and RAS (~30%) are the most common driver mutations in sporadic MTC. In the remaining cases, driver mutation appears to be quite heterogeneous (Minna et al., 2022). BRAF V600E is a common mutation seen in follicular thyroid cancer. Very few cases of BRAF V600E MTC have been reported in the literature. One case was reported in the United States (Robbins et al., 2020) and one case in Korea (Cho et al., 2014). On the contrary, Goutas et al. documented an extraordinary 68.2% occurrence of the BRAF V600E mutation among 55 sporadic MTC cases. However, many experts suggest that this finding is likely a technical anomaly. Overall, this case adds evidence that downstream mutations in the MEK/ERK pathway without RET alteration may initiate tumorigenesis across both follicular and parafollicular thyroid cells.

### Poster 0157

*Thyroid Cancer, Case Study, Poster*

#### **Rare Case of Multiple Endocrine Neoplasia Type 2A Diagnosis in a Geriatric Patient Emphasizes Importance of Early Genetic Testing**

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MEN-2A is a rare familial cancer syndrome that affects multiple endocrine organs, typically the thyroid, adrenal glands, and parathyroid. The age of onset for MEN-2A is early adulthood. Physiologically, MEN-2A is a hereditary syndrome typically indicated by the presence of two or more specific endocrine tumors. Genetically, MEN-2A is caused by a missense gain-of-function mutation of the REarranged during Transfection (RET) proto-oncogene. We present a case of an 81-year-old woman diagnosed with multiple endocrine neoplasia 2A (MEN-2A). The patient underwent genetic testing with a positive detection of C1859G>A (p.Cys620Tyr) showing an increased risk of endocrine cancer. Previously, diagnosis of MEN-2A across all phenotypes has only been shown to occur from adolescence to middle age. This report emphasizes the importance of preliminary screenings and genetic testing due to the oddity of this unexpected diagnosis in a geriatric patient typically diagnosed in young adulthood.

### Poster 0158

*Thyroid Cancer, Case Study, Poster*

#### **Diagnostic Conundrum: Pulmonary Metastasis from Thyroid Cancer Masquerading as Benign Adenomatoid Nodules on Pathology**

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Multinodular goiter (MNG) represents a common thyroid disorder characterized by enlargement of the thyroid gland and presence of multiple nodules. While most nodules are benign, a subset may harbor malignant potential, posing diagnostic challenges for clinicians. Fine needle aspiration (FNA) and molecular testing have emerged as valuable tools in evaluating thyroid nodules, aiding in risk stratification and guiding management decisions.

We present a case of a 78-year-old female, without prior radiation exposure or family history of thyroid cancer, who presented to the Endocrine clinic for postsurgical hypothyroidism. She had a history of MNG and neck ultrasound showed a solid, isoechoic nodule with smooth margins measuring 6.6cm in the left lobe and two nodules measuring 3.4cm and 2.1cm in the right lobe, without associated lymphadenopathy. Thyroid-stimulating hormone (TSH) was 2.8 mIU/mL. FNA of the left nodule yielded findings of atypia of undetermined significance, and molecular analysis using Thyroseq demonstrated the presence of NRAS and EIF1AX mutations, raising suspicion for malignancy. However, subsequent total thyroidectomy pathology reported benign adenomatoid nodules with some areas of hypercellularity without evidence of malignancy, corroborated by two independent pathologists. Several months later, the patient underwent chest computed tomography (CT) to investigate chronic dyspnea on exertion, which revealed numerous bilateral metastatic lung nodules, with the largest measuring 1.8cm. A positron emission tomography (PET) scan demonstrated mild activity in the nodules (SUV 2.3) however, no primary fluorodeoxyglucose (FDG) avid tumor was identified. The thyroglobulin level measured at this juncture was elevated at 1025.2ng/mL. Subsequent radioactive iodine (RAI) scan revealed diffuse uptake in the bilateral lung fields, confirming metastatic thyroid cancer. The patient underwent dosimetry-based RAI therapy, resulting in a decrease in thyroglobulin level to 170.9ng/mL two months post-RAI.

Multifocal pulmonary metastasis of thyroid cancer, devoid of primary intrathyroidal cancer or metastases elsewhere, is exceedingly rare, with very few cases reported in literature. This case highlights the need for accurate diagnostic techniques in scenarios lacking pathological confirmation yet exhibiting malignant clinical characteristics. Based on the mutations detected in our patient, it is probable that she had metastatic follicular or hurthle cell thyroid carcinoma despite a benign pathology report.

**Poster 0159***Thyroid Cancer, Case Study, Poster***A Novel Case of Redifferentiation of Anaplastic Thyroid Cancer Followed by Surgery and Treatment with Radioactive Iodine**

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**Introduction**

Anaplastic thyroid cancer (ATC) is a rare and aggressive thyroid tumor which usually develops from dedifferentiation of papillary thyroid cancer (PTC) secondary to the accumulation of somatic mutations. The *BRAF* V600E mutation is found in 40-50% of ATC. Treatment with dabrafenib and trametinib in a non-randomized study demonstrated an overall survival (OS) of 14.5 months, with neoadjuvant treatment resulting in a one year survival of 83% in a small case series. The efficacy of radioactive iodine (RAI) following BRAF-directed therapy and surgery is unclear.

**Case Description**

A 64-year-old male presented with cough, dyspnea, and dysphagia. PET/CT showed a 7.5 cm thyroid mass, with cervical, hilar and mediastinal lymphadenopathy, as well as multiple pulmonary and bone metastases. Endobronchial biopsy of his lung metastases was diagnostic of ATC with a *BRAF* V600E mutation, therefore initial treatment was non-surgical with external beam radiation, and systemic therapy with dabrafenib and trametinib. Follow-up imaging showed a mixed response, and treatment was complicated by multiple hospitalizations and treatment interruptions. After ten months of systemic therapy, fine needle aspiration biopsy of neck nodal disease revealed differentiated thyroid cancer. Four months later he underwent total thyroidectomy, left neck dissection, and mediastinal dissection, with histopathology showing a mix of classical PTC, poorly differentiated thyroid carcinoma, high grade differentiated follicular cell derived thyroid carcinoma, and anaplastic thyroid cancer. He received 150 mCi of RAI two months after surgery and his post-treatment I-131 scan with SPECT CT showed a mix of RAI-avid and non-RAI-avid metastases. There was further disease progression and he died 6 weeks later, with an overall survival of 20 months from the time of diagnosis.

**Discussion**

Recent advances in the treatment of ATC have resulted in improved overall survival rates, particularly in patients who are candidates for BRAF-directed therapy. A retrospective cohort study reported improved survival in patients with ATC treated with neoadjuvant BRAF-directed therapy followed by surgery. Our case is the first report of the use of RAI following redifferentiation with BRAF-directed therapy and surgery, with RAI uptake into some of the metastases.

**Poster 0160***Thyroid Cancer, Case Study, Poster***Rare Case Of Cutaneous Metastasis In Medullary Thyroid Cancer**

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**INTRODUCTION**

Cutaneous metastases are rare in any type of thyroid malignancies, and of those reported, majority are seen in papillary cancers. We report a case of cutaneous metastasis in medullary carcinoma of the thyroid.

**CASE DESCRIPTION**

44 y/o male presented with left ear pain and swelling in the neck. CT scan showed enlarged thyroid gland with infiltrating features

concerning for thyroid malignancy with enlarged cervical lymph nodes. Fine Needle Aspiration of the left thyroid nodule and cervical lymph node showed Medullary Thyroid Carcinoma (MTC). Patient did not have any family history of MTC or Multiple Endocrine Neoplasia syndromes. Parathyroid hormone, Calcium and Metanephrine levels were in normal range. He underwent total thyroidectomy with left neck dissection. Pathology showed 5.2 cm MTC, 4/12 lymph nodes involved, largest focus of 3.8 cm with extranodal extension and positive tumor margins. Pre-operative calcitonin levels were 133 pg/mL which improved to 6.5 post-operatively. RET M918T mutation was seen.

3 months after completion of radiation therapy, he presented with severe scalp pain and a red exophytic indurated nodule on the right parieto-occipital scalp which was unresponsive to topical steroids and oral antibiotics. Suspecting cutaneous metastatic disease, further evaluation for recurrence was undertaken. Calcitonin levels returned elevated at 1405 pg/mL and CT imaging revealed multiple lesions in liver and lung consistent with metastatic disease. A liver biopsy showed metastatic MTC and biopsy of the skin lesion was deferred to avoid worsening the pain in that site as it would not alter management in that time. He started on Selpercatinib treatment and imaging 3 months later showed response to treatment with decrease in the size of liver and lung metastases. Calcitonin levels were also undetectable. His scalp lesion also reduced in size and scalp pain had resolved, proving that this was a cutaneous metastasis of MTC.

**DISCUSSION**

Medullary thyroid cancer is a rare thyroid malignancy and cutaneous metastasis are even rarely reported in this disease or any other type of thyroid cancer. Most of reported cutaneous metastasis in thyroid cancer are seen in papillary and follicular types. Scalp is the most common site of cutaneous metastasis from any type of thyroid cancer and indicates poor prognosis. This highlights the importance of awareness of this rare site of metastasis of MTC which needs a high index of suspicion. His diagnosis of progressive systemic disease perhaps could have been delayed without this suspicion of cutaneous metastasis.

**Poster 0161***Thyroid Cancer, Case Study, Poster***Significant Clinical Response to Crizotinib in Recurrent, Metastatic Papillary Thyroid Cancer with CCDC30-ROS1 Fusion Mutation**

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**Introduction:** ROS1 mutations have only recently been described in Papillary Thyroid Cancer (PTC) for the first time<sup>1</sup> and limited data exists on ROS1 targeted Tyrosine Kinase Inhibitor (TKI) therapy in PTC. The TKI Crizotinib has classically been used for ALK-positive non-small cell lung cancer. There is currently limited experience in its use for thyroid cancer and to our knowledge this is the first case of Crizotinib use in PTC with ROS1 mutation.

**Case:** Our case involves a 41-year-old female with aggressive PTC, stage pT3N1bMx with extensive disease in the thyroid bed and later found in the chest, mediastinum, and pelvis. She underwent hemithyroidectomy in October 2016 and completion thyroidectomy in March 2017. Over the next two years, she underwent three additional neck surgeries for recurrent bulky disease and received adjuvant radioactive iodine prior to a final surgery in April 2019. She

continued to show uptake in the thyroid bed, neck, and pelvis on imaging 2 months later, concerning for residual metastatic disease. Multidisciplinary discussion was held May 2019 and systemic therapy was recommended. Genomic sequencing found a CCDC30-ROS1 fusion mutation and Crizotinib was started with significant response after just 2 months. Thyroglobulin (TG) decreased from 2011 to 1391 ng/mL. At 4 months, TG decreased to 795 ng/mL. Restaging scans showed decreased vascularity and size of a diffusely enhancing pelvic mass from 7x4.3cm to 6x2.7cm, and shrinkage in mediastinal lymph nodes (LN) from 3.2x3.5cm to 1.1x1.5cm and 1.9x2.4cm to 0.7x1.6cm, respectively. After 7 months, TG reached a nadir of 369 ng/mL. During the next several months, TG rose to 809 ng/mL, concerning for progression. Imaging at 13 months showed increased size of hilar LNs and an increase in TG to 1492 ng/mL, at which point a change in therapy was recommended. Overall, Crizotinib slowed disease progression in our patient for approximately 12 months.

**Discussion:** To our knowledge this is only the third reported case of ROS1-mutated PTC<sup>2</sup> and the first case treated with Crizotinib. This case demonstrates the potential impact of genetic testing and targeted therapies for cases of PTC refractory to conventional treatments.

### Poster 0162

*Thyroid Cancer, Case Study, Poster*

#### **Diagnostic Discrepancy: A Case of Coexisting Papillary and Anaplastic Thyroid Carcinoma**

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Anaplastic thyroid cancer is known for its aggressive nature that leads to poor prognosis and is not uncommon to find coexisting differentiated thyroid cancer. Here we present a case initially diagnosed with papillary thyroid cancer, later turned out to have anaplastic thyroid carcinoma too, which could have approached differently if known earlier.

A 77-year-old female was admitted for a large left papillary thyroid cancer which was diagnosed from a fine needle aspiration (FNA) 8 months before the admission. CT chest and neck demonstrated solid, lobulated heterogeneously enhancing 5.0 x 4.1 cm mass in the left side of the neck involving the left thyroid, causing mild deviation of nearby structure. She underwent left hemithyroidectomy and neck dissection. The tumor involved the trachea, tracheal-esophageal groove, and skeletal muscles. Two lymph nodes out of 27 were positive for metastatic thyroid carcinoma. Interestingly, pathology from surgical biopsy revealed three different types of thyroid carcinoma: 5% of anaplastic, mainly in the extrathyroid area, 25% of differentiated high-grade papillary, and 70% of clear cell type papillary carcinoma. The patient's hospital course was complicated with an acute left middle cerebral artery infarct postoperatively. She developed hypothyroidism, so started levothyroxine 25 mcg. The patient was discharged to a long-term care facility for hospice care.

There was a significant delay between the onset, first diagnosis, and surgery of her thyroid mass as the patient lost follow-ups a few times, which might have caused cancer transformation in the meantime. The mean interval between the FNA and surgery was 52 days per Yuan F. Liu et al. Also, it was less likely to get the tissue sample of anaplastic carcinoma from FNA as it only consisted of 5% of the mass. In addition, there has been research showing relatively large false negative results from FNA for large nodules. We can argue that the patient would have benefited from core needle biopsy rather than FNA for its large size. We can also consider developing a scoring system for patients who have a higher chance of having

coexisting anaplastic thyroid cancer to get further diagnostic tests before considering treatment.

### Poster 0163

*Thyroid Cancer, Case Study, Poster*

#### **The Enigma of Distant Metastases in Medullary Thyroid Cancer: Low Calcitonin Levels as a Deceptive Indicator**

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#### Introduction

Calcitonin levels can be used as an indicator for regional neck metastasis versus distant metastasis in patients with medullary thyroid cancer (MTC).

#### Clinical Case

A 61-year-old man with hypertension was diagnosed with a 0.6 cm left lobe medullary thyroid cancer with central and left lateral neck metastases with extranodal extension at age 53. He had no germline mutation. Prior to surgery his calcitonin was 255 pg/mL and CEA was 5 ng/mL. Post-operatively these calcitonin and CEA levels decreased to 5 pg/mL and <1 ng/mL, respectively. The year following his initial surgery, he underwent a repeat left neck dissection for cervical node metastases. Two years after the repeat neck dissection, he was found to have recurrence in a left submandibular node, left periauricular mass, neck scar on the left, and liver. Next generation sequencing in the liver tissue was positive for RET p.M918T. Despite these extensive distant metastases his calcitonin level was only 36 pg/mL and CEA level was 1 ng/mL. Due to distant metastases, he was enrolled into the LOXO study but was disenrolled three months later due to elevated liver enzymes. He then enrolled in the BLU study during which time his calcitonin and CEA levels became undetectable and his liver and lungs metastases remained stable in size. Following completion of the BLU study, he started Pralsetinib 100 mg three tablets daily. His current calcitonin and CEA levels remain undetectable and imaging studies show no progression of distant metastases.

#### Discussion

Distant metastases can rarely occur in patients with MTC with a calcitonin level less than 150 pg/mL. Physicians should pursue additional imaging studies even if calcitonin level is less than 150 pg/ml if there is clinical suspicion for distant progression of disease.

### Poster 0164

*Thyroid Cancer, Case Study, Poster*

#### **A Rare Presentation: Papillary Thyroid Cancer Initially Identified As Left Hip Pathological Fracture**

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**Introduction:** Papillary thyroid cancer (PTC) is the most prevalent type of thyroid malignancy, constituting 80-85% of cases, with incidence rates varying among populations. Females are disproportionately affected, with a 2 to 3 times higher prevalence than males, possibly influenced by hormonal and genetic factors. Improved diagnostic methods contribute to the rising incidence rates observed globally.

**Case Description:** A 75-year-old woman was referred to the endocrinology clinic due to metastatic PTC, initially diagnosed after a left hip pathological fracture. She experienced chronic left hip

pain, exacerbated at night and relieved by movement. Imaging revealed lytic lesions, prompting surgical fixation and subsequent biopsy confirming metastatic carcinoma of thyroid origin. Further investigations unveiled additional lesions in the thyroid, kidney, and adnexa, with abnormal thyroglobulin levels. Bilateral thyroidectomy revealed papillary carcinoma with no extrathyroidal extension, prompting initiation of replacement therapy, radioactive Iodine and Denosumab.

**Discussion:** PTC commonly presents as a thyroid nodule, often asymptomatic or with localized symptoms. While bone metastases are rare at diagnosis, they signify advanced disease and poorer prognosis. Vigilance for metastases, especially in aggressive PTC cases, is crucial for timely intervention. This case underscores the importance of thorough evaluation and multidisciplinary management in metastatic PTC, emphasizing the need for further research to improve outcomes and address diagnostic challenges.

### Poster 0165

*Thyroid Cancer, Case Study, Poster*

#### **Redifferentiation Effect of Larotrectinib: A case report of a 19 y/o male with an NTRK1 pathogenic fusion**

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#### **Introduction**

Papillary Thyroid Carcinoma (PTC) is the most common cause of thyroid malignancy, and the most common metastatic site is the lung. Metastatic thyroid cancers may dedifferentiate and become radioactive-iodine (RAI) resistant. A redifferentiation effect can be observed with inhibitors of the mitogen-activated protein kinase pathway in thyroid cancers with point mutation in oncogenes and inhibitors targeting oncogenic fusion genes. Neurotropic Tyrosine Receptor Kinase 1 (NTRK1) represents a minority of oncogenes causing PTC. We report the case of a patient with metastatic RAI-refractory NTRK-rearranged thyroid cancer who received Larotrectinib for redifferentiation therapy.

#### **Clinical Case**

We present a case of a 19 y/o man with no family history of thyroid cancer or history of radiation to the neck or chest area. He was incidentally found with abnormal cervical lymph nodes (LN). The Neck US showed an ill-defined left lobe nodule, measuring 3.0 cm with microcalcifications. It also showed LNs that were completely replaced by tumors on Left cervical levels 3 and 4. The abnormal LN were solid and had chaotic blood flow and calcifications. The FNA of the Left lobe nodule and the dominant LN were positive for PTC. He underwent a total thyroidectomy with a left neck dissection. The pathology showed papillary thyroid cancer, a classical variant extending into the strap muscles, with negative angiovascular invasion. He had LN metastasis to 13/72 with positive ENE.

The appropriately suppressed post-op thyroglobulin was 112.4 ng/ml, with a low concentration of thyroglobulin Ab, 11 IU/ml. The CT chest showed scattered subcentimeter pulmonary nodules, which were too small for biopsy.

Molecular analysis by DNA and RNA next-generation sequencing identified a pathogenic NTRK1 fusion. Whole Body Dosimetry did not show RAI avid disease. The patient received Larotrectinib for three months with the goal of cancer differentiation and subsequent RAI therapy. The repeated diagnostic Whole-Body scan after the therapy showed RAI avid disease.

The patient underwent RAI therapy with a therapeutic activity of 200 mCi. The stimulated thyroglobulin was 126 ng/ml, and the

thyroglobulin Ab was 15 IU/ml. The post-treatment scan showed diffuse uptake throughout the bilateral lungs. A CT chest after RAI therapy showed a significant decrease in the size and number of the bilateral punctate pulmonary nodules.

#### **Discussion**

Larotrectinib-induced a remarkable RAI reuptake in the lungs. The patient tolerated the therapy well, with no reported side effects, and experienced a significant reduction in the size and number of bilateral pulmonary nodules.

### Poster 0166

*Thyroid Cancer, Case Study, Poster*

#### **Anaplastic Thyroid Cancer Presenting as Cranial Nerve Palsies**

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**Introduction:** Anaplastic thyroid cancers (ATC), accounting for 1.7% of thyroid cancers in the United States, are extremely aggressive, with an overall one-year survival of 20%. In 90% of cases, regional or distant spread is present at diagnosis. Sites include perithyroidal fat and muscle, lymph nodes, oropharyngeal structures, and great vessels of the neck. We are presenting a unique case of ATC presenting as multiple cranial nerve palsies secondary to carotid artery involvement.

**Case Presentation:** An 87-year-old female presented with a 6-week history of glossoplegia, impaired movement, and dysphonia. Laboratory workup was unrevealing. Nasal endoscopy revealed an immobile right vocal cord. CT Neck with IV contrast identified a 2.2cm thyroid mass, biopsied as papillary thyroid carcinoma. CT angiogram demonstrated severe basilar artery stenosis and complete intracranial left vertebral artery occlusion. MRI exhibited a pituitary macroadenoma extending into the left cavernous sinus and highlighted complexities involving the tongue and palatine tonsil; subsequent right tongue base biopsy was negative. There was abnormal enhancement of cranial nerve VI, vascular loop near cranial nerve IX, and edema along cranial nerve XII on the right.

PET scan showed a 2cm intensely FDG avid nodule in the right thyroid lobe and nonspecific increased uptake around the right carotid artery, impacting the carotid artery and cranial nerves X and XII. Because of the location, a needle biopsy nor an open biopsy was feasible. Total thyroidectomy revealed papillary thyroid carcinoma progressing to ATC with a significant squamous component with extrathyroidal extension, perineural invasion, and lymph vascular invasion. One central compartment lymph node contained a tumour with no extracapsular disease. A high-dose iodine scan showed no uptake in the carotid mass, suggesting a squamous cell component. External beam radiation targeted the carotid lesion, and targeted therapy with anti-BRAF plus anti-MEK was initiated.

**Discussion:** This intricate case with diagnostic challenges reveals an unusual presentation of ATC, depicting its aggressive nature and diverse symptomatology. Diagnostic challenges were evident in determining the etiology of our patient's dysphagia alongside cranial nerve palsies. We highlight the complexity of managing ATC cases and the necessity for an interdisciplinary approach, allowing for tailored interventions to improve outcomes.

### Poster 0167

*Thyroid Cancer, Case Study, Poster*

#### **Follicular Thyroid Neoplasm with Aggressive Bone Metastasis**

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### INTRODUCTION

We present an extremely rare case of a follicular thyroid carcinoma presenting with aggressive bone metastasis.

### CASE PRESENTATION

52-year-old female with no known medical history initially presented for evaluation of a left scalp mass and enlarging anterior neck mass. The neck mass was present for the past 6 years, but progressively enlarged causing mild dyspnea when supine and dysphagia to solids for the past one year. A CT of the neck revealed a goiter with substernal extension and invasion of the right internal jugular vein. A subsequent thyroid ultrasound demonstrated goitrous enlargement of the right thyroid lobe with heterogeneous nodules, hypervascularity and scattered marginal calcifications. Thyroid function tests revealed a normal TSH and a borderline low FT4. Cytology from a FNA was consistent with a follicular thyroid neoplasm.

A CT Head revealed a 5 cm x 4 cm lytic mass along the posterior midline and another 3.3 cm x 2 cm lytic mass along the left calvarial cortex with invasion of the scalp soft tissue. Subsequent imaging revealed an incidental 10.1 cm x 6 cm x 8 cm lytic sacral mass and a

3.6 x 3.2 x 5.2 cm lytic left iliac lesion invading the left gluteal musculature. There was no clear evidence of another primary lesion on other lab testing or imaging. A core biopsy of the sacral mass had pathology with positive stains for TTF, galectin 3, HBME1, and thyroglobulin supporting a diagnosis of metastatic thyroid carcinoma.

### DISCUSSION

Follicular thyroid carcinoma is more common in women and usually appears in the fifth and sixth decades. Chronic iodine deficiency may also increase individual risk. Metastasis occurs via vascular invasion with rate of distant hematogenous dissemination reported as 6-20%. The most common sites involved are spine (33.9%), pelvis (30.5%) and skull (27.1%). In some cases, widespread metastasis has already occurred at the time of diagnosis. Sacral metastases are extremely rare, with literature consisting of only a few case reports. All patients presenting with thyroid mass should be thoroughly evaluated for any evidence of metastasis and disease burden, as in this case, the patient's sacral and iliac masses were incidental findings given absence of symptoms.

# Thursday, October 31, 2024

## Poster 0168

*Autoimmunity, Basic, Poster*

### The TSH Receptor Interacts Directly With The IGF-1 Receptor Complex

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**Introduction:** It is well known that TSH and IGF-1 signaling synergize. The TSH receptor (TSHR) and IGF-1 receptor (IGF-1R) are expressed on orbital fibroblasts and their synergy has been explained by a poorly defined “cross talk”, reported to be mediated via  $\beta$ -arrestin, linking both receptors together. Evidence suggests that the resulting signal enhancement is involved in the inflammatory pathogenesis of Thyroid Eye Disease (TED) (1).

**Objective:** We have evaluated whether TSHR and IGF-1R can interact directly in a constitutive arrestin independent state.

**Methods & Results:** We first used a modeling approach and docked the leucine rich domain (LRD) of the TSHR ectodomain (ECD) to the cryo-EM structure of the active-state IGF-1R dimer complex followed by molecular dynamics (MD) simulations. This revealed highly stable docked structures allowing us to build a TSHR-IGF-1R complex using our own recent model of the full-length TSHR (2, 3). To then assess the stability of this heterodimeric complex a 3000ns MD simulation showed that not only the stability of the interacting ectodomains but also revealed the reduced proximity of the TSHR and IGF1R transmembrane domains (TMD) further indicating a stable active receptor complex.

In order to validate our modelling data, we next performed co-immunoprecipitation studies with anti-TSHR and anti-IGF-1R mAbs using cells expressing the TSHR and the IGF1R and compared them with cells that expressed only the TSHR-ECD (which is unable to bind  $\beta$ -arrestin) and the IGF1R complex. We detected a 362kD complex protein in the immunoprecipitation positive for both antibodies, and which was clearly present in the full length TSHR and the TSHR-ECD-only expressing cells and absent from controls. Furthermore, we also found co-localization of TSHR and IGF1R in the TSHR-ECD-only cells again evidencing direct interaction.

**Conclusion:** These data show that TSHR-IGF1R interaction has more than one mode of “cross talk” - indirect via arrestin as suggested by others but also direct electrostatic/Van der Waals interactions via the TSHR-ECD structures. Understanding these two modes of interaction in depth and their physiological consequences is of prime importance in the pathogenesis of TED and its therapeutic control.

## Poster 0169

*Autoimmunity, Translational, Poster*

### IFN $\alpha$ shapes thyroglobulin peptide repertoire into an immunogenic repertoire triggering autoimmune thyroiditis

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Einstein College of Medicine, USA, <sup>2</sup>University of Pisa, Italy

**Objective:** Autoimmune thyroid diseases (AITD) arise from an interplay between genetic and non-genetic triggers. IFN $\alpha$ , a key cytokine produced in response to viral infections, emerged as a

major AITD trigger. Our group discovered that IFN $\alpha$  activates the unfolded protein response and autophagy/lysosomal pathways in thyroid cells, triggering thyroglobulin (Tg) degradation. Tg antigenicity is influenced by its degradation into immunogenic peptides. However, the mechanisms that shape the Tg antigenic repertoire are not known. We hypothesized that viral infections can trigger AITD by inducing local thyroidal production of IFN $\alpha$  leading to degradation of Tg into immunogenic peptides.

**Methods:** We employed *in vitro* studies in ML-1 thyroid cells and *in vivo* studies using the NOD.H-2<sup>h4</sup> mouse model. To assess IFN $\alpha$ -induced degradation of Tg, we treated ML-1 cells with IFN $\alpha$  in the presence or absence of lysosomal inhibitors (chloroquine, [CQ]), and evaluated thyroidal Tg levels by western blot and immunostaining. To assess if IFN $\alpha$ -induced Tg degradation triggered the release of immunogenic peptides, we exposed ML-1 cells to IFN $\alpha$  in the presence and absence of lysosomal inhibitors, and examined expression of Tg and Tg.2098, a key immunogenic peptide, by immunostaining. Finally, we compared the development and severity of experimental induced thyroiditis (EAT) between NOD.H-2<sup>h4</sup> mice treated with IFN $\alpha$  and IFN $\alpha$  + CQ. EAT was evaluated based on T-cell cytokines production in response to Tg/Tg.2098, autoantibodies (Abs) to Tg and thyroid histology.

**Results:** IFN $\alpha$  treatment of thyroid cells triggered Tg degradation; lysosomal inhibition restored Tg protein levels. Immunostaining showed that IFN $\alpha$ -induced degradation of Tg was accompanied by detection of Tg.2098, while blocking Tg degradation reduced Tg.2098 levels. These studies suggest that IFN $\alpha$  can trigger Tg degradation into immunogenic peptides including Tg.2098. Moreover, mice treated with IFN $\alpha$  showed increased T-cell responses and Tg Abs compared with mice treated with IFN $\alpha$  + CQ and with control mice. Moreover, mirroring our findings in ML-1 cells, we detected increased levels of thyroidal Tg in IFN $\alpha$  + CQ compared with IFN $\alpha$ -treated mice.

**Conclusions:** Our studies reveal a new mechanism by which virally induced IFN $\alpha$  can shape the Tg peptide repertoire into an immunogenic repertoire triggering AITD.

## Poster 0170

*Autoimmunity, Translational, Poster*

### Effect on Th1 and Th2 Chemokines Secretion by Rapamycin, Mycophenolic Acid, or Glucocorticoids in Primary Retro-Orbital Cells Obtained from Patients with Graves' Ophthalmopathy

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**Objective:** Cytokines and chemokines play a key role in the pathogenesis of Graves' Ophthalmopathy (GO), and cytokines stimulate the T-helper (Th)1 and Th2 chemokines release from retro-orbital cells. We aimed to investigate the effects of rapamycin, mycophenolic acid and/or glucocorticoids on the secretion of Th1

and Th2 chemokines in human primary cell cultures obtained from GO patients.

**Methods:** We established primary cultures of retro-orbital fibroblasts, preadipocytes and myoblasts from 6 patients with GO, and we evaluated the effect of increasing concentrations of rapamycin and/or mycophenolic acid and/or glucocorticoids (alone or in combination) on the secretion of the prototype Th1 (CXCL10) and Th2 (CCL2) chemokines.

**Results:** We showed that in the primary GO retro-orbital cells, CXCL10 was undetectable in the supernatants, whereas it was induced dose-dependently by interferon (IFN)-gamma, but not by tumor necrosis factor (TNF)-alpha. The combination of IFN-gamma and TNF-alpha had a significant synergistic effect on CXCL10 secretion.

Differently, a low level of CCL2 were found in basal condition, and it was induced in a dose-dependent manner by TNF-alpha (but not by IFN-gamma alone), while the combination of TNF-alpha+IFN-gamma had a significant synergistic effect on CCL2 release.

The co-treatment with mycophenolic acid, rapamycin, or glucocorticoids (in a pharmacological range), in the presence of TNF-alpha+IFN-gamma, led to a dose-dependent inhibitory effect on the chemokines release.

Moreover, a synergistic inhibitory effect on the chemokines release was observed by combining mycophenolic acid or rapamycin and/or with glucocorticoids.

**Conclusions:** Our results show the therapeutic role of mycophenolic acid or rapamycin with glucocorticoids in GO patients, that could be reached through their immune-modulatory effect on Th1 and Th2 chemokines secretion in retro-orbital cells.

### Poster 0171

*Autoimmunity, Translational, Poster*

#### Targeting CD4+ T cell IL21 Signaling to Halt Hashimoto's Thyroiditis Progression

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Hashimoto's thyroiditis is one of the most common autoimmune endocrinopathies, affecting 15% of the U.S. population. However, no treatments exist to halt disease progression or address the underlying immunopathogenesis, as has become the standard of care for many other autoimmune diseases. We used single cell and spatial RNA sequencing of human thyroid specimens to delineate key immune interactions and signaling pathways in HT. We identified T-follicular helper (Tfh, CD4<sup>+</sup>IL21<sup>+</sup>ICOS<sup>+</sup>PD1<sup>+</sup>BCL6<sup>+</sup>CXCR5<sup>+</sup>) cells as early mediators of HT, orchestrating the formation of tertiary lymphoid structures (TLS). Cellchat analysis showed significant interleukin 21 (IL21) – IL21R, CXCL13 – CXCR5/3, and CD40LG – CD40 signaling from CD4<sup>+</sup> Tfh cells to B and effector T cells in inflamed thyroid tissues. In addition, Tfh cells appeared early in disease progression (euthyroid TPO antibody positive patients with HT), while CD8<sup>+</sup> T cells were increased in later disease (hypothyroid TPO antibody positive patients). Spatial transcriptomics confirmed that Tfh CD4<sup>+</sup> cells expressing *IL21* and *CXCL13* were central to TLS in early stage HT. We then turned to our unique mouse model of HT, in which mice with a dominant negative mutation in the *AIRE* (autoimmune regulator) gene develop spontaneous thyroiditis due to altered negative selection of self-reactive T cells. Importantly, thyroiditis in NOD.AIR-EGW mice recapitulates key features of human HT, including lymphocytic infiltration, hypothyroidism, TPO antibody positivity, and female sex bias, but does not require excess iodine for disease development. As in patients, scRNAseq of thyroid immune infiltrates in

NOD.AIRE<sup>EGW</sup> mice revealed T, B, and myeloid cells, with a prominent IL21+ CD4+ T cell population. Flow cytometry analyses confirmed increased Tfh cells in thyroid infiltrates of NOD.AIRE<sup>EGW</sup> mice compared to age and sex matched NOD wildtype controls. Furthermore, deletion of CD4+ T cells and genetic deletion of IL21 signaling in NOD.AIRE<sup>EGW</sup> mice prevented thyroiditis development. Based upon these data, we tested the effect of ruxolitinib, a clinically-approved janus kinase (JAK) inhibitor that prevents downstream JAK/STAT activation in immune cells following IL21 stimulation, on thyroiditis development in our mouse model. Indeed, ruxolitinib effectively halted thyroiditis and presents a potential near-term therapeutic approach to stop autoimmune disease progression in patients with HT.

### Poster 0172

*Autoimmunity, Translational, Poster*

#### Memory Stem-like Progenitor Exhausted CD8+ T cells Drive Chronicity in Hashimoto's Autoimmune Thyroid Disease

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Hashimoto's thyroiditis (HT) is an autoimmune disease affecting up to 15% of the population and the most common cause of thyroid gland dysfunction. While HT is clinically defined by chronic lymphocytic infiltration, the mechanisms driving continued propagation of self-reactive immune effectors remains elusive. Memory progenitor exhausted T cells (Tpex) are antigen experienced CD8<sup>+</sup> T cells that uniquely possess a capacity for self-renewal and differentiation to cytotoxic CD8<sup>+</sup> effectors. Such Tpex cells have been implicated in chronic viral infection and cancer immune responses. We hypothesize that these cells are also seen in HT and potentiate the chronic, progressive autoimmunity that defines HT.

We evaluated thyroid immune infiltrates in patients with no thyroid disease, early HT (+immune infiltrate, +TPO antibody positive, but euthyroid) or late HT (+immune infiltrate, +TPO antibody, with hypothyroidism) using single nuclei RNA sequencing (snRNAseq) of benign thyroid surgical specimens and flow cytometry of fresh tissue from thyroid fine needle aspirates. SnRNAseq revealed thyroid follicular cells and diverse immune infiltrates comprised of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells, and myeloid cells. Notably, we found increased CD8<sup>+</sup> T cells in HT compared to healthy controls, with increased absolute counts and relative percentages correlating with progression from early (euthyroid) to late stage (hypothyroid) HT. This suggested that differences in the CD8<sup>+</sup> T cell population may distinguish individuals who have progression of their autoimmunity compared with those who remain euthyroid.

Subclustering of CD8<sup>+</sup> T cells identified clusters of Tpex (*IL7R<sup>+</sup> CD44<sup>+</sup> TCF7<sup>+</sup> SLAMF6<sup>+</sup> SELL<sup>+</sup> TOX<sup>+</sup>*) and effectors (*IFNG<sup>+</sup> FAS<sup>+</sup> PRFI<sup>+</sup>*), as well as a terminally exhausted subset (*LAG3<sup>+</sup> HAVCR2<sup>+</sup> PDCDI<sup>+</sup>*). Furthermore, trajectory analysis showed that progression from Tpex to effector CD8<sup>+</sup> T cells expressing cytotoxicity genes (*IFNG, PRFI*) was significantly increased in thyroid immune infiltrates from subjects with late stage HT but not early HT or healthy controls. We then confirmed Tpex and effector CD8<sup>+</sup> populations using flow cytometry in patients with HT and healthy controls. In summary, we now extend a role for memory Tpex cells, key drivers of immune chronicity in viral infections and cancer, to thyroid autoimmunity and propose them as a potential therapeutic target in autoimmune endocrinopathies.

**Poster 0173***Autoimmunity, Translational, Poster***Serum Proteomic Analysis Reveals Insights into the Mechanism of Action of Teprotumumab, an Insulin-Like Growth Factor-1 Receptor Inhibitor, in Patients with Chronic, Low Disease Activity Thyroid Eye Disease (TED)**

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**Background:** TED presents with various degrees of severity and activity, with chronic cases posing challenges in diagnosis and treatment. Insulin-like growth factor-1 receptor (IGF-1R) pathogenic signaling plays a key role in TED. Teprotumumab, an IGF-1R inhibitor, demonstrated disease improvement in a trial of patients with chronic, low disease activity TED recently (NCT04583735). This trial represents a significant step, demonstrating reduced proptosis for a population traditionally treated with decompression surgery and recalcitrant to pharmacotherapy. Teprotumumab's impact on biomarkers and signaling pathways remains to be fully understood. In this study, we examine serum proteomics to elucidate global pathways impacted by teprotumumab in low disease activity TED patients.

**Methods:** Serum samples from placebo and teprotumumab-treated subjects (20 in Placebo and 41 in Teprotumumab) were collected at baseline and Weeks 3, 12 and 24 and were analyzed on the Olink Explore 3072 platform, and serum IGF-1 levels were analyzed with the R&D Quantikine assay.

**Results:** In teprotumumab-treated samples, drug target engagement was validated and confirmed through the IGF-1 immunoassay. Modulation of IGF-1 pathways (i.e., soluble IGF-1R, and insulin-like growth factor binding proteins [IGFBPs] 1-3) were also noted post-teprotumumab treatment in the Olink assay. Additionally, teprotumumab treatment repressed key proteins that were previously found to be elevated in TED tissues, including proteins involved in collagen formation and extracellular matrix (ECM) production, such as COL1A1, OMD, and MMP1 (decreased by 2.07, 1.82 and 1.60-fold vs placebo after 24 week treatment, respectively).

**Conclusion:** Previous TED studies have demonstrated collagen accumulation leads to an expansion of the ECM which causes destructive tissue remodeling, a hallmark of the disease. Our findings underscore the pivotal role of IGF-1R activation in the disease and confirm target engagement and modulation with teprotumumab in these patients with chronic TED. Global proteins associated with the disease were altered by teprotumumab, particularly in pathways related to IGF-binding proteins and ECM which ultimately may lead to disease modification. These insights deepen our understanding of teprotumumab's therapeutic mechanisms and its implications for the management of chronic TED, potentially paving the way for more targeted interventions and improved patient outcomes.

**Poster 0174***Autoimmunity, Translational, Poster***GenSci098-a potent TSHR antagonistic antibody for the treatment of TED**

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**Objective:** The stimulation of TSHR by TSHR-stimulating antibody (TSAb) is key to the induction of orbital phenotypes seen in Thyroid eye disease (TED). TSHR, due to its limited tissue distribution and its role in TED, serves as a promising target for developing therapeutics against TED. Here, we aim to develop a potent TSHR

antagonistic antibody that might possess advantages over existing therapeutic options for the treatment of TED.

**Methods:** In *in vitro* studies, receptor binding and cAMP assays were used to investigate the binding and antagonistic activities of GenSci098 across species. The blocking effects of GenSci098 on hyaluronic acid (HA), IL-6 and IL-8 secretion were evaluated in TSAbs-stimulated primary human orbital fibroblasts (OFs) isolated from active and inactive TED patients. In *in vivo* efficacy studies, we have adopted an acute M22-induced hyperthyroidism mouse model to test the inhibitory effects of GenSci098 on T4 production. We also conducted pre-clinical studies to evaluate the toxicity and pharmacokinetics of GenSci098.

**Results:** In the receptor binding assay, GenSci098 showed great across species binding activity to TSHR in receptor-overexpressing HEK293 cells. In the cAMP assay, GenSci098 showed excellent blocking activities on M22-stimulated human TSHR-expressing HEK293 cells. In addition, GenSci098 exhibited comparable blocking efficacy as teprotumumab on HA, IL-6, and IL-8 production in TED-Igs treated OFs from both active and inactive patients. The antagonistic activity of GenSci098 on TSHR *in vivo* was confirmed in a M22-induced hyperthyroidism mouse model, with minimum and maximum effective doses at 0.5 mg/kg and 3mg/kg respectively. The half-lives of GenSci098 in mice (327h) and monkeys (462h) support a potential once-monthly dosing frequency in human. Finally, GenSci098 was proved to be safe and well-tolerated in the mouse and monkey tox studies, with no signs of hypothyroidism.

**Conclusion:** GenSci098 has demonstrated comparable efficacy as teprotumumab in improving HA secretion from retro-orbital fibroblasts of TED patients and alleviated the thyroid hormone secretion in acute GD mouse model with low safety risks. More importantly, no hypothyroidism was observed with GenSci098 in mouse and monkey tox studies. Therefore, GenSci098 might be a promising drug for further development in the treatment of TED and Grave's disease.

**Poster 0175***Autoimmunity, Translational, Poster***Single-cell transcriptomics defines disease-specific cellular heat shock response states in autoimmune thyroid diseases and thyroid cancer**Jin Zhou<sup>\*1</sup>, Fangyi Han<sup>2</sup>, Xicheng Song<sup>3</sup>, <sup>1</sup>Department of Endocrinology, Yantai Yuhuangding Hospital of Qingdao University, China, <sup>2</sup>Yue Bei People's Hospital Postdoctoral Innovation Practice Base, Southern Medical University, China, <sup>3</sup>Department of Otorhinolaryngology, Head and Neck Surgery, Yantai Yuhuangding Hospital of Qingdao University, China

**Objective:** Heat shock response is an evolutionarily conserved survival program that is activated in response to proteotoxic stress, which is implicated in various physiological and pathological processes. However, cellular heat shock response states in autoimmune thyroid diseases and thyroid cancer remain to be fully defined. Single-cell RNA sequencing provides a novel cell biology and genetic data basis for elucidating the pathogenesis of thyroid disease.

**Methods:** This study established a single-cell atlas of the human thyroid from Graves' disease (GD), Hashimoto's thyroiditis (HT), papillary thyroid cancer (PTC), anaplastic thyroid cancer (ATC), uncovering heat shock response states in different cell types.

**Results:** Here, we identified the heterogeneity in cellular heat shock response states in the context of autoimmune thyroid diseases and thyroid cancer at a single-cell level. Heat shock protein HSPB1<sup>+</sup> thyroid epithelial cell subset was found both in thyroid autoimmunity and cancer. *In vitro*, the expression of HSPB1 was up-regulated in

thyroid epithelial cells and thyroid cancer cells during acute heat stress, and HSPB1 was secreted from the cells into the thyroidal tissue microenvironment mainly through exosomes. Heat shock protein HSPA1A<sup>+</sup> CD8<sup>+</sup> T cell subset was predominantly enriched in thyroid tumors, and HSPA1A enabled to impair antitumor immunity of CD8<sup>+</sup> T cells, suggesting a potential role of HSPA1A-based heat shock response in immunotherapy efficacy. Furthermore, we found the notable presence of HSPA1A<sup>+</sup> macrophage subset in GD and HT. HSPA1A promoted the conversion of macrophages to inflammatory phenotype, thus contributing to thyrocyte destruction. Besides that, a unique thyroid cancer cell subpopulation was defined in ATC, which specifically expressed a set of cancer-testis antigens.

**Conclusion:** Taken together, our study sheds light on the state of cellular heat shock response that might prompt the pathogenesis and new therapeutics of autoimmune thyroid diseases and thyroid cancer.

### Poster 0177

*Disorders of Thyroid Function, Basic, Poster*

#### Transcriptome Analysis of a Novel Hyperthyroid Mouse Induced by TSH Overexpression

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**Objective:** Hyperthyroidism is fundamentally caused by activation of TSH receptor (TSHR). The details of TSHR signaling remain to be elucidated. We aimed to clarify its molecular mechanism through transcriptome analyses for hyperthyroid mice that we generated by overexpressing TSH.

**Methods:** To generate hyperthyroid mice, we performed TSH overexpression for C57BL/6J mice via hydrodynamic gene delivery with pLIVE-TSHB and pLIVE-CGA vectors. Control mice were injected with pLIVE-Empty vector. Measurements of thyroid function and histological analysis were conducted at 1 week and 4 weeks after TSH overexpression. To elucidate mechanisms of action of anti-thyroid drug, transcriptome analyses using RNA sequencing were performed for the thyroid glands of thiamazole (MMI)-treated hyperthyroid mice.

**Results:** The hydrodynamic gene delivery successfully caused hyperthyroidism at least for 4 weeks, which was verified by increased serum free T4 and T3 along with elevated serum TSH levels. In addition, our hyperthyroid mice developed goiter. Changes in thyroid histology included increases in follicle size and follicular epithelial cell height at 1 week, while follicle size was similarly increased but follicular epithelial cell height was decreased at 4 weeks.

Thereafter, we obtained thyroid transcriptome dataset from control mice, hyperthyroid mice, and MMI-treated hyperthyroid mice. Unexpectedly, MMI treatment caused slight changes in clustering and principal component analyses, which resulted in a small number of differentially expressed genes. On the other hand, clear changes in thyroid transcriptome were observed between control mice and hyperthyroid mice. The enrichment analyses shed light on cell cycle,

PI3K/Akt pathway, and Rap1 pathway that could associate with goiter development.

In addition, among genes crucial to thyroid hormone secretion, *Slc26a4* was exclusively upregulated in hyperthyroid mice at 1 week and 4 weeks after TSH overexpression. We performed TSH overexpression for *Slc26a4* knockout mice to investigate its pathophysiological significance, which revealed that *Slc26a4* knockout mice developed hyperthyroidism and goiter in a similar manner.

**Conclusion:** In this study, we generated a new mouse model of hyperthyroidism and obtained the information on thyroid transcriptome. As we did not observe significant changes in known genes involved in thyroid hormone secretion, our datasets might include unrecognized regulatory genes of thyroid function.

### Poster 0178

*Disorders of Thyroid Function, Basic, Poster*

#### Improvement of Free Thyroxine Measurement Quality Through CDC Clinical Standardization Programs

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**Objective:** Thyroid function tests are among the most requested tests in patient care, and reliability of these measurements are crucial for appropriate diagnosis and management of thyroid disorders. In response to concerns from the clinical and research community about the quality of thyroid function tests, the CDC Clinical Standardization Programs (CSP) has created the hormone standardization (HoSt) program for free thyroxine (FT4) in partnership with the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC). CDC CSP recently assessed the current state of FT4 testing. The study has demonstrated that all study participants showed a negative mean bias to the CDC FT4 reference measurement procedure (RMP), with immunoassays (IAs) showing a higher magnitude of bias ( $-20.7 \pm 0.9\%$ ) than LC-MS based lab-developed tests (LDT) ( $-4.7 \pm 1.1\%$ ). This highlights the critical need for measurement standardization to improve accuracy and comparability of FT4 measurements.

**Methods:** Results of the FT4 interlaboratory comparison study were normalized to the CDC RMP results (recalibrated in silico by linear regression). In addition, assay-specific reference intervals (RI) and the RI determined by the CDC FT4 RMP were used to estimate disease-state classification among the 40 samples using for the study pre- and post-recalibration, respectively. To further advance FT4 standardization activities, CDC CSP successfully initiated Phase 1 of the HoSt program for FT4.

**Results:** Recalibration of FT4 assays improved their performance with mean percent bias improving profoundly (IA average:  $0.0 \pm 0.8\%$ , LDT average:  $0.1 \pm 1.1\%$ ). Thyroid disease status was underestimated in 12.5% of samples on average (range: 0–37.5%) pre-calibration, which reduced to 1.3% on average (range: 0–10%) after recalibration. Participants agreed on the classification of only 53% of samples pre-recalibration, which improved to 86% post-recalibration.

**Discussion/Conclusion:** The data suggest that the agreement among FT4 assays can notably be improved through assay recalibration to the FT4 RMPs operated by the CDC CSP and the IFCC reference laboratory network. The recalibration can improve consistency in patient classification. CDC CSP is now offering Phase 1 sets of serum-based materials with values assigned by CDC FT4 RMP that can be used by assay manufacturers to further assess performance and perform recalibration if needed.

**Poster 0179***Disorders of Thyroid Function, Basic, Poster***Incidence and Prevalence of Graves' Disease: Analysis of a United States Commercial Insurance Claims Database**Lesley-Ann Miller-Wilson<sup>\*1</sup>, Joel Arackal<sup>2</sup>, Paola Mina-Osorio<sup>1</sup>, Ruby Grewal<sup>2</sup>, Brett Venker<sup>2</sup>, <sup>1</sup>Immunovant, Inc., USA, <sup>2</sup>Roivant Sciences, Ltd., USA

**Objective:** Graves' Disease (GD) is an autoantibody-mediated disorder and the most common cause of hyperthyroidism. Excess thyroid hormone production and the autoantibodies themselves contribute to the thyroidal and extrathyroidal symptoms of GD. The objective of this study was to estimate the prevalence and incidence of GD in the United States (US), and the proportion of patients treated with antithyroid drugs (ATD) or thyroid ablation.

**Methods:** This retrospective study used Inovalon data from 2016 through 2022, covering over 200 million lives and containing professional and institutional medical and pharmacy claims from commercial, Medicare Advantage, and Medicaid payers. Patients having at least 2 claims with diagnosis codes for thyrotoxicosis (hyperthyroidism) separated by at least 30 days, and a claim for treatment with thionamides (methimazole or propylthiouracil) or thyroid ablation (radioactive iodine [RAI] or thyroidectomy) were identified as having GD. We conducted a prevalence estimation for 2022 and an incidence estimation for 2021 for patients aged 18 years or older with continuous enrollment from 2016 through 2022.

**Results:** The estimated raw prevalence rate of GD was 257.5 per 100,000 persons. Extrapolating this to the US population using census data gives an adjusted prevalence rate of 284.1 per 100,000 persons in 2022. The raw incidence rate in 2021 was 16.8 patients per 100,000 persons, corresponding to an adjusted rate of 18.7 per 100,000 persons. In the adjusted incident cohort, 91.8% were treated with ATD within the first year after diagnosis, 5.2% received RAI, and 3.0% underwent thyroidectomy.

**Discussion and conclusions:** Based on the adjusted prevalence and incidence rates in this study, an estimated 934,042 adults were living with GD in the US in 2022, including 61,406 adults diagnosed in 2021. Patient identification relied on International Classification of Diseases coding and the dataset was skewed toward commercially insured and Medicaid patients; therefore, older patients are likely underrepresented. However, the validity of the dataset used in this analysis strengthens the epidemiologic estimations observed in this study. Treatment utilization rates in the incident cohort were consistent with recent evidence suggesting a paradigm shift in the primary treatment of GD away from ablative therapy and towards increased ATD use.<sup>1</sup>

**Poster 0180***Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster***Exploring the Effects of Thyroid Hormones on Oligodendrocyte Progenitor Cell Differentiation for Potential Therapeutic Use in Myelin Repair**Ziyu Zhu<sup>\*</sup>, Achala Dharmasiri, Matt Zupan, Meredith Hartley, University of Kansas, USA

**Objective:** Oligodendrocytes are critical for proper nervous system function, and their dysfunction is linked to various neurological disorders, such as multiple sclerosis. Thyroid hormones (TH) are known to promote myelination during development by stimulating oligodendrocyte progenitor cell (OPC) differentiation into oligodendrocytes (OL). Understanding the role of TH in oligodendrocyte differentiation could have important therapeutic implications for these

disorders. Although recent research has demonstrated that TH promotes myelin repair in demyelination mouse models, the mechanisms by which TH acts on OPCs in the adult brain following myelin damage are not fully understood. To address this limitation, we aim to utilize single-cell RNA sequencing to explore the mechanism of promoting effects of TH, and other nuclear receptor ligands (NR ligands), on OPC differentiation, and assess these promoting effects with histology analysis.

**Methods:** We treated OPCs isolated from P7-8 Sprague-Dawley rats with TH or other NR ligands after 4 days of proliferation to promote differentiation. Single-cell RNA sequencing was performed after 1 day of differentiation, and we used various analysis tools to process transcriptomic profiles to identify the key pathways and genes involved in TH regulation of OPC differentiation. To evaluate the differentiation of OPCs induced by TH and other NR ligands, we utilized immunofluorescence staining to determine the populations of OPC-OL lineage cells after 6 days of differentiation.

**Results:** Based on transcriptomics data, 162 KEGG pathways and 24 Gene Ontology biological processes were identified as involved in T3 treatment. By identifying TH-induced OLs and comparing OL lineage cells isolated from TH-treated OPCs, a small panel of pathways and genes were identified specific to TH-induced OPC differentiation. The promoting effect of TH on OPC was also confirmed by the increased population of OLs in the histology study.

**Discussion:** The preliminary results demonstrated a panel of genes and pathways regulated by T3 that were associated with OPC differentiation. We plan to improve our single-cell treatment procedures and validate the key pathways with follow-up experiments. These findings may provide novel insights into the mechanisms underlying TH-induced OPC differentiation and may lead to the development of new therapeutic strategies for demyelination disorders.

**Poster 0181***Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster***Investigating the Effect of Sob-AM2 on the Central Nervous System Lipid Turnover for Successful Remyelination**Nishama Mohotti<sup>\*</sup>, Rashmi Binjawadagi, Disni Dedunupitya, Meredith Hartley, University of Kansas, USA

**Objective-** Demyelination is a hallmark feature in many neurodegenerative diseases, where disruption of myelin sheath leads to subsequent impairment in neuronal signal transduction. Sob-AM2 is a thyroid hormone agonist that has previously shown to promote remyelination. Myelin is heavily enriched in lipids; thus, demyelination can alter the lipid populations and homeostasis in the central nervous system (CNS). Therefore, assessing lipid turnover is essential to investigate the efficiency of remyelination. Thyroid hormone is known to regulate lipid metabolism in the periphery; however, little is known about its regulation of lipids in the CNS during remyelination. Our main objective in this study is to identify Sob-AM2-induced CNS lipid changes and their importance for successful remyelination.

**Methods-** We have used the *Plp1-iCKO-Myrf* genetic mouse model of demyelination for this study. Healthy (Cre-) and demyelinating (Cre+) mice were treated with control chow or Sob-AM2 chow (estimated daily dose of 84 µg/kg body weight) 2 weeks post-tamoxifen treatment. Mice were euthanized at 12 and 18 weeks post-tamoxifen injections, and brain and spinal cord tissues were collected. Brain and spinal cord lipids were extracted using the Bligh and Dyer lipid extraction method with minor modifications. Extracted phospholipids, sphingolipids, and cholesterol esters (CE) were analyzed using liquid chromatography-mass spectrometry

(LC-MS), and sterols were analyzed using gas chromatography-mass spectrometry (GC-MS).

**Results-** In the brain, Sob-AM2 treatment normalized classes of structural lipids that were disrupted during demyelination, such as phosphatidylethanolamine (PE) and phosphatidylinositol (PI). Disrupted signaling lipids such as phosphatidylserine (PS) and ether-linked phosphatidylethanolamine (ePE) were also normalized by Sob-AM2 treatment. Furthermore, the administration of Sob-AM2 induced a rapid clearance of CEs that were accumulated during brain demyelination. In contrast, Sob-AM2 had a limited effect on spinal cord lipid turnover. This observation is correlated with the extensive myelin damage observed in the spinal cords of *P1pl-iCKO-Myrf* mouse model.

**Discussion/Conclusions-** This study confirms that Sob-AM2-induced remyelination is associated with greater normalization of lipid levels compared to endogenous remyelination. Further studies are required to identify specific lipid regulatory mechanisms of Sob-AM2, which are crucial in developing effective therapeutics to promote successful remyelination.

### Poster 0182

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

#### The loss of silencing mediator of retinoid and thyroid hormone receptors (SMRT) in cerebellar Purkinje cells results in developmental disorder

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**Objective:** Thyroid hormone (TH) is essential for brain development, guiding brain maturation through dynamic changes in gene expression. THs bind to thyroid hormone receptors (TRs) in the nuclei and, together with transcriptional coregulators, dictate the transcription of target genes. Alongside abnormalities in TH action via TRs, mutations in coregulators have also implicated in brain developmental disorders. Recently, *de novo* genetic variants in nuclear coregulators have been discovered in pediatric patients with neurodevelopmental disorders. Particularly noteworthy is the silencing mediator of retinoid and thyroid hormone receptors (SMRT), a critical corepressors of the TR. However, the precise mechanism of SMRT action in the brain remains incompletely understood.

**Methods:** We generated a model in which SMRT is knocked out specifically in cerebellar Purkinje cells by crossing *L7/pcp2-Cre* mice, which express Cre only in cerebellar Purkinje cells, with SMRT<sup>loxP/loxP</sup> mice. We then conducted behavioral and electrophysiological experiments to determine the impact of SMRT on development.

**Results:** No growth or developmental abnormalities were observed in these mice. Subsequently, we performed the rotarod tests to evaluate cooperative movement and motor learning, one of the major cerebellar functions, and found that the mice exhibited normal cooperative movement and motor learning. In addition, we conducted social behavioral tests, which have recently been attracting attention as a novel cerebellar function, and found that these mice exhibit mild social behavioral abnormalities. Furthermore, we performed electrophysiological analysis using the slice patch clamp method to characterize the neurophysiology of Purkinje cells caused by SMRT deletion. The results showed an increase in membrane excitability. In addition, while no morphological abnormalities were observed at the macroscopic level, an increase in the number of spines was observed upon histologic evaluation.

**Discussion/Conclusion:** These results indicate that deletion of SMRT in Purkinje cells causes various symptoms of cerebellar ataxia by inducing neurophysiological abnormalities. SMRT is a critical corepressor whose actions in Purkinje cells are critical for normal development and electrophysiological functioning.

### Poster 0183

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

#### Thyrocye-specific Bmal1 Deletion induces metabolic alterations in mice

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**Objective:** Thyroid hormones play a crucial role in metabolic regulation, and the thyroid gland is regulated by the circadian clock. However, the effects of disruptions in thyroid clock on metabolism remain unclear. This study aims to explore how thyroid-specific deletion of the core circadian gene *Bmal1* affects metabolic processes.

**Methods:** A conditional thyrocye specific *Bmal1* knock out mouse model (T-Bmal1<sup>-/-</sup>) was established, which were fed either a normal diet (ND) or a high-fat diet (HFD) over a 10-week period. Levels of thyroid hormone, glucose tolerance and insulin sensitivity were evaluated. Adipose tissue, thyroid, and liver specimens were collected for biochemical, histological, and gene expression analyses.

**Results:** Compared with HFD-control mice, HFD-T-Bmal1<sup>-/-</sup> group exhibited elevated serum T4 levels and hepatic T3 levels (P<0.05). T-Bmal1<sup>-/-</sup> male mice on HFD displayed improved glucose tolerance and insulin sensitivity, along with reduced total and HDL cholesterol levels compared to controls (P<0.05). Liver histology in T-Bmal1<sup>-/-</sup> mice showed fewer vacuoles and reduced lipid droplets compared to controls. Hepatic metabolomics analysis revealed significant differences in hepatic phospholipid metabolic pathway between T-Bmal1<sup>-/-</sup> and control groups, which was consistent under ND and HFD feeding. qPCR and WB analysis revealed reduced expression of *Cd36* and *Acs11* in hepatic tissues, and elevated expression of fatty acid catabolism-related genes *Ucp3* and *Acot1* in BAT (P<0.05).

**Conclusions:** The present study demonstrated that thyrocye-*Bmal1* deletion can lead to disruptions in thyroid hormone levels and significant metabolic alterations. These results highlight the intricate role of the thyroid clock in metabolic disorders.

### Poster 0184

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

#### Molecular Effects of Thyroid Hormone and Histone Methyltransferase Dot1L during *X. tropicalis* Metamorphosis

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Epigenetic modifications play a pivotal role in embryonic development. Among histones regulations, H3K79 methylation is performed by the highly conserved protein known from yeast to human: Disruptor of Telomeric Silencing-1 like (Dot1L). Despite its association with childhood leukemia and adult cancer, Dot1L's function remains enigmatic. Dot1L gene is regulated by thyroid hormone (T3) during metamorphosis in *Xenopus tropicalis*, a quintessential model for post-embryonic development.

Our previous findings have revealed that Dot1L is a co-activator of thyroid receptor (TR). Moreover, Dot1L expression is directly regulated by T3 at the transcription level. Notably, Dot1L

knockdown inhibits tadpole development, leading to premature death before metamorphosis. My project aims to understand the role of endogenous Dot1L and the associated molecular mechanisms during *Xenopus* metamorphosis.

To address this issue, we generated Dot1L mutant animals using CRISPR/Cas9 gene-editing approach and obtained a frog line with an 18 bp in-frame deletion in the coding methyltransferase domain. We observed that homozygous mutant tadpoles lacked any H3K79 methylation, demonstrating that the mutation inactivates the enzyme and confirms Dot1L as the exclusive methyltransferase for H3K79 methylation. Importantly, mutant tadpoles died before the initiating metamorphosis, similarly to our earlier observation with Dot1L knockdown animals, suggesting that H3K79 methylation is essential for tadpole development prior to metamorphosis.

We are currently investigating if Dot1L deficiency affect T3 signaling and metamorphosis by treating wild type and mutant pre-metamorphic tadpoles with exogenous T3, focusing on intestinal remodeling and hindlimb development. Furthermore, employing ChIP-seq assays, I am identifying Dot1L methylation targets in the genome to determine if and how Dot1L affects T3-signaling globally during *Xenopus* development.

These studies should deepen our understanding of Dot1L's multifaceted functions and its contribution to metamorphosis in *Xenopus tropicalis* and mammals post-embryonic development.

#### Poster 0185

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

##### **Quantification of mouse brain cholesterol esters in a demyelinating mouse model upon Sob-AM2 treatment**

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**Objective:** Multiple Sclerosis (MS) is caused by the inflammatory demyelination of the cholesterol-rich myelin sheath that wraps around neurons. Upon demyelination, high levels of cholesterol esters (CEs) are observed in the central nervous system. This project focuses on understanding cholesterol ester levels in the brain upon treatment with Sob-AM2, a thyroid hormone agonist, in the iCKO-Myrf-Sox10 mouse model.

**Method:** A genetic mouse model based on the inducible, conditional ablation of the *Myrf* gene was used to produce demyelinating and healthy mouse groups. The Sob-AM2 drug was subcutaneously injected at a 0.1 mg/kg mouse dose once daily for five weeks. Clinical signs of mice were scored while giving the injections. The left brain hemisphere was directly subjected to homogenization, and a Percoll gradient was used to isolate microglial cell fraction from the right brain hemisphere. The Bligh and Dyer lipid extraction protocol was used to isolate lipids. An internal standard-based quantitative method was used to measure the CE levels in mouse brains and microglia using UPLC-ESI-MS/MS.

**Results:** The average clinical scoring for Sob-AM2-treated mice in the demyelinated mouse group was significantly lower than that of vehicle-treated mice. The average total CE levels of mice with demyelination was higher at 38.87 nmol/mg tissue for vehicle-treated mice, and it was 23.84 nmol/mg tissue for Sob-AM2-treated mice. Each of the 21 CE types between Sob-AM2-treated vehicle-treated mice with demyelination, showed a significant difference between the two groups for low-abundant CEs (CE 14:0, 16:0, 16:1, 18:3, 20:0, 20:1, and 22:5) but not for the highly abundant CEs (CE 22:6, 20:4, 20:5, and 20:6) in the brain homogenate. Ongoing work is focused on optimizing and measuring CEs in the enriched microglia fraction.

**Discussion/conclusion:** This study shows how CE levels significantly change with Sob-AM2 treatment in demyelinated mouse brains. Currently, we are optimizing mass spectrometric methods to quantify CE levels specifically in microglial cells. Further investigations on CE levels in microglial cells will reveal how Sob-AM2 regulates CE metabolism in microglia during demyelination.

#### Poster 0186

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

##### **Thyroid Hormone Dosage Effects on Oligodendrocyte Progenitor Cell Differentiation and Remyelination**

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**Objective:** Thyroid hormones (THs) represent a treatment option for neurodegenerative diseases that involve demyelinating events such as multiple sclerosis. THs are known to promote oligodendrocyte precursor cell (OPC) differentiation and myelination but are also detrimental to oligodendrogenesis in high doses. Therefore, this study aims to identify a tolerated TH dosage that can improve remyelination in a mouse model of demyelination and further define its effects on OPC differentiation.

**Methods:** An induced conditional knock-out *Myrf* fl/fl; Plp1-CreERT (iCKO-Myrf) mouse model of demyelination was used to identify a tolerated TH dose that improves remyelination without disrupting the OPC pool. The effects of TH dosing were evaluated using behavioral assessments such as rotarod, horizontal ladder, weights, and disease severity scoring. Mice in the 10-week experimental time-point were treated with EdU water to label proliferating and newly formed cells. Brain and spinal cord tissue was collected at 10- and 24-weeks post tamoxifen injection for immunofluorescence staining.

**Results:** In the 10-week experiment, the 0.06 ppm T3 treatment was identified as a tolerated T3 dose based on disease severity scoring and normalized weights of experimental groups. Rotarod and horizontal ladder results of all groups were analyzed. Immunofluorescence was performed to quantify OPCs and oligodendrocytes in brain tissue collected at 10-weeks post tamoxifen.

**Discussion:** The behavioral results from the iCKO-Myrf model demonstrated a tolerated T3 dose that could potentially be used in the T3 treatment of demyelination. Mice collected in the 10-week experimental group were used to define how T3 affects the OPC and oligodendrocyte populations in the central nervous system. The 24-week experimental groups will be used to define the effects of the tolerated dosage of T3 on remyelination by immunofluorescence, BlackGold staining, and electron microscopy. These findings may help lead to the development of new therapeutic strategies for the treatment of demyelinating diseases utilizing thyroid hormones.

#### Poster 0187

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*

##### **The Thyroid Increases the T<sub>3</sub>/T<sub>4</sub> Ratio in Response to Short-Term Overnutrition to Mitigate Hypothyroidism**

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Obesity, which affects >40% of the U.S. population, is increasingly understood as an endocrine disorder. The field has long focused on the effects of thyroid status on obesity, but much less is

known about obesity's effects on thyroid function, though we have known for decades that thyroid hormones (THs) are regulated by nutrient sensing to modulate energy expenditure to match energy intake. One would expect strong TH upregulation to counteract diet-induced weight gain, but this is *not* consistently reported in obesity studies. Thus, we ***hypothesized that overnutrition impairs thyroid function, preventing a sustained increase in TH levels.*** We tested this hypothesis in male C57Bl/6J mice fed a high-fat diet and sucrose water. Strikingly, overnutrition decreased serum T<sub>4</sub> after just 5 days—and progressively induced mild hypothyroidism, with increased thyroid stimulating hormone (TSH) and goiter, within 3 weeks. Concomitantly, intrathyroidal T<sub>4</sub> levels significantly decreased within 10 days. Furthermore, we found increased expression of several ER stress-related proteins, including BiP, p-eIF2 $\alpha$ , and PDI, whereas expression of the TH precursor thyroglobulin (TG) was unchanged, despite high TSH stimulation. These results suggest that TG upregulation was blunted because overnutrition-induced ER stress impaired protein translation. Remarkably, though T<sub>4</sub> was low, the thyroid maintained normal serum T<sub>3</sub> by increasing the T<sub>3</sub>/T<sub>4</sub> ratio on TG. We also observed pronounced histological and vascular changes, which would promote TH availability. We have seen similar histological changes in preliminary female mouse studies and, notably, in human thyroids, strongly correlating, in the latter case, with BMI. Collectively, our findings show that overnutrition induces mild hypothyroidism, despite the struggling thyroid's best efforts to adapt. Existing data suggest that low T<sub>4</sub> alone can be problematic, particularly in metabolic tissues that rely on serum T<sub>4</sub> to generate intracellular T<sub>3</sub>. Reversibility of this state is being investigated in ongoing experiments. The causal role that overnutrition plays in thyroid impairment and decreased TH availability in the pathogenesis of obesity has scarcely begun to be elucidated. Thyroid function has far-reaching effects on whole-body energy balance and thus has untapped therapeutic potential. Our work sheds new light on how overnutrition changes thyroid function and highlights the thyroid's remarkable adaptability.

#### Poster 0188

##### *Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster* **Thyroid Hormone Action on Microglia in Mechanisms of Myelin Repair**

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**Objective:** Microglia are innate immune system macrophages that play a crucial role in central nervous system remyelination. It has been recently suggested that thyroid hormone (TH) induces phagocytosis in microglia by activating the TREM2 pathway. TREM2 is a cell surface receptor on microglia that switches these cells away from a pro-inflammatory state and towards an anti-inflammatory, phagocytotic, restorative phenotype. During demyelination, microglia phagocytose and process myelin debris, which is necessary to initiate proper myelin repair. Additionally, we have data from an animal model showing that cholesterol esters accumulate during demyelination, and that treatment with Sob-AM2 reduces this accumulation. Our lab is interested in further exploring the role of TH action in microglia and elucidating a novel mechanism for how TH agonists promote the clearance and metabolism of myelin debris.

**Methods:** We isolated primary microglia from rat pups and treated them with thyroid hormone and myelin. A phagocytosis assay was developed by adding fluorescent beads to the microglia and analyzing the number of beads engulfed by the cells. The effect of TH on microglia morphology is being studied by immunostaining

primary microglia and analyzing their shape with Image J. The effect of TH on the microglia transcriptome is being studied by performing RNA sequencing on primary microglia. Cholesterol metabolism in microglia is being studied by adding isotopically labelled cholesterol and cholesterol ester to primary microglia and using mass spectrometry to analyze the resulting metabolites produced by the cells.

**Results:** The phagocytosis assay showed that TH as well as myelin debris increased the phagocytic activity of primary microglia. Following up with studying the phenotype and transcriptome of TH treated microglia will allow us to identify genes of interest and potential pathways involved in this myelin debris phagocytosis. We will also present data from the mass spectrometry assay showing how thyroid hormone affects cholesterol ester metabolism in primary microglia.

**Discussion:** These experiments will characterize the genotypic and phenotypic effects of TH under demyelinating conditions. Overall, we hope to better understand the role of TH action on microglia to enable the development of better treatments for demyelinating diseases.

#### Poster 0189

##### *Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster* **Comprehensive Evaluation of Thyroid Hormone Action Using Hypothyroid Mice**

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**Objective:** Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with the normal function of hormones. Disruption of thyroid hormone (TH) actions by EDCs is being highlighted. For example, TH activity has been detected from the environmental water in multiple countries. We generated a mouse model to elucidate TH disruption mechanisms by EDCs.

**Methods:** We administered 3,3',5-triiodo-L-thyronine (LT3) via drinking water to C57BL/6J mice treated with 6-propyl-2-thiouracil (PTU) (hypothyroid mice) and without (euthyroid mice). TH actions were evaluated through growth curves and TH-responsive gene expressions. Furthermore, we visualized changes in the hypothalamus-pituitary-thyroid (HPT) axis as enlargement of the thyroid gland and follicular dysmorphology and further determined by thyroid function tests.

**Results:** We administered 0.1  $\mu$ g/mL of LT3 as a supplemental dose or 1  $\mu$ g/mL as a high dose to euthyroid mice for 4 weeks, but we unfortunately observed slight changes in their phenotypes. To increase the sensitivity for determining TH actions, we analyzed hypothyroid mice treated with PTU for 4 weeks, which revealed that 0.1  $\mu$ g/mL of LT3 co-administration significantly restored growth retardation, changes in the HPT axis, and changes in TH-responsive gene expressions.

Thus, we could evaluate TH actions in various organs via detailed analyzes of hypothyroid mice. Furthermore, we improved this model through following experiments. To shorten the induction period of hypothyroidism, we treated mice with sodium iodide as well as PTU for either 1 week or 2 weeks. We found that PTU monotreatment for

2 weeks was enough to induce hypothyroidism and significant changes in phenotypes. To search more sensitive TH-responsive genes, we performed RNA sequencing for the liver, the heart, the cerebrum, and the gastrocnemius muscle of hypothyroid mice generated by this regimen.

**Conclusions:** We established an *in vivo* system for evaluating TH actions. As our previous study highlighted endocrine-disrupting potential of 3,3',5-triiodoacetic acid (TRIAc) (Environ Sci Technol. 2022;56:13709-13718), we clarified TRIAC's disruptive mechanism as cooperation of depletion of circulating endogenous THs via negative feedback and heterogeneous distribution of TRIAC among different organs (iScience. 2023;26:107135). The improved model and comprehensive analyses of TH-responsive genes can contribute to further research.

### Poster 0190

*Disorders of Thyroid Function, Clinical, Poster*

#### Management of Thyroid Dysfunction Due to Immune Checkpoint Inhibitors: Lessons from the Real-World Experience

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**Objective:** Immune checkpoint inhibitors (ICIs) frequently cause immune-related adverse events involving the thyroid gland (thyroid irAEs). We previously reported clinical features of thyroid irAE including representative clinical course (Thyroid. 2017; 27: 894-901), predictive factors and relationship to good prognosis (PLoS One. 2019; 14: e0216954), and delayed-onset with chemotherapy combination (Endocr J. 2023; 70: 323-332). Here we further elucidated best practices for management of thyroid irAE.

**Methods:** Retrospective cohort analyses were performed using the medical records of patients who received PD-1 blockade therapy with nivolumab, pembrolizumab, or atezolizumab as monotherapy at Kyoto University Hospital until 2020.

**Results:** Of recruited 639 patients, overt thyroid irAEs were observed in 70 patients (11.0%). After exclusion of patients according to criteria, we analyzed 50 patients by dividing into the following groups: thyrotoxicosis with subsequent hypothyroidism (Toxic-Hypo, n = 21); thyrotoxicosis without subsequent hypothyroidism (Toxic, n = 9); and hypothyroidism without prior thyrotoxicosis (Hypo, n = 20). The Toxic-Hypo group developed thyroid irAEs earlier than the Toxic group (26 vs 91 days;  $p < 0.001$ ) and had higher serum free T4 levels (3.210 vs 1.880 ng/dL;  $p = 0.011$ ). Anti-thyroglobulin antibodies (TgAbs) at thyroid irAE onset were more commonly positive in the Toxic-Hypo group (93.3%) than in the Toxic group (0.0%;  $p = 0.005$ ) and Hypo group (44.4%;  $p = 0.007$ ). The Toxic-Hypo group developed severe hypothyroidism and required larger levothyroxine doses than the Hypo group (75 vs 25 µg/day;  $p = 0.007$ ).

According to these results, we predicted that patients with positive TgAbs who developed severe thyrotoxicosis within 4 weeks after the first ICI administration would develop subsequent severe hypothyroidism. We treated 4 such patients with prompt LT4 replacement, characterized by LT4 initiation after thyrotoxicosis improvement and quick dose titration. Their euthyroid state was successfully maintained, in contrast with patients receiving conventional replacement.

**Conclusion:** Rapid-onset severe thyrotoxicosis in patients with TgAbs correlated with a high likelihood of subsequent hypothyroidism due to thyroid irAEs. Prompt LT4 replacement is a therapeutic option to prevent a severely hypothyroid state.

### Poster 0191

*Thyroid Hormone Action, Metabolism and Regulation, Translational, Poster*

#### LASN01 is a novel, clinical stage antibody that blocks inflammatory cytokine and chemokine release in *in vitro* studies using orbital fibroblasts from thyroid eye disease (TED) patients

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**Objective:** Infiltration of immune cells and the pronounced Th1-immune response is a key pathogenic feature of TED and an area of ongoing therapeutic drug research. In particular, the upregulation of chemokines and cytokines such as IL-6, IL-8 and MCP-1/CCL2 is believed to promote recruitment and activation of immune cell populations leading to prolonged inflammation and orbital tissue expansion and remodeling. Based on the role of IL-11 as a fibro-inflammatory mediator in other disease settings, we investigated whether IL-11 was involved in chemokine and cytokine release by orbital fibroblasts from TED patients and whether treatment with LASN01, a fully human, clinical stage antibody that blocks the IL-11 receptor (IL-11R), would mitigate this process.

**Methods:** Primary orbital fibroblasts (OF) were isolated from tissue obtained after TED patient decompression surgeries. A broad panel of 96 cytokines was first analyzed after stimulation of orbital fibroblasts with IL-11 + IGF-1 alone, or in the presence of LASN01 or anti-IGF1R antibody, teprotumumab. Quantitative ELISA's were then performed to assess IL-6 and MCP-1/CC12 release, specifically.

**Results:** Stimulation with the combination of IL-11 + IGF-1 led to increased release of multiple cytokines including IL-6, IL-8, MCP-1/CCL2 and BAFF. LASN01 blocked release of numerous chemokines and cytokines, to the same or even greater degree as that seen with the approved anti-IGF1R antibody, teprotumumab. Follow-up analysis using quantitative ELISA revealed that LASN01 significantly ( $P < 0.0001$ ) blocked IL-6 and MCP-1/CCL2 release, whereas teprotumumab had no effect, consistent with no role for the IGF-1 pathway in stimulating production of these cytokines.

**Conclusions:** This data suggests IL-11 may be an important factor in the inflammation-mediated orbital tissue remodeling in TED and that IL-11 may be upstream of IL-6 release by orbital fibroblasts. The ability of LASN01 to block the release of multiple cytokines, whereas teprotumumab did not, indicates that LASN01 may provide a unique and differentiated treatment for TED that is not addressed by IGF-1 receptor blockade alone.

### Poster 0192

*Thyroid Hormone Action, Metabolism and Regulation, Translational, Poster*

#### Thermogenic Gene Expression in Human Neck Adipose Tissue in Relation to Circulating and Local Thyroid Hormone Levels

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**Objective:** With the growing incidence of diabetes and metabolic syndrome, highly active metabolic tissues like brown adipose tissue (BAT) have been proposed as potential treatment avenues. Rodent studies have shown that thyroid hormone (TH) is a key regulator in the activation and growth of BAT. It is unknown whether circulating TH and TSH levels reflect BAT gene expression and are associated

with its activity in humans. This study aimed to find correlations between serum TH and TSH, local adipose tissue TH concentrations and RNA expression of thyroid-signaling and thermogenic genes in deep perithyroidal adipose tissue (BAT) compared to subcutaneous neck adipose tissue (WAT) in adult humans.

**Methods:** We measured serum TSH, T3 and T4 levels, and collected deep peri-thyroidal and subcutaneous neck adipose tissue from 16 patients who underwent thyroidectomy as part of their standard care. We measured adipose tissue TH (T4, T3) concentrations using liquid chromatography/mass spectrometry and thermogenic gene expression using bulk RNA sequencing.

**Results:** There were no significant associations between serum TSH and thermogenic or thyroid-signaling genes in either deep or subcutaneous neck adipose tissue. We found a negative correlation between serum TSH and expression of leptin receptor and PR-domain-zinc-finger-protein-16-receptor genes in deep, but not subcutaneous neck adipose tissue. Serum TSH was not correlated with adipose tissue T3 and T4 concentrations. There was a significant positive correlation between deep neck fat T4 and expression of uncoupling-protein-1 and beta-3-adrenergic-receptor genes ( $p = 0.01$  and  $p = 0.04$ , respectively), but not local T3 levels. We found negative correlations between local T3 and thermogenic pathways in deep and subcutaneous neck fat. In addition, there were positive correlations between thermogenic pathways and T4 concentrations in deep fat.

**Conclusion:** Measurement of thermogenic gene expression in perithyroidal deep neck adipose tissue can be useful for studying BAT activity in humans. TH concentrations in adipose tissue do not reflect serum TSH, however, their relationship with thermogenic gene expression in human BAT requires further investigation. To our knowledge, this is the first study to measure adipose tissue TH concentrations and evaluate correlations with thermogenic gene expression in human BAT.

### Poster 0193

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*  
**Adiponectin receptors agonist, AdipoRon, regulates cardiac lipid metabolism via thyroid hormone dependent mechanism**

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Hypothyroidism is one of the key risk factors for developing cardiovascular diseases (CVDs) such as atherosclerosis, ischemic heart, or heart failure. Hypothyroidism treatment involves constant thyroid hormone (TH) supplementation, usually triiodothyronine (T3) or thyroxine (T4). TH action in the cell is facilitated by TH transporters, such as monocarboxylate transporter 8 (MCT8), and TH receptors (TR). These proteins were also shown to regulate metabolism by controlling the expression of enzymes involved in such processes as lipid trafficking, synthesis, and utilization. Furthermore, obese patients with hypothyroidism have been shown to have lower level of adiponectin, an adipokine secreted by adipocytes, that regulates insulin sensitivity as well as balances glucose and lipid metabolism. Therefore, the aim of this project is to determine if adiponectin receptors agonist, AdipoRon, is involved in lipid metabolism regulation in hypothyroid cardiomyocytes in TH-dependent manner. To accomplish that, we have used left ventricles from 3-month-old female Wistar-Kyoto rats that underwent thyroidectomies to develop hypothyroidism. Additionally, some animals were given T4 (2µg/100g body weight/day) or simultaneously T4 and AdipoRon (25µg/100g body weight/day) intraperitoneally for 4 weeks after thyroidectomy. AdipoRon treatment elevated MCT8 protein level and gene expression, but at the same time decreased TR $\alpha$  and did not affect TR $\beta$  protein levels in

cardiomyocytes compared to T4 only treated group. No changes in TR-dependent lipogenic genes expression, such as transcription factor sterol regulatory element binding transcription factor 1 (*Srebp1l*) or *Cd36* transporter, were detected, that corresponds with constant TR $\beta$  level. On the other hand, AdipoRon supplementation decreased gene expression and protein level of adipose triglyceride lipase (ATGL), a rate-limiting enzyme of triglyceride (TAG) lipolysis, and elevated gene expression of *G0s2*, a protein inhibitor of ATGL. Moreover, gene expression and protein level of diglyceride acyltransferases (DGAT1 and 2), involved in last step of TAG synthesis, were also downregulated by AdipoRon action compared to T4 treatment alone, leading to a conclusion that observed changes are TR $\alpha$  dependent. Taking together, obtained results suggest that AdipoRon, through activation of different TR isoforms, can modulate lipogenesis and lipolysis in cardiomyocytes during hypothyroidism.

### Poster 0194

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*  
**Menopause is Associated With Disc Degeneration in the Lumbar Spine. Can PRP and 8-Prenylnaringenin (phytoestrogen) be a Disease Modifying Treatment?**

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#### Background

Several studies have demonstrated the clinical significance of estrogen as it relates to intervertebral disc degeneration.

Degenerative disc disease (DDD) remains a leading cause of chronic back pain.

The intervertebral disc is composed of an annulus fibrosus that surrounds a nucleus pulposus, anchored to each other by cartilage endplates. The nucleus pulposus, composed primarily of water, proteoglycans such as aggrecan, and type II collagen, provides vertebrae with the elasticity and stability.

Various explanations have been offered to the origins of disc degeneration, including progressive deterioration, nutritional deficiencies, genetic predispositions, and hormone-related processes.

Women who are estrogen-replete are more likely to maintain intervertebral disc height than estrogen deficient women.

#### Aim

The aim of this study is to evaluate the efficacy of PRP treatment in patients with low back pain and menopause versus patients with low back pain that received intradiscal PRP and 8-prenylnaringenin treatment.

#### Methods

We evaluated 40 menopausal female patients who presented non-specific low back pain that had no relief after physiotherapy (ESWT, MLS) and NSAIDs medication and we divided them in two groups of 20 patients (group 1 that had only intradiscal PRP) and a second group of 20 patients that had intradiscal PRP and 8-prenylnaringenin treatment for 6 months.

Patients were injected with 2 mls of PRP (48 mls of venous blood, obtained under aseptic technique, centrifuged for 2 minutes at 3450 rpm. From the resulting 25 mL PRP, there was another spin at 3550 rpm, 5 minutes and the resulting 2 mls were administered intradiscal, using echographic guidance.

For group 2 patients were administered 8-prenylnaringenin 1 tablet a day for 6 months (Menover - SWP).

Patients who had received PRP injection and Menover medication showed improvement in their scores at the 6 months follow up with no complications.

#### Results

The study showed improve of symptoms in terms of NRS and ODI. Only one patient had pain above 5 in NRS and there was no value > 20% on ODI after 6 months. One patient complained of nausea.

MRI was used to analyse 25 discs, height was recorded, disc degeneration was evaluated using Pfirrmann grading system.

#### Conclusions

Menopause is associated with disc degeneration

PRP injection and Menover is a good treatment for the management of the patient with menopause and low back pain.

Limitations of this study: small number of patients involved, patients who would like to have hormone therapy and many patients are reluctant to spinal injection.

#### Poster 0195

*Thyroid Nodules and Goiter, Basic, Poster*

#### Association Between Shoulder Calcification Tendinopathy and Benign Thyroid Cysts

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**Background** It appears that there is an association between thyroid cysts and shoulder calcification tendinopathy.

**Aim** To assess the association of thyroid disorders and shoulder calcification tendinopathy.

**Methods** We evaluated 20 patients (group 1) who presented shoulder pain and movement restrictions (calcific tendinopathy confirmed by shoulder ultrasound) and 20 patients (group 2) with general orthopaedic affections (other than shoulder pain) whom we asked if they have an underlying thyroid condition. The assessment was conducted by an orthopaedic surgeon. An endocrinologist also evaluated 20 patients (group 3) with thyroid dysfunction (thyroid nodules, thyroid cysts), randomly chosen, to assess if they present any shoulder pain.

All of the participants answered the questionnaire on the following variables: age, gender, body mass index (BMI), occupation, physical activity, presence of thyroid disorders, shoulder disorders, smoking and alcohol.

All patients had ultrasound of the shoulder and the thyroid.

Group 1 consisted of 18 female patients between 20-65 years old, of whom 3 presented bilateral symptoms, and 10 had the non dominant side affected and 2 male patients.

Out of the 18 female patients, 2 (11,11%) had benign thyroid cysts (ultrasound appearance), 4 had thyroid nodules (22,22%) and 1 one had thyroiditis (5,55%).

Group 2 consisted of 18 female patients between 20-80 years old, without any shoulder complaints, of whom

None had thyroid cysts, 1 had nodules (5,55%) and none had thyroiditis.

Group 3 consisted of 20 female patients, aged from 20-65 years old, know with benign thyroid cysts (5 patients), hypothyroidism (10 patients) and nodules (5 patients).

Of these patients 3 patients had supraspinatus calcific tendinopathy (thyroid cysts), 2 had joint pain (1 benign thyroid nodules and 1 patient with thyroiditis).

**Results** When comparing the thyropathy group with the control and rotator cuff groups, there is a specific association between the presence of thyroid disorders (cysts) and shoulder tendinopathy (calcific tendinitis). By calculating relative risk, it is possible to state that an individual with thyropathy has a higher chance of developing frozen shoulder.

**Conclusions** Thyroid disorders and benign thyroid cysts are risk factors significantly associated with calcific tendinopathy, rising the chances to 3 times of developing the above condition.

Thyroid cysts are common findings but whenever a shoulder calcific tendinopathy is diagnosed without an obvious overuse cause, thyroid should be considered.

Patients with thyroid dysfunction should be questioned for musculoskeletal complaints and referred to a specialist if necessary.

#### Poster 0196

*Thyroid Nodules and Goiter, Basic, Poster*

#### Behavior of the Genes CLDN1, TIMP1 and KRT19 Among the Different Categories of the Bethesda System in Thyroid Nodules

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The Bethesda System for Reporting Thyroid Cytopathology allows for the categorization of thyroid nodules based on cytology. Although approximately 90% of detected nodules are benign lesions, thyroid cancer might be present in around 5% of cases. From 20 to 25% of thyroid nodules submitted to fine-needle aspiration (FNA) result in an indeterminate diagnosis, with a risk of malignancy ranging between 5% and 30%. Uncovering the molecular patterns hidden behind nodules from the different Bethesda System categories could help guide diagnosis and treatment options for patients.

**Objective.** Evaluate the gene expression profiles of CLDN1, TIMP1, and KRT19 in thyroid nodule FNA samples from the various Bethesda System categories.

**Methods.** CLDN1, TIMP1, and KRT19 gene expression were assessed by RT-qPCR in FNA thyroid nodule samples. Cytological diagnosis was determined by a pathologist, and clinical data were retrieved to establish further associations.

**Results.** 92 FNA samples were analyzed: 32 were categorized as Bethesda 2, 17 as Bethesda 4, 7 as Bethesda 5, and 32 as Bethesda 6. For CLDN1, significant differences in gene expression were observed among the Bethesda System groups ( $p < 0.05$ ). Post-hoc comparisons revealed significant differences among all the groups ( $p < 0.05$ ). Regarding TIMP1, post-hoc comparisons revealed significant differences between groups 4 and 5 ( $p = 0.0004$ ) and between groups 4 and 6 ( $p = 0.0019$ ). Additionally, there was a significant difference between group 2 and groups 4, 5, and 6 ( $p < 0.05$ ). For KRT19, post-hoc comparisons showed significant differences between groups 2 and 4, as well as between groups 4 and 6 ( $p = 0.0010$  and  $p = 0.0001$ , respectively).

**Conclusion.** These findings demonstrate that the expression of CLDN1, TIMP1, and KRT19 varies significantly among different groups of the Bethesda system in thyroid nodules. These results highlight the significance of considering molecular heterogeneity when evaluating thyroid nodules. This consideration may have clinical implications for risk stratification and patient management.

#### Poster 0197

*Disorders of Thyroid Function, Translational, Poster*

#### Transmission of different deletions in the SLC16A2 gene

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**Objective:** Monocarboxylate transporter 8 (MCT8) deficiency is a rare X-linked disorder caused by mutations in the *SLC16A2* gene and is characterized by neurodevelopmental and thyroid hormone abnormalities. Identifying *SLC16A2* mutations at an early age is essential for early treatment. Large deletions in *SLC16A2* are identified in 13% of patients. We encountered the perplexing transmission of different deletions in *SLC16A2* by a mother heterozygous only for

one deletion. We propose a change in prenatal testing of *SLC16A2* deletions.

**Methods:** Nanopore long-read sequencing.

**Results:** A ~5Kb hemizygous deletion on Xq13.2 including exon 3 and 4 of *SLC16A2*, was identified by Array-CGH and confirmed by qPCR in a male patient with MCT8 deficiency and his clinically normal heterozygous mother. Analysis of segregation showed that this defect occurred *de-novo* on the X-chromosome inherited from the maternal grandfather, haplotype-1. Prenatal testing of another male fetus during a subsequent pregnancy failed to show this deletion and the pregnancy was deemed normal. However, after birth, the male infant exhibited clinical and laboratory manifestations of MCT8 deficiency. A full-length assessment of his *SLC16A2* gene revealed a different deletion encompassing exon 2, while exons 3 and 4 were intact. Long-read sequencing of the mother's lymphocyte gDNA revealed that in addition to the haplotype-1 with exon 3-4 deletion, the haplotype-2 inherited from her mother presented mosaicism for exon 2 deletion as a *de-novo* postzygotic defect. Mosaicism in the maternal germline would involve the presence of germinal cells with one of the X-chromosomes being haplotype-1 with exon 3-4 deletion, and the other X being haplotype-2 harboring the new exon 2 deletion. Homologous recombination between these two X-chromosomes before meiosis presumably led to the X-chromosome inherited by the younger affected son, in which exon 2 deletion is in the background of haplotype-1.

**Discussion:** The very large size of intron 1 of *SCL16A2*, ~100kb, and the presence of multiple mobile and repetitive elements potentially facilitate the frequent occurrence of recombination. Considering the devastating course of this disease, targeted sequencing of the entire *SLC16A2* gene instead of only genotyping for a known pathogenic variant should be recommended for prenatal diagnosis of familial MCT8 deficiency harboring *SLC16A2* deletions.

### Poster 0198

*Iodine Uptake and Metabolism, Basic, Poster*

#### Urinary Iodine Concentration And Thyroid Status In 880 Patients From The Longitudinal Adult Health Study (Elsa-Brasil)

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**Summary:** Iodine is an essential micronutrient in the synthesis of thyroid hormones, directly affecting organic metabolic processes from the prenatal period to aging, including embryogenesis, growth and physical, neurological and cognitive development. Urinary iodine concentration (UIC), a marker of nutritional intake, is known to be a predictor of thyroid dysfunction. Objectives: This work aims to evaluate urinary iodine concentration in Brazilian adults from the Adult Health Study (ELSA-Brazil), correlating it with sociodemographic factors and thyroid status. Method: Analysis of 880 participants aged 35 to 74 years from six Brazilian capitals involving urinary iodine concentration and thyroid status assessed based on serum TSH and T4L levels.

**Results:** Among the participants, 51.8% were women, the average age was 52.1 (9) years. According to the WHO classification, 523 (59%) have more than adequate levels of iodine, that is, between UIC >200 and 299mcg/L, 206 (23%) with excessive levels, and only 22 (2.5%) deficient (<100mcg/L). The median UIC was 221.8 mcg/L. In women of childbearing age (35-44 years), we found 22% in deficiency conditions (<150mcg/L) and 35% in excess conditions (>250mcg/L). Participants who did not consume fruit daily (p 0.05),

as well as vegetables (p 0.013) had a higher prevalence of excess iodine. No differences were detected in UIC according to thyroid status.

**Conclusion:** The research confirms that Brazil reached the target for population iodine supplementation, including part of the population presenting excessive levels, however, without evidence of a direct link between iodine concentration and thyroid dysfunction. Of the participants who did not consume fruits and vegetables daily, 28% were in a situation of excess urinary iodine concentration, probably due to greater consumption of ultra-processed foods rich in added sodium.

### Poster 0199

*Iodine Uptake and Metabolism, Translational, Poster*

#### Imaging-guided mesenchymal Stem Cell-mediated Sodium Iodide Symporter (NIS) Gene Transfer targeting Hypoxia in Glioblastoma

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Glioblastoma multiforme (GBM) is characterized by significant tumor heterogeneity at cellular and molecular levels – a central phenomenon linked to treatment failure and tumor recurrence. Hypoxia is a predominant feature of GBM, promoting its aggressiveness, chemo- and radioresistance, and is known to support GBM stem cell survival. Hypoxia and related signaling pathways are therefore important therapeutic targets in GBM. As central part of the tumor microenvironment, mesenchymal stem cells (MSC) have emerged as cellular-based vehicles for the delivery of therapeutic genes, such as the sodium iodide symporter (NIS), in cancer therapy due to their inherent migratory and tumor homing capabilities. As theranostic gene, NIS represents one of the oldest and most successful targets for non-invasive radionuclide-based molecular imaging and therapy. In our recent work we showed NIS to be highly effective as reporter and therapy gene, allowing therapeutic application of <sup>131</sup>I or alternative radionuclides <sup>188</sup>Re or <sup>211</sup>At as well as detailed non-invasive *in vivo* tracking of MSCs by <sup>123</sup>I-scintigraphy/SPECT and <sup>124</sup>I- or <sup>18</sup>F-TFB-PET.

Based on the important role of hypoxia and hypoxia-related HIF signaling in the pathogenesis of GBM, in the present study we have used multiparametric imaging to characterize regions of tumor hypoxia by <sup>18</sup>F-FMISO-PET and its correlation with <sup>124</sup>I-PET-monitored recruitment of MSCs genetically engineered to express NIS under control of a synthetic hypoxia-inducible promoter (HIF-NIS-MSC).

Subcutaneous GBM xenograft mouse models were established by implantation of patient-derived GBM cells. Areas of hypoxia were characterized *in vivo* by <sup>18</sup>F-FMISO-PET and correlated with *ex vivo* pimonidazole staining. HIF-NIS-MSCs were labelled with CMFDA and injected i.v., wild-type-MSC or NIS-specific inhibitor perchlorate served as controls. Coregistration of <sup>18</sup>F-FMISO-PET imaging with <sup>124</sup>I-PET imaging 48 h after HIF-NIS-MSC injection demonstrated significant induction of NIS-mediated <sup>124</sup>I-accumulation in hypoxic areas

showing effective MSC recruitment into these sites. This was confirmed by fluorescence microscopy as well as *ex vivo* NIS immunostaining and  $^{124}\text{I}$ -autoradiography.

In conclusion, we have shown the potential to therapeutically target the critical areas of hypoxia in GBM by MSC-based NIS gene delivery under the control of a hypoxia-responsive promoter guided by PET-based imaging of hypoxic regions.

## Poster 0200

*Disorders of Thyroid Function, Clinical, Poster*

### Risk of Mortality Associated with Anti-thyroid Drugs, Radioactive Iodine, and Surgery for Hyperthyroidism: A Systematic Review and Network Meta-analysis

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**Objective:** Hyperthyroidism can be treated with anti-thyroid drugs (ATD), radioactive iodine (RAI), or surgery. We aimed to evaluate the long-term outcomes of these treatments through systematic review and network meta-analysis.

**Methods:** PubMed, EMBASE, Web of Science, and the Cochrane Library were searched from inception to March 20, 2024. Primary outcome was all-cause mortality. Secondary outcomes were cancer mortality and MACE. Eligible studies compared at least two treatments in adults with hyperthyroidism and reported outcomes of interest. Two reviewers independently screened, extracted data, and assessed risk of bias, with conflicts resolved by a third reviewer. Hazard ratios (HR) and confidence intervals (CI) were extracted. A random effects network meta-analysis was used to synthesize the effect sizes.

**Results:** Among 4921 screened studies, nine observational studies (186,199 patients) were eligible. In seven studies (164,303 patients) reporting all-cause mortality, surgery conferred a lower risk than ATD (HR, 0.44; 95% CI, 0.36-0.52; p-value, <0.001) or RAI (HR, 0.51; 95% CI, 0.43-0.61, p-value < 0.001). RAI did not significantly reduce all-cause mortality compared with ATD (HR, 0.86; 95% CI, 0.73-1.01; p-value, 0.07). In two studies (121,592 patients) evaluating MACE, both RAI (HR, 0.60; 95% CI, 0.37-0.99; p-value, 0.04) and surgery (HR, 0.76; 95% CI, 0.59-0.97; p-value, 0.03) were associated with lower risk than ATD. No significant difference in MACE was observed when comparing surgery with RAI (HR, 1.27; 95% CI, 0.74-2.13; p-value 0.37). In three studies (23,374 patients) assessing cancer mortality, neither surgery (HR, 0.98; 95% CI, 0.76-1.27; p-value, 0.88) nor RAI (HR, 1.03; 95% CI, 0.84-0.1.27; p-value, 0.78) were associated with lower risk when compared with

ATD. Similarly, no significant difference in cancer mortality was observed when comparing surgery with RAI (HR, 0.95; 95% CI, 0.82-1.10; p-value, 0.49).

**Conclusions:** In hyperthyroid patients, surgery was associated with lower all-cause mortality and MACE risks than ATD. Surgery was associated with lower all-cause mortality risk than RAI, but MACE risk did not differ. Compared to ATD, RAI was associated with reduced MACE risk but not all-cause mortality. No significant differences in cancer mortality were found across three treatments. Surgery and RAI may offer better long-term outcomes than ATD.

## Poster 0201

*Iodine Uptake and Metabolism, Translational, Poster*

### Transcriptional Reprogramming Using a New Dual NIS Agonist Enhances Radioiodide Uptake and Facilitates Greater Predictive Utility for Thyroid Cancer Recurrence

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**Objective:** New approaches are needed to enhance radioiodide (RAI) ablation of aggressive thyroid cancer. Previously, we reported that valosin-containing protein inhibitors (VCPi) such as disulfiram markedly increase sodium iodide symporter (NIS) activity to promote RAI uptake. Disulfiram inhibits NPL4 activity – a critical VCP cofactor – via its copper bound diethyldithiocarbamate metabolite Cu(DDC)<sub>2</sub>. We hence hypothesised that disulfiram and its metabolites increase RAI uptake by interfering with ER-Associated Degradation (ERAD) via a VCP/NPL4 pathway, permitting more NIS protein to be trafficked to the plasma membrane. Here, our aim was to determine the mechanistic impact and clinical relevance of utilising Cu(DDC)<sub>2</sub> in RAI therapy.

**Methods:** We used RNA-Seq to identify Cu(DDC)<sub>2</sub>-regulated transcriptional pathways. NIS function was monitored in wild-type BALB/c mice via Technetium-99m pertechnetate (<sup>99m</sup>Tc) uptake following intravenous (IV) administration. TCGA was appraised for Cu(DDC)<sub>2</sub>-gene interactions in papillary thyroid cancer (PTC).

**Results:** RNA-Seq revealed potent transcriptional responses in Cu(DDC)<sub>2</sub>-treated 8505C cells (*n*=4661; *P*<0.05). TaqMan RTPCR confirmed induction of transcription factors (TF) with key roles in regulating NIS expression, such as PAX8, in thyroid cancer cells and human primary thyrocytes. In support, Cu(DDC)<sub>2</sub> was unable to induce NIS mRNA or  $^{125}\text{I}$  uptake when PAX8 was depleted. Surprisingly, Cu(DDC)<sub>2</sub> retained activity in the absence of NPL4 but not VCP. Previously, we induced thyroidal <sup>99m</sup>Tc-uptake in BALB/c mice via Cu(DDC)<sub>2</sub> treatment. Here, IV administration of Cu(DDC)<sub>2</sub> increased thyroidal TFs, including PAX8 and CREM, indicating a mechanism for enhancing NIS function *in vivo*. LASSO regression using TCGA identified a 22-gene riskscore based on

Cu(DDC)<sub>2</sub>-associated TFs; revealing a worse prognosis in RAI-treated PTC [Hazard Ratio=11.6; 95%CI, 5.80-23.31; *P*=4.7E-12; *n*=256]. Critically, incorporating both TF and VCP/proteostasis genes generated a dual riskscore with increased sensitivity (90.48%) and specificity (94.85%) for recurrence. Multivariate analysis reinforced the superior performance of this dual riskscore as an independent predictive factor in RAI-treated PTC [Hazard Ratio=20.58; 95%CI, 9.13-46.39; *P*=3.09E-13; *n*=211].

**Conclusion:** Our work demonstrates that a new dual NIS agonist targets transcriptional and VCP pathways to enhance RAI uptake, with clinical relevance to impact therapy and patient stratification for predicting recurrence.

## Poster 0202

*Thyroid Cancer, Basic, Poster*

### Thyroid Cancer is Associated with Sex-Specific Spatial Molecular Immune Responses

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**Background/Objective:** Thyroid Cancer (TC) has a strong sex-dimorphism with an incidence that is 3-4 times higher in females although males generally have more aggressive disease. The molecular basis for this observation is enigmatic and current approaches to treatment and surveillance are not sex-specific. The objective of this study was to characterize the spatial immune landscape by sex within the tumor microenvironment(TME) of TC.

**Methods:** In this IRB=approved prospective cohort study, we collected clinical, molecular data and paired tumor-normal tissues from patients undergoing thyroidectomy for high-risk thyroid nodules(Bethesda V-VI) or with diagnosed TC. Based on final pathology, only patients with TC of epithelial origin were included. Flow cytometry was performed. For a subset of patients NanoSting Digital Spatial Profiling(NDSP) was employed to elucidate the molecular and spatial characteristics of the immune landscape within TME.

**Results:** Thirty-Eight patients were enrolled(23 female/15 male); 11 were excluded (9 had benign tumors, 1 lymphoma, 1 MTC). Average female age was 49yr(SD19) and male was 47yr SD16)(*p*=0.806). *BRAF V600E* was present in 5(38%) females and 7(88%) males (*p*=0.067); *NRAS* in 2 females(15%) and no males (*p*=0.505); *TERT* was present in 2(25%) males and no females(*p*=0.133). In TME, TIGIT+CD8 T-cells and dividing NK cells were significantly higher in males (2.34 vs 0.87, *p*=0.048; 9.67 vs 1.29, *p*<0.001, respectively); whereas there was a trend towards mature NK cells being higher in females (2.54 vs 1.08, *p*=0.074). Spatial molecular profiling using NDSP revealed significant sex-differences in expression of immune response-related genes within TME. In the non-tumor tissue, *HLA-DRB* (antigen-presentation to T-cells) was significantly lower in males (*p*=0.001); at tumor-border *KRT* (keratin) was lower in men (*p*=0.04), and within the tumor core *CCND1*(regulator of cell cycle) was lower (*p*=0.04), whereas *PECAMI*(promotes tumor proliferation) (*p*=0.04), *IFNARI*(Type 1 interferon)(*p*=0.04), *CD68* (macrophage marker) (*P*=0.04) and *B2M*(NK cells inhibition) (*p*=0.019) were higher in males compared to females.

**Conclusion:** Patients with TC exhibit sex-specific molecular and spatial immune profiles within the TME. Males demonstrate a

predominance of inhibitory immune markers, while females a higher frequency of effector immune cells. Our finding could have implications for individualized, sex-specific therapies for patients with aggressive TC refractory to standard therapy.

## Poster 0203

*Thyroid Cancer, Basic, Poster*

### The crosstalk between SPPI<sup>+</sup> macrophages and FAP<sup>+</sup> fibroblasts participating in the sensitivity of post-radiotherapeutic immunotherapy for anaplastic thyroid cancer

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**Objective:** Anaplastic thyroid cancer (ATC) is a rare yet lethal subtype of thyroid cancer, representing the primary cause of mortality among thyroid cancer patients. The treatment options for ATC remain limited. Although immune checkpoint inhibitors have shown therapeutic potential in various tumors, their effectiveness in ATC is relatively constrained.

**Methods:** We performed single-cell RNA sequencing (scRNA-seq) on samples from ATC patients, individuals with papillary thyroid cancer (PTC), and healthy thyroid tissue. We used genetic engineering to create a conditionally inducible ATC murine model in a C57BL/6 background, which was genotyped by TPO-cre/ERT2; *Braf*<sup>CA/wt</sup>, *Trp53*<sup>ex2-10/ex2-10</sup> (TBP). We also conducted scRNA-seq of TBP murine model. Our analyses integrated these findings with 7 public thyroid cancer datasets to construct a comprehensive scRNA-seq atlas of thyroid cancer across human samples and mouse models. Additionally, we evaluated the synergistic effects of radiotherapy and immunotherapy using ATC mouse models, and extended this investigation to ATC patients receiving combined treatments. Pre- and post-treatment scRNA-seq analyses were conducted, and the spatial distribution of tumor cells was further examined using multiplex immunofluorescence to corroborate our results.

**Results:** Our preliminary research found that radiotherapy can sensitize immunotherapy for anaplastic thyroid cancer. Data from our comprehensive scRNA-seq of thyroid cancers reveal that SPPI<sup>+</sup> tumor-associated macrophages (TAMs) and FAP<sup>+</sup> cancer-associated fibroblasts (CAFs) play pivotal roles within the ATC microenvironment and are critical to the radiosensitization of immunotherapy. Radiotherapy combined with immunotherapy significantly reduced the content of tumor-infiltrating SPPI<sup>+</sup> TAMs and FAP<sup>+</sup> CAFs. Through interaction analysis, SPPI<sup>+</sup> TAMs and FAP<sup>+</sup> CAFs were identified as the two subtypes with the strongest interaction, with the LGALS9-SLC1A5 ligand-receptor pair playing a vital role in this process. The spatial distribution of the corresponding cell types also validated our findings. Moreover, the prediction role of LGALS9 in immunotherapy was also confirmed in our validation cohorts.

**Discussions:** we propose that SPPI<sup>+</sup> macrophages regulate FAP<sup>+</sup> fibroblasts via LGALS9-SLC1A5 to participate in the radiosensitization in immunotherapy for ATC, providing potential targets for biomarkers and cancer treatment of ATC.

## Poster 0204

*Thyroid Cancer, Basic, Poster*

### Breaking Resistance to Immune Checkpoint Inhibitor Therapy in Papillary Thyroid Cancer

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**Background:** While most patients with differentiated thyroid cancer (DTC) are successfully treated with surgery and radioactive iodine therapy, a subset develop metastatic and progressive disease that portends poor disease-specific survival (10% at 10 years) and for which there are few effective treatment options. Immune checkpoint inhibitors (ICIs) are a new form of cancer immunotherapy that have revolutionized outcomes for many patients with advanced solid malignancies, but, disappointingly, have not proven effective in DTC. We hypothesized that combination treatment with ICI and CpG, a toll-like receptor (TLR) agonist that reverses suppressive myeloid cell activity and increases antigen presentation, could improve anti-tumor immune responses.

**Methods:** We used a syngeneic murine BRAF<sup>V600E</sup> papillary thyroid cancer model to test the effect of combination ICI + CpG therapy on tumor growth and anti-tumor immune responses *in vivo*. Groups of 6wk old 129/SvmJ tumor-bearing mice were randomized to treatment with anti-mouse programmed death protein (PD1; 10mg/kg/dose, i.p., twice weekly) or isotype control antibody, and CpG (1ug/dose, peritumoral, 5 doses) or vehicle control, once tumors reached 50mm<sup>3</sup>. Primary outcomes were tumor growth, assessed by caliper measurement thrice weekly, and frequency of intratumoral and spleen immune effector and suppressor cells evaluated by flow cytometry and immunofluorescence.

**Results:** As in patients, anti-PD1 monotherapy of murine PTC tumors failed to significantly decrease tumor growth compared to isotype antibody treatment (p=ns). By contrast, mice treated with combination anti-PD1 + CpG had significantly smaller tumors than anti-PD1 alone beginning at day 12 and persisting until end of treatment at day 21 (p < 0.01). In addition, combination anti-PD1 + CpG therapy increased intratumoral IFN $\gamma$ <sup>+</sup> CD44<sup>+</sup> CD8<sup>+</sup> T cells (p < 0.05), a key population associated with effective anti-tumor immunity. Concurrent with this, we found reduced populations of CD11b<sup>+</sup> Gr1<sup>+</sup> myeloid derived suppressor cells in anti-PD1 + CpG treated compared to anti-PD1 alone or isotype treated mice (p < 0.05).

**Conclusion:** In summary, TLR agonist CpG effectively sensitized PTC to ICI therapy *in vivo* and increased tumor immune infiltration by effector T cells. These studies provide a foundation for translational approaches to improve the efficacy of ICI treatment in patients with DTC.

## Poster 0205

*Thyroid Cancer, Basic, Poster*

### Exposure to Bisphenol A Promotes the Proliferation and Tumorigenesis of Papillary Thyroid Carcinoma by producing ROS and Activating NOX4/MAPK and NOX4/PI3K/AKT Axes

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**Objective:** Bisphenol A (BPA) is a widely-used retardant in industrial goods and daily necessities. Although considerable researches have been conducted on the endocrine-disrupting effects and carcinogenicity of BPA, the mechanisms by which BPA induces the occurrence and development of thyroid cancer remain unclear. This study aims to explore how BPA promote the proliferation and tumorigenesis of papillary thyroid carcinoma.

**Methods:** The current research investigated the cancer-promoting activity of BPA on human Nthy-ori 3-1, TPC-1 and BCPAP cells using CCK-8, EdU incorporation assays, colony-forming assay, wound healing assay and western blot. RNA sequencing analyses were performed on the control and BPA-treated Nthy-ori 3-1 cells for 48h. Evaluation of changes in intracellular oxidative stress levels

after BPA treatment using DCFH-DA dye method and western blot. Finally, N-acetyl-L-cysteine (NAC) was used to explore the effects of ROS on cell proliferation.

**Results:** CCK8, EdU and colony-forming assays confirmed the toxicity of environmentally relevant doses of BPA on the proliferation of human normal follicular epithelial cell line (Nthy-ori 3-1) and PTC-derived cell lines (TPC-1 and BCPAP) dependent on the dose and time. Wound healing assay showed that BPA exacerbated the aggressiveness of PTC cells in a time-dependent manner. BPA altered the level of oxidative phosphorylation and oxidative stress response which was further proven by public databases and RNA-seq bioinformation analysis. Western blot showed that BPA could up-regulate the expression of NOX4, and activate the MAPK and PI3K/AKT axes. The expression of inflammation-related indicators (ICAM-1) has also increased. Furthermore, the intervention of NAC could inhibit cell proliferation and block the signaling pathways.

**Discussion:** This study demonstrated that exposure to environmental concentrations of BPA induced ROS production targeting NOX4, which activated the MAPK and PI3K/AKT axis to promote the proliferation and migration of papillary thyroid carcinoma. These findings might be helpful in clarifying the potential mechanism of BPA exposure leading to papillary thyroid cancer and comprehensively assess its health risks. And it could provide sufficient basis for the revision of standards for the use of BPA products and the formulation of environmental pollution. However, further research is needed on in-depth mechanisms, biomarkers, and in vivo detection.

## Poster 0206

*Thyroid Cancer, Basic, Poster*

### Low Bisphenol A doses produce diverse pleiotropic effects on anaplastic-derived thyroid cells and control follicular epithelial thyroid cells

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Bisphenol A (BPA), a ubiquitous synthetic endocrine-disrupting chemical, may increase susceptibility to thyroid cancer. However, little is known about the effects of BPA on thyroid cells, particularly malignant cells. Our aim was to evaluate the effects of low doses (0.1–1.0  $\mu$ g/ml) on the TP53-mutated cell line derived from anaplastic thyroid carcinoma (8505-C) and on the normal thyroid follicular epithelial cell line (Nthy-ori-3-1). Different concentrations, including the Specific Migration Limit (SML) = 1.0  $\mu$ g/ml (the maximum allowed amount of a substance in food), were tested in technical and biological triplicates after 24h, 48h, and 72h of exposure. The Trypan Blue assay, which assesses cell membrane integrity, and the CCK-8 assay, based on metabolic activity, were used to analyze cell viability. Apoptosis rates were cytologically determined using Hoechst 33342 and propidium iodide double staining. The BRDU assay was used to determine cell proliferation rates. Migration and invasion analyses were performed using a wound healing assay in monoculture. BPA produced non-monotonic cytotoxic effects in both thyroid cell lines. However, while an SML dose of 1.0  $\mu$ g/ml decreased Nthy-ori-3-1 viability by 50% at the 24h and 48h time points, the same concentration reduced the viability of 8505-C cells by 80% after 48h of exposure. The CCK-8 assay confirmed the sensitivity of 8505-C to BPA, with only 33% and 39% of viable cells remaining after 24h and 48h of exposure to 1.0  $\mu$ g/ml, respectively. The rate of apoptotic cell death was more pronounced in 8505-C cells than in control cells at all tested BPA concentrations. Surprisingly, BPA promoted the proliferation of 8505-C cells. Doses of 0.8  $\mu$ g/ml and 0.1  $\mu$ g/ml produced increases in absorbance of 143% and 113%, respectively, at 24h; 1.0  $\mu$ g/ml produced an increase of 151%

after 48h. The SML dose of BPA increased the wound healing rates of Nthy-ori-3-1 (62%) and 8505-C (33%) after 48h. This increase persisted in 8505-C cells after 72h but disappeared in Nthy-ori-3-1 cells. We suggest that the pleiotropic effects of low-dose BPA exposure, especially in mutated cells, may be related to the incidence and clinical characteristics of thyroid cancer, contributing to the selection of more harmful cells.

[https://youtu.be/LN35nn7\\_sOA](https://youtu.be/LN35nn7_sOA)

## Poster 0207

*Thyroid Cancer, Basic, Poster*

### GPT-4 Accuracy and Completeness of American Thyroid Association Guidelines for Management of Thyroid Cancer

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**Objective:** GPT-4 is a large multimodal model that uses publicly available data and data licensed from third party providers to generate predictions in the form of human-like responses. It has demonstrated the ability to synthesize medical knowledge. However, the accuracy and completeness of GPT-4 in providing recommendations for the management of patients with thyroid cancer is unknown. The objective is to assess the agreement between GPT-4 responses and the most recent American Thyroid Association (ATA) Guidelines for anaplastic thyroid cancer, medullary thyroid carcinoma, differentiated thyroid cancer and thyroid nodules to further understand the role of artificial intelligence in healthcare applications.

**Methods:** Recommendations and their grades of evidence were extracted from the most recent ATA management guidelines. Corresponding questions were identified and inputted into GPT-4. Two independent reviewers graded the GPT-4 generated outputs for accuracy and completeness on a Likert scale of 1 to 5 (1 - completely incorrect to 5 - correct) and 1 to 3 (1 - incomplete to 3 - comprehensive), respectively. Ratings were summarized with descriptive statistics and the measurement of agreement between reviewers was calculated using Cohen's Kappa.

**Results:** Across all recommendations (n=283), median accuracy rating was 4 with mean rating of 3.56 of 5, indicating an accuracy of more correct than incorrect. Cohen's kappa was 0.65, indicating substantial agreement. Median completeness rating was 2 with mean rating of 2.30 of 3, indicating a completeness of adequate to comprehensive. Cohen's kappa was 0.78, indicating substantial agreement.

**Discussion/Conclusion:** Results demonstrate the potential of ChatGPT as a supportive tool in responding to basic questions about the management of thyroid cancer. However, further research and model development are needed to correct inaccurate responses. Moreover, despite a high completeness score, extensive caution should be taken given the risk of artificial hallucinations in which partially incorrect recommendations are stated using confident language.

## Poster 0208

*Thyroid Cancer, Basic, Poster*

### Proto-oncogene regulation of thyroid cancer cell motility through altered focal adhesions

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**Objective:** Thyroid cancer progression is dependent on cell motility, a highly complex process that involves the co-ordination of multiple signalling pathways, cell adhesion, and actin dynamics. The proto-oncogene pituitary tumor-transforming gene (PTTG)-binding factor (PBF/PTTG1IP) potently stimulates thyroid cancer cell migration and invasion. We recently used Pbf-knockout (KO) mouse embryonic fibroblasts (MEFs) to show that PBF is also required for physiological cell movement. Phosphoproteomic and RNA-Seq analyses of Nthy-ori 3-1 thyroid cells revealed that PBF upregulation altered expression and phosphorylation of key adhesion and cytoskeletal proteins. We hypothesised that PBF is a physiological regulator of cell adhesion and its overexpression in thyroid tumours promotes cell motility via altered adhesion.

**Methods:** We utilised CRISPR/Cas9-mediated PBF-KO TPC-1 human papillary thyroid carcinoma cells and Pbf-KO MEFs in the analysis of cell adhesion and spreading on fibronectin-coated plates.

**Results:** TPC-1 PBF-KO cells exhibited markedly decreased cell-substrate adhesion at multiple time points up to 4 hours compared with control TPC-1 cells. We then assessed focal adhesions (FAs), the large protein complexes that link the cell cytoskeleton to the extracellular matrix. Immunofluorescence staining of focal adhesion kinase (FAK), vinculin and paxillin revealed alterations in FA structure and distribution. In comparison with control cells, which displayed numerous, elongated FAs aligned with actin fibres, PBF-KO TPC-1 cells had fewer and shorter FAs located predominantly around the cell periphery. In addition, LifeAct-GFP live-cell imaging and cell spreading assays suggested that TPC-1 PBF KO cells had impaired cell spreading and loss of cell polarity. In support of this, Pbf-KO MEFs also demonstrated decreased cell-substrate adhesion, significantly altered FAs and reduced cell spreading.

**Conclusions:** Collectively, these data provide new mechanistic insights into the regulatory role of PBF in thyroid cancer cell motility through cell adhesion dynamics. These findings also highlight potential novel avenues to therapeutically target PBF-regulated pathways in thyroid tumorigenesis.

## Poster 0209

*Thyroid Cancer, Basic, Poster*

### Site-Specific HRAS Q61R Activation Promotes Cell Proliferation via Activation of the PI3kinase/AKT/mTOR Pathway and TP53 Inactivation in Medullary Thyroid Cancer

Andrea Ruiz- Jurado, Montserrat Olaya Herrera, Joseph Kidd, Theresa Guise, Marie-Claude Hofmann, Mimi HU, Rozita Bagheri-Yarmand<sup>\*</sup>, The University of Texas MD Anderson Cancer Center, USA

**Objective:** RAS proteins are GTPases that function as molecular switches regulating proliferation and cell survival. Activating RAS mutations are found in 20-30% of human cancers. Activating mutations in specific hotspots of the RAS genes are found in sporadic medullary thyroid cancers (MTC), usually occurring in tumors with wild-type *RET* and rarely in those harboring a *RET* mutations. *HRAS-Q61R* is the most common *HRAS* mutation in MTC. The impact of *HRAS-Q61R* subcellular localizations on the pathogenesis of MTC is unknown. Our objective is to investigate how *HRAS-Q61R* activated at various subcellular localizations affects the biological outcome of *HRAS* signaling in MTC.

**Methods:** We generated constructs that encoded for constitutively active *HRAS-WT* or *HRAS-Q61R* fused to specific tethering signals to target *HRAS* to the plasma membrane (PM), Golgi complex(GA), and endoplasmic reticulum (ER). We then established MTC-MZCRC1 cells that stably expressed *HRAS-WT* (wild-type) or *HRAS-Q61R-Flag* tagged directed to the PM, GA, and ER by these

specific localization signals. Additionally, we established MTC- TT cells expressing native HRAS-WT or HRAS-Q61R mutations. We examined the targeted expression of HRAS-Q61R derivatives by real-time RT-PCR, western blot, and immunofluorescence. We also studied the effects of HRAS-Q61R derivatives on cell proliferation and signaling pathways.

**Results:** We observed an increased proliferation rate of MTC-MZCRC1 cells expressing the HRAS-Q61R mutation in the PM and the Golgi but not in the ER. The tumor suppressor TP53 protein levels were significantly decreased by HRAS-Q61R localized in the PM and Golgi but not when directed to ER compared to HRAS-WT. Forced expression of native HRAS-WT and HRAS-Q61R mutation in TT cells resulted in higher pAKTS473 and p-p70S6K phosphorylation, suggesting that activation of AKT and mTOR is a crucial consequence of HRAS signaling in MTC.

**Discussion/Conclusions:** Our results suggest that expression of HRAS-Q61R mutation directed to the endoplasmic membrane and Golgi controls cell proliferation/survival. However, this control is not observed when the mutations are expressed in the endoplasmic reticulum. Furthermore, HRAS-Q61R expression inactivates TP53 depending on the subcellular localization, which may cause resistance to TP53-mediated apoptosis. These findings could have implications for the development of novel therapeutic strategies for HRAS-mutated MTC.

#### Poster 0210

*Thyroid Cancer, Basic, Poster*

##### **Metabolic Reprogramming Contributes to Resistance Towards Lenvatinib in Thyroid Cancer**

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**Objective:** Lenvatinib is a multikinase inhibitor used for the treatment of metastatic progressive thyroid cancer (TC). The objective response rate to lenvatinib of up to 65% is transient and most patients eventually progress. Patients with progressive metastatic disease are characterized by increased glucose uptake evidenced by 18-Fluorodeoxyglucose Positron Emission Tomography, suggesting enhanced metabolism. We hypothesized that changes in cancer metabolism may play a role in resistance to Lenvatinib (LR).

**Methods:** We induced LR in human TC cell lines (THJ29T and TPC1) by continuous exposure to increasing concentrations of the drug over several months, achieving a clinically relevant resistance factor of >2.5. We performed unsupervised metabolomics using mass spectrometry (MS) and compared metabolic profiles of LR and parental Lenvatinib sensitive (LS) cells using principal component analysis. RNA sequencing was done to compare the transcriptome in LR vs LS cell lines. Seahorse analysis was performed to analyze oxidative phosphorylation (OXPHOS) and glycolysis. Western blotting was performed to evaluate the expression of OXPHOS markers. P-values of  $\leq 0.05$  were considered statistically significant.

**Results:** Untargeted metabolomics profiling revealed that LR cell lines clustered separately from LS paternal lines, suggestive of different metabolic signature. RNAseq revealed significant enrichment in metabolic pathways (enrichment score >3.5,  $p < 0.0001$ ) in the LR cells as compared to LS cell line. Butanoate and fatty acid metabolism as well as steroid biosynthesis were significantly upregulated in LR vs LS (enrichment scores of >4.5,  $p < 0.0001$ ). Metabolism profiling showed a significant overactivation of OXPHOS in resistant cells (THJ29T LR vs LS:  $4013 \pm 306$  vs  $2293 \pm 334$ ,  $p < 0.001$ ; TPC1 LR vs LS:  $3999 \pm 358$  vs  $1774 \pm 208$ ,  $p < 0.0001$ ), while glycolysis rate remained similar ( $p > 0.05$ ). Consistently, immunoblotting

revealed at least 2-fold overexpression of key components of respiratory chain, including complex I NDUFB8 ( $p = 0.02$ ), complex III UQCRC2 ( $p = 0.006$ ), and complex V ATP5A ( $p = 0.05$ ) in LR cells vs LS-TC.

**Conclusions:** Metabolic plasticity has a prominent role in resistance to Lenvatinib in TC. Activation of metabolic pathways is associated with enhanced OXPHOS in LR models. Exploration of mechanisms fueling OXPHOS in TC may form a basis for targeted therapies aimed at overcoming LR.

#### Poster 0211

*Thyroid Cancer, Basic, Poster*

##### **Differential activity of specific inhibitors of transcription regulating cyclin-dependent kinases in thyroid cancer cells**

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**Objective:** "Superenhanced" transcription of oncogenes by aberrant looping of upstream enhancer elements to transcriptional regulatory regions is a mechanism of oncogene overexpression. Non-selective cyclin-dependent kinase inhibitors (CDKi) that target transcriptionally regulatory CDKs, including CDK7, 9, 12, and 13, reduce mRNA levels of superenhanced oncogenes have activity versus thyroid cancer cells as part of their activities. We hypothesized that more specific inhibitors of CDKs would have differential activities in thyroid cancer cells and may be suitable for further preclinical studies.

**Methods and Results:** We selected thyroid cancer cell lines with a variety of genetic drivers for initial screening studies with CDK7/12/13 (THZ1) and CDK9 (AZD4573) inhibitors. IC<sub>50</sub> values ranged from 5-100 nM for THZ1 for all cell lines, and 6 of 8 cell lines for AZD4573, with inhibition of nuclear RNAPII phosphorylation and evidence of reduced cell migration. 8505C and TPC1 cells were selected for more detailed studies based on their expression of two common thyroid oncogenes, BRAF<sup>V600E</sup> and RET fusions, respectively. In these cells, SR4835 and AZD4573 were more effective than the specific CDK7 inhibitor YKL-5-124 at reducing cell survival, migration, proliferation, and inducing apoptosis. Treatment with SR4835 was the most potent, induced DNA damage, and resulted in cyclin K loss.

**Conclusion:** These data suggest that specific inhibitors of CDK12/13, and CDK9, are capable of inhibiting thyroid cancer growth and inducing apoptosis. Further studies evaluating the potential efficacy of these more specific inhibitors are warranted in thyroid cancer.

#### Poster 0212

*Thyroid Cancer, Translational, Poster*

##### **Unique Molecular Landscape of Thyroid Cancer in African Americans: A Cross-Institutional Large-Cohort Genomic Analysis**

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**Objective:** Emerging research from the SEER database suggests that African American (AA) patients with thyroid cancer have worse outcomes than their White (W) counterparts, even when controlling for age, sex, and socioeconomic factors. Few studies have explored the genetic and morphologic landscape of thyroid cancer in AA patients, highlighting the need for an enhanced understanding of the

molecular underpinnings of thyroid cancer across diverse study cohorts. Here, we hypothesize that the landscape of genetic drivers of thyroid cancer in AA patients is different from that of W patients.

**Methods:** We analyzed the frequency of *BRAF*<sup>V600E</sup> and *RAS* driver mutations and distribution of histopathologic subtypes for thyroid cancer patients by reported race in two large thyroid cancer sequencing cohorts: the Tempus multimodal database and The Cancer Genome Atlas.

**Results:** While papillary thyroid carcinomas (PTC) are the most common histologic subtype overall in both cohorts, the Tempus multimodal database demonstrates increased prevalence of follicular thyroid carcinoma in AA patients. There is a corresponding decreased prevalence of PTC in AA patients relative to the entire Tempus multimodal database, and within the PTC category, AA patients have increased prevalence of follicular variant PTC and decreased prevalence of classical papillary histology. Follicular-patterned thyroid cancers are typically associated with *RAS* mutations and fewer lymph node metastases. Compared to the entire Tempus multimodal database, AA patients show decreased frequency of *BRAF*<sup>V600E</sup> and increased frequency of *RAS* mutations. Consistent with the *RAS* mutations, AA patients show fewer lymph node metastases. AA patients in a smaller cohort, The Cancer Genome Atlas, also trend toward increased follicular-patterned tumors.

**Discussion/Conclusion:** Altogether, we have identified a shift in the landscape of thyroid cancer in AA patients toward *RAS*-driven follicular-patterned tumors, which could be a result of both social determinants of health and genetic factors contributing to different disease phenotypes. The underlying cause of these differences should be further evaluated with the goal of rethinking how we diagnose, prognose, and treat thyroid cancer for diverse populations.

### Poster 0213

*Thyroid Cancer, Translational, Poster*

#### **Role of the ETV5/p38 Signaling Axis in BRAF-Mutated Anaplastic Thyroid Cancers**

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**Background and Objective:** The *BRAF*<sup>V600E</sup> mutation drives 35% of anaplastic thyroid cancers (ATC). Combination treatments with *BRAF*<sup>V600E</sup> and MEK inhibitors induce impressive tumor size reduction in these tumors, but drug resistance poses a significant challenge in many patients. We hypothesize that *BRAF*-mutated ATC tumor cells express multiple oncogenic pathways that can be used to bypass the *BRAF*/MEK inhibition. Therefore, signaling networks in *BRAF*-mutated cells need to be deciphered to identify additional targetable proteins for novel therapeutic strategies, which are still urgently needed.

**Methods:** We searched The Cancer Genome Atlas (TCGA) and NCBI GEO for novel signaling pathways/molecules associated with overexpression of ETV5, a transcription factor downstream of the activated MAPK pathway. Pathway/marker validation was performed in poorly differentiated thyroid carcinoma (PDTC) and ATC cells using qPCR and western blotting. Differential expression of specific genes was also tested after downregulation of ETV5 (shRNA). Novel drugs were also identified and tested in vitro on

*BRAF* inhibitor-resistant PDTC/ATC cells and in vivo in a transgenic mouse model of ATC.

**Results:** In silico transcriptome analysis showed a strong correlation between the *BRAF* mutation, ETV5 expression, and activation of the p38 pathway ( $p < 0.001$ ), which was confirmed by western blotting in PDTC and ATC cells. Down-regulation of ETV5 inhibited p38 activation as well as that of its regulatory kinases (MKK3/MKK6). It also increased ATF2/ATF7 phosphorylation, indicating activation of the apoptotic pathway. Among three different p38 inhibitors tested in vitro, ralimetinib was the most effective (IC<sub>50</sub> @ 15 μM). Treatment combining ralimetinib and dabrafenib (a *BRAF*<sup>V600E</sup> inhibitor) resulted in significant synergy in preclinical models as measured by high throughput screening (cell lines) and best tumor responses in ATC animal models.

**Conclusions:** We have identified a connection between the MAPK and the p38 pathways, which relies on ETV5 expression. Activation of the MAPK/ETV5 axis by the *BRAF*<sup>V600E</sup> mutation upregulated the p38 pathway, which may contribute to additional cell survival/proliferation and resistance. Combining inhibitors targeting *BRAF*<sup>V600E</sup> (such as dabrafenib) and p38 activity showed synergistic effects, yet enhancing the specificity of the latter will be crucial to pave the way for a novel strategy in treating *BRAF*-mutated ATC and PDTC thyroid cancers.

Funded by the Petrick/MDA Anaplastic Thyroid Cancer Funds and DOD #HT9425-23-1-0675.

### Poster 0214

*Thyroid Cancer, Translational, Poster*

#### **Targeting the MAPK and DNA Repair Pathways in Poorly Differentiated and Anaplastic Thyroid Cancer Cells**

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**Background:** Poorly differentiated thyroid carcinomas (PDTC) and anaplastic thyroid carcinomas (ATC) are rare but very aggressive thyroid tumors. Around 35% of these tumors harbor the *BRAF*<sup>V600E</sup> mutation. Treatment combining dabrafenib and trametinib to target *BRAF*<sup>V600E</sup> and MEK kinases is initially effective, however most patients progress. Short-term cultures (72 h) of PDTC and ATC cells with dabrafenib and/or trametinib indicated that DNA damage recognition and repair enzymes were upregulated by these drugs, which might contribute to additional genomic instability. We tested the long-term effects of dabrafenib on the occurrence of DNA damage and subsequent repair in surviving cancer cells. We also hypothesized that berzosertib, a drug that impairs the ability of dividing cells to recognize DNA damage, would reduce their viability due to accumulation of damaged DNA.

**Method:** We established dabrafenib-resistant ATC cells by culturing them long-term in presence of 5 μM dabrafenib. To evaluate differential protein expression and follow the development of resistance pathways, we performed reverse phase-protein arrays (RPPA) at 0, 2, 4, 6 and 8 months of treatment. Western blots quantified and confirmed the expression/phosphorylation of relevant DNA damage recognition and repair proteins. We tested dose combinations of dabrafenib with berzosertib, a selective inhibitor of the DNA damage recognition protein ATR.

**Results:** Drug resistance occurred around 3 months of treatment. We observed increased expression of DNA damage recognition

proteins such as ATM (Ataxia-telangiectasia mutated), ATR (Ataxia Telangiectasia and Rad3-Related Protein), PARP-1 (Poly [ADP-ribose] polymerase 1), and gH2AX over time. DNA repair enzymes such as exo- and endonucleases were also upregulated. Interestingly, TP53 expression was simultaneously downregulated. Berzosertib combined with dabrafenib showed synergistic effects in decreasing cells viability, including dabrafenib-resistant cells.

**Conclusion:** These results confirm that kinase inhibitors lead to DNA damage and upregulation of DNA repair pathways. Concomitant downregulation of TP53 expression prevents cellular senescence and apoptosis. These events might contribute to emergence of secondary mutations through faulty DNA repair in absence of cell death and cause drug resistance. Therefore, combination treatments of dabrafenib with an ATR inhibitor such as berzosertib might be useful to prevent or eliminate drug resistance in aggressive thyroid cancers and other BRAF-mutated solid tumors.

Funded by the Petrick/MDA Anaplastic Thyroid Cancer Funds.

## Poster 0215

*Thyroid Cancer, Translational, Poster*

### Association Between Polygenic Risk Score and Clinical Outcomes in Papillary Thyroid Cancer

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**Objective:** Genome-wide association studies (GWAS) have identified germline variants involved in the development of papillary thyroid carcinoma (PTC) that can be used to construct a polygenic score (PGS) for estimating the overall PTC risk of an individual. The purpose of this study is to assess whether there is an association between germline risk defined by PGS and survival outcomes for PTC.

**Methods:** Patients with newly diagnosed PTC who presented to the University of Texas MD Anderson Cancer Center for treatment between 1999-2014 were included in the study cohort. Genomic DNA was extracted from buffy coat cells isolated from peripheral blood samples. Genotyping for germline polymorphisms were performed using the Omni1-Quadbead chip. Germline risk for PTC was estimated with a previously validated PGS calculated from 10 single nucleotide polymorphisms (SNPs) identified through GWAS. The Wilcoxon test and Kruskal-Wallis test were conducted to assess the relationship between PGS and family history of thyroid cancer. Linear regression analysis was conducted to analyze the association between PGS and clinicopathological characteristics. Multivariable Cox proportional hazards models were used to relate PGS to PTC-specific and overall survival.

**Results:** 366 patients were included in the study. Median PGS was higher in patients with a self-reported family history of thyroid cancer (median PGS, -1.38; range, -2.69 to -0.40) but did not differ significantly compared with patients lacking such history (median PGS, -1.43; range, -3.05 to 0.55). Based on the linear regression analysis, increasing PGS was significantly associated with multifocality ( $P = 0.0452$ ) and N1 disease ( $P = 0.0091$ ) at diagnosis. PGS was significantly associated with PTC-specific survival in univariable analyses. However, PGS did not achieve statistical significance in the multivariable models after adjusting for clinicopathologic variables for both overall survival and PTC-specific survival.

**Conclusion:** Our findings suggest that PGS is associated with disease extent at presentation, but it is not independently associated with survival outcomes.

## Poster 0216

*Thyroid Cancer, Translational, Poster*

### Metabolomic Profiling of Paraffin-Embedded Thyroid Tumors Identifies Hallmarks of Cancer Progression

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**Objective:** Metabolic reprogramming is a hallmark of cancer. A deeper understanding of tumor metabolic profiles is often limited by the scarcity of large-scale metabolomic studies. Leveraging the abundance of formalin-fixed-paraffin-embedded (FFPE) tissue samples when compared to fresh-frozen tissue (FFT), this study presents the first extensive FFPE metabolomic analysis of thyroid cancers.

**Methods:** We performed a clinical-genomic-metabolomic analysis of patients with differentiated (papillary-PTC, follicular-FTC and oncocytic-OCT), poorly differentiated (PDTC) and anaplastic thyroid cancer (ATC). Patients were clinically characterized, and 90% had a custom-targeted next-generation-sequencing assay covering over 400 cancer genes. FFPE samples underwent untargeted metabolomics analysis using LC-MS. Metabolomics data were quality-controlled, with retention times identified and annotated using Compound Discoverer, and analyzed using *limma*.

**Results:** Ninety patients (n=90) covering the entire spectrum of thyroid neoplasia, i.e., benign adenoma, NIFTP, PTC (classic, tall-cell, follicular subtypes), FTC, OCT, PDTC, ATC, and 10 matched normal-thyroid (NT) controls were analyzed. We first proved that metabolomics of FFPE tumors is feasible and accurate; for example, an observed ~184-fold increase in saccharopine levels in FFPE OCT samples ( $\log_2FC=7.53$ ;  $q=1.48E-6$ ) aligns with previous studies on OCT using FFT. No significant metabolic differences were identified when comparing BRAFV600E-mutant (n=25) vs. RAS-mutant (n=19) tumors across histologies. Importantly, we identified 272 unique metabolites differentially abundant, and clear metabolic phenotypes across the nine histologies compared to NT. Purine salvage pathways were activated in ATC and PDTC, evidenced by increases in guanosine ( $\log_2FC=1.74$ ;  $q=0.003$ ), GMP ( $\log_2FC=1.54$ ;  $q=0.004$ ), and GDP ( $\log_2FC=1.11$ ;  $q=0.02$ ), without the accumulation of ribose-5-phosphate. Conversely, tricarboxylic acid cycle (TCA) and fatty acid metabolic intermediates were reduced, as indicated by decreases in cis-aconitate ( $\log_2FC=-3.83$ ;  $q=1.42E-7$ ), citrate ( $\log_2FC=-2.39$ ;  $q=1.56E-4$ ), eicosanoate ( $\log_2FC=-1.93$ ;  $q=0.002$ ), and suberic acid ( $\log_2FC=-3.12$ ;  $q=2.51E-10$ ). These findings suggest that in ATC and PDTC, glucose-derived carbons may primarily fuel nucleotide biosynthesis via the purine salvage pathway, resulting in diminished TCA intermediates and reduced fatty acid synthesis and oxidation.

**Discussion-Conclusion:** Our study demonstrated the feasibility of performing metabolomics from FFPE samples in thyroid cancer. While *BRAF* and *RAS* mutations did not cause metabolic divergence, distinct metabolic phenotypes were observed across histologies. Aggressive thyroid cancers exhibited deregulated purine biosynthesis, presenting potential therapeutic targets.

## Poster 0217

*Thyroid Cancer, Translational, Poster*

### A Novel Approach for the Study of Anaplastic Thyroid Carcinoma via Generation of Patient-Derived Thyroid Tumor Organoids

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**Introduction:** Anaplastic thyroid carcinoma (ATC) is a rare but aggressive form of thyroid cancer. While ATC constitutes less than 2% of thyroid cancer diagnoses, it accounts for up to 50% of all thyroid cancer-associated deaths, with a 5-year survival of less than 10%. Many ATC cases arise from pre-existing papillary thyroid carcinoma through anaplastic transformation; however this process is not well understood. An improved understanding is critical for improving patient mortality.

**Objective:** Our objective was to develop a novel method of studying ATC using patient-derived ATC tumor organoids. Organoid models are three-dimensional culture systems that enable modeling of tissue heterogeneity and structure complexity but have not yet been established for ATC. We hypothesize that patient-derived ATC organoids can provide an effective platform for characterizing anaplastic transformation and growth. We report a novel method of culturing ATC organoid models from patient-derived specimens.

**Methods:** The tumor specimen was collected from a 62-year-old female undergoing palliative tracheostomy for biopsy proven ATC. Surgical specimens were dissociated into single cells via mechanical and enzymatic digestion and seeded into Cultrex BME collagen matrix droplets. The organoids were cultured in growth medium enriched with growth factors for thyroid cells including TSH, Wnt surrogate, and R-spondin, as mentioned in previous literature.

**Results:** After culturing in organoid medium, the organoids exhibit hyperproliferation over at least 1 week of growth and maintained viability after at least 1 passage to date. Successful induction of a tumor phenotype will be confirmed through qPCR and IHC of markers associated with anaplastic thyroid carcinoma.

**Discussion:** We report the first generation of an organoid model for anaplastic thyroid carcinoma, which can be used as a model to study ATC malignant transformation. Transcriptomic and metabolomic analyses will be performed to identify key metabolic pathways involved in anaplastic transformation and growth. We plan to utilize this platform to identify therapeutic targets to prevent anaplastic transformation and treat poorly differentiated thyroid cancers.

## Poster 0218

*Thyroid Cancer, Translational, Poster*

### Redox State of Serum Albumin Cys34 and Its Influence on Ferroptosis in Differentiated Thyroid Cancer

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**Objective:** Serum albumin cysteine 34 (Cys34) physiologically exists in three primary forms: the free thiol form (human mercaptalbumin, HMA), the disulfide form with a small thiol compound (primarily cysteine) known as human non-mercaptalbumin1 (HNA1), and higher oxidized forms with Cys34 in sulfinic or sulfonic acid states termed human non-mercaptalbumin2 (HNA2, present only in trace amounts *in vivo*). However, the clinical significance of the redox state of albumin Cys34 in differentiated thyroid carcinoma (DTC) remains unclear. In this study, we investigated the association between the redox state of albumin Cys34 and the progression of DTC, and evaluated the therapeutic potential of its interventional modulation.

**Methods:** A retrospective cohort study involving 99 DTC patients was conducted to assess the relationship between albumin Cys34 redox state and progression-free survival (PFS). *In vitro* studies using the DTC cell line 8505C assessed the effects of HMA and HNA1 on cell survival. *In vivo* experiments involved murine models transplanted with 8505C thyroid cancer cells. The mice were fed a diet lacking cysteine, cystine, and methionine to prevent HMA conversion to HNA1. Tumor size and HMA concentration were measured.

**Results:** The patient cohort study indicated that higher HMA concentrations were associated with improved PFS. *In vitro*, HMA-enriched culture conditions induced iron-dependent regulated cell death termed ferroptosis, characterized by decreased glutathione synthesis, which in turn promoted lipid peroxidation. These effects were reversed by ferroptosis inhibitors. In contrast, under HNA1-enriched conditions, glutathione synthesis was maintained, lipid peroxidation did not occur, and the cells proliferated, suggesting that cysteine bound to the Cys34 disulfide bond in HNA1 was utilized for glutathione synthesis. *In vivo*, sulfur amino acid restriction maintained high HMA levels and reduced tumor size.

**Discussion/Conclusion:** The serum albumin Cys34 redox state significantly impacts ferroptosis induction in DTC. Sulfur amino acid restriction enhances HMA levels, leading to ferroptosis and tumor shrinkage. Personalized dietary control and targeted modulation of albumin Cys34 redox state could represent novel strategies for advancing DTC treatment.

## Poster 0219

*Thyroid Cancer, Translational, Poster*

### Exposomic Analysis of Thyroid Cancer: Correlating histopathological characteristics with persistent environmental organic pollutants

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**Objectives:** Preliminary data have shown elevated concentrations of ubiquitous environmental chemicals in differentiated thyroid cancer when compared to normal controls. This study sought to correlate the presence of persistent organic pollutants with histopathological characteristics in differentiated thyroid cancer.

**Methods:** Retrospective review of de-identified human archived cryopreserved specimens of differentiated thyroid cancer (n=60, 20 per subtype, including Papillary Thyroid Carcinoma, Follicular Carcinoma, Follicular Variant of Papillary Thyroid Carcinoma). High-resolution exposomic analysis to quantify the amount of multiple environmental contaminants was performed using gas chromatography-mass spectrometry (GC-MS). Annotation of raw spectra was performed by mapping mass-to-charge ratios and retention times to an in-house library of pure chemical standards run on the same instrument. Annotated signals were only analyzed if they were detected in  $\geq 70\%$  of samples. ANOVA and linear regression were used to assess the relationship between chemical abundance and histologic characteristics.

**Results:** 288 unique chemicals were identified in the samples, and 73 had significant correlation with histopathologic characteristics. 33 contaminants were associated with tumor variant, 16 with number of tumors, 13 with lympho-vascular invasion (LVI), 12 with tumor size, 7 with extra-thyroidal extension (ETE), and 4 with multifocality. 8 chemicals were identified to have more than one significant correlation with histopathologic characteristics. The chemicals with the most associations were propylparaben (common preservative;

LVI, ETE, size, number of tumors), 3-hydroxycarbofuran (pesticide; multifocality, size, number of tumors), and 4-aminobiphenyl-1 (discontinued color additive; LVI, size, number of tumors).

**Conclusions:** Multiple environmental chemicals have been identified at higher concentrations in differentiated thyroid cancer cryopreserved specimens. More than a quarter, including common chemicals such as propylparaben, were found to correlate with histopathologic characteristics associated with more aggressive disease. More studies are needed to assess the role of these contaminants in thyroid carcinogenesis and tumor characteristics associated with these environmental organic pollutants.

### Poster 0220

*Thyroid Cancer, Translational, Poster*

#### **Routine Mutation Analysis Reveals Germline and Somatic Variants Associated with Altered Risk: Results in 265 Thyroid Cancers**

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**Objective:** Molecular interrogation of pathologic samples has become routine for some malignancies in many centers and results in increased capability to guide postoperative treatment and surveillance. Here we reviewed the results of routine mutation analysis for patients who had thyroid malignancies to identify both somatic and germline variants that might be associated with aggressive histology.

**Methods:** Consecutive patients who underwent surgery for thyroid cancer from 2014-2021 and whose tumors were submitted for OncoPrint next generation sequencing analysis were included. Clinicopathologic variables, genomics, referral patterns, and outcomes were retrospectively analyzed. For genes associated with possible familial syndromes, suspicion for germline variants (GVs) was defined by a variant allele frequency of 45-55%. High-risk subtypes - including poorly differentiated thyroid cancer (PDTCC), anaplastic, or tall cell variants, were identified, and genomic characteristics were evaluated.

**Results:** 265 patient tumors underwent OncoPrint testing. 47 (17.7%) had suspected GV. The GV cohort median age was 51 and 66% of patients were female. 15.8% demonstrated vascular invasion, 0 had perineural invasion, 32.4% had lymphatic invasion, 54.5% had lymph node involvement, 13% exhibited gross extrathyroidal extension, 17.4% had positive margins, and 15.2% experienced a recurrence. There were no statistically significant age, sex, or pathologic differences between the GV cohort and GV negative patients; however, more PDTCCs were found in the GV cohort (6.4% vs 1.4%, p=0.030). 29 (10.9%) total high-risk subtypes were identified, of which 27.6% had a suspected GV. Notably, all *FLT3* (1/1-tall-cell), *JAK3* (1/1-PDTC), *TSC1* (1/1-anaplastic), and *PDGFRA* (1/1-tall-cell) suspected GV. *BRAF*, *PIK3CA*, and *TP53* were the most frequent somatic/driver mutations among high-risk lesions. 11/47 (23.4%) were sent for confirmatory testing by referral to medical genetics. Previously diagnosed cases of Cowden syndrome and BRCA1 were detected by OncoPrint screening.

**Discussion/Conclusion:** Routine oncogene analysis of thyroid cancer specimens is associated with a 17.7% likelihood of identifying a potential germline mutation which may help guide treatment and follow-up of patients with thyroid cancer. Furthermore, given the higher incidence of associated oncogene mutations in aggressive histologies, further investigation into the role of these mutations in thyroid cancer development is warranted.

### Poster 0221

*Thyroid Cancer, Translational, Poster*

#### **Tumor Cell Origin of Anaplastic Thyroid Cancer Squamous Subtype and Novel Targeted Therapy Options Revealed by Patient-derived Xenografting**

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**OBJECTIVE:** Squamous cell carcinoma (SCC) in the thyroid, recently characterized as a subtype of anaplastic thyroid cancer (ATC), are rare but highly malignant tumors that respond poorly to chemoradiotherapy. Hence, TSCC is mostly fatal shortly after diagnosis. In absence of BRAF mutation, the tumor-cell-origin of TSCC is uncertain and spread from extra-thyroid locations cannot be excluded. Here, we present data supporting a direct transition of SCC from papillary thyroid carcinoma (PTC) and first characterization of TSCC in a patient-derived xenograft (PDX) mouse model.

**METHODS:** Human tumor biopsies were subcutaneously engrafted in immunodeficient NOG mice. Protein expression was monitored by immunohistochemistry (IHC) on primary and transplanted FFPE tumor tissue sections. Mutation analysis was performed by whole exome sequencing (on PDX) or using the GMS560 panel recently launched by Genomic Medicine Sweden (on cells captured from tissue sections). Targeted drug treatment based on mutation profile was tested on third generation PDX.

**RESULTS:** A 70-years-old female presented a mixed PTC/SCC and a synchronous vulvar SCC. Likely pathogenic mutated genes were identical in PTC and TSCC (*KEAP1*, *STK11* and *RB1*) but entirely different in the genital cancer (*NOTCH*, *RHOA*, *HUWE1*, *FAT1*, *TERT* and *TP53*). *BAP1* and *PTPRC* mutations present in TSCC only indicated subclonality. IHC showed for PTC: NKX2-1<sup>+</sup>, PAX8<sup>+</sup>, P40<sup>+</sup>, P63<sup>+</sup>; for TSCC: NKX2-1<sup>-</sup>, PAX8<sup>+</sup>, P40<sup>+</sup>, P63<sup>+</sup>. Both thyroid tumor components were negative of *BRAF* mutation.

Only one out of eight engrafted advanced-stage TC (3 PTC, 2 FTC, 1 PDTC, 2 ATC) was successfully established and propagated as PDX. The primary tumor was an invasive TSCC (T3N1bM0) with no signs of differentiated TC. Driver mutations comprised *PIK3CA*, *CDKN2A* and *NFE2L2*. PDX recapitulated the tumor phenotype. Combined treatment with cabozantinib and GDC-0326, a PI3K inhibitor, significantly reduced PDX growth whereas single drugs were inefficient. Remarkably, monotherapy with glutaminase inhibitor CB-839 (telaglenastat) had the best therapeutic effect of all drugs. CB-839 suppressed NQO1 and CDH2/N-cadherin overexpression in SCC tumor cells.

**CONCLUSIONS:** Progression of PTC to SCC features multiple mutations some of which not previously recognized in thyroid cancer. The predominating NRF2/KEAP1 pathway is druggable and potentially optional for ATC patients with squamous tumor subtype.

### Poster 0222

*Thyroid Cancer, Translational, Poster*

#### **EpCAM Signaling Regulates Tumor Progression, Metastasis, and Stemness in Anaplastic Thyroid Cancer**

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**Objective:** Epithelial cell adhesion molecule (EpCAM) is a pleotropic transmembrane glycoprotein comprising an extracellular domain (EpEX), a single transmembrane domain, and an intracellular domain (EpICD). In several types of cancer, including colon cancer, high EpCAM expression is associated with tumor progression, metastasis, immune evasion, and overall poor prognosis. Thyroid cancer accounts for 90% of all endocrine malignancies and has a high 5-year survival rate. However, a rare but aggressive form of thyroid cancer, anaplastic thyroid cancer (ATC, < 2% of thyroid cancer), has a mean survival time of only 3-6 months after diagnosis. This study focused on the potential role of EpCAM in ATC disease pathogenesis.

**Methods:** Immunostaining on a thyroid cancer tissue array (TMA) was performed and four ATC cell lines (MDA-T178, MDA-T245, MDA-T264, and MDA-T265) were used to verify expression of EpCAM in ATC. EpCAM-neutralizing antibody EpAb2-6 and BRAF inhibitor dabrafenib were used to suppress EpCAM expression for cell growth and invasion *in vitro* and in a metastatic animal model of ATC *in vivo*.

**Results:** We observed that ATC samples exhibited a marked loss of membrane EpEX along with increased nuclear and cytoplasm accumulation of EpICD, as compared to non-ATC tissues in the TMA. EpEX induced phosphorylation of EGFR, HGFR and Wnt receptors in ATC cells to promote cell growth and invasion activity. EpAb2-6 suppressed regulated intramembrane proteolysis of EpCAM and shedding of the EpEX and EpICD in ATC cells, while combined treatment of EpAb2-6 and BRAF inhibitor dabrafenib coordinately induced apoptosis, while inhibiting invasion and stemness characteristics. Combination of EpAb2-6 and dabrafenib significantly inhibited lung metastasis and prolong survival in an animal model of metastatic ATC.

**Conclusion:** Our study outlines the molecular mechanisms underlying EpCAM signaling promotion of ATC tumor progression, metastasis, and stemness. Our findings illuminated the functions and mechanisms of EpCAM cleavage-mediated signaling and suggested that was likely involved in ATC progression, metastasis, and stemness. EpAb2-6 may improve the therapeutic efficacy of BRAF inhibitor, dabrafenib, in ATC. Our results further suggested that EpCAM may be a valuable therapeutic target for ATC.

## Poster 0223

*Thyroid Cancer, Translational, Poster*

### Transcriptome analysis of FNA to identify candidate genes related to prognosis of papillary thyroid microcarcinoma

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**Objective:** RNA sequencing is important for predicting the prognosis of papillary thyroid microcarcinoma (PTMC). The study aimed to investigate important candidate genes involved in prognosis of PTMC patients preoperatively.

**Methods:** Total RNA was extracted from 8 fine needle aspiration (FNA) samples of PTMC with lymph node metastases (LNM) and 7 FNA samples of PTMC without LNM, followed by RNA sequencing. The differentially expressed genes (DEGs) were identified. Gene set enrichment analysis (GSEA) was performed to identify the biological pathways, and protein-protein interaction (PPI) networks

were constructed. Key genes showing a strong correlation with the LNM of PTMC were identified.

**Results:** In the 15 FNA samples, The RNA-seq yielded a mean of 94.46% of the clean reads mapped to the reference genome. A total of 775 genes were identified as differentially expressed: 631 (49.81%) were upregulated and 144 (50.19%) were downregulated (LNM vs. Control). Significance analysis of GO enrichment of DEGs revealed 101 significantly enriched entries, and DEGs were assigned to 130 KEGG pathways, of which 6 were significantly enriched (padjust<0.05). The protein-protein interaction network sorted the nodes, and some genes have prominent gene expression abnormalities and were associated with thyroid cancer: PLXNA4, SEZ6L2, HECW2, ABI3BP, SIX1, PTPRB, KDR and CREB3L1 genes.

**Conclusions:** Our study demonstrated that transcriptome analysis is feasible for the FNA specimens of PTMC patients, and can be used to investigate important candidate genes involved in LNM of PTMC patients. Several genes including PLXNA4, SEZ6L2, HECW2, ABI3BP, SIX1, PTPRB, KDR and CREB3L1 might be used as the prognosis biomarkers of PTC.

## Poster 0224

*Thyroid Cancer, Translational, Poster*

### Thyroid Cancer: Role of Neutrophil Extracellular Traps and Neutrophil-Related Mediators

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**Objective:** Neutrophils cover a central role in inflammation and cancers thanks to their several mediators, such as myeloperoxidase (MPO), pentraxin-3 (PTX3), matrix metalloproteinase-9 (MMP-9), and neutrophil extracellular traps (NETs). Therefore, we aimed to evaluate NETs and neutrophil-related mediators as possible biomarkers in thyroid cancer (TC).

**Methods:** We enrolled 23 healthy controls (HCs), and 27 patients with multinodular goiter (MNG), 21 with differentiated TC (DTC), and 27 with dedifferentiated TC (De-DTC).

The serum levels of all subjects have been investigated for: free DNA (dsDNA), nucleosomes, citrullinated histone H3 (CitH3), and MPO-DNA complexes (NETs indicators), and MPO, PTX3, MMP-9 and granulocyte-monocyte colony-stimulating factor (GM-CSF) (as neutrophil-related mediators).

**Results:** We have obtained the following **results:** 1) NETs indicators resulted higher in the serum levels of DeDTC patients with respect to HCs; 2) CitH3 levels were elevated in DeDTC and DTC patients (vs HCs and MNG patients); 3) DeDTC patients showed higher levels of MPO-DNA complexes and nucleosomes (vs HCs, MNG patients); and MPO-DNA complexes resulted increased in DeDTC patients (also vs DTC patients); 4) DeDTC patients had higher MPO levels with respect

to HCs; 5) DTC and DeDTC patients showed higher levels of PTX3, MMP-9 and GM-CSF levels (vs HCs); 6) patients with metastatic disease at diagnosis had higher levels of dsDNA, nucleosomes and MPO-DNA complexes with respect to non-metastatic patients.

**Conclusion:** Our findings suggested a relation of NETs to the malignancy and severity of TC. Moreover, the levels of neutrophil-related mediators were elevated in TC compared to MNG and HCs. These results support the involvement of the neutrophilic inflammation in TC.

### Poster 0225

*Thyroid Cancer, Translational, Poster*

#### **Role of cGAS-STING pathway in anaplastic thyroid cancer progression**

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**Objective:** Anaplastic thyroid carcinoma (ATC) is a rare yet highly lethal malignancy with limited therapeutic options. Although ATC is derived from differentiated thyroid cancers, the underlying mechanisms remain elusive. Emerging data support that the innate immunity mediated by cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) DNA sensing pathway could play a role in cancer progression. Our study explored potential roles of this pathway in the progression of differentiated thyroid cancer to dedifferentiated ATC.

**Methods:** We developed a tamoxifen (TAM)-inducible mouse model (*Thrb<sup>PV/PV</sup>Pten<sup>thy-/-</sup>Trp53<sup>thy-/-</sup>TPO-Cre<sup>ERT2</sup>* mice; designated as RU3 mice) to monitor the progression of thyroid cancer from the differentiated cancer to ATC. We also induced orthotopic tumors by papillary thyroid cancer (PTC) and ATC cells for analysis. The role of the cGAS-STING pathway in cancer progression was studied by lentiviral transduction, immunohistochemistry, flow cytometry and cell proliferation assays.

**Results:** We found that TAM-induced RU3 mice exhibited decreased survival as compared to those uninduced. Histological analyses of TAM-induced RU3 tumors showed characteristics of ATC, whereas the uninduced exhibited differentiated cancer phenotypes. The protein levels of cGAS, STING and its downstream effector interferon regulatory transcription factor 3 (IRF3) were decreased in TAM-induced RU3 tumors. Flow cytometric analyses showed reduced filtration of CD4<sup>+</sup> and CD8a<sup>+</sup> T cells in ATC tumors. Consistently, orthotopic tumors induced by ATC cells developed tumors faster with markedly increased tumor size than those induced with differentiated thyroid cancer cells. IHC analysis showed reduced cGAS protein levels in ATC cells-induced tumors and virtually lacking infiltration of CD4<sup>+</sup> and CD8a<sup>+</sup> T cells. We also demonstrated exogenously expressed interferon B1 potently suppressed cell proliferation in ATC, indicating that reduced expression of IFNB1 caused by suppression of cGAS-STING could lead to increased ATC tumor growth. These findings indicate that cGAS-STING signaling is attenuated as thyroid cancer progressed from differentiated cancer to ATC, supported by the findings that STING expression was elevated in human PTC and suppressed in human ATC.

**Discussion/Conclusion:** We showed the suppression of cGAS-STING signaling contributing to the progression of ATC via regulation of cell proliferation and immune modulation. The anticancer effect of IFNB1 suggests potential new therapeutic approaches for ATC.

### Poster 0226

*Thyroid Cancer, Translational, Poster*

#### **Novel Approach for Study of Thyroid Carcinogenesis via BRAFV600E Transduction of Patient-Derived Normal Thyroid Organoids**

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BRAF V600E is the predominant genetic mutation implicated in thyroid carcinomas. However, more than 50% patients do not respond to BRAF/MEK inhibition. Furthermore, a comprehensive understanding of the pathways involved in BRAF-driven tumorigenesis has not yet been characterized that would allow for effective alternatives for treatment. Three-dimensional culture systems, also known as organoid models, recapitulate tissue heterogeneity. We hypothesized that patient-derived thyroid organoids can be an effective platform for studying early events in thyroid carcinogenesis. We report a proof-of-concept protocol as a novel approach to model thyroid carcinogenesis through BRAFV600E transduction of patient-derived thyroid organoids.

Three normal thyroid specimens were collected from adult patients undergoing thyroidectomy for papillary thyroid cancer (mean age = 32.3, range 22.9 – 48.2). The surgical specimens underwent mechanical and enzymatic dissociation. We compared the growth of the thyroid organoids in Wnt 3a, Wnt surrogate, and CHIR99021 in addition to other growth factors mentioned in the previous literature. Our results show that the thyroid organoids faithfully express TTF-1 and other related markers of thyroid differentiation. These organoids have been observed to be capable of being passaged at least 4 times and grown in culture for at least 3 months. To induce tumorigenesis, we performed lentiviral transduction of the BRAFV600E mutation. BRAF-induced thyroid organoids show an increased rate of growth and viability compared to control. The hyperproliferation and abnormal morphology in these organoids are suggestive of follicular thyroid neoplasm.

Our platform provides a novel framework to study early events in papillary thyroid carcinogenesis related to BRAF mutation. We will report the single-cell transcriptomic analyses and metabolomic analyses to determine the key metabolic pathways involved in tumorigenesis. Ultimately, we hope to leverage the unique advantages provided by our organoid platform to identify therapeutic targets and perform drug screening, which is critical for discovering novel targets for BRAF inhibition-resistant thyroid cancers.

### Poster 0227

*Thyroid Cancer, Translational, Poster*

#### **Cabozantinib in Primary Human Cell Cultures from Anaplastic Thyroid Carcinoma**

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**Objective:** Anaplastic thyroid cancer (ATC) is a very aggressive tumor with a median survival of about 6 months; therefore its treatment is extremely challenging. In the last years, great progresses

have been obtained thanks to the in-depth knowledge of the pathways involved in the phases of tumour initiation and progression of ATC. In this context, *in vitro* studies permit a good preclinical evaluation of the antineoplastic effect of the drugs.

We aimed to test the antineoplastic effect of the multikinase inhibitor cabozantinib, that acts against tyrosine kinase receptors involved in growth, angiogenesis and metastatic progression of tumour. Cabozantinib was recently approved for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma, not eligible or refractory to radioactive iodine who have progressed during or after prior systemic therapy.

**Methods:** The experiments were conducted in continuous ATC cell lines (8305C and CAL-62 lines), and in primary human ATC cells obtained from surgical thyroidal samples of three females and two males with ATC (55–81 years) with a tumour size range of 6–14 cm, at the moment of first surgical operation.

**Results:** We firstly showed a good antineoplastic effect *in vitro* of cabozantinib in both continuous and primary ATC cells. Indeed, cabozantinib showed a good activity in inhibiting the proliferation of the tumoral cells as well as in increasing their apoptosis.

**Conclusion:** Personalization therapy is the future approach to be used in the treatment of patients, and *in vitro* studies will aid in the application of this new promising approach.

## Friday, November 1, 2024

**Poster 0228***Surgery, Basic, Poster***OCCULT LYMPH NODE MICROMETASTASES AND RELATED FACTORS IN PATIENTS WITH cT1aN0M0 PAPILLARY THYROID CARCINOMA UNDERWENT TOETVA PROCEDURE: FROM GUIDELINES TO CLINICAL PRACTICE***Hien Nguyen<sup>\*1,2</sup>, Hau Nguyen<sup>1,2</sup>, Duong Pham<sup>1</sup>, Tan Nguyen<sup>1</sup>, Quang Le<sup>1,2</sup>, <sup>1</sup>Hanoi Medical University, Vietnam, <sup>2</sup>Hanoi Medical University Hospital, Vietnam*

**Objective:** Aim to assess the incident of central lymph node micrometastases (CLNM) and related factors in patients with cT1aN0M0 papillary thyroid carcinoma (PTC) undergoing transoral endoscopic thyroidectomy vestibular approach (TOETVA).

**Methods:** A cross-sectional study was performed in 680 patients with early stage cT1aN0M0 PTC undergoing transoral endoscopic thyroidectomy vestibular approach in Oncology Center – Hanoi Medical University Hospital, between January 2020 and December 2023. The clinical, pathological characteristics and mid-term results including surgical outcomes and the rate of recurrence were recorded.

**Results:** The mean age was  $36.5 \pm 8.2$  (13–67) years. Females accounted for 96%. The mean tumor size was  $6.3 \pm 1.8$  (2–10)mm. Total thyroidectomy was applied in 54 cases (7.9%), and conservative thyroidectomy accounted for 626 cases (92.1%). The median number of harvested lymph nodes in ipsilateral and bilateral CND groups is 5 (IQR: 3–7) and 7 (IQR: 3–10). The median number of micrometastase nodes was 2 (IQR: 1–3). The rate of occult lymph node metastases was 32.1% and rate of high number CLNM (>5 nodes) was 2.6%. On average, thyroiditis significantly increased the number of harvested lymph nodes by  $7.3 \pm 4.2$  (range: 1–24) ( $p = 0.002$ ). Young age (<29 years old), tumor size >5mm on ultrasound, and location in lower lobe significantly increased the likelihood of occult lymph node micrometastase ( $p < 0.05$ ). Univariate and multivariate logistic regression revealed that big tumor size and young age (<29 years old) were independent risk factor of high number CLNM with  $p < 0.05$ . With median follow-up time was 17 (4–50) months, 4 recurrence cases were recorded with 2 cases in high number CLNM groups (11.1%).

**Conclusion:** CLNM occurs frequently even in early-stage cT1aN0M0 PTC with a rate of 32.1%. Factors like young age, tumor size >5mm, and tumor location in the lower lobe increase the risks of CLNM. 2 patients experienced recurrence in high number CLNM groups, accounting for 11.1%.

**Poster 0229***Surgery, Case Study, Poster***Primary Thyroid Epithelioid Angiosarcoma of Non-Alpine Origin: A Case Report***Emery Boudreau<sup>\*1</sup>, Darcy Kerr<sup>1</sup>, Theodora Pappa<sup>2</sup>, Thierry Alcindor<sup>3</sup>, Meredith Sorensen<sup>1</sup>, <sup>1</sup>Dartmouth Hitchcock Medical Center, USA, <sup>2</sup>Brigham and Women's Hospital, USA, <sup>3</sup>Brigham and Women's, USA*

**Introduction:** Thyroid angiosarcoma (TAS) is a rare, aggressive malignancy that demonstrates endothelial cell differentiation. It accounts for less than 1% of all sarcomas and has a poor prognosis.

TAS is predominantly seen in individuals from Alpine countries of northern Europe accounting for 2-10% of all thyroid malignancies in this population<sup>1</sup>. It more often affects women, is associated with iodine deficiency with resultant goiter, ionizing radiation, polyvinyl chloride and thorium dioxide exposures<sup>2</sup>. Given its rarity, especially in non-Alpine regions, literature regarding the natural progression of TAS and treatment is limited.

**Case Presentation:** A 67-year-old female with history of osteoporosis and seizure disorder was found to have a left-sided thyroid nodule in 2021. Ultrasound demonstrated bilateral thyroid nodules measuring 6.5 x 4 x 3.7 cm on the left, and sub centimeter on the right. Biopsy was recommended but never done. The patient noticed a rapid increase in size over 1-2 months in 2023 and globus sensation and presented to the ED. Biopsy at that time was suspicious for anaplastic thyroid malignancy. Preoperative PET was negative for metastatic disease.

She underwent a total thyroidectomy; a 6cm nodule occupied the left thyroid lobe with rightward tracheal shift and no extrathyroidal extension. Final pathology resulted as epithelioid angiosarcoma with negative margins. An ARID1A nonsense mutation was found on genetic testing. By analogy with other high-grade sarcomas, adjuvant radiotherapy was recommended by a multidisciplinary tumor board for a potential cure of her locally advanced malignancy. The patient ultimately chose to continue with surveillance only, with no evidence of recurrence on most recent imaging.

**Discussion:** TAS is extremely rare, particularly from the non-Alpine region with fewer than 100 cases reported in the literature. Published data on genetic features of TAS is very limited, with no recurrent alterations identified to date. An ARID1A mutation, as detected in this patient, encodes a protein involved in chromatin remodeling and the activation of a variety of downstream genes. ARID1A is altered in 17% of angiosarcoma patients<sup>3</sup>. This report provides new information on the genetic profile of one case of TAS and adds to the limited information regarding TAS in non-Alpine regions.

**Poster 0230***Surgery, Clinical, Poster***Impact of the COVID-19 Pandemic on Thyroid Surgery for Medicare Beneficiaries***Anthony Saxton<sup>\*</sup>, Alberto Monreal, Hadiza Kazaure, Randall Scheri, Duke University, USA*

**Objective:** The COVID-19 pandemic disrupted endocrine surgical care in the United States. Little is known about the resulting national case deficit for Medicare beneficiaries related to thyroid surgery and the financial impact on healthcare providers.

**Methods:** Data were extracted from the Medicare Provider Utilization and Payment Dataset for thyroid surgeries from 2010-22. Reimbursements were adjusted for inflation to 2023 United States dollars. Utilization rates were calculated as annual thyroid surgery cases per 10,000 Medicare beneficiaries. Cochran-Armitage tests evaluated case volume trends from 2010-19. Linear regression models were created from 2010-19 utilization to evaluate expected thyroid case demand from 2020-22, and were compared to actual utilization rates to calculate case deficits.

**Results:** In the ten years preceding the COVID-19 pandemic, national thyroid surgery volume for Medicare beneficiaries decreased gradually from 34,649 cases in 2010 to 28,160 in 2019

( $p < 0.001$ ). The pool of Medicare beneficiaries increased 2.7% annually during that time, leading to an average annual decline in the utilization rate of -4.6% from 7.33 in 2010 to 4.58 in 2019.

During the first year of the COVID-19 pandemic in the United States in 2020, Medicare claims for thyroid surgeries decreased by -18.8% (22,866 cases), with a -20.5% decrease in utilization rate to 3.64. In the subsequent two years, case volumes remained stagnant with 22,958 cases in 2022 and a utilization rate of 3.53. Procedures with the largest annual decline from 2019 to 2022 included unilateral lobectomy with contralateral subtotal lobectomy (-15.3%), total thyroidectomy (-9.4%), and thyroidectomy with radial neck dissection (-7.4%).

Between 2020-22, an estimated 7,150 thyroid surgery case deficit was incurred for Medicare beneficiaries, leading to \$5,906,109 in decreased Medicare provider revenues ( $p < 0.001$ ). Case volumes have not yet caught up to expected demand, with 96% of expected cases for Medicare beneficiaries performed in 2022.

**Discussion/Conclusion:** The COVID-19 pandemic had a substantial impact on the provision of thyroid surgery for Medicare beneficiaries, with decreased financial support of endocrine surgery practices in excess of \$5.9 million for the procedures alone. Case volumes have not recovered to expected levels in 2022, which raises concerns about delay in care and disease progression for Medicare beneficiaries with thyroid neoplasia.

### Poster 0231

*Surgery, Clinical, Poster*

#### **The Role of Pre-Operative Vitamin D Levels on Post-Operative Symptomatic Hypocalcemia in Patients with Hyperthyroidism**

Chad Griesbach<sup>\*1</sup>, Jhon Martinez-Paredes<sup>1</sup>, Kristina Nikolova<sup>1</sup>, Ginger Coleman<sup>2</sup>, Sahi Puvvala<sup>3</sup>, Stacey Milan<sup>1,3</sup>, Baylor Scott & White Medical Center, USA, <sup>2</sup>South Texas VA Medical Center, USA, <sup>3</sup>Baylor College of Medicine, USA

**Objective:** We aimed to evaluate the impact of preoperative vitamin D levels on the risk of developing post-surgical symptomatic hypocalcemia in patients with hyperthyroidism who underwent thyroidectomy over the last 5 years at one institution.

**Methods:** A retrospective chart review was performed for patients with diagnosis of hyperthyroidism who underwent total thyroidectomy between 2018 to 2023. A total of 104 patients met the inclusion criteria: 74 were diagnosed with Graves' disease (GD) and 30 had toxic multinodular goiter (TMG). Patients undergoing parathyroidectomy were excluded. Clinical variables included preoperative laboratory results, intraoperative findings, and postoperative symptoms. We conducted descriptive statistics, Pearson correlation analysis, and a logistic regression model.

**Results:** The mean age was 46 ( $\pm 17$ ) years, mean BMI 29.9 ( $\pm 7.3$ ), and female gender comprised 89% of the sample. Almost two-thirds of patients (60.5%) presented with low preoperative vitamin D levels ( $< 30$ nmol/L), with a mean level of 28nmol/L. A total of 53 patients (51%) received high-dose vitamin D supplementation before surgery. Postoperative hypocalcemia was diagnosed in 13 patients (12.5%). A higher BMI correlated with low preoperative vitamin D levels ( $p$ -value $< 0.01$ ). Our logistic regression analysis failed to demonstrate an association between developing postoperative hypocalcemia and clinical variables including low preoperative vitamin D levels, obesity, or preoperative vitamin D supplementation ( $p$ -value $> 0.05$ ). Subgroup analysis within patients with GD and TMG showed similar results ( $p$ -value $> 0.05$ ).

**Discussion/Conclusion:** Post-operative hypocalcemia is a well-recognized occurrence following total thyroidectomy. Several studies have investigated the role of vitamin D deficiency and the risk of

post-operative hypocalcemia, however, only a few have analyzed patients with hyperthyroidism. Graves' patients exhibit elevated bone turnover, which may result in hungry bone physiology and heightened risk of hypocalcemia. Based on our results, we are unable to conclude that patients with hyperthyroidism undergoing total thyroidectomy who have pre-operative vitamin D of 50ng/mL or greater have decreased risk of symptomatic hypocalcemia. However, our study is limited by a small number of patients experiencing post-operative hypocalcemia and by retrospectively available data. Authors still feel that routine vitamin D supplementation is valuable. Further investigation should be considered, including establishing a protocol for routine preoperative vitamin D optimization.

### Poster 0232

*Surgery, Clinical, Poster*

#### **Comparative Efficacy, Safety, and Oncological Outcomes of Percutaneous Thermal and Chemical Ablation Modalities for Recurrent Metastatic Cervical Lymphadenopathy in Thyroid Cancer**

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**Objective:** Thermal and chemical ablation techniques may consolidate recurrent metastatic cervical lymph nodes as alternatives to repeat neck dissection in thyroid cancer patients. This meta-analysis aims to compare the efficacy and safety across modalities.

**Methods:** Five databases were searched for studies on radiofrequency (RFA), microwave (MWA), laser (LA) and ethanol ablation (EA) treating metastatic cervical nodes from thyroid cancer. Outcomes analyzed included treatment response, oncologic control, and complications. Random effects meta-analytical pooling was conducted.

**Results:** 25 studies ( $n=1061$  nodes) examining four ablation methods. Patients showed comparable baseline characteristics and initial lymph node sizes from 0.96-1.28cm. All modalities achieved substantial node volume reduction (88.4%) and disappearance (62.8%), with significant biochemical decline (from 6.01 to 1.13 ng/ml thyroglobulin,  $p=0.18$  between groups). MWA showed the highest volume reduction (99.4%) and disappearance rate (87.6%) versus slower efficacy of RFA (93.0%, 72.1%), LA (77.9%, 62.5%) and EA (81.8%, 58.4%). New malignancy/metastases risks ranged from 0.03%-1.3% without between-group differences ( $p=0.52$ ). Major complications were absent; transient voice changes (0.05%-10.6%) and neck pain (0.0%-5.9%) were the primary issues. However, overall complication rates significantly varied by modality (1.1%-10.6%;  $p=0.003$ ).

**Conclusions:** Thermal and chemical ablation show substantial capacity for metastatic lymph node debulking, offering a potentially less morbid non-surgical alternative to neck re-dissection. Additional prospective data would verify long-term equivalence to revision neck dissection and stratification by concomitant Hashimoto's and genomic mutation. Clarifying optimal patient selection and standardizing prognostic indexing could further enhance utilization.

### Poster 0233

*Surgery, Clinical, Poster*

#### **Implementation of Scarless Robotic Thyroid Surgery in the United States: The Initial 10-year Experience**

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**Objective:** The appeal of innovative and trendy robotic thyroid surgery has not met the success of transitioning into a mainstream

surgical technique in the US over the past 2 decades. Such failure is multifactorial but attributed to a lack of competency training, mentorship, and standardization of technique which are not innate flaws in the technology of the robotic platform or the design of the technique itself. Many surgeons have given up and many providers remain skeptical or unaware of its value.

**Methods:** After a dedicated 6-month of international training with simulations, animal labs, and proctorship, the robotic thyroid technique was implemented in the US at an academic institution through deliberate efforts in preparation, pilot, and transition phases. The indications have expanded gradually to include higher index cases such as metastatic thyroid cancer requiring central and lateral neck lymph node dissections as well as large goiters substernal in nature or measuring up to 10 cm. Safety and oncologic outcomes were the primary objectives. The technique was offered in a non-biased manner depending on the patient's preferences and values.

**Results:** A series of 852 cases (489 partial vs 363 total thyroid & 52 modified radical neck dissection) have been performed from 2015-2023. Average age 38.3 (17-74), BMI 26.2 (15-49), Indications for surgery: Cancer (N=356, 42%) Graves (N=71, 8%), symptomatic or toxic goiter (N=192, 23%), and indeterminate nodule (N=213, 25%). Average lymph node harvest is 7 (2-32) for central and 27 (9-74) for lateral neck dissection. In this cohort, 3 patients had cancer recurrences. Routine thyroid cases were performed as an outpatient. Permanent hypoparathyroidism (N=3, 0.5%). Open conversion (N=4, 0.5%). Seroma needing a needle aspiration (N=6, 0.7%, no routine drains). There was no mortality, postop hematoma, permanent recurrent laryngeal injury, infection, tracheal injuries or esophageal injuries.

**Discussion:** Similar to other novel techniques, robotic thyroid surgery can be safely and impactfully implemented in the US despite its demographic and pathologic diversities. The benefits seem to be beyond cosmesis with improved complication rates, oncologic outcomes, quality of life measures, and faster discharge and recovery, especially after more extensive operations. Long-term oncologic outcomes need further evaluation.

### Poster 0234

*Surgery, Clinical, Poster*

#### Limited Thyroidectomy Achieves Equivalent Survival to Total Thyroidectomy for Localized T1 Medullary Thyroid Cancer

Jessan Jishu\*, Mohammad Hussein, Salmanfaizee Sadakkadulla, Solomon Baah, Yaser Bashumeel, Eman Toraih, Emad Kandil, Tulane University School of Medicine, USA

The optimal surgical approach for localized T1 medullary thyroid cancer remains unclear. Total thyroidectomy is standard, but limited thyroidectomy may minimize morbidity while maintaining oncologic control. This retrospective analysis utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry to identify 2,702 MTC patients including 398 patients with T1N0/1M0 MTC treated with total thyroidectomy or lobectomy/subtotal thyroidectomy from 2010-2019. Cox regression analyses assessed thyroid cancer-specific and overall mortality. The majority (89.7%) underwent total thyroidectomy, while 10.3% had lobectomy/subtotal thyroidectomy. Nodal metastases were present in 29.6%. Over a median follow-up of 8.75 years, no significant difference was observed in cancer-specific mortality (5.7% vs 8.1%,  $p=0.47$ ) or overall mortality (13.2% vs 12.8%,  $p=0.95$ ). On multivariate analysis, undergoing cancer-directed surgery was associated with significantly improved overall survival (HR 0.18,  $p<0.001$ ) and cancer-specific survival (HR 0.17,  $p<0.001$ ) compared to no surgery. However, no significant survival difference was seen between total thyroidectomy and lobectomy/subtotal thyroidectomy for overall

mortality (HR 0.77,  $p=0.60$ ) or cancer-specific mortality (HR 0.44,  $p=0.23$ ). Extent of surgery also did not impact outcomes within subgroups stratified by age, gender, T stage, or nodal status. Delayed surgery >1 month after diagnosis was associated with worse overall survival ( $p=0.012$ ). For localized T1 MTC, lobectomy/subtotal thyroidectomy appears to achieve comparable long-term survival to total thyroidectomy in this population-based analysis. Delayed surgery is associated with worse survival and additional neck dissection showed no benefit for this select group of patients. Selective use of limited thyroidectomy may allow avoidance of morbidity from total thyroidectomy while maintaining oncologic efficacy. A personalized approach weighing potential risks and benefits of lobectomy versus total thyroidectomy is warranted.

### Poster 0235

*Surgery, Clinical,*

#### Evaluation of two different treatment strategies of inferior parathyroid gland during central neck dissection of thyroid cancer: active autotransplantation or preservation in situ

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**Objective:** Postoperative permanent hypoparathyroidism due to dysfunction of the parathyroid glands is the serious complication after total thyroidectomy plus central neck dissection (CND). Whether *in situ* preservation or autotransplantation of inferior parathyroid gland (IPTG) more effective in prevent permanent hypoparathyroidism is unclear. The object of this study was to determine the effect of *in situ* preservation of IPTG using "TBP layer" (layer of thymus-blood vessel-inferior parathyroid gland) concept on the incidence of permanent hypoparathyroidism.

**Methods:** The autotransplantation group included patients with primary papillary thyroid carcinoma who underwent total thyroidectomy with CND routinely autotransplanting IPTG between January 2015 and December 2019. The preservation group included patients who underwent total thyroidectomy with CND using "TBP" layer concept to preserving IPTG between January 2015 and December 2019. Incidence of postoperative permanent hypoparathyroidism and central neck lymph node (CNLN) recurrence in the two groups were compared.

**Results:** There were 308 patients in the autotransplantation group and 626 patients in the preservation group. The rate of IPTG preservation *in situ* was significantly lower in the autotransplantation group compared with the preservation group (21.4% vs. 85.2%,  $P<0.001$ , in the left side; 22.5% vs. 84.6%,  $P<0.001$ , in the right side). Permanent hypoparathyroidism rate was 1.9% (6/308) in the autotransplantation group compared with 0.0% (0/626) in the preservation group ( $P<0.001$ ). CNLN recurrence rate was 0.0% (0/308) versus 0.2% (1/626) respective ( $P=0.482$ ).

**Conclusion:** "TBP layer" concept is an effect method to prevent permanent hypoparathyroidism after total thyroidectomy plus CND and guarantee the completeness of CND.

### Poster 0236

*Surgery, Clinical, Poster*

#### The Effect of Perioperative Education of Neck, Oropharyngeal and Laryngeal Rehabilitation Exercises on Quality of Life in Patients Undergoing Thyroidectomy

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**Objective:** Explore effect of perioperative education of neck, oropharyngeal and laryngeal rehabilitation exercises on swallowing and other aspects of quality of life in patients undergoing thyroidectomy, and evaluate the safety of the rehabilitation exercise program. This study aims to provide effective guidance for perioperative rehabilitation exercise education for patients undergoing thyroidectomy in clinical practice.

**Methods:** This study formulates a neck, oropharyngeal and laryngeal rehabilitation exercises program for patients undergoing thyroidectomy and conducts an open-label, single-center, prospective randomized controlled trial. 334 thyroid surgery patients are randomly divided into the rehabilitation education group (n=165) and the control group (n=169) for interim analysis. Patients in the rehabilitation education group receive neck, oropharyngeal and laryngeal rehabilitation exercises education one day before and after surgery, while patients in the control group are only informed that they can move their neck freely. Follow-up visits conducted at 1 week, 1 month, 3 months and 6 months after surgery. The MDADI and THYCA-QoL completed by both groups during follow-up are used to assess and analyze postoperative swallowing-related quality of life and other aspects of quality of life. Postoperative pain, surgical scar conditions, and postoperative drainage are analyzed to evaluate the safety of the rehabilitation exercise program using the GPS, POSAS and postoperative drainage tube retention time.

**Results:** A total of 327 patients are included in the mid-term analysis. MDADI total score in the rehabilitation education group is higher than that in the control group at 1 month after surgery, with a statistically significant difference between the two groups ( $P < 0.05$ ). The emotional subscale and functional subscale also show consistent results. There is no statistically significant difference in MDADI scores between the two groups at 1 week, 3 months and 6 months after surgery. Additionally, no statistically significant difference is found between the two groups in other scales at all four follow-up time points.

**Conclusion:** Perioperative education of neck, oropharyngeal and laryngeal rehabilitation exercises helps improve daily swallowing-related functions in patients early after thyroid surgery (1 month after surgery), enhancing swallowing-related quality of life, particularly improving emotional and social functions related to swallowing. Meanwhile, the exercise program demonstrates good safety.

### Poster 0237

*Surgery, Clinical,*

**Assessing the Correlation Between 18F-Choline PET/CT and Surgical Outcomes for Parathyroid Adenoma Localization in Primary Hyperparathyroidism Patients with Negative or Inconclusive Conventional Imaging: A Retrospective Study of 70 Cases at a High-Complexity Hospital in Bogotá, Colombia (2023)**

Juan Santivañez\*, *Fundacion santa fe de Bogota, Colombia*

**Introduction:** Primary hyperparathyroidism (PHPT) is characterized by autonomous secretion of parathyroid hormone, leading to hypercalcemia, and hypophosphatemia ranging from mild to severe spectrum, with increased morbidity in bone, renal, cardiovascular, and neuropsychological aspects. The majority of PHPT cases are caused by benign parathyroid tumors, with surgical excision being the definitive and cost-effective curative option. Multiple imaging modalities may be necessary for surgical planning, including neck ultrasound, parathyroid scintigraphy, neck computed tomography, and recently, 18F-choline PET/CT. This study addresses the effectiveness of 18F-Choline PET/CT in locating parathyroid adenomas in patients with primary hyperparathyroidism (PHPT). It

underscores the importance of accurate localization for successful surgical intervention and introduces positron emission tomography as a promising tool in cases where conventional imaging results are inconclusive.

**Methodology:** A retrospective observational study enrolled 70 patients diagnosed with PHPT, underwent surgical intervention, and evaluated using conventional imaging techniques and 18F-Choline PET/CT. We used the data from electronic records sourced from surgery, pathology, radiology, hospital medical records systems, and laboratory results.

**Results:** The 18F-Choline PET/CT exhibited a high accuracy in identifying adenomas, especially in cases involving multiple lesions or parathyroid hyperplasia, where conventional imaging methods reduced short pinpointing of the surgical lesion. The positive correlation observed with surgical outcomes, along with the sustained improvement in postoperative biochemical parameters, underscores the utility of this modality in the comprehensive management of surgical planning, execution, and overall success.

**Conclusion:** The 18F-Choline PET/CT emerges as an invaluable diagnostic tool in the surgical planning of PHPT, significantly improving disease cure rates. Despite the inherent limitations of retrospective studies, the capability of this technique to address diagnostic challenges, optimize surgical planning, and contribute to successful clinical outcomes underscores its potential positive impact on the comprehensive management of PHPT.

### Poster 0238

*Surgery, Clinical, Poster*

**Radiofrequency Ablation of Benign Thyroid Nodules: Risk of Progression to Indeterminate or Malignant Cytology**

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**Introduction:** Radiofrequency (RFA) is a safe and effective treatment strategy for reducing nodule volume and alleviating symptoms of benign thyroid nodules. Limited evidence exists in the potential risk of progression of disease following RFA and predictors for the same.

**Methods:** A single institution prospective cohort study was performed between 2019 and 2023. Patients with Bethesda II cytology who underwent RFA were included. These patients were followed up for a minimum of 12 months. Post-RFA fine needle aspiration (FNA) was performed in all patients. The primary outcome measure was incidence of progression to indeterminate (Bethesda III, IV) or malignant (Bethesda V, VI) categories following RFA.

**Results:** A total of 312 thyroid nodules underwent FNA and were identified as Bethesda II cytology followed by RFA. Post-ablation FNA was performed at a median period of 9.5 months (IQR: 5.1-16.1 months). The cytology analysis revealed that 12 cases (3.84%) progressed from Bethesda II to Bethesda III. The median VRR at 24-, 36-, 48-, and 60-months after RFA was 85.2%, 87.9%, 85.8%, and 88% respectively. There was no significant difference in the VRR at the last follow-up between Bethesda II and III thyroid nodules ( $p=0.07$ ). Due to the small number of post-RFA Bethesda III cytology patients, analysis to identify predictors for progression was not possible.

**Conclusion:** RFA is an effective and safe treatment option for benign thyroid nodules. Rarely, there may be progression to indeterminate or malignant cytology. Further studies with a larger sample size are needed to better characterize this subgroup of patients.

## Poster 0239

WITHDRAWN

technique for thyroid surgeries. It holds the potential for comparable oncological outcomes and superior QOL, cosmetic, and functional outcomes. However, robust evidence supporting this hypothesis is scarce.

**Methods:** We collected data from patients diagnosed with papillary thyroid carcinoma who underwent hemithyroidectomy with central compartment dissection at PUMCH between December 2019 and January 2023. After applying propensity-score matching, a total of 424 cases were included. For oncological outcomes, patients in both groups were prospectively followed through regular outpatient visits. The QOL, functional, and cosmetic outcomes were assessed using a cross-sectional online questionnaire including EORTC-THY34 for QOL, PSAQ for cosmetic outcomes, SIS-6 for swallowing functions, and VHI-10 for voicing functions. We further compared oncological outcomes, QOL, functional, and cosmetic outcomes between these two groups.

**Results:** A total of 274 cases provided validated responses: 141 underwent the GTAE approach, and 134 underwent the CO (conventional open) approach. Patients in the GTAE group were 2 years younger and had a slightly lower body mass index. The operation time was approximately 60 minutes longer in the GTAE group. Costs were higher in the GTAE group, primarily due to extended postoperative hospital stays and recurrent laryngeal nerve monitoring. Notably, there was no difference in complications between the two approaches. No recurrence reported in both groups. Rates of suspicious recurrence in both groups remained low and showed no significant differences (2.55% vs. 1.57%,  $p>0.05$ ). Patients with the GTAE approach reported better body image and less joint pain (EORTC-THY34), better swallowing (SIS-6), and better cosmetic outcomes (PSAQ). Voice outcomes showed no difference between these two approaches (VHI-10).

**Conclusion:** Compared to the CO approach, hemithyroidectomy with central compartment dissection via the GTAE approach maintains comparable oncological outcomes while offering better QOL, cosmetic benefits, and functional outcomes.

## Poster 0241

*Surgery, Clinical, Poster*

**Saving Parathyroids during Trans Oral Endoscopic Thyroidectomy Vestibular Approach – TOETVA**

*Narendra Lohokare\*, Siddhakala Hospital, India*

**Objective:** To study advantage of enhanced vision in TOETVA with Indo Cyanine Green (ICG) angiography to reduce incidence of parathyroid injury.

**Methods:** In our series of 74 patients Parathyroids were identified and confirmed using ICG. ICG angiography helped check the vascular anatomy and perfusion status. Parathyroids were graded from 0 to 2 as per viability & perfusion status.

**Results:** Use of advanced vision of endoscopy & ICG helped in correctly identifying & confirming the parathyroids with more accuracy there by avoiding injury and ultimately hypoparathyroidism. This was statistically significant. Initially ICG Angiography showed vascular anatomy & perfusion status and at a later stage confirmed the perfusion & Viability which helped in deciding the requirement of auto transplantation. Incidence of permanent or transient hypoparathyroidism was very less (< 1%, < 3%) in our study.

**Conclusion:** Parathyroid visualization & confirmation was more reliable with better vision endoscopy and ICG during TOETVA thus reducing injury incidence.

## Poster 0240

*Surgery, Clinical, Poster*

**Gasless Trans-axillary Endoscopic versus Conventional Open Thyroidectomy for Thyroid Cancer patients: a Propensity Score-matched Analysis of Quality of Life, Functions, Cosmetic and Oncological Outcomes**

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**Objective:** Thyroid cancer predominantly affects young females who seek surgical intervention not only for excellent oncological outcomes but also for a high quality of life (QOL) and favorable cosmetic and functional outcomes. The gasless trans-axillary endoscopic (GTAE) approach is a commonly used remote access

**Poster 0242***Surgery, Clinical, Poster***Extent of Thyroidectomy for Solitary Papillary Thyroid Carcinoma Confined in the Isthmus**

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**Objective:** The optimal extent of surgical resection for patients with isthmus-confined PTC remains a topic of debate. The aim of this study is to evaluate the clinical and pathological characteristics, surgical complications, and recurrence rates in relation to the extent of surgical resection in patients diagnosed with isthmus-confined PTC.

**Methods:** A total of 426 patients who underwent thyroidectomy for isthmus lesions at our hospitals from 2013 to 2022 were included in the present study. Exclusion criteria included large tumor size (>4cm), suspected clinically positive lymph nodes, non-PTC, and additional lesions in lobes other than the isthmus. Complication rates, clinicopathologic features, and recurrence rates were compared among the total thyroidectomy, lobectomy, and isthmusectomy groups. To further refine our comparative analysis, we employed propensity score matching (PSM), resulting in two distinct groups for comparison: Thyroidectomy (TT) and Lobectomy (L) group vs. Isthmusectomy (I) group, each comprising 129 patients. This approach was used to reduce heterogeneity in the diverse characteristics of isthmus lesions.

**Results:** Among 426 patients, 93 underwent total thyroidectomy (TT), 36 underwent lobectomy (L), and 297 underwent isthmusectomy (I). In the 258 propensity score-matched patients, there were no differences in tumor size between TT/L group and I group (1.1±0.7cm vs 1.0±0.5cm, p=0.07). The rate of central lymph node metastasis was higher in the TT/L group compared to the I group (48.1% vs. 37.2%, p=0.102). In the TT/L group compared to the I group, the incidence of major complications such as transient/permanent hypocalcemia (14.0%/4.7% vs. 0%/0%, p<0.001) and transient vocal cord palsy (3.1% vs. 0%, p=0.131) was higher. The median follow-up period was 3.01 years, and local recurrence or distant metastasis was not observed.

**Conclusions:** These results suggested that isthmusectomy might be an acceptable procedure in selected patients with isthmus-confined PTC. Further study will be needed to assess the oncologic outcomes with long-term follow-up data.

**Poster 0243***Surgery, Clinical, Poster***Chylous Leak after a Modified Radical Neck Dissection for Thyroid Cancer – A Single Institution Experience**

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**Objective:** A chylous leak after a modified radical neck dissection (mRND) is a rare complication. Our aim was to report on treatment of patients with a chylous leak after a mRND in our tertiary cancer center.

**Methods:** Altogether 372 patients (166 males, 206 females; 13-89 (mean 49) years of age) were treated because of a medullary or differentiated thyroid cancer with a mRND during 20-year period (from 2005 to 2024) at the Institute of Oncology Ljubljana. The

subject of our retrospective study were ten patients (3 men, 7 females; 64-76 years of age) who had a chylous leak after a mRND. A chylothorax occurred in two of ten patients. Surgical procedure in order to cure a chylous leak had to be done in six cases, while a leak resolved after conservative measures in four cases.

**Results:** A mRND was done in 372 patients: at the time of total thyroidectomy in 301 patients and because of a regional recurrence in 71 patients. Altogether 425 (353 unilateral, 36 bilateral) mRNDs was done. A mRNDs was done on the right and left side in 54% and 46%, respectively. Histology revealed a papillary cancer in 80% of patients, medullary cancer in 15% and other entities in 5% of patients. Surgery was performed by eight surgeons. Each of them performed 10-113 mRNDs. A chylous leak occurred in 0-3 (median 1) cases per surgeon. Two surgeons had three cases of chylous leakages. One of them performed 39 and the other 109 mRNDs. Frequency of leakages did not correlate with patients' age, gender or tumor histology. A leakage more often occurred on the left side. A statistical trend for more often chylous leak was found in cases with mRND done because of a cancer recurrence in lymph nodes, as well as in one of our eight surgeons.

**Conclusion:** After a mRND because of medullary or differentiated thyroid cancer a chylous leak occurred in 2.6% of patients and 2.3% of mRNDs. Surgical procedure in order to cure a chylous leak had to be performed in 60% of patients with a chylous leak and in 1.6% of patients after a mRND.

**Poster 0244***Surgery, Clinical, Poster***Hypocalcemia Post Total Thyroidectomy: A Ten-Year, Single Institution Experience with a PTH-Guided Calcium and Calcitriol Supplementation Protocol**

Rockey Dahiya<sup>\*</sup>, Victor Bernet, Ejigayehu Abate, Sarika Rao, Jeffrey Janus, Michael Heckman, Hannah Sledge, John Casler, Ana-Maria Chindris, Mayo Clinic, USA

**Objective:** To determine the effectiveness of a parathyroid hormone (PTH)-guided Calcium (Ca) and calcitriol supplementation protocol in reducing the incidence of hypocalcemia after total thyroidectomy (TT) and establish the optimal cutoff value for 4-hour PTH (4h-PTH) for predicting hypocalcemia.

**Methods:** Single-institution, retrospective chart review of patients who underwent TT between 2008 and 2023. Patients with history of parathyroid disease, previous thyroid and parathyroid surgery and known history of vitamin-D deficiency were excluded. 148 patients operated before and 735 after the protocol implementation were included in the study. Total serum Ca < 8 mg/dl was defined as hypocalcemia. The 4h-PTH was used to stratify patients as low (>30pg/mL), intermediate (30-15 pg/mL) and high (<15pg/mL) risk for hypocalcemia and determine the Ca and calcitriol regimen. Demographic information, pre- and post-operative characteristics, and outcomes were recorded. Fisher's exact test and Wilcoxon rank sum test were used to compare the characteristics between the 2 groups. Multivariate logistic regression model was used to account for confounding variables. Area under curve (AUC) was used to determine optimal 4h-PTH value as predictor of hypocalcemia.

**Results:** Pre-protocol patients had lower BMI compared to protocol group (median 27.5 vs. 28.9 kg/m<sup>2</sup>, p=0.046), otherwise there were no significant differences in the pre-operative and operative characteristics; and in the surgical indication between groups. The incidence of hypocalcemia and hypocalcemia-related hospital readmissions were significantly lower in the protocol vs. pre-protocol group 9.9% vs. 20.9% (p<0.001) and 0.9% vs. 4.7% (p=0.004) respectively. 3% of patients in the low-risk group experienced

hypocalcemia compared to 23% in the high-risk group. A 4h-PTH of 11 pg/mL was associated with 0.763 sensitivity and 0.753 specificity in predicting hypocalcemia (AUC=0.797, 95% CI).

**Discussion/Conclusion:** Hypocalcemia is the most common complication post TT, contributing to prolonged hospital stay, readmissions, increased morbidity and mortality.(1, 2) Serum PTH has been used as predictor for hypocalcemia however there is no general consensus regarding timing of measurement and cutoff value. Broadly accepted guidelines regarding Ca and vitamin-D supplementation protocols are lacking. Hereby we report a PTH-guided Ca and calcitriol supplementation protocol as an effective approach in reducing hypocalcemia events and hypocalcemia-related readmission.

## Poster 0245

*Surgery, Clinical,*

### **Bilateral Superficial cervical plexus block for conduct of thyroidectomy and parathyroidectomy surgeries: A prospective randomised clinical study**

*Ashutosh Chaurasia, Ashish Kannaujia, Rudrashish Haldar\*, SGP GIMS, India*

**Objectives:** Thyroid & parathyroid surgeries are generally performed under general anaesthesia. However, for a selected group of patients, these surgeries can be performed under bilateral superficial cervical plexus. We aimed to determine the feasibility, effectiveness and safety of ultrasound guided bilateral superficial cervical plexus block along with sedation for surgery of thyroid and parathyroid.

**Methods:** 43 adult patients received ultrasound guided bilateral superficial cervical plexus block using 0.5% bupivacaine. Dexmedetomidine was used for sedation to keep the patient comfortable. The efficacy of the block was assessed by pinprick method and surgery was allowed after adequate effect. General anaesthesia with endotracheal tube was administered if block was inadequate after 20 minutes or anytime during surgery if needed. Intraoperative discomfort, postoperative pain, nausea, vomiting, surgeon's and patient satisfaction with the technique were noted.

**Results:** Out of 43 cases, general anaesthesia was required in 2 patients before the incision (failed block) and in 5 cases during surgery due to prolonged duration (1), difficulty in dissection (3) and frequent deglutition (1). 36 cases were successfully conducted under ultrasound guided bilateral superficial cervical plexus block with 6 cases requiring some intervention during surgery while 30 cases requiring none. All 36 successful cases remained communicative and responsive to verbal commands. Postoperative mean VAS score for pain on arrival in PACU was  $1.94 \pm 1.39$  with the maximum score reaching at 6 hr after surgery being  $2.11 \pm 1.01$ . None of the patients required rescue analgesia. Surgeons' satisfaction with operative conditions on 5-point Likert's scale was good (53%), very good (17%) and excellent in 8% cases. There was minimal incidence of other postoperative complications.

**Conclusion:** Bilateral superficial cervical plexus block for thyroid and parathyroid surgeries with sedation is feasible, effective and safe in properly selected group of patients. The block is easy to learn and has minimal complications.

## Poster 0246

*Surgery, Clinical, Poster*

### **NON RECURRENT LARYNGEAL NERVE – A SERIES OF 9 CASES IN OUR TERTIARY CENTER**

*Sunil Unnithan\*, Kerala ENT Research Foundation, India*

Recurrent laryngeal nerve (RLN) is a branch of the vagus, that recurs around the subclavian artery on the right and the arch of aorta

on the left. It innervates all the laryngeal muscles except the cricothyroid. Nonrecurrent laryngeal nerve (NRLN) is a rare entity with a reported incidence of 0.3–0.8% on the right side and 0.004% on the left side. It was first reported by Steadman in 1823. It's intraoperative diagnosis is a challenge and hence we present a series of 9 cases of NRLN in our tertiary center.

Our center has done over 1500 total thyroidectomy cases over last 10 years (2012-2022). Non Recurrent Laryngeal nerve was identified in 9 out of 1500 cases, 0.6% incidence. Of the 9 cases, 8 were females. All the above cases had NRLN on the right with four being Type 2b and three Type 2a (Avisse's types of NRLN). All the above patients underwent doppler study post-op but none had any vascular anomaly. All were intraoperative diagnoses and had uneventful post operative period.

## Poster 0247

*Surgery, Clinical, Poster*

### **Enhanced Parathyroid Identification in Endoscopic Thyroidectomy: A Comparative Analysis of AI Models Across Different Surgical Approaches**

*Chenyi Wang<sup>\*1,2</sup>, Jian Cao<sup>1</sup>, Xiaodong Yang<sup>1</sup>, Kewei Jiang<sup>1</sup>, Shan Wang<sup>1</sup>, <sup>1</sup>Peking University People's hospital, China, <sup>2</sup>Stanford University, USA*

**Objective:** The objective of this study is to develop and validate an artificial intelligence (AI) model that enables the real-time identification of parathyroid glands during endoscopic thyroidectomy, aiming to reduce surgical complications associated with parathyroid gland damage.

**Methods:** Our team analyzed approximately 14,000 images of parathyroid glands, derived from 120 endoscopic thyroidectomy videos that utilized oral, breast, and axillary approaches. These images were annotated by a junior endocrine surgeon and further reviewed and filtered by two senior surgeons to ensure precise identification. The images, sourced from eight different hospitals, contribute to the dataset's diversity and representativeness. An independent validation cohort was also included, consisting of 15 full-length videos (five from each approach). AI algorithms such as YOLO V3, Faster R-CNN, and SOLQ were evaluated, with the best-performing model, based on a transformer architecture, selected for detailed analysis. This architecture was particularly noted for its ability to mitigate recognition challenges posed by occlusion and blood contamination during surgeries.

**Results:** The optimized AI model achieved an Average Precision (AP) of 0.423 (IoU threshold range 0.50:0.95), an AP of 0.949 for IoU of 0.50, and an Average Recall (AR) of 0.473 for IoU range 0.50:0.95. It operated at a frame rate of xxx FPS on an NVIDIA TITAN RTX GPU using FP32 precision, demonstrating its practicality for real-time application in surgical environments.

**Conclusions:** The AI model significantly enhances the intraoperative visibility of parathyroid glands during endoscopic thyroidectomies, thus minimizing the risk of unintended gland damage—a frequent complication in thyroid surgeries. Its real-time functionality supports immediate surgical decision-making, thereby improving surgical safety and outcomes. Moreover, the model serves as a valuable educational tool for residents, enhancing their skills in recognizing parathyroid glands. The incorporation of this advanced AI technology into surgical procedures marks a novel step towards enhancing the accuracy and safety of thyroid surgeries.

**Poster 0248***Thyroid Cancer, Basic, Poster***Identification and Validation of a Necroptosis-related Prognostic Signature in Thyroid Cancer via Single-Cell Sequencing**Chenyi Wang<sup>\*1,2</sup>, Kewei Jiang<sup>3</sup>, Shan Wang<sup>3</sup>, <sup>1</sup>Peking University People's Hospital Peking University People's Hospital, China, <sup>2</sup>Stanford University, USA, <sup>3</sup>Peking University People's Hospital, China

**Objective:** To identify and validate a prognostic signature based on necroptosis-related genes in thyroid cancer using single-cell sequencing and comprehensive genomic data analysis.

**Methods:** Thyroid cancer transcriptome and clinical data were obtained from UCSC Xena, including FPKM expression profiles, count data matrices, CNV data, and survival information for 496 tumor and 55 normal tissues. Data were preprocessed with log2 normalization and annotated using UCSC Xena's gene symbol annotations. Additional insights were gained from single-cell RNA sequencing data set GSE184362 available on GEO, which included samples from primary tumors, adjacent normal tissues, metastatic lymph nodes, and subcutaneous metastases from 11 patients. Key genes identified from these analyses were further validated using quantitative PCR and immunohistochemistry in 40 independent patient cohort.

**Results\*\*:** This analysis identified six necroptosis-related genes (AXL, TNFRSF1B, TLR3, BCL2, CD40, SPATA2) that correlate significantly with survival outcomes in thyroid cancer. Moreover, an interaction between lncRNA00667 and miR19a was found to regulate SPATA2 expression, impacting the TNF- $\alpha$  signaling pathway.

**Discussion/Conclusion:** The necroptosis-related genes validated in this study contribute to a novel prognostic signature in thyroid cancer, enhancing our understanding of its pathophysiology and providing potential new targets for therapy. The elucidation of the lncRNA00667/miR19a/SPATA2 axis introduces a new layer of regulatory complexity, suggesting novel avenues for targeted therapeutic interventions.

**Poster 0249***Surgery, Clinical, Poster***Uncontrolled Hyperthyroidism During Total Thyroidectomy: A Systematic Review and Meta-analysis**Eddy Lincango<sup>\*1</sup>, Luis Figueroa<sup>2</sup>, Cristina Arias<sup>3</sup>, Domenica Herrera Hernandez<sup>4</sup>, Emily Rivadeneira<sup>5</sup>, Francisco Rivadeneira Proano<sup>5</sup>, Pedro Torres<sup>5</sup>, Domenica Brito<sup>5</sup>, Bryan Vallejo<sup>6</sup>, Luis Serrano<sup>1</sup>, Adela Casas-Melley<sup>1</sup>, Dustin Huynh<sup>1</sup>, Julie Sosa<sup>7</sup>, Benzon Dy<sup>8</sup>, Minerva Romero<sup>9</sup>, Sophie Dream<sup>10</sup>, Carmen Solorzano<sup>11</sup>, Juan Brito<sup>6</sup>, <sup>1</sup>Department of Surgery, University of Central Florida/HCA Healthcare, USA, <sup>2</sup>CaTaLiNA Research: Cancer de tiroides en Latinoamerica, Ecuador, <sup>3</sup>Medical school, Universidad del Azuay, Ecuador, <sup>4</sup>Medical school, Universidad Católica del Ecuador, Ecuador, <sup>5</sup>Medical school, Universidad Central del Ecuador, Ecuador, <sup>6</sup>Knowledge and Evaluation Research Unit, Mayo Clinic, USA, <sup>7</sup>Department of Surgery, University of California San Francisco (UCSF), USA, <sup>8</sup>Department of Surgery, Mayo Clinic, USA, <sup>9</sup>Department of Surgery, Weill Cornell Medicine New York Presbyterian Brooklyn Methodist Hospital, USA, <sup>10</sup>Surgical Oncology, Department of Surgery, Medical College of Wisconsin, USA, <sup>11</sup>Department of Surgery, Vanderbilt University Medical Center, USA

**Objective:** The ATA and AAES guidelines recommend achieving euthyroid status in hyperthyroid patients before thyroidectomy to

reduce the risk of complications. They are primarily based on the historical evidence that surgical manipulation could potentially precipitate an increased metabolism. This study assessed the perioperative outcomes of hyperthyroid patients who were euthyroid compared to those who were not before thyroidectomy.

**Methods:** Medline, Embase, Scopus, and Cochrane were searched from inception to July 2023 to identify experimental and observational studies focusing on the impact of incompletely treated hyperthyroidism during total thyroidectomy. Any medical therapy before surgery, but radioiodine, was included. We excluded patients who had previous thyroid surgery. Incompletely treated hyperthyroidism was defined as elevated free T3 or T4 immediately before surgery. Random-effects model to consolidate dichotomous variables with odds ratios (OR) and continuous variables with mean differences (MD), along with their 95% confidence intervals (95%CI), were performed. The risk of bias was assessed using the Newcastle Ottawa Scale.

**Results:** We included eight retrospective cohort studies involving 1,336 patients, of whom 33.6% were incompletely treated for their hyperthyroidism at the time of thyroidectomy. Most of these uncontrolled hyperthyroid patients were female (65%) with an average age of  $38.73 \pm 2.8$ . Graves' Disease was the predominant etiology (96%). The mean preoperative TSH was  $0.28 \pm 0.1$  mIU/L, FT4 was  $3.33 \pm 0.64$  ng/dL, and FT3 was  $67.65 \pm 22.41$  pg/mL

There was one case of thyroid storm after surgery but no mortalities. No significant differences emerged in any postoperative complications including, temporary hypocalcemia (OR:0.50, 95% CI:0.20 - 1.29, I2: 42.7%, n=521), permanent hypocalcemia (OR:0.46, 95%CI:0.11 - 1.96, I2: 0.0%, n=727), temporary hoarseness (OR: 1.46, 95%CI: 0.59 - 3.64, I2:0.0%, n=541) permanent hoarseness (OR:0.74, 95%CI: 0.13-4.34, I2:0.0%, n=727), hematoma risks (OR:0.27, 95%CI: 0.06-1.28, I2:0.0%, n=541), length of stay (MD:-0.0, 95%CI: -0.2-0.2, n=379), and operative time (MD: -5.6, 95%CI:-15.4 - 4.3, n=674). The risk of bias was moderate in six studies and high in two.

**Conclusions:** While achieving a euthyroid state is the ideal goal, current low-to-moderate quality evidence suggests that total thyroidectomy does not result in significant harm when performed on actively hyperthyroid patients. However, clinicians should still carefully weigh the risks and benefits on a case-by-case basis, considering the patient's overall health.

**Poster 0250***Thyroid Cancer, Clinical, Poster***Quality of Life in Patients with Differentiated Thyroid Cancer Undergoing Total Thyroidectomy in Ecuador**Eddy Lincango<sup>\*</sup>, Martin Lescano Ruiz, Wladimir Lescano Silva, Ana Ortiz Burbano, Juan Iglesias, Jorge Salazar, CaTaLiNA Research: Cancer de tiroides en Latinoamerica, Ecuador

**Objective:** Thyroid cancer arises from the uncontrolled growth of neoplastic cells in the thyroid gland. While the five-year survival rate stands at 98%, overdiagnosis has resulted in a rise in its incidence, leading to an increase in surgical procedures that negatively affect the quality of life of patients with this relatively non-lethal cancer. This aspect remains underexplored in Latin America. Therefore, we aimed to assess the health-related quality of life in patients with differentiated thyroid cancer undergoing total thyroidectomy at Ecuador's largest referral hospital.

**Methods:** A cross-sectional study was conducted from 2021 to 2022, utilizing the EUROQOL 5-D (EQ-5D) scale and health-adjusted life years (HALYs). The surveys were performed during the one-year follow-up period. Patients with differentiated thyroid

cancer who underwent total thyroidectomy, with or without radioiodine therapy, were included. Those who were hypothyroid, hyperthyroid, or experienced permanent hypocalcemia were excluded. EQ-5D and HALYs were categorized based on the presence of no problems, mild, moderate and severe health problems, and low, moderate and high disease burden, respectively.

**Results:** A total of 500 patients were enrolled (95% female, mean age 45.7 years). Among them, 53% had T1a or T1b tumors, and 52% were overdiagnosed. 82% had stage I and II. Central neck dissection was performed in 63% of cases, and 17% underwent lateral neck dissection. Only 10% had distant metastasis at diagnosis. One-third of the patients reported at least mild health problems. No severe health problems were found. The overall mean EQ-5D score was 0.93. HALYs analysis revealed a high disease burden in 26% of cases, with an average of 3.34 years lost. Stage, tumor size, and lymph node dissection significantly impacted quality of life, while stage and lymph node dissection affected HALYs. No significant associations were found with sociodemographic characteristics.

**Conclusion:** One-third of the Ecuadorian population undergoing total thyroidectomy for differentiated thyroid cancer experienced mild to moderate health problems and a high disease burden. Hence, strategies to reduce overdiagnosis and surgical complications warrant evaluation. Given Ecuador's high incidence of thyroid cancer within Latin America, these findings may be relevant for neighboring countries as well.

#### Poster 0251

*Surgery, Clinical, Poster*

##### **Pectoral Nerve II Block after Robot-Assisted Transaxillary Thyroidectomy: A Prospective, Randomized Controlled Trial**

JA SUNG BAE\*, Kwangsoon Kim, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of

**Objective:** Effective pain management with minimal opioid use is crucial in postoperative care, especially for surgeries like robot-assisted transaxillary thyroidectomy (RATT), which pose unique challenges in managing surgical flap-related pain. Regional analgesic techniques, such as the pectoral nerve II (PECS II) block, have shown promise in addressing these challenges, potentially improving patient outcomes and recovery quality.

**Methods:** In a prospective, randomized controlled trial at a tertiary medical center known for its expertise in RATT, 90 patients aged 19–60 years scheduled for elective RATT were initially considered. After excluding 7 patients for medical conditions or high body mass index, 83 participants were randomized into two groups: 42 in the PECS II block group and 41 in the non-block group. The primary outcome measured was postoperative pain intensity, with secondary outcomes including opioid consumption and quality of recovery, assessed via post-surgical Visual Analog Scale pain scores at specified intervals and the Korean version of the Quality of Recovery-15 (QoR-15K) questionnaire administered at discharge.

**Results:** The block group experienced significantly lower postoperative pain scores at 1, 4, and 24 hours after surgery compared to the non-block group. Additionally, the block group had reduced opioid requirements, particularly noted in the Post-Anesthesia Care Unit. The QoR-15K questionnaire highlighted improved pain management outcomes in the block group, though other aspects of recovery, such as physical comfort and emotional status, were comparable between both groups.

**Conclusions:** The PECS II block significantly enhances the recovery experience for patients undergoing RATT by effectively managing postoperative pain and reducing opioid requirements. This analgesic technique represents a valuable addition to postoperative

pain management strategies for RATT surgeries, aligning with current healthcare priorities to minimize opioid use and mitigate associated risks.

#### Poster 0252

*Thyroid Cancer, Clinical, Poster*

##### **Redefining T3b (Strap Muscle Invasion): Tumor Size as a Key Factor in Differentiated Thyroid Carcinoma Prognosis**

JA SUNG BAE\*, Joonseon Park, The Catholic University of Korea, Seoul St. Mary's Hospital, Republic of Korea

**Objective:** The present study aimed to clarify the impact of T3b (tumor invasion to strap muscles) differs according to the tumor size in DTC by analyzing prognosis including disease-specific survival (DSS), disease-free survival (DFS), overall survival (OS).

**Methods:** Patients with T1, T2, T3a, and T3b categories in pathologic reports were included according to the 8th edition of the AJCC/UICC TNM staging system. 6,282 patients with PTC who underwent thyroid surgery at Seoul St. Mary's Hospital from September 2000 to December 2017 were retrospectively reviewed. T3b was stratified into three subcategories: T3b-1 ( $\leq 2$ cm), T3b-2 (2–4 cm), and T3b-3 ( $> 4$ cm), using the same criteria as for T1, T2, and T3a. We compared DSS, DFS, OS across all T subcategories and introduced a modified T category that reclassifies T3b-1 into T1'. Predictive performance was evaluated using Harrell's concordance index (c-index) and time-dependent Receiver Operating Characteristic (ROC) curves. The primary endpoint was comparison of DSS among the T subcategories, and the secondary endpoint was the comparison of predictive performance of DSS between classic and modified T categories.

**Results:** T3b-1 ( $\leq 2$ cm) showed no significant difference in mortality compared to T1 and all survival curves (DSS, DFS, and OS) were ranked in order, T1, T3b-1, T2, T3a, T3b-2, and T3b-3. Both c-index and the area under the time-dependent ROC curve demonstrated superior performance in the modified T category compared to the classic T category (0.8961 vs. 0.8959 and 0.8573 vs. 0.8518, respectively).

**Conclusion:** This study elucidates that the influence of T3b on Disease-Specific Survival (DSS) is contingent on tumor size, a determinant in the AJCC/UICC TNM staging system. Tumors measuring 2cm or smaller within the T3b category may warrant downstaging, and the adoption of a modified T category could enhance prognostic staging accuracy over the existing T category.

#### Poster 0253

*Thyroid Nodules and Goiter, Case Study, Poster*

##### **Resolution of Sleep Apnea After Radiofrequency Ablation of Goiter: A Case Report**

Kamran Ali<sup>1,2</sup>, Daniel Ma<sup>\*2</sup>, Lindsay McCullough<sup>2,3</sup>, James Herdegen<sup>2,3</sup>, Sean Wrenn<sup>1,2</sup>, <sup>1</sup>Rush University Medical Center, Department of Surgery, USA, <sup>2</sup>Rush Medical College of Rush University, USA, <sup>3</sup>Rush University Medical Center, Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, USA

**Introduction:** Obstructive sleep apnea (OSA) and nontoxic multinodular goiter are common clinical issues that often coexist. Treatments of both conditions have evolved over time, but continuous positive airway pressure (CPAP), oral appliances, or surgical therapy are often needed. Radiofrequency ablation (RFA) of the soft palate and base of tongue has been applied as an alternative therapy for

mild to moderate cases of OSA. Thyroid RFA is an increasingly utilized non-operative intervention for thyroid nodules and goiter, but to date has no established therapeutic benefit for OSA.

**Case Description:** A 59 year old female with known history of multinodular goiter and moderate OSA was referred to our endocrine surgery clinic. The goiter was found to have mediastinal extension, documented longitudinal growth of dominant nodule, cosmetic deformity of neck, and compression symptoms. The patient underwent thyroid RFA as nonoperative treatment for her goiter (maximum wattage 60 W, 22:46 total ablation time). Within a month of her procedure, she also reported a significant subjective reduction in apneic events and then underwent a formal home sleep study demonstrating an apnea-hypopnea index change from 15.8/hr at diagnosis to 2.9/hr currently, signifying resolution of her OSA. Her treated nodule had 92% volume reduction on 18 month follow up visit.

**Discussion:** To our knowledge, this is the first reported case of OSA cured in a patient undergoing RFA for goiter. OSA has complex systemic and anatomic risk factors. In particular, goiter-associated sleep apnea remains inadequately described in the literature and warrants further investigations on prevalence and management. Large nodules can cause collapse of the upper airway during sleep, especially when there is substernal involvement. Thyroidectomy remains the most definitive treatment for goiter, and some studies suggest secondary efficacy in treating OSA. RFA is now established as a first-line option for symptomatic thyroid nodules but prior to this case had no described benefit to OSA symptoms. This report illustrates that thyroid RFA could be offered to patients as both an effective nonsurgical option for goiter (to treat nodules) as well as a potential cure for their OSA to free them from nightly CPAP usage.

#### Poster 0254

*Thyroid Nodules and Goiter, Case Study, Poster*

##### **Follicular Epithelial Dysplasia with RET/PTC1 Rearrangement in Hashimoto's Thyroiditis**

*Kristina Kuklova\*, Tarunya Vedere, Faripour Forouhar, Giao Phan, UConn Health, USA*

**Introduction:** A 61-year-old woman was found to have a hypermetabolic left thyroid nodule after undergoing PET scan for melanoma which was otherwise negative. She had no history of head/neck radiation and was clinically and biochemically euthyroid. Neck ultrasound showed heterogeneous echostucture with a 1.4 cm isoechoic solid left thyroid nodule with multiple punctate echogenic foci.

**Description of Case:** FNA biopsy of the thyroid nodule showed atypia of undetermined significance (Bethesda Category III), marked by follicular cells with nuclear enlargement, nuclear membrane irregularity, and chromatin clearing. Molecular profiling with ThyGeNEXT demonstrated RET/PTC1 (CCDC6-RET\_1) translocation which estimated >95% malignancy risk. After a discussion of surgical options, the patient chose hemithyroidectomy. Final pathology showed Hashimoto's thyroiditis (HT) with multifocal follicular epithelial dysplasia, with the largest measuring 1.5 mm, intermixed with HT inflammatory changes.

**Discussion:** HT (chronic lymphocytic thyroiditis) is the most common autoimmune thyroid disease and cause of hypothyroidism. Papillary thyroid carcinoma (PTC) occurs not uncommonly in HT, although controversies exist on whether the association is causal vs. coincidental. Follicular epithelial dysplasia (FED), first termed by Chui et al. in 2013, describes a premalignant lesion with HT-related atypia consisting of microscopic foci exhibiting cytological and architectural atypia, but without invasive growth nor papillae formation. RET/PTC rearrangements are common mutations found in PTC and assumed to be definitive markers for PTC. This axiom has been challenged by several studies showing that RET/PTC

rearrangements can be detected in some benign adenomas and in HT. These studies suggest that RET/PTC rearrangements might not be sufficient for cancerous transformation. In our patient, the presence of the RET/PTC1 translocation in the setting of FED and HT suggests that RET/PTC1 was an indicator of the precancerous transformation process before developing into a true carcinoma. In the era of molecular profiling of indeterminate nodules, this premalignant possibility should be discussed with patients as it might affect the type of operation they pursue. Irrespective of the nature of this condition, a conservative lobe-sparing treatment was justified by the size of the lesion, and the patient will undergo active surveillance. Further studies are necessary to understand the malignant potential of FED.

#### Poster 0255

*Thyroid Nodules and Goiter, Case Study, Poster*

##### **Thyroid Nodule Hematoma Following Fine Needle Aspiration in a Thrombocytopenic Patient Causing Respiratory Distress and Thyrotoxicosis: A Cautionary Tale**

*Soumya Kurnool\*, Jessica Hansen, Niharika Vennelaganti, Charles Choe, Karen McCowen, University of California, San Diego, USA*

**Introduction:** Fine needle aspiration (FNA) of thyroid nodules is well-tolerated but carries risk of hematoma, particularly for those prone to bleeding, as demonstrated here.

**Case Description:** A 64-year-old woman with transfusion-dependent hypoplastic myelodysplastic syndrome underwent evaluation for a left 1.4cm solid hypoechoic TR-5 nodule. Despite a platelet transfusion hours earlier for platelet count 13,000/mm<sup>3</sup>, 2 FNA passes resulted in a small hematoma. Neck pressure was applied, however 2 days later, she developed dysphagia, neck swelling and fever. Computed-tomography scan showed rightward tracheal deviation and compression due to a 4.6cm left thyroid hematoma. The patient was intubated for respiratory distress. She was managed non-surgically due to bleeding risk and received dexamethasone 8 mg 3 times daily for 48 hours followed by a taper. She also received tranexamic acid and platelet transfusions to maintain platelets above 50,000/mm<sup>3</sup>. Thyroiditis from hematoma trauma led to TSH 0.09 uIU/mL and free T4 >7.77 ng/dL 3 days after FNA. She was extubated after two days with improving dysphagia and was asymptomatic within a week. One month later, after transient hypothyroidism, she was euthyroid. Nodule cytology was follicular lesion of undetermined significance. No further thyroid biopsy has been attempted.

**Conclusion:** Massive hematoma post thyroid FNA is rare, with few case reports in those with end-stage renal disease or anticoagulation who experienced respiratory compromise and required surgical evacuation. Hematomas are usually due to venous extravasation from intranodular thin-walled vessels or arterial-venous shunts, though rarely hemodynamically significant bleeding could be from thyroid artery injury. There are no clear guidelines of minimum platelet counts prior to thyroid FNA. Interventional Radiology guidelines suggest maintaining platelets above 20,000/mm<sup>3</sup> for low bleeding risk procedures such as thyroid FNA and 50,000/mm<sup>3</sup> for higher bleeding risk procedures. Despite a same-day platelet transfusion, this patient's thrombocytopenia significantly increased bleeding risk. This case also involved thyroiditis due to trauma which has not been described in other case reports of hemorrhage after FNA, as those patients underwent prompt surgical evacuation of hematoma or thyroidectomy.

In conclusion, transfusion-dependent patients may warrant a higher minimum platelet count of 50,000/mm<sup>3</sup> prior to thyroid FNA to reduce bleeding risk.

**Poster 0256***Thyroid Nodules and Goiter, Case Study, Poster***Posterior substernal goiter as a rare cause of pleural effusion***Sualeha Khalid\*, Emily Japp, University of Maryland School of Medicine, USA*

Substernal goiters typically follow the path of least resistance and preferentially extend into the anterior mediastinum; only 10-15% extend into the posterior mediastinum. We present a rare case of a posterior mediastinal goiter causing pleural effusion.

A 73-year-old female was referred to the emergency department by her pulmonologist after she was found to have recurrent pleural effusion and increased dyspnea. She had a history of multinodular goiter with mediastinal extension and subclinical hyperthyroidism, for which she took methimazole 5 mg daily. Her goiter had been slowly growing since 1990, however she remained asymptomatic for about 30 years. Prior evaluation included radioactive iodine uptake scans showing increased metabolic activity in the right thyroid extending into the chest, and a cold nodule in the left inferior pole with subsequent negative fine needle aspiration. On physical exam, both cervical thyromegaly, and Pemberton's sign were negative. Laboratory evaluation showed low free T4 of 0.66 (0.9-1.7 ng/dL) and normal TSH 1.14 (0.27-4.2 mIU/mL). CT scan revealed substernal extension of a lobulated, partially calcified left lobe of the thyroid measuring 3.5 x 4 cm, and intrathoracic extension of a heterogenous and calcified right lobe measuring 11 x 10 x 14 cm, with distortion of the right hilum, atelectasis of the right lung and large right pleural effusion. Subsequent PET scan confirmed inferior right thyroid gland extending into chest and displacing lung parenchyma however did not demonstrate significantly increased metabolic activity. Thoracentesis removed 1.5 liters of transudative fluid with cytology negative for malignancy. Patient is planned for future surgical resection via thoracotomy with possible sternotomy, and total thyroidectomy, since radioactive iodine would not significantly reduce the volume of substernal goiter.

Differential diagnosis of posterior mediastinal mass is broad and includes conditions such as neurogenic tumors, non-neurogenic tumors like lymphoma and sarcoma, and vascular conditions like aortic aneurysm. Posterior mediastinal goiter can be differentiated from other mediastinal masses with radioactive iodine uptake scan (using I-123 vs pertechnetate) and CT imaging. Substernal goiter is an important clinical entity to be aware of and monitor, as it can progress and impinge on vital organs.

**Poster 0257***Thyroid Nodules and Goiter, Clinical, Poster***Radiofrequency Ablation as the First-Line treatment for Autonomously functioning thyroid nodules: A Latin American Experience**

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**Objective:** This study aims to assess the effectiveness and safety of RFA for AFTNs in different countries across Latin America.

**Methods:** A retrospective, multicenter cohort study was conducted on patients with a single AFTN that was histologically confirmed as benign and treated with a single session of RFA. The study included an analysis of patient demographics, sonographic characteristics of the nodules, thyroid profile assessment at each follow-up visit, evaluation of clinical symptoms to determine the achievement of a euthyroid state and measurement of nodule volume reduction.

**Results:** Our study enrolled 97 patients with a solitary, benign AFTN. The Volume Reduction Percentage consistently increased over the follow-up period, with medians of -49.3%, -74.7%, -80.1%, and -90.5% at 1, 3, 6, and 12 months, respectively. The rate of resolution of hyperthyroidism or TSH normalization levels in the case of pretoxic nodules was 95.9%. Most patients (60.2%) achieved normalization of their TSH levels within one month of follow-up, followed by three months (30.6%). Notably, volume at baseline  $\geq 20$  mL did not affect the achievement of hyperthyroidism resolution. In bivariate analyses, a higher VRP at the 3-month follow-up was associated with the resolution of hyperthyroidism and energy delivered  $\geq 700$  Joules/mL. Only six patients (6.1%) experienced complications.

**Conclusions:** This multicenter study indicates that RFA represents an effective and safe treatment modality for patients with AFTN, irrespective of baseline volume, age, or composition. The success of the intervention may be linked to the VRP and the delivered energy.

**Poster 0258**

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### Poster 0259

*Thyroid Nodules and Goiter, Clinical, Poster*

#### **Comparison of Sedation and Non-Sedation Approaches in Patients Undergoing Radiofrequency Ablation for Thyroid Nodules: A Retrospective Cohort Study**

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**Objective:** In recent years, radiofrequency ablation (RFA) has gained popularity as a minimally invasive treatment modality for symptomatic benign thyroid nodules and select cases of thyroid cancer. The use of conscious sedation during RFA for thyroid nodules is a topic of ongoing debate. However, the necessity of sedation for RFA has been questioned, as some studies have suggested that the procedure can be performed effectively and safely without sedation. Therefore, this retrospective cohort study aims compare the procedural outcomes, patient-reported pain scores, and complications, between patients who underwent RFA with sedation and those who had the procedure without sedation.

**Methods:** A retrospective cohort study was conducted, including patients who underwent RFA for thyroid nodules between January 2019 and December 2023. Inclusion criteria were: (1) age  $\geq$  18 years, (2) presence of a symptomatic benign thyroid nodule or a cytologically indeterminate nodule, and (3) RFA performed as the primary treatment modality. The study population was divided into two groups: sedation group (patients who received sedation during RFA) and non-sedation group (patients who underwent RFA without sedation).

**Results:** A total of 429 patients (336 females, 93 males) with a mean age of  $57.3 \pm 13.8$  years were included in the study. The mean procedural time was significantly shorter in the non-sedation group compared to the sedation group ( $25.3 \pm 6.8$  minutes vs.  $35.7 \pm 9.2$  minutes,  $p < 0.001$ ). The median patient-reported pain score during the procedure was higher in the non-sedation group. However, there was no significant difference in pain scores at 24 hours post-procedure between the two groups ( $p = 0.15$ ). The overall complication rate was 3.0% (13 patients), with no significant difference between the sedation and non-sedation groups (3.4% vs. 2.2%,  $p = 0.56$ ). There were no statistically significant differences in the rates of specific complications between the sedation and non-sedation groups ( $p > 0.05$  for all comparisons).

**Discussion/Conclusion:** Conscious sedation is a valid option for pain tolerance during an RFA procedure and does not increase the risk of complications. Our findings support the safety and feasibility of performing RFA without sedation in patients, potentially optimizing patient experience while maintaining favorable outcomes.

### Poster 0260

*Thyroid Nodules and Goiter, Clinical, Poster*

#### **Polyamine and Methionine Metabolism Gene Expression Analysis in Thyroid Tumors**

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**Objective:** Polyamine levels are elevated in thyroid cancers and highest in poor prognostic subtypes including poorly differentiated and anaplastic thyroid cancers. Methionine, a methyl donor and nutrient important for nucleic acid synthesis, is an essential precursor for polyamine synthesis. The interplay of these metabolic pathways may be a proxy of tumor aggressiveness. There is a lack of data evaluating the interplay of polyamine and methionine metabolism in thyroid cancer and the impact on clinical outcomes. We hypothesized polyamine and methionine metabolism gene expression may be directly correlated with thyroid tumor cytologic, molecular, and clinical risk.

**Methods:** The Afirma Genomic Sequencing Classifier (GSC) whole exome database was analyzed for polyamine and methionine metabolism gene expression from cytologically indeterminate ((B)ethesda III/IV - ITN) molecularly benign (GSC-B) (n=30,259), molecularly suspicious (GSC-S) (n=15,815), and malignant (B V/VI, n=1,621) fine needle biopsy specimens. Additionally, patient samples with Afirma testing from an integrated interventional thyroid practice (n=464) were analyzed to assess the correlation between polyamine and methionine gene expression and histopathologic features including vascular invasion and lymph node metastasis.

**Results:** Among malignant nodules, BVI and *BRAF* V600E-mutant (*BRAF*+) nodules exhibited high expression of genes involved in methionine salvage (*MTAP*), methyl group transfer (*PRMT5*, *NTMT1*) and folate metabolism (*MTHFR*). In contrast, high expression of polyamine catabolism genes (*SMOX*, *OAZ2*, *OAZ1*) and arginase expression (*ARG1*) were associated with a lower likelihood of *BRAF*+ or BVI cytopathology ( $p < 0.001$  for all). High *MTAP* expression was directly associated with a higher likelihood of malignancy relative to ITN GSC-S, independent of *BRAF* status ( $p < 0.001$ ); and was also higher in BV/VI or ITN GSC-S samples lacking mutant *BRAF* expression relative to GSC-B ( $p < 0.001$ ). Additionally, high *MTAP* gene expression was associated with a higher likelihood of vascular/extra-thyroidal invasion or lymph node metastasis ( $p = 0.02$ ).

**Discussion/Conclusions:** Higher expression of methionine salvage pathway genes is associated with greater cytologic risk and clinically aggressive behavior whereas polyamine catabolism gene expression conferred less risk. Future work seeks to leverage these data to further risk stratify those patients with ITN and molecularly suspicious tumors who may be more likely to present with clinically aggressive thyroid cancer.

### Poster 0261

*Thyroid Nodules and Goiter, Clinical, Poster*

#### **External Validation of a Natural Language Processing Enhanced Algorithm to Identify Appropriateness of Thyroid Ultrasound**

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**Objective:** To externally validate a Natural Language Processing (NLP) powered computable phenotyping algorithm to identify the appropriateness of thyroid ultrasound (TUS) using electronic medical records (EMRs) from the University of Florida (UF) Health.

**Methods:** We conducted a retrospective cohort study involving adults who underwent an initial TUS at the University of Florida between 2017 and 2021. We identified 8284 patients with TUS and randomly selected 200 to complete the external validation. Chart review was conducted by human annotators to determine the appropriateness of the TUS orders, categorizing them as appropriate (aTUS) or inappropriate (iTUS) based on predefined criteria.

The rule-based NLP algorithm, developed at Mayo Clinic and focusing solely on visit diagnoses and reasons for the exam sections, was subsequently deployed in our UF-annotated cohort to categorize the appropriateness of the TUS. Performance metrics were calculated, including Sensitivity, Specificity, Positive Predictive Value (PPV), and Accuracy. We conducted a quality assessment of the potentially misclassified iTUS cases by the NLP algorithm.

**Results:** We included 200 patients for the final analysis, mostly females (79%) with a median age of 50 years. Human ground truth assessment identified 192 (96%) aTUS and 8 (4%) iTUS. The most frequent reasons for aTUS were thyroid abnormalities on routine physical exams (80, 41.7%), work-up of thyroid nodules (17, 8.9%), and incidental imaging findings (15, 7.8%). The main reasons for iTUS included globus sensation and thyrotoxicosis, accounting for 50% of iTUS cases. When deployed, the NLP algorithm showed a sensitivity of 91%, specificity of 75%, PPV of 99%, and overall accuracy of 90%. Analyzing potentially misclassified iTUS cases, we found instances where evidence supporting the TUS order was present in the clinical notes but not in visit diagnoses or reason for the exam section.

**Discussion/Conclusion:** External validation of a rule-based NLP algorithm for assessing the appropriateness of TUS orders revealed an overall accuracy of 90%. Potential misclassification of iTUS occurred due to the limited clinical record data input for the NLP algorithm. These findings represent initial steps toward developing models that include clinical notes for TUS appropriateness assessment. Overall, iTUS was infrequent.

## Poster 0262

*Thyroid Nodules and Goiter, Clinical, Poster*

### Systematic Assessment of Thyroid Biopsy Appropriateness In Clinical Practice

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**Objective.** Evaluate the appropriateness of thyroid nodule biopsy in clinical practice

**Methods:** Retrospective evaluation of electronic health records of a random sample of 479 adult patients who underwent thyroid nodule biopsy at a single academic institution between 2017 and 2023. Exclusions included prior thyroid biopsies, hyperthyroidism, pregnancy, or missing thyroid nodule ultrasound features. The appropriateness of biopsy was categorized using an established step-wise framework that includes the following steps. Initially, biopsies were first classified according to ACR-TIRADS recommendations as either (1) likely appropriate or (2) likely inappropriate. Biopsies deemed likely appropriate based on ultrasound assessment may be further categorized as (3) possibly inappropriate if patients have a high Carlson Comorbidity Index, are undergoing chemotherapy, or have end-stage kidney, renal, or heart disease. If these patient factors are present and the nodule does not meet ultrasound-driven biopsy recommendations, biopsies are classified as (4) extremely

inappropriate. Biopsies initially considered likely inappropriate may be re-evaluated as likely appropriate in the presence of additional factors (e.g., patient preference, transplant candidacy).

**Results.** 232 met the inclusion criteria. The majority of patients were female (82%), with a median age of 61 years. Ordering clinicians were predominantly from ENT (30%), primary care (27%), and endocrinology (27%).

Following thyroid biopsy appropriateness assessment using ultrasound criteria by ACR-TIRADS, 83% (193/232) were deemed likely appropriate, while 17% (39/232) were classified as likely inappropriate.

Upon incorporating additional factors, the distribution of appropriateness shifted. Among the 39 likely inappropriate biopsies, 1 was classified as extremely inappropriate due to factors associated with limited life expectancy. Additionally, 16 were reclassified as likely appropriate due to clinical factors, leaving 23/232 as likely inappropriate (10%).

A total of 178/232 (77%) were considered likely appropriate based on ultrasound features and clinical factors, while 13% (30/232) were classified as possibly inappropriate as they were deemed appropriate by ultrasound features but occurred in patients with limited life expectancy.

**Conclusion.** Nearly 8 out of 10 biopsies were deemed likely appropriate after considering both ultrasound and clinical factors. Approximately 1 out of 10 occurred in patients with limited life expectancy. Findings highlight the need to explicitly consider patient and ultrasound factors in decision-making.

## Poster 0263

*Thyroid Nodules and Goiter, Clinical, Poster*

### Distinct Molecular Profiles of Thyroid Nodules in Patients Under 21 Years of Age

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**Introduction:** Thyroid nodules (TN) are rare in children and carry a higher risk of malignancy (~25%) compared to adults (~5-10%). This study aimed to assess molecular differences related to malignancy in TN from patients < and ≥ 21 yrs.

**Methods:** Cytologic and molecular differences were assessed in 177,227 TN samples tested by the Afirma Genomic Sequencing Classifier (GSC). Genome-wide differential gene expression (DGE), mutation profiles, and expression signatures were compared between < and ≥ 21 yrs patients using Fisher's exact and Wilcoxon rank tests.

**Results:** There were 1,583 < 21 yrs patients (median age 18.9 yrs (IQR 17.1-20.0; 80.3% female)) and 175,644 ≥ 21 yrs patients (median age 59.3 yrs (IQR 46.0-69.0; 77.5% female)). Among cytologically indeterminate TN (ITN), 56% of < 21 yrs patients were GSC-(S)uspicious compared to 31% of ≥ 21 yrs (p<0.001). ITN GSC-S in < 21 yrs had more frequent fusions (13.6% vs 5.7%, p<0.001), particularly *ETV6::NTRK3* (5%) and *CCDC6::RET* (2.7%), as well as *ALK* fusions (1%). Within Bethesda V/VI nodules, *RET* and *NTRK3* fusions were enriched in < 21 yrs (19.6% vs 7.9%, p<0.001); predominantly *CCDC6::RET* (13%). *BRAFV600E* was equal among age groups (~50%).

Sequence variants were also enriched in < 21 yrs (44.8% vs 37.0%, p<0.001), notably of *DICER1* (10.0% vs 1.5%, p<0.001) including those associated with poorly differentiated thyroid histology (codons 1709/1705/1813; 7.2% vs 0.7%, p<0.001).

Transcriptionally, < 21 yrs TN expressed higher ERK and MYC activity and cell cycle-related pathways (adjusted  $p < 0.05$ ). DGE identified overexpression of genes associated with cell cycle-related gene sets (e.g. KEGG cell cycle, G2-M). Among the subset of thyroid nodules with *NTRK*, *RET*, or *ALK* fusions, < 21 yrs was associated with higher expression of angiogenesis, epithelial-mesenchymal transition, and cell cycle gene sets (adjusted  $p < 0.05$ ).

**Conclusion:** Thyroid tumors from younger patients are unique by having more than double the prevalence of targetable fusions (*NTRK* and *RET*), high-risk somatic *DICER1* variants, and higher expression of cell cycle-related gene sets. As BRAFness was similar across age groups, the identification of distinct molecular drivers that increase malignancy risk underscores the importance of comprehensive molecular profiling in patients < 21 yrs.

## Poster 0264

*Thyroid Nodules and Goiter, Clinical, Poster*

### Radionuclide Therapy With I-131 In Patients With Autonomously Functioning Thyroid Nodules And Normal FT4 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 hormone (FT4) blood level.

**Methods:** In this study 131 cytological benign AFTNs in 116 pts (100 female and 16 male) with normal FT4 level have been treated with a fixed I-131 doses (370 MBq). Clinical exam, ultrasonography with color Doppler (US), fine needle aspiration biopsy (FNAB), TSH, FT4, FT3, anti-TPO, anti-Tg, anti-TSH receptor and thyroid scan (scintigraphy) have been performed in all pts before and 6 months after I-131 therapy.

**Results:** The median age of the pts was 61 (range 35 - 90) years. AFTNs were located more frequently in the right thyroid lobe (73 nodules) than in the left lobe (58 nodules). In 19 pts a solitary AFTN has been found on ultrasonography and the other 97 patients had AFTNs in multinodular goiter. 15 pts had two AFTNs. On post I-131 therapy thyroid scan in 80 AFTNs complete therapy effect has been observed, but in 51 AFTNs a scintigraphically partial effect has been noted. Statistical analysis showed a significant reduction in the thyroid ( $p = 2.8179E-24$ ) and AFTNs ( $p = 4.0351E-06$ ) volume after I-131 therapy. TSH value significantly increased ( $p = 3.0081E-05$ ) and FT4 value significantly decreased ( $p = 3.1438E-05$ ) after I-131 therapy. FT3 ( $p = 0.3757$ ), anti-TPO ( $p = 0.7615$ ) and anti-Tg ( $p = 0.1412$ ) and anti-TSH receptor ( $p = 0.1182$ ) values did not change significantly.

**Conclusion:** This study shows that radionuclide therapy with I-131 in pts with AFTN and normal FT4 blood level is a very effective modality. The effect of the I-131 therapy on AFTNs can be evaluated with a thyroid scan 6 months after I-131 therapy.

## Poster 0265

*Thyroid Nodules and Goiter, Clinical, Poster*

### Shared decision making for patients with thyroid nodules considering biopsy: a pilot multicenter randomized trial

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**Objective:** Evaluate the feasibility of a multicenter randomized trial and provide a preliminary estimate of the effects of an encounter-shared decision-making (SDM) tool on the management of patients with thyroid nodules.

**Methods:** A pilot trial at the University of Florida, Gainesville, and Mayo Clinic, Rochester, assigned medical encounters of patients with thyroid nodules and their clinicians to either the use of a SDM tool (intervention) or usual care (UC, control). The SDM tool, designed for the encounter, summarizes the situation, displays thyroid cancer risk according to ultrasound findings, and outlines management options' risks and benefits. The primary outcome was study procedure feasibility. Secondary outcomes included the quality of the decision-making process and diagnostic decisions. Outcomes were assessed by patient and clinician surveys, medical record review, and videographic analyses of visits.

**Results:** Study procedures were successfully implemented. We enrolled 90 patients, with 86 analyzed, 43 in each arm (80% women, mean age 57 [16] years) and 17 clinicians. Mean thyroid nodule size was 2.1 cm (1.5).

In the SDM tool group, the average thyroid nodule knowledge correct response rate was 72% vs 65% in the UC group ( $p = 0.215$ ). Thyroid cancer risk perception was accurate for 70% of participants in the SDM group vs 54% in UC ( $p = 0.101$ ). Furthermore, 60% of SDM participants reported reduced worry about thyroid cancer after the visit, compared to 44% in UC ( $p = 0.179$ ).

Patient involvement in decision-making, assessed via video recordings using the OPTION Scale (1-100 scale, higher levels indicating higher patient involvement), was greater in the SDM group (34) than in UC (27) ( $p < 0.001$ ). Choice awareness, indicating discussion of alternative diagnostic options, occurred in 91% of SDM recordings versus 65% of UC ( $p = 0.008$ ).

Immediate biopsy was chosen by 40% of patients in the SDM group, compared to 51% in UC ( $p = 0.386$ ). Patient satisfaction was high, decisional conflict moderate and clinician satisfaction moderate in both groups. Encounter duration averaged 22 minutes, in both groups.

**Conclusion:** Implementation of study procedures for a multicenter randomized trial of the SDM tool was feasible. Preliminary outcomes indicate the tool may positively impact the care of patients with thyroid nodules.

## Poster 0266

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**Poster 0267***Thyroid Nodules and Goiter, Clinical, Poster***A Scoping Review of Patient Quality of Life Following Molecular testing or Surgery for Individuals with Indeterminate Thyroid Nodules***Raisa Chowdhury<sup>\*1</sup>, Khadija Brouillette<sup>1</sup>, Kayle Payne<sup>2</sup>, Veronique-Isabelle Forest<sup>3</sup>, Richard Payne<sup>3</sup>, <sup>1</sup>McGill University Faculty of Medicine and Health Sciences, Canada, <sup>2</sup>McGill University Department of Psychology, Canada, <sup>3</sup>McGill University Department of Otolaryngology-Head and Neck Surgery, Canada*

**Objective:** The objective of this scoping review was to identify and analyze the health-related quality of life (HrQOL) outcomes in patients with indeterminate thyroid nodules (ITNs) who are expected to undergo or have undergone surgery or molecular testing.

**Method:** A comprehensive search was conducted on PubMed, Scopus, PsychINFO, and Embase to identify relevant studies. The search terms included “thyroid neoplasms” or “thyroid nodule” and “molecular testing” or “surgery” and “quality of life.” The included articles were analyzed for their main study objective, study design, participant characteristics, and main results.

**Results:** Eight studies were included in this scoping review. Four evaluated the quality-adjusted life years (QALYs) for patients with ITNs. Three of these studies found that molecular testing slightly improved QALYs compared to surgery, while one study found no difference. Two studies assessed surgical HrQOL outcomes and reported that patients with ITNs who were expected to undergo surgery favored surgical procedures, while those who underwent surgery experienced impaired HrQOL. Two studies evaluated molecular testing in patients with ITNs and found that the final molecular test result significantly impacted HrQOL outcomes. Patients with suspicious molecular test results had worse symptoms of goiter, anxiety, and depression, while those with benign results had preserved quality of life scores.

**Conclusion:** This scoping review highlights the importance of considering HrQOL outcomes in the management of patients with ITNs. Notably, while molecular testing QOL appears comparable to surgery, a notable discrepancy arises when molecular testing yields benign results. Specifically, patients with benign molecular test results exhibit superior QOL compared to those with suspicious

results, potentially suggesting a pivotal role for molecular testing in enhancing patient well-being. Further research is warranted to explore these findings and their implications for shared decision-making in ITN management.

**Poster 0268***Thyroid Nodules and Goiter, Clinical, Poster***Consensus Radiofrequency Ablation Reporting Guidelines for Thyroid Nodules Using a Delphi Approach***Kendyl Carlisle<sup>1</sup>, Rebecca Kowalski<sup>\*1</sup>, Q. Hu<sup>2</sup>, Sophie Dream<sup>3</sup>, Jonathan Russell<sup>4</sup>, Steven Hodak<sup>5</sup>, Yinin Hu<sup>1</sup>, <sup>1</sup>University of Maryland Baltimore, Department of Surgery, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Department of Surgery, USA, <sup>3</sup>Medical College of Wisconsin, Department of Surgery, USA, <sup>4</sup>Johns Hopkins University, Department of Otolaryngology, USA, <sup>5</sup>NYU Langone Health, Department of Medicine, USA*

**Objective:** Radiofrequency ablation (RFA) has become increasingly popular for symptomatic benign, hyperfunctioning, and even small, low-risk malignant thyroid nodules. However, best practice recommendations on data collection and outcomes reporting are lacking. As RFA becomes more popular in thyroid disease, it is important to monitor and report outcomes for quality improvement and research. The objective of this study was to generate consensus guidelines for thyroid RFA data collection for purposes of quality assurance and collaborative research.

**Methods:** We recruited an interdisciplinary panel of experienced RFA practitioners through the North American Society for Interventional Thyroidology. Using a modified Delphi process, experts created and iteratively revised a data collection form encompassing items from the pre, intra, and post-procedural phases. Emphasis was placed on brevity and preference for parameters that are universally accessible to both community and academic-based practitioners. Items with >70% (strongly-agree) or 100% (agree) consensus for inclusion were retained. The Delphi process and the final reporting instrument were built on REDCap.

**Results:** Ten panelists completed five Delphi rounds to produce 36 items for basic RFA reporting. Panelists reported practice volumes between 10-72 RFA cases/year (median:22.5) and participated from 9 institutions. All 10 panelists voted strongly-agree for retention on 68% (n=36) of included items. The final instrument was divided into three forms: 1. Pre-procedure (n= 17 items), 2. Immediate post-procedure (n=8 items), and 3. Follow-up (n=11 items) intended for longitudinal repeated use.

**Conclusions:** Three data collection forms for thyroid RFA were created through an interdisciplinary consensus. Adoption by new and established interventionalists may facilitate collaborative and standardized outcome reporting, clinical trial design, and aid in defining metrics for procedure success and failure.

**Poster 0269***Thyroid Nodules and Goiter, Clinical, Poster***Trends, risk factors and outcomes of the diagnostic work of patients with thyroid nodules***Sanaa Badour<sup>\*1</sup>, Xingke Liu<sup>1</sup>, Kylie Harrall<sup>1</sup>, Yi Guo<sup>1</sup>, Ramzi Salloum<sup>1</sup>, Juan Brito Campana<sup>2</sup>, Dejana Braithwaite<sup>1</sup>, Naykky Singh Ospina<sup>1</sup>, <sup>1</sup>University of Florida, USA, <sup>2</sup>Mayo Clinic, USA*

**Objective:** Evaluate trends and outcomes of the diagnostic workup of patients with thyroid nodules, and assess multi-level factors associated with the diagnostic process.

**Methods:** A retrospective cohort study of adult patients in the OneFlorida+ Data Trust (2015-2021) who underwent incident thyroid ultrasound and were found to have thyroid nodules across 18-month follow-up. We excluded patients with prior thyroid nodules or thyroid cancer. Separate multivariable logistic regression models were used to identify patient and health system factors associated with 1) thyroid biopsy post-ultrasound and 2) thyroid cancer diagnosis post-biopsy. Secondary analyses evaluated trends in the proportion of patients undergoing ultrasound, subsequent biopsy and thyroid cancer diagnosis.

**Results:** We identified 67,238 patients with thyroid nodules on ultrasound. Of these, 14,516 (22%) underwent biopsy and 1,383 (9.5%) had a thyroid cancer diagnosis post-biopsy. The strongest factors associated with biopsy were social vulnerability index (SVI; higher levels indicate more vulnerability) and Charlson Comorbidity Indices (CCI). Increase in SVI at patient and facility levels was associated with decrease in the odds of thyroid biopsy [OR(95%CI): 0.42(0.37-0.49) and 0.32(0.28-0.38), respectively]. Patients with mild, moderate, and severe CCI had increased odds of biopsy post-ultrasound [OR(95% CI): 1.32(1.25, 1.38), 1.56(1.46, 1.67), 1.72(1.61, 1.83), respectively], compared to patients without comorbidities. As for thyroid cancer, there were increased odds of diagnosis post-biopsy among patients with mild, moderate, and severe CCI [OR(95% CI): 7.92(6.58, 9.54), 12.99(10.41, 16.20), 14.90(12.00, 18.50), respectively]. Overall, trends for thyroid ultrasound, subsequent biopsy and cancer diagnosis appear stable during our study period.

**Discussion/Conclusion:** On average, 2 out of 10 patients with thyroid nodules on ultrasound underwent biopsy, and 1 out of 10 were found to have thyroid cancer. Utilization trends of thyroid ultrasound, thyroid biopsy, and thyroid cancer diagnoses have remained consistent throughout the seven-year study period. Both patient-level and healthcare facility-level social vulnerability negatively impacted thyroid biopsy utilization. Furthermore, patients with more comorbidities were significantly more likely to undergo thyroid biopsy and receive thyroid cancer diagnosis, which may seem counterintuitive considering the elevated competing risk of mortality from other factors in comorbid patients with thyroid nodules.

## Poster 0270

*Thyroid Cancer, Clinical, Poster*

### **Medullary Thyroid Cancer: Clinicopathological Profile of a Cross-Sectional Study at a Single Center, 2000–2024, Imbanaco Clinic, Cali – Colombia**

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**Background and Aims:** Medullary thyroid cancer (MTC) is a neuroendocrine tumor originating from the parafollicular or C cells of the thyroid gland, representing 1-2% of all thyroid cancers. This study aimed to describe the clinical, histopathological, and immunohistochemical profiles of MTC patients treated at the Imbanaco Clinic, Cali, Colombia, from 2000 to 2024.

**Method: Study Design:** Descriptive cross-sectional study.

**Study Population:** Adult male and female patients over 18 years old who underwent total thyroidectomy after an MTC diagnosis. Sampling: Non-probabilistic by convenience, based on consecutive clinical records.

**Statistical Analysis:** Data were processed using IBM SPSS 29.0. Levene's test assessed variance homogeneity, and Shapiro-

Wilk confirmed normality. T-tests (Student's or Welch's) were used for continuous variables, while Fisher's exact or Chi-square tests were used for categorical variables. Confidence intervals were set at 95%, and statistical significance was established at  $P < 0.05$ .

**Results:** 21 patients included, 18 (85.7%) were female and 3 (14.3%) were male. 85.7% of the patients were aged 45 years or older. 23.8% of patients had tumors between 1-2 cm, while 76.2% had tumors larger than 2 cm. The mean tumor size was 3.2 cm (SD 1.58). The TNM classification revealed that the most frequently observed stages among the patients were 28.6% at T2N0aM0, 14.3% at T1bN0aM0, 9.5% at T1bN1aM0, and 9.5% at T4bN1bM1. Metastasis was found in 47.6% of patients, primarily involving the cervical lymph nodes (52.4%). The mean Ki67 proliferation index was 6.29% (SD 4.99).

Histopathological findings showed amyloid production, calcifications, nodular cell proliferation, and lymphocytic thyroiditis. Immunohistochemical markers, including thyroglobulin (52.4%), calcitonin (95%), chromogranin (90.5%), and synaptophysin (66.7%), were positive in significant portions of patients. The T-student analysis revealed a significant difference in age between patients with tumors larger than 2 cm and those with tumors between 1-2 cm (mean difference: -15.2 years,  $P < 0.05$ ). No significant difference was observed in the Ki67 proliferation index. The overall mortality rate was 19%, while the survival rate was 71.4%.

**Conclusions:** This study provides valuable insights into the clinicopathological and immunohistochemical profiles of MTC patients. The findings underscore the relationship between larger tumor size and older age

## Poster 0271

*Thyroid Cancer, Clinical, Poster*

### **Outcomes in Thyroid Cancer Patients According to 7th and 8th Edition AJCC/TNM Classifications: A Retrospective Cohort Study in a Single Center. Imbanaco clinic. Cali, Colombia**

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**Objective:** The 8th edition of the AJCC/TNM system (TNM-8) introduces significant changes compared to the 7th edition (TNM-7), which has been in global use for approximately 10 years. The aim of this study was to evaluate the patterns of recurrence and remission using the 7th and 8th editions of the AJCC/TNM system in a cohort of thyroid cancer patients in Colombia, from January 2016 to December 31, 2021.

**Materials and Methods:** This observational, analytical, retrospective, single-center study included thyroid cancer patients aged over 18 years at a high-complexity institution in Cali, Colombia. The period of study was from January 2016 to December 31, 2021. The outcomes (recurrence, remission) and the percentage of excellent response to treatment were evaluated according to the updates of the AJCC/TNM system, along with the concordance between these editions.

**Results:** A total of 116 patients were included, 84.5% (98/116) of whom were female, with an average age at diagnosis of  $50.6 \pm 16.5$  years. 92.2% (106/116) had papillary carcinoma. The average dose of radioactive iodine was  $63.4 \pm 35.0$  mCi. Using TNM-8, 82 (70.6%) patients were reclassified as Stage I, 32 (27.5%) as Stage II,

1 (0.9%) as Stage III, and 1 (0.9%) as Stage IV. After an average follow-up of  $13.2 \pm 2.8$  months, 80.1% (93/116) remained in remission. 19.8% (23/116) met the criteria for recurrence, and 43.9% (51/116) met criteria for an excellent response. Upon applying TNM-8, 100% of patients in Stages III and IV experienced recurrence. There were no statistically significant differences between the 7th and 8th editions of the AJCC/TNM system.

**Conclusions:** In our cohort, 72.4% of patients were reclassified into lower stages. All patients in Stages III and IV according to TNM-8 experienced disease recurrence at the time of follow-up. All patients with an excellent response were in Stages I and II according to TNM-8.

**Keywords:** Thyroid neoplasms; cancer staging; local recurrence.

#### Poster 0272

WITHDRAWN

#### Poster 0273

WITHDRAWN

#### Poster 0274

*Thyroid Cancer, Clinical, Poster*

#### **Selpercatinib Dose Adjustments and Associated Exposure-Response in Patients with Advanced *RET*-mutant Medullary Thyroid Cancer**

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**Objective:** Selpercatinib is a highly selective and potent RET kinase inhibitor that has shown superior progression-free survival (PFS) in patients with *RET*-mutant medullary thyroid cancer (MTC) over cabozantinib/vandetanib. Here, we report the results of an exploratory analysis to investigate the exposure-response relationship following dose adjustments.

**Methods:** We studied patients with MTC treated with selpercatinib in two prospective trials (LIBRETTO-001 [NCT03157128] and LIBRETTO-531 [NCT04211337]). Patients received a starting dose of 160 mg twice daily; dose reductions to 120 mg, 80 mg and 40 mg twice daily were permitted. We developed exposure-response models to characterize the relationship between selpercatinib at clinically relevant exposures and efficacy endpoints (overall response rate [ORR] and PFS). The average selpercatinib exposure over time was represented by steady-state exposure parameters: area under the plasma concentration-time curve over 24 hours (AUC<sub>24</sub>) and maximum and minimum selpercatinib concentrations. Additionally, the exposure parameters were averaged over the last 10 doses during treatment or prior to safety/efficacy events. Exposure-response analyses were conducted using a stepwise logistic regression for ORR, and Kaplan-Meier plots for each exposure parameter for PFS.

**Results:** Of 495 treated patients (LIBRETTO-001, n=312; LIBRETTO-531, n=183), 210 (42%) underwent dose reduction. The median time to first dose reduction was 3 months. Compared with patients without dose reduction, patients who dose reduced were older (median age [range]: 61 [21-86] vs 54 [12-90] years) and on therapy longer (median time [range]: 34 [1-61] vs 22 [0-67] months). The most common adverse events leading to dose adjustments were alanine and aspartate aminotransferase elevation, hypertension and drug hypersensitivity.

In the 494 patients included in the ORR exposure-response analysis, the response rate was 74% (364 responders); the probability of response increased with increasing selpercatinib exposure (AUC<sub>24</sub>) ( $P < 0.05$ ). Exploratory analysis of PFS in 495 patients (145 events) by exposure metrics showed no significant relationship with PFS probability across exposure quartiles.

**Discussion/Conclusion:** Our analyses did not find any correlation between selpercatinib exposure and PFS but suggested that higher exposure was associated with better response rates. For patients experiencing toxicity on selpercatinib, dose adjustment to reduce exposure may allow ongoing clinical benefit without a decremental impact on PFS.

## Poster 0275

*Thyroid Cancer, Translational, Poster*

### A Sensitive Liquid Chromatography Tandem Mass Spectrometry Method (LC-MS/MS) for Plasmatic Lenvatinib Measurement Allows Drug Monitoring in Patients with Thyroid Cancer

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**Objectives:** No data are available on the pharmacokinetic (PK)/bioavailability of Lenvatinib in patients with radioiodine-refractory thyroid cancer (RAIR-TC) treated with Lenvatinib.

This preliminary retrospective study aims to evaluate the PK profile of Lenvatinib in a real-life scenario, in order to validate the clinical application of the method.

**Methods:** We enrolled 23 patients with RAIR-TC, treated for an average time of 45 months (range 6-96) with Lenvatinib. At the time of sampling, daily doses were 4 mg in 3, 10 mg in 8, 14 mg in 4, 18 mg in 1, 20 mg in 4, and 24 mg in 3 patients.

Lenvatinib was taken by all patients between 8.00 pm and 11.00 pm and the plasma samples were collected the following morning within 9.00 am at multiple time points for each patient, for a total of 51 samples. Samples were collected using sodium heparinized tubes and plasma was stored at -80°C until assay. Detection of Lenvatinib was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using 250 µL of plasma, after analytical validation of the assay.

**Results:** The steady-state exposure of Lenvatinib increased proportionally with increasing dose, suggesting a linear PK, with a plateau phase when exceeding the dosage of 20 mg (R 0.8038,  $P < 0.0001$ ). The analysis demonstrated similar Lenvatinib plasma levels among patients treated with the same dosage, independently of age and body mass index. Median Lenvatinib levels were 37±17.1 ng/mL in patients on 4 mg, 85.4±20.6 in patients on 10 mg, 128.5±31.4 in patients treated with 14 mg, 208.6 ± 48.9 in patients on 20/24 mg. An intra-patient concentrations stability was observed when comparing multiple samplings at the same drug dosage. Moreover, the data showed a good intraindividual correlation between dosage modifications of Lenvatinib and variations in plasma levels.

**Discussion:** These results indicate for the first time that plasmatic Lenvatinib concentrations can be effectively measured by LC-MS/MS assay in patients with RAIR-TC. The quantification assay could be crucial for patients requiring dose titration, and to explain differences in drug efficacy and/or in the development of toxicities among patients.

## Poster 0276

*Thyroid Cancer, Clinical, Poster*

### RAF Family Fusions in Thyroid Carcinomas: Clinicopathological Analysis of 16 Patients

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**Objective:** MAPK pathway activation from *BRAF* alterations plays a central role in thyroid carcinoma pathogenesis. While

*BRAF*<sup>V600E</sup> mutations characterize ~40-60% of papillary (PTC) and anaplastic (ATC) thyroid carcinomas, *RAF*-family fusions are rare. Given novel pan-*RAF* inhibitors and the recently observed responses to *MEK* inhibitors in *BRAF*-fusion melanomas, a better understanding of *RAF*-fusion thyroid carcinomas is necessary.

**Methods:** Retrospective case series including all thyroid carcinoma patients identified at an NCI-designated cancer center with a *BRAF/RAF1/ARAF* fusion between 2018-2024. Clinicopathologic, treatment, and outcome data were analyzed using descriptive statistics and Kaplan-Meier methods.

**Results:** *RAF*-family fusions were identified in 16 patients with thyroid carcinoma (PTC in 14/16 and ATC in 2/16): 8 in primary and 8 in metastatic tumors. None had *BRAF*<sup>V600E</sup>. The fusion involved *BRAF* in 14/16 and *RAF1* in 2/16, most commonly with *SND1* (n=4) and *MKRN1* (n=3). Two fusions were detected at progression after multi-targeted TKIs but lacked earlier testing (i.e. potentially acquired).

Median age at diagnosis was 50 years (range 13-86) and 50% were female. PTCs presented with stage I (n=4) or II (n=7) disease. ATCs presented with stage IVB (n=1) or IVC (n=1). All primary tumors were surgically resected. At initial resection of cervical lymph nodes, pN status was: 1/11 N0, 2/11 N1a, and 8/11 N1b. Distant metastases developed in 9/14 PTCs and 1/2 ATCs, including 3/9 PTCs and 1/1 ATC at initial presentation, most frequently involving lungs (8/10) and mediastinal lymph nodes (5/10). Median time to distant metastasis for PTCs was 43 months (range 0-254).

All PTCs received I<sup>131</sup> (median cumulative activity 196 mCi). Neck-directed radiotherapy was administered to 4/14 PTCs and 1/2 ATCs. 7/14 PTCs and 2/2 ATCs received systemic therapy, including: *MEK* inhibitors (n=2), *BRAF*+*MEK* inhibitors (n=1), pan-*RAF* then *MEK* inhibitors (n=1), pan-*RAF* inhibitor (n=1), and multi-targeted TKI(s) (n=5). In 1 PTC with neck recurrence invading sternocleidomastoid muscle, 1 month of neoadjuvant trametinib facilitated a less morbid surgery. 11/14 PTCs (median follow-up: 94 months) and 2/2 ATCs (15 and 25 months follow-up) patients were still alive.

**Conclusion:** Our findings support further investigation into the prognosis and optimal management of thyroid carcinomas with *RAF* family fusions.

## Poster 0277

*Thyroid Nodules and Goiter, Clinical, Poster*

### Clinical Performance of the Afirma Genomic Sequencing Classifier (GSC) in Pediatric Patients With Cytologically Indeterminate Thyroid Nodules

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**Objective:** Cytologically indeterminate thyroid nodules (ITN) in pediatrics carry a higher risk of malignancy (~30-60%) compared with adult ITN (13-34%). The 2015 ATA pediatric thyroid nodule guidelines recommend surgical resection for ITN. The Afirma GSC was validated in patients ≥ 21 yrs with a 96% negative predictive value (NPV) for malignancy when benign (GSC-B), allowing patients to avoid unnecessary thyroid surgery. Here, we evaluated the performance of Afirma GSC in pediatric patients with ITN.

**Methods:** Forty-nine ITN from patients < 21 yrs sent for Afirma GSC testing had histopathology or clinical follow-up data collected. Afirma GSC ensemble classifier and Xpression Atlas (XA – the GSC molecular variant and fusion panel) data were analyzed for all

samples (though XA data is not reported clinically for GSC-B cases). For Afirma GSC-B cases that avoided surgery, a two-year clinical follow-up with exam and/or ultrasound was a surrogate for a true negative (TN) result.

**Results:** Nine males and 40 females (ages 12-20 yrs, median 18.5 [IQR 17.3-19.8]) had 30 GSC-B and 19 GSC-suspicious (S) cases. Histopathology determined that 14 (73.7%) were malignant (true positive, TP) and five (26.3%) were benign (false positive, FP). All GSC-B cases were either histologically (n=9) or clinically benign (TN). All 14 malignancies were GSC-S (sensitivity 100% [95% CI 77-100%]); 30/35 clinically or histologically benign cases were GSC-B (specificity 86% [95% CI 70-95%]). NPV for a GSC-B result was 100% [95% CI 88-100%]. Genomic alterations were not detected by XA in the 30 benign samples. One of five FP samples had a *DICER1* p.E183Q variant. Among the 14 TP samples, there were 7 papillary thyroid carcinomas (PTC; n=1 with *FGFR2::VCL* fusion and n=1 *PPP1R21::ALK* fusion (previously unreported in thyroid cancer); 1 oncocytic carcinoma (*PAX8::PPARG* fusion); 1 NIFTP; 2 follicular variant PTC; and 3 follicular thyroid carcinomas (n=1 with *PAX8::PPARG* fusion, n=2 with *NRAS* p.Q61K).

**Conclusion:** In older adolescents with ITN, the Afirma GSC showed excellent performance when defining a true negative result by histology or clinical follow-up. Our findings indicate that an Afirma GSC-B result appears reassuring and may allow for a more conservative management strategy in younger patients with ITN.

## Poster 0278

*Thyroid Cancer, Clinical, Poster*

### Overcoming Thyroid Overdiagnosis: Developing and Deploying Large Language Models for Incidental Thyroid Nodule Identification

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**Objective:** An important driver of thyroid nodules and cancer overdiagnosis is the finding of incidental thyroid nodules (ITNs) in different types of non-thyroidal imaging modalities. To facilitate the study of the frequency and downstream outcomes of ITNs, we trained Large Language Models (LLM) to identify ITNs in imaging reports.

**Methods:** We identified 56,418 radiology reports from non-thyroid related imaging studies that included neck window evaluation, from adult patients with no prior history of nodular thyroid conditions, across Mayo Clinic sites between January 2017 and October 2023. We created an enriched dataset of 300 imaging reports, of which 41.67% (125/300) included ITNs cases, and developed a consensus-based ground truth. Subsequently, we used a two-step approach that included 1) fine-tuning four pre-trained LLMs (BERT, BioBERT, BioCLinicalBERT, and GatorTron) to identify any thyroid incidental findings (e.g., thyroiditis or ITN) and 2) implementing Llama 2, a Question-Answering model (Q&A), to identify ITNs among the reports with any incidental finding. Our dataset was split 66.66% (200/300) for a training set for fine-tuning our models, and 33.33% for a testing set (100/300) for performance evaluation. Additionally, the models were deployed across all the initially identified reports.

**Results:** Among the used LLMs, GatorTron showed the highest performance metrics with an accuracy of 95% and F-1 score of 95% in classifying any incidental finding. Subsequently, the Q&A model, employing Llama2, achieved an accuracy of 90% and F-1 score

95% in identifying ITN findings within these reports. When deployed in all the available reports, out of 56,418 studies, 11.30% (6,377/56,418) had an incidental finding, and 9.50% (5,361/56,418) had ITNs with the following imaging-type distribution: 88.11% Computerized Tomography (4,724/5,361), 5.72% Positron Emission Tomography scan (307/5,361), 3.11% magnetic resonance (167/5,361), and 3.04% nuclear medicine and ultrasound (163/5,361).

**Discussion/conclusion:** We successfully trained and deployed LLMs that accurately identify ITNs from imaging reports. Their deployment into the entire healthcare system enhances their potential to elucidate ITN frequency at scale and inform future interventions to mitigate thyroid cancer overdiagnosis. Further enhancements to the model will focus on extracting detailed ITN characteristics, such as size, to provide additional information for these efforts.

### Poster 0279

*Thyroid Nodules and Goiter, Clinical, Poster*

#### Leveraging artificial intelligence to categorize thyroid cytology results from fine-needle aspiration biopsy reports within a large healthcare system

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**Objective:** To develop a Natural Language Processing (NLP) pipeline to classify cytology results from Fine-needle Aspiration Biopsy (FNAB) reports and explore the epidemiology of these outcomes among patients with thyroid nodules.

**Methods:** We identified 2,979 reports from patients undergoing their initial FNAB at Mayo Clinic sites between January 2019 and December 2022. Among these, 123 FNAB reports were manually selected, ensuring at least 20 reports from each 2023 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) category. The cohort was further enriched with 120 ChatGPT3.5 generated synthetic reports to bolster the dataset with less common scenarios (e.g., medullary thyroid cancer). A consensus-based ground truth was developed by human annotators. Subsequently, we developed a rule-based NLP pipeline and fine-tuned Llama 2, a pre-trained large language model (LLM), to classify FNAB reports into six categories: I) Nondiagnostic, II) Benign, III) Atypia of Undetermined Significance, IV) Follicular neoplasm, V) Suspicious for Malignancy, and VI) Malignant. Our dataset was split 74% into a training cohort (n=180, including the 120 synthetic reports and 60 original reports), and 26% into a testing cohort (n=63). We evaluated the performance using the testing set and deployed the model in the entire initial cohort (n=2,979) to evaluate the overall distribution of the categories.

**Results:** Our model achieved 100% precision, recall, accuracy, and F-1 score in classifying according to TBSRTC. Upon deployment, we estimated the following yearly distribution of FNAB (n=2,979): 19.3% in 2019 (n=575), 22.9% in 2020 (n=683), 25.6% in 2021 (n=761), 24.7% in 2022 (n=736), and 7.5% in 2023 (n=224). The overall distribution per category was as follows (n=2,979): 9.4% non-diagnostic (n=279), 66.4% benign (n=1,979), 5.3% atypia of undetermined significance (n=159), 5.7% follicular neoplasm (n=168), 2.5% suspicious for malignancy (n=76), and 10.7% malignant (n=318).

**Discussion/conclusion:** We developed an accurate NLP model for extracting FNAB results at scale. This advancement has the potential to explore the epidemiology of FNAB results across diverse settings (e.g., private vs. academic). Moreover, it enables the

exploration of downstream outcomes for each category, including the identification of patients with indeterminate thyroid nodules, the utilization of molecular testing, and their subsequent outcomes.

### Poster 0280

*Thyroid Cancer, Clinical, Poster*

#### Thyroid Cancer Invading the Airway: Common Features and Outcomes of Surgical Treatment in a Single Center Experience

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**Objective:** is to describe common features and characteristics of patients with thyroid cancer (TC) invading the trachea and/or larynx.

**Methods:** Clinical records of 22 patients who underwent surgery for TC invading the trachea and/or the larynx at St. Petersburg State University Hospital between years 2014 and 2023 were analyzed.

**Results:** The male to female ratio was 8:14. 16 patients (73%) were treated for papillary thyroid cancer (PTC), 3 for poorly differentiated thyroid cancer (TC), 2 for anaplastic thyroid cancer (ATC) and 1 for sporadic medullary thyroid cancer (MTC). Of the 16 cases of PTC tall cell variant was the most common (n=9, 56%). 4 cases of PTC were of the oncocyctic variant, 2 of the conventional and 1 of the follicular variant.

11 patients (50%) had primary surgery, each case involving circular resection of the trachea. 6 of the 11 primary patients were first diagnosed with thyroid nodules by ultrasound imaging a number of years prior (range 2-29 years), none of them had FNA performed at the time of diagnosis and most did not undergo regular ultrasound scans. Among the 11 patients with repeat surgery 4 underwent laryngectomy and 7 had circular tracheal resection. For 3 of the 11 patients primary thyroid surgery was performed 11, 14, and 40 years prior and no records of primary treatment or histological examination results were available.

18 patients were available for follow up. 6 patients with PTC are disease-free. 2 patients with local recurrence of PTC undergo regular ultrasound and CT scans and show no signs of disease progression. 3 patients are presently receiving thyrosine kinase inhibitors (1 MTC, 1 PTC, 1 poorly differentiated TC). 6 patients have died (4 PTC, 1 ATC, 1 poorly differentiated TC), 1 of them of unrelated causes.

**Conclusion/Discussion:** A number of patients in the examined cohort appear to have had either a lengthy history of thyroid cancer unverified by FNA, leading up to its invasion into the airways, or primary thyroid surgery with no proper histological examination of the removed tissue and no postoperative patient follow up. The existence of advanced disease may thus be partially related to low patient compliance and a lack of proper diagnostic, monitoring and follow up algorithms. Other factors such as histological characteristics and a relatively high proportion of male patients with advanced thyroid cancer appear in line with known trends.

### Poster 0281

*Thyroid Cancer, Clinical, Poster*

#### How response to therapy status changed over 5 years of follow-up in a German collective of differentiated thyroid cancer patients after surgery and radioiodine therapy (RAIT)

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**Objective:** The aim of our study was to investigate how response to therapy status changed over 5 years of follow up in a cohort of German differentiated thyroid cancer (DTC) patients after surgery and radioiodine therapy (RAIT) and to determine if initial ATA risk classification and stratification is able to estimate the 5 year response in DTC patients in a German population.

**Methods:** We retrospectively analyzed 69 patients who were referred to our tertiary referral center for initial RAIT and had a follow-up for 4-7.1 years (median 5.35 years). Patients were classified into risk categories and the therapy response was determined according to ATA. We compared the 5 year response results to the responses 1 year after therapy.

**Results:** Out of 51 patients that had an excellent response to therapy at one year, 43 (84%) remained excellent response while 7 (14%) were reclassified as indeterminant response and 1 (2%) demonstrated a structural incomplete response.

39/49 (80%) ATA low risk patients and 6/10 (60%) intermediate risk patients showed an excellent response 5 years after therapy. None of the indeterminant responses or biochemical incomplete responses developed a structural incomplete response. In the 5 patients with structural incomplete response to initial therapy, who receive additional therapies, 2 patients (40%) transitioned to biochemical incomplete response.

**Discussion/Conclusion:** The clinical outcomes predicted by ATA risk stratification and response to therapy in this German cohort are very consistent with previously published studies in other population groups. Initial response to therapy is predictive of the 5-year response to therapy outcomes in this German cohort of patient with differentiated thyroid cancer.

## Poster 0282

*Thyroid Cancer, Clinical, Poster*

### Could quantitative superb microvascular imaging or shear wave elastography help to identify grown suspicious thyroid nodules measuring $\leq 10$ mm? A cross-sectional study

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**Objective:** How to identify ACR TI-RADS 4-5 (TR4-5) nodules  $\leq 10$  mm that have increased in size is an important issue in clinical work. Our study investigated whether superb microvascular imaging (SMI) and shear wave elastography (SWE) could help differentiate grown and stable TR4-5 thyroid nodules measuring  $\leq 10$  mm.

**Methods:** Each nodule underwent ultrasound examination for SMI and SWE. VImax means higher VI in transverse or longitudinal section. SWV-ratio means the ratio of thyroid nodule and peripheral gland. Growth was defined as a growth rate  $> 2$  mm/y or an increase in size of  $> 3$  mm in the largest dimension.

**Results:** Of all 61 TR4-5 TNs, 31 (50.8%) were defined as grown nodules. SWV-ratio and VImax were significantly different between the grown and stable groups ( $p < 0.05$ ). The AUC of VImax and SWV-ratio were 0.672 and 0.755 (95% CI: 0.540-0.787, 0.628 to 0.856, respectively). Using a SWV-ratio cut-off of  $\leq 1.25$  to identify grown TNs, the specificity, sensitivity, PPV, NPV, and accuracy were 58.1%, 90.0%, 85.7%, 67.5%, and 73.8%. With the use of a VI cut-off of  $> 14.4$  to identify grown TNs, the specificity, sensitivity, PPV, NPV, and accuracy were 83.9%, 53.3%, 65.0%, 76.2%, and 68.9%, respectively.

**Conclusion:** Grown ACR TI-RADS thyroid nodules measuring  $\leq 10$  mm presented rich blood flow and low shear wave velocity, more prospective research with large sample size should be conducted to study the value of SMI and SWE in managing suspicious thyroid nodules.

## Poster 0283

*Thyroid Cancer, Clinical, Poster*

### Diagnostic Value of Molecular Testing for Evaluating Thyroid Nodules Greater Than 4 Centimeters

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**Objective:** Molecular testing (MT) of thyroid nodules is widely utilized to avoid unnecessary thyroidectomies, owing to its high negative predictive value. Nevertheless, the reliability of MT in larger nodules, which tend to have a higher incidence of malignancy, remains uncertain. This study aims to evaluate the efficacy of MT in diagnosing thyroid nodules exceeding 4 centimeters in size.

**Methods:** We conducted a retrospective analysis of patients who underwent fine needle aspiration (FNA) of thyroid nodules at our institution from 2015 to 2023. We included nodules measuring at least 4 centimeters in their largest dimension. The analysis incorporated results from both Gene Expression Classifier and Genetic Sequence Classifier versions of the Afirma assay. Non-invasive follicular thyroid neoplasms with papillary-like nuclear features were classified as malignant. Normally distributed variables were reported as mean  $\pm$  standard deviation, while non-normally distributed variables are presented as median with the first and third quartiles (Q1, Q3).

**Results:** Our study included 371 patients: 51.4% white, 45.1% black, and 71.2% female, with an average age of  $55 \pm 16$  years. The median size of the nodules was 4.7 (4.3, 5.5) centimeters. Thyroidectomy was performed on 155 patients (41.8%), revealing a malignancy rate of 27.1%. 57 (15.4%) nodules were categorized as Bethesda III, with 57.9% subsequently undergoing molecular testing (MT) that showed a suspicious malignancy rate of 32.4%. Additionally, six nodules (1.6%) were categorized as Bethesda IV, with half receiving MT that revealed a suspicious rate of 50%. Including patients biopsied outside our institution, we identified 78 patients with large nodules and a Bethesda score of III or IV, along with corresponding surgical pathology. Nodules deemed suspicious by MT had a malignancy rate of 53.8% (28/52), whereas those classified as benign exhibited a 19.2% malignancy rate (5/26). Of the five malignant nodules misclassified as benign by MT, two were papillary carcinomas, one was a follicular carcinoma, one a poorly differentiated carcinoma, and one a microcarcinoma.

**Conclusion:** A negative result from molecular testing may not conclusively rule out malignancy in thyroid nodules larger than 4 centimeters. Therefore, physicians should use caution when ordering and interpreting molecular testing results for larger thyroid nodules.

## Poster 0284

*Thyroid Cancer, Clinical, Poster*

### The Absence of TPO Antibodies Marks the Role of Immune Evasion in the Development of Aggressive Thyroid Cancers of Follicular Origin: An International Surgical Series

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**Objective:** Our studies suggest that TPO antibodies participate in humoral immunity and could limit the progression of thyroid cancers of follicular origin (TCFO) when found in high titers. The present work evaluates the specific role of TPO antibodies on the development of aggressive (AGG) and non-aggressive (NAG) TCFO.

**Methods:** We retrospectively collected data on preoperative TPO, age, sex and surgical pathology from post-thyroidectomy patients operated in 2 countries [USA: (2007-2013) and Greece (2021-2023)]. We split our subjects in AGG thyroid cancers [distant metastasis, extensive lymph node involvement (LNs)( $\geq 10$  or  $\geq 6$  with a ratio of involved/total dissected  $\geq 75\%$ ),  $\geq 2$  treatments with I-131 and/or large structural local recurrence]; the remainder of TCFO were deemed NAG. Non malignant lesions by histology (BEN) served as controls. TPO titers were subgrouped in: very low (VL)( $< 1$  IU/ml), low (L)(1 - 10 IU/ml), intermediate (IN)(10 - 30 IU/ml), high (HI)(30-300 IU/ml) and very high (VH)( $\geq 300$  IU/ml). The frequency of AGG thyroid cancers was compared between these subgroups.

**Results:** We reviewed 11,212 surgeries and n=1943 subjects had available preoperative TPO measurements: n=995 (51.2%) had TCFO out of whom, n=73 were AGG (7.3%). Overall, our TCFO patients were younger compared to BEN (45.7 $\pm$ 14.6 vs. 47.7 $\pm$ 15.1 years respectively) as were those with AGG vs. NAG tumors (40.2 $\pm$ 15.3 vs. 46.2 $\pm$ 14.5 years). Furthermore, 55.6% of males (259/466) and 49.5% of females (736/1487) had TCFO, p=0.02. AGG tumors were significantly more frequent in VL (p=0.018) and less frequent in H (p=0.016) subgroups.

**Discussion:** High TPO titers appear protective against, while very low TPO titers appear to boost aggressive thyroid cancers of follicular origin (TCFO) development. This could be due to tumor evasion of humoral immunity exhibited by such cancers, a mechanism that could be protective, even against auto-immunity, which is a defective form of immunity.

## Poster 0285

*Thyroid Cancer, Clinical, Poster*

### DESCRIPTION OF FIFTY YEARS OF EXPERIENCE IN THE MANAGEMENT OF THYROID DIFFERENTIATED CARCINOMA IN CHILDREN AND ADOLESCENTS IN THE REAL WORLD

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Distinguishing patients who require closer monitoring and rigorous therapeutic measures from those who should be spared from excessive treatment is crucial in the management of thyroid cancer. However, limitations of the current initial risk stratification (IRS) and dynamic risk stratification (DRS) methods challenge the management of pediatric patients with thyroid cancer (pDTC), where this issue is particularly important. To improve the monitoring parameters, we retrospectively evaluated the predictive markers for

persistent disease in a consecutive series of patients with pDTC treated at a single institution.

We reviewed the records of 178 patients with pDTC who underwent the same standard management protocol to establish their risk using the stratification system of the 2015 American Thyroid Association pDTC guidelines (IRS) and DRS guidelines for adults. We characterized the early outcome risk (EDRS) after 1–3 years and a late outcome (LDRS) after  $\geq 10$  years of follow-up.

125 patients had sufficient recorded data to permit IRS. The mean age at diagnosis was 14 years, 98 (78.4%) were female, and 114 (91.2%) had papillary thyroid carcinomas. The tumor size was 2.4 $\pm$ 1.41 cm, 80 (64%) had cervical metastases, and 21 (16.8%) had distant metastases at diagnosis. IRS classified the majority of patients (108, 86.4%) as intermediate- or high-risk. EDRS was closely associated with IRS, with favorable responses predominating in the low- and intermediate-risk groups and unfavorable responses predominating in the high-risk group (p=0.0001). We observed that 86.11% of the 36 patients evaluated for LDRS maintained this response (p=0.074). A serum post operative Tg (sPOTg) level of 12.5 ng/mL predicted persistent disease with a sensitivity of 73.3% and specificity of 81.1%, along with tumor margins (p=0.007) and the number of affected lymph nodes (p=0.032).

In conclusion, we confirmed a positive relationship between IRS and disease persistence, demonstrating that EDRS is a good predictor of LDRS and pDTC patient outcomes, in addition to the number of affected lymph nodes, resected tumor margins, and sPOTg levels.

## Poster 0286

*Thyroid Cancer, Clinical, Poster*

### Metabolic Parameters on PET/CT Correlate with Biochemical Response to Selpercatinib in Patients with Advanced Medullary Thyroid Cancer

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**Objective:** The introduction of selpercatinib, a RET-specific tyrosine kinase inhibitor, has significantly improved the prognosis of patients with advanced medullary thyroid cancer (MTC). Despite improving progression-free survival in most patients, the response can be challenging to predict. The aim of this study was to assess for correlation between volumetric and metabolic parameters on Positron Emission Tomography/Computer Tomography (PET/CT) and response to selpercatinib.

**Methods:** In this single-centre retrospective review, all patients treated with selpercatinib for metastatic MTC were assessed. Patients with Gallium-68-DOTA-(Tyr3)-octreotate (<sup>68</sup>Ga-DOTA-TATE) or Fluorine-18-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) PET/CTs  $< 18$  months prior to selpercatinib treatment were included. Patient and treatment data were collected and pathological uptake on

PET/CTs was quantified. Per scan, Standardized Uptake Value (SUV)<sub>max</sub>, SUV<sub>mean</sub>, Total Lesion Activity (TLA) and Metabolic Tumor Volume (MTV) were determined and assessed for correlation with several response measures.

**Results:** Of the 15 patients, mean age at diagnosis was 47 ( $\pm$ 16) years; 10 (67%) were female and all had RET-mutated cancers (3/15 [20%] with MEN2). At final follow up, patients had distant metastases in bone (11 [73%]), liver (10 [67%]), lungs (6 [40%]), and brain (3 [20%]). Four patients (27%) had died. Response rates were; partial response (PR) 10/15 (67%); stable disease (SD) 4/15 (27%); and intolerant 1/15 (7%). A total of 18 PET/CTs (14 <sup>68</sup>Ga-DOTATATE PET/CTs, 4 <sup>18</sup>F-FDG PET/CTs) were performed prior to selipercatinib treatment. A total of 289 lesions were identified; 216 skeletal, 49 nodal, 18 hepatic and 6 lung lesions. Within the <sup>18</sup>F-FDG cohort, a high SUV<sub>max</sub> and SUV<sub>mean</sub> correlated with a shorter time to biochemical response (calcitonin nadir) ( $p < 0.001$ ,  $p = 0.024$ , respectively). In the <sup>68</sup>Ga-DOTATATE cohort, the opposite was observed for SUV<sub>max</sub>, where lower avidity correlated with a shorter time to biochemical response ( $p = 0.025$ ). In addition, high MTV on <sup>68</sup>Ga-DOTATATE PET/CT trended with a lower disease-specific survival ( $p = 0.065$ ). The PET parameters did not significantly predict RECIST classification (SD or PR) ( $p > 0.05$ ).

**Conclusion:** Metabolic and volumetric parameters on PET/CT prior to selipercatinib treatment may assist in predicting the time to calcitonin nadir. Larger studies are required to determine whether PET parameters can predict structural response to treatment.

### Poster 0287

*Thyroid Cancer, Clinical, Poster*

#### Evaluating the Prognostic Significance of Cyfra 21-1 Changes and Genetic Mutations in Thyroid Cancer Patients

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**Objective:** Cyfra 21-1 is an established tumor marker for monitoring cancer progression and response to treatment. This study aimed to investigate the prognostic implications of changes in cyfra levels and the influence of BRAF and TERT mutations on thyroid cancer patient outcomes.

**Methods:** From the single tertiary hospital, a cohort of 57 patients was retrospectively analyzed, categorizing based on a  $\geq 10\%$  increase in cyfra levels. We assessed disease progression and mortality rates in correlation with these changes and the presence of BRAF and TERT mutations.

**Results:** The average change in cyfra levels was  $0.018 \pm 1.620$ , which alone did not significantly correlate with progression rates (39.29% vs. 31.03%,  $p = 0.708$ ). Patients with a  $\geq 10\%$  increase in cyfra levels who also had BRAF mutations exhibited a higher progression rate (50%) compared to those with smaller changes (33.33%) without statistical significance. ( $p = 0.746$ ) However, TERT mutations significantly influenced progression rates, particularly in patients with less than a 10% increase in cyfra levels (progression rate 77.78%  $p = 0.004$ ). Mortality rates were low across all groups, but slightly higher in patients with TERT mutations and cyfra increase (14.29%) compared to those without cyfra increase without statistical significance ( $p = 0.438$ ).

**Conclusion:** Changes in cyfra levels alone were not sufficient to predict patient outcomes. However, TERT mutation was associated with a significant increase in progression rates, especially in patients with minimal changes in cyfra levels. These findings underscore the potential of incorporating genetic markers such as TERT to enhance the prognostic accuracy of cyfra measurements in clinical settings.

### Poster 0288

*Thyroid Cancer, Case Study, Poster*

#### A Rare Case Of Mixed PTC Sub-Types: An Evolving New Entity

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**Introduction:** Papillary thyroid carcinoma (PTC) is the most common thyroid neoplasm, and is typically characterized by its indolent nature and favorable survival. In recent years, more aggressive subtypes of PTC have been recognized and research surrounding the definition, prognosis, and management of PTC subtypes is continuously evolving. The tall cell, columnar cell, and hobnail subtypes of PTC are associated with more unfavorable outcomes. We present a rare case of a patient with all three PTC subtypes coexisting within the same tumor.

**Case Description:** A 55 year-old male initially presented with a thyroid nodule and fine needle aspiration (FNA) reporting PTC, he subsequently underwent a total thyroidectomy that revealed gross involvement of the tracheal cartilage and the left recurrent laryngeal nerve. Pathology reported PTC of the tall cell subtype with lymphatic and perineural invasion. While awaiting radioactive iodine (RAI), and within 8 weeks of thyroidectomy, he returned with a new-onset hard, painless lump in his neck at level 4. Ultrasonography revealed a suspicious 1 cm soft tissue nodule, and neck CT reported up to four different suspicious soft tissue deposits. FNA of two of these lesions were positive for PTC. Thyroglobulin was low at 0.5 ng/mL despite disease present, indicating likely de-differentiation of disease. We requested a second histopathology review of the original specimen which reported three different subtypes of PTC: hobnail, columnar, and tall cell which was the most predominant. There were no anaplastic features and molecular studies showed TERT and BRAF positive. RAI was deemed to be of low utility given disease de-differentiation. Prior to deciding on a course of treatment with systemic therapy or external beam radiation, the patient will undergo further staging.

**Discussion:** A review of existing literature revealed limited reports of mixed PTC subtypes within patients, highlighting the rarity and complexity of such cases. Mixed PTC subtypes present a novel challenge in terms of management and prognosis, and prompts further research into the histopathology and prevalence of such tumors.

### Poster 0289

*Thyroid Cancer, Case Study, Poster*

#### Monoallelic Pathogenic c.5712dup Mutation in the Ataxia Telangiectasia Mutated (ATM) Gene as a Risk Factor for Metachronous Thyroid and Breast Cancer - A First Report

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The Ataxia Telangiectasia Mutated (*ATM*) gene is an oncosuppressor located on chromosome 11q23 involved in DNA repair by activating DNA damage response pathways. Pathogenic *ATM* gene variants are common and have a prevalence of approximately 1%. There is a strong association between *ATM* variants and the risk of malignancy development. The c.7271 mutation was found to have the highest association with breast cancer while other variants have been found to be associated with thyroid but not increased breast cancer risk.

We describe the first case report of a c.5712dup monoallelic pathogenic mutation in the *ATM* gene as a risk factor for metachronous thyroid and breast cancer.

The patient was a young female who underwent total mastectomy at age 35 for a Grade 1 ER PR Positive Her 2 Negative Invasive Mucinous Carcinoma of the right breast. She underwent 49-gene testing (Invitae) and was found to be a heterozygous carrier of a pathogenic monoallelic *ATM* gene mutation (c.5712dup (p.Ser1905-Ilefs\*25)). She was hence followed up more closely with surveillance PET-CT which found an FDG-avid focus in the right thyroid. Ultrasound thyroid showed a 0.6cm indeterminate right lower pole nodule and Fine Needle Aspiration Cytology was Atypia of Undetermined Significance (AUS). She was counselled for right hemithyroidectomy and final histology showed papillary microcarcinoma. She was the index case and there was no history of radiation exposure in her family.

Unlike the more common *BRCA1* and *PTEN* mutations, *ATM* represents a rarer mutation. This is the first case of a c.5712dup variant predisposing to the development of metachronous papillary thyroid and breast cancer. This case demonstrates the importance of genetic testing in young patients with a first primary breast malignancy. Detection of an *ATM* gene mutation like the c.5712dup variant necessitates a high index of suspicion for a secondary thyroid malignancy and carries screening implications for the offspring of these individuals. Further studies would be valuable to establish precise and comprehensive estimates of cancer risks associated with *ATM* gene mutations as this can facilitate recommendations for the identification, surveillance, and potential preventive treatment of high-risk individuals with a first primary malignancy.

## Poster 0290

*Thyroid Cancer, Case Study, Poster*

### **A Rare and Difficult Diagnosis: Primary Fibrosarcoma Masquerading as Riedel's Thyroiditis and Anaplastic Carcinoma**

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**Introduction:** Fibrosarcoma of the thyroid are rare cancers with very few cases reported in the literature. Here we present a case of primary fibrosarcoma of the thyroid masquerading as Riedel's thyroiditis and anaplastic carcinoma.

**Description of the case:** A 66-year-old-woman initially presented to an outside hospital with 8 months of progressive dysphagia and neck swelling and was found to have a large solid and cystic mass arising from the right thyroid lobe. After an initial non-diagnostic fine needle biopsy, she underwent a right lobectomy from which the diagnosis of Riedel's thyroiditis was made. She was treated with prednisone 60 mg daily. In the subsequent months she suffered an episode of hypoxic respiratory failure leading to cardiac arrest. She

received a tracheostomy and a PEG feeding tube was placed. She presented to our hospital for tracheostomy bleeding seven months after the initial diagnosis. MRI demonstrated invasion of thyroid mass into thyroid cartilage, paraglottic fat, base of the epiglottis, and posterior infiltration of the prevertebral fat and upper esophagus. The aggressive nature of the thyroid mass in spite of treatment called into question the original diagnosis and prompted a core needle biopsy which revealed spindle cells and was interpreted as sarcomatoid type anaplastic carcinoma. However, a review of the initial surgical specimen from her right hemithyroidectomy and additional staining in conjunction with her subsequent clinical course revised her final diagnosis to be fibrosarcoma. The diagnosis of fibrosarcoma was supported by diffusely positive TP53 staining and negative keratin and PAX-8 staining. She received radiation therapy and chemotherapy but succumbed to sepsis 19 months after her initial presentation.

**Discussion:** Previous case reports have described anaplastic thyroid cancer mimicking Riedel's thyroiditis and vice versa; this case adds fibrosarcoma as a contender when approaching a large, rapidly growing thyroid mass with predominantly spindle cells on pathology. Given the rarity of all three diagnoses, proactive investigation of aberrant TP53 expression, staining for epithelial cell markers such as cytokeratin, and close follow up to assess for response to the chosen therapy should be arranged when there is diagnostic uncertainty.

## Poster 0291

*Thyroid Cancer, Case Study,*

### **Papillary Thyroid Cancer Presenting As Thyroid Abscess**

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## Introduction

Thyroid cancer is most frequently detected in females (3:1) and makes up about 1% of all newly diagnosed malignant disorders. Papillary carcinomas are considered "well-differentiated" and are responsible for between 80-85% of all thyroid malignancies.

## Case presentation

A 43 years old female years patient presented to our Emergency department with a complaint of a sudden anterior neck swelling with difficulty of breathing of 10days duration. The patient couldn't maintain her saturation with atmospheric air. Progressively she couldn't breath by herself.

## Diagnostic assessment

Neck ultrasound shows markedly enlarged right thyroid lobe with multiple different sized nodules largest >5cm in AP diameter and there is surrounding collection with internal echo debris . The left lobe appears normal.

FNAC from the mass showed impression of suppurative inflammation.

## Treatment

With an impression of thyroiditis with abscess collection and rule out anaplastic thyroid cancer, an initial dose of Hydrocortisone 200 mg IV shot given.

The intraoperative finding was: Adhesion between the platysma muscle and external layer of deep fascia, around 400 ml of super infected hematoma, both lobes were necrotic except small thyroid tissue remnant over bilateral upper lobes.

The hematoma drained, necrotic tissue removed, the trachea was free especially centrally. She was extubated on the next day of surgery.

### Outcome and Follow-up

The patient was seen after 12 days of the surgery, the wound was getting better.

She was put on suppressive dose of levothyroxine.

She is now on her 11<sup>th</sup> post surgery month with no sign regrowth or metastasis.

The patient didn't take radio-iodine ablation therapy because it is not available in the country.

### Discussion

Given the relative resistance of the thyroid gland to infection, acute suppurative thyroiditis/thyroid abscess is an exceptionally rare condition. Due to its protective capsule, abundant blood supply, extensive lymphatic drainage, and high iodine content, the thyroid gland is naturally resistant to infection. The most prevalent malignant thyroid tumor with respect to age at presentation is papillary thyroid carcinoma (PTC). Patients are typically diagnosed with this tumor during the third and fifth decades of life. Most patients with this tumor present with painless anterior neck mass. High index of suspicion for thyroid cancer presenting as an abscess is important to act early in this group of patients.

### Learning Points:

Still if timely appropriate actions are taken the patients life could be saved and leave long as this cancer is differentiated one and grows slowly.

### Poster 0292

*Thyroid Cancer, Case Study, Poster*

#### Successful Redifferentiation of Radioactive Iodine Resistant Papillary Thyroid Cancer with BRAF/MEK Inhibition: A Case Report

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**Introduction:** Tyrosine kinase inhibitor (TKI) therapy has emerged as a promising strategy to treat radioactive iodine (RAI) resistant papillary thyroid cancer (PTC). We present a case of RAI-resistant PTC that successfully redifferentiated with BRAF/MEK inhibition therapy.

**Case Description:** 59-year-old male was diagnosed with PTC with tall cell features and esophageal and laryngeal nerve involvement. The patient underwent initial surgery in 2016 and received I-131. Post-RAI whole body scan (WBS) showed uptake in the thyroid bed with no visible metastases.

Surveillance imaging with neck US and CT chest in 2017 showed cervical and mediastinal lymphadenopathy and bilateral pulmonary nodules, the largest 1.1 cm in the left lingula. PET scan showed avidity in the lingula nodule and lymph nodes. Biopsy of the lingula lesion confirmed metastatic papillary thyroid cancer. He underwent repeat neck dissections and received additional I-131. Post-RAI WBS showed uptake in the neck without mediastinal or lung uptake.

Molecular analysis showed BRAF V600E and TERT promoter mutations. Treatment with dabrafenib/trametinib (BRAF/TERT inhibition) started in 2022. 6 week follow-up I-123 WBS showed new uptake in the superior mediastinum although no lung uptake, which led to the administration of the third course of I-131 RAI. Tg levels increased from <1 to 22, interpreted as re-differentiation. CT showed a decrease in the neck and lung lesions, with the most recent CT showing only subcentimeter lung nodules and lymph nodes.

**Discussion:** We believe our case contributes to the literature for successful re-differentiation of RAI-resistant metastatic PTC with

BRAF V600E and TERT mutations, using dual TKI-based therapy with dabrafenib and trametinib. It is unclear if the response of the lung metastases was due to RAI, as there was no uptake visible, or due to the TKI therapy itself. Currently, no consensus guidelines have been published regarding the timing of or necessity for redifferentiation therapy in RAI-resistant cases on TKI therapy, hence any data on successful treatment remain critical for clinicians.

### Poster 0293

*Thyroid Cancer, Case Study, Poster*

#### Neoadjuvant Selective RET Inhibitor for Medullary Thyroid Cancer: A Case Report

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**Introduction:** In 2020 two selective RET inhibitors - selpercatinib and pralsetinib - were approved by the FDA for the treatment of advanced RET mutated medullary thyroid cancer (MTC). There is little data to support their use in other clinical contexts of MTC. Four cases of neoadjuvant therapy has been described recently. Here we present a case of neoadjuvant pralsetinib followed by surgery for a patient with initially presenting with loco-regionally metastatic MTC.

**Case Report:** A 47-year-old man presented with a feeling of a lump in the throat and supra-clavicular swelling. Neck biopsy revealed hyalinized fibrous tissue containing small solid nests and trabecules of small epithelioid tumorous cells, with morphology and immunohistochemical patterns consistent with MTC. FDG PET CT demonstrated a hypermetabolic 6 cm right thyroid tumor that merged with superior mediastinal lymphadenopathy, and a right supra-clavicular mass impinging on the right jugular vein (T4aN1bM0 Stage IV). A somatic RET C2753T>C mutation was found. Serum Carcinoembryonic antigen (CEA) and calcitonin levels were 219 ng/mL (normal reference: <5.0 ng/mL) and 13,341 pg/mL (normal reference: <10 pg/mL), respectively. He was treated with pralsetinib at 400 mg once a day without significant side-effect, with repeat PET-CT showing a partial response and decreased uptake in both tumor masses within 3 months. After 7 months of treatment, and following further response, he underwent total thyroidectomy, right neck and retrosternal dissection, revealing several viable tumor deposits in the neck and mediastinum, representing either lymph nodes completely replaced by metastasis, tumor deposits or ectopic thyroid tissue completely replaced by tumor, without any viable disease within the resected thyroid gland. Calcitonin level was 8.8 pg/mL one month after surgery. The patient was taken off pralsetinib and no future follow-up has yet been carried out.

**Discussion:** This case provides 'proof-of-concept' to the feasibility of neoadjuvant treatment with a selective RET inhibitor in sporadic metastatic Ret-mutated MTC. Neoadjuvant therapy can reduce the risk of disease progression before definitive treatment, potentially improving long-term outcomes. The neoadjuvant treatment led to tumor shrinkage, rendering the surgery feasible with minimal morbidity. Our experience lends support to the idea that agnostic treatments against driver-oncogenes may become an integral part of the multi-disciplinary treatment of thyroid cancer.

Further clinical trials are required to establish the safety, efficacy, and long-term outcomes with this approach.

**Poster 0294***Thyroid Cancer, Case Study, Poster***A Unique Presentation of Unilateral Thyroid Lymphoma***John Woodley\*, UCSF Fresno, USA*

Primary Thyroid Lymphoma (PTL) is a rare malignancy of the thyroid gland that accounts for less than 5% of all thyroid malignancies. A large majority of PTL cases are of B-cell origin with approximately 98% of all cases being Non-Hodgkin's Lymphoma. In a retrospective analysis between 2004 and 2015 by Vardell et al., 68% of diagnosed PTL cases were histologically diffuse large B-cell lymphoma (DLBCL) with 10% being follicular lymphoma, 10% being marginal zone or mucosa-associated lymphoma tissue (MALT) lymphoma and 3% being small lymphocytic lymphoma. On clinical presentation, PTLs traditionally present as a rapidly enlarging, uniform neck mass with possible symptoms of compression such as dysphagia, hoarseness, or dyspnea. Occasionally, B symptoms and peripheral lymphadenopathy may also be present. In this case report, we highlight the clinical course of a patient who initially presented to the clinic with a rapidly enlarging unilateral neck mass that ultimately revealed MALT lymphoma of the right thyroid without evidence of malignancy on the left.

**Poster 0295***Thyroid Cancer, Case Study, Poster***METASTATIC PAPILLARY THYROID CANCER PRESENTING AS CAUDA EQUINA SYNDROME: A CASE REPORT***Samantha Patricia Go-Soco\*, Kurt Bryan Tolentino, Roy Raoul Felipe, Mikhail Lew Ver, St. Luke's Medical Center - Global, Philippines***Introduction**

Papillary thyroid cancer is the most common type of thyroid malignancy worldwide and usually presents as a painless enlarging

nodule or mass. Metastatic disease is rare at the onset of diagnosis, only present in about 1-2% of diagnosed thyroid cancers.

**Case Presentation**

A 49 year old male with no comorbidities complained of lower back pain with initial workup revealing vertebral body compression with spinal canal stenosis, with an anterior paraspinal soft tissue at the T2 and L5 along with a positive TB quantiferon result favoring tuberculous spondylodiscitis. He denied fever, cough, or weight loss; eventually managed as Pott's disease and was started on Anti-Koch's regimen. Despite treatment for 4 months, the patient noted worsening of lower back pain now with difficulty ambulating, constipation and urinary urgency. He was advised admission for emergent surgery due to symptoms of cauda equina syndrome. Lateral rectus palsy was noted during physical exam, hence a brain scan was requested which revealed a skull base lesion. Now entertaining the possibility of malignancy, cancer markers were requested (TSH, CEA and AFP all normal, with elevation of PSA at 5.46) and PET scan was done with attenuation of the thyroid gland and the soft tissue paraspinal mass. During laminectomy, specimens were sent for cultures which returned negative, with histopathology showed metastatic carcinoma. Anti-Koch's regimen was discontinued, and patient was referred to Endocrinology. Thyroid ultrasound done showed multiple TIRADS 4 nodules, and IHC stains positive CK7, Thyroglobulin, PAX8, TTF-1, favoring thyroid as the primary carcinoma. Patient underwent total thyroidectomy with a final histopathology of papillary thyroid cancer, encapsulated follicular variant. On follow up, patient underwent RAI therapy, with post-RAI scan showing no iodine-avid thyroid tissue, but with uptake on the skull base, pelvis and right femur and was subsequently started on levothyroxine therapy.

**Discussion**

We report an unusual case of papillary thyroid cancer initially presenting as severe back pain leading to cauda equina syndrome. Although metastasis is the most common cause of tumors in the spine, having it as the initial presentation of thyroid cancer is rare, and metastatic workup of spinal lesions should include the thyroid.

# Friday, November 1, 2024

## Poster 0296

*Autoimmunity, Case Study, Poster*

### Conversion of Hashimoto's thyroiditis to Graves' disease; a rare phenomenon

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#### Introduction

Hashimoto's thyroiditis and Graves' disease are autoimmune diseases with potential for interconversion. Conversion from Graves' disease to Hashimoto's thyroiditis is more common than the vice versa. We are presenting a case of a patient in whom Hashimoto's thyroiditis shifted to Graves' disease.

#### Case presentation

A 63-year-old female was diagnosed with HT 10 years ago and was treated with levothyroxine 112 mcg daily, however, the dose of levothyroxine was tapered down to 50 mcg daily. She was referred to an endocrinologist for excessive eye tearing, fatigue, muscle weakness, and palpitations.

On examination, she had periorbital edema along with conjunctival injection, and inflammation of the caruncle. Her TSH was suppressed at 0.010 mcU/ml (0.4-4.2), free T4 elevated to 2.8 ng/dl (0.6 – 1.5) and had elevated antibodies including TRAb at 32.20 IU/L and thyroid stimulating immunoglobulin Antibody (TSI Ab) at 7.5 IU/L. CT scan of the orbit showed proptosis secondary to thyroid orbitopathy and her Doppler imaging of the thyroid was consistent with hyperemia. Consequently, levothyroxine was discontinued, and she was started on methimazole.

#### Discussion

Conversion from HT to GD is very rare. The reason behind this conversion remains debatable. More than 50% - 70% of patients with GD also have TPOAb and TgAb, [1], similarly, TRAb is detected in 10% of HT cases.[2] Patient who had conversion from HT to GD have both TSAb and TRAb that cause thyroid in a push and pull state and favors the antibody which is higher in concentration. [3] Thyroid gland recovery from HT injury and start responding to TSAb leading to the conversion to GD. Given, TSAb has higher affinity to TSH receptor than as compared to TSH. [3] Studies have reported a positive correlation between levothyroxine dose and the appearance of de novo TSAb or an increase in TSAb. [4,5]

#### Conclusion

A high index of suspicion should be raised in patients with HT, especially if levothyroxine demand is decreasing. Further testing for GD autoantibodies and meticulous clinical examination should help in the early diagnosis of the conversion.

## Poster 0297

*Autoimmunity, Clinical, Poster*

### Improvements in Quality of Life with Teprotumumab in Patients with Chronic, Low Disease Activity TED With a Proptosis Response

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**Objective:** In thyroid eye disease (TED) patients, proptosis and diplopia can impact quality of life (QoL) over several years. In the phase 4 trial of teprotumumab (NCT04583735) in patients with disease duration 2-10 years and clinical activity score (CAS)≤1, proptosis was significantly reduced with teprotumumab vs placebo. Proptosis response (≥2mm improvement) was observed in 63% of teprotumumab vs 25% of placebo patients. We assessed QoL improvements in proptosis responders and non-responders.

**Methods:** Data from teprotumumab-treated patients was included in this post hoc analysis. Patients were to receive 8 infusions of teprotumumab. At baseline, weeks 12 and 24, the Graves' ophthalmopathy quality of life questionnaire (GO-QoL) was used to measure total, visual-function (VF)-related, and appearance (AP)-related QoL. Improvements >10 points were defined as clinically meaningful. Mean improvements from baseline were calculated for responders and non-responders. Patients were categorized as higher or lower baseline QoL based on medial total score, and improvements in total, VF and AP at week 24 were calculated for these subgroups. Differences between responders/non-responders and between higher/lower baseline QoL patients were compared using t-test.

**Results:** Of 42 teprotumumab patients, 26 were proptosis responders, and 16 were non-responders. At baseline, mean (SD) total, AP and VF scores were lower in responders vs non-responders: Total: 64.0 (24.6) vs 70.1 (16.0), AP: 45.0 (30.5) vs 48.8 (28.7); VF: 83.1 (23.9) vs 91.7 (9.9). At week 24, responders had clinically meaningful, moderate improvements from baseline: total GO-QoL mean (SD) 10.6 (18.4), AP 11.1 (24.8) and VF 10.1 (22.4) points. In non-responders, total score improved by 5.6 (16.5), AP by 7.7 (29.3), and VF 3.0 (10.7) points; difference was not significant between responders and non-responders.

At baseline, 20 and 22 patients were categorized as higher and lower QoL groups, respectively. Those with lower baseline GO-QoL had greater improvements than those with higher baseline GO-QoL, although differences between the groups were only significant for VF: total, mean (SD) 14.1 (21.8) vs 3.6 (10.1), p=0.06; VF, 14.9 (24.5) vs 0.1 (6.7), p<0.02; AP, 12.8 (32.5) vs 6.9 (17.4), p=0.48.

**Conclusions:** Clinically meaningful improvements in total GO-QoL, VF- and AP-related scores were noted in proptosis responders, with smaller improvements for non-responders. Patients with lower baseline GO-QoL experienced greater improvements than those with higher baseline GO-QoL.

## Poster 0298

*Autoimmunity, Clinical, Poster*

### Increasing Incidence of Pediatric Graves' Disease in the U.S.: An Epidemiological Analysis of 2007-2022 Outpatient Insurance Claims

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**OBJECTIVES:** This study aims to investigate the reported increase in incidence of pediatric Graves' disease in the U.S., assessing epidemiological trends and distribution patterns based on sex, age group, census-designated geographical region, urban/rural setting, and health insurance plan type.

**METHODS:** This retrospective cohort study utilized the Merative™ Marketscan® outpatient insurance claims database, from 2007 to 2022. Pediatric (age <18) patients diagnosed with Graves' disease were identified using ICD-9 and ICD-10 codes. Annual

incidence rates were analyzed over the study period to detect temporal trends. Incidence rates were further stratified by demographic and systemic variables: sex, age, census-designated region, urban/rural setting, and insurance plan. Statistical methods included t-tests, ANOVA, and linear regression models to identify significant trends and differences across subgroups.

**RESULTS:** A total of 20,147 new diagnoses of pediatric Graves' disease were identified during the 15-year study period. The average annual incidence rate was 19.81 per 100,000 (SD = 6.92), with an observed increase of 0.99 per 100,000 annually ( $p < 0.01$ ). Marked sex differences in incidence were observed ( $p < 0.001$ ); females exhibited greater incidence (mean = 29.13 per 100,000) and rate of change ( $b = 1.28$ ,  $p < 0.01$ ) compared to males (mean = 10.79 per 100,000). Both sexes exhibited increasing incidence rate with age; adolescents (13 to <18 years) had highest incidence (34.40 per 100,000) compared to other age groups ( $p < 0.001$ ) among both sexes. Children covered under Point of Service (POS) plans showed highest incidence rates at 1.33 per 100,000 ( $p < 0.05$ ). No significant differences were observed across geographic regions ( $p = 0.125$ ), or urban (19.96 per 100,000) or rural (18.51 per 100,000) settings ( $p = 0.560$ ).

**DISCUSSION/CONCLUSION:** This study delineates and quantifies a rising trend in the incidence of pediatric Graves' disease in the U.S. Significant variations by gender, age, and insurance type were observed, but geographic variables did not show significant differences. Greatest average incidence and rate of change were observed among females, adolescents, patients in the Northeast region, and patients with POS insurance. This study underscores the importance of monitoring Graves' disease trends and patterns to facilitate early detection and management strategies. Further research is needed to elucidate genetic and environmental factors underlying these epidemiological trends.

### Poster 0299

*Autoimmunity, Clinical, Poster*

#### **University of Pittsburgh Real World Experience with Teprotumumab: Outcomes and Side Effects**

*Sahana Parthasarathy\*, Esra Karslioglu French, UPMC, USA*

**Objective:** Thyroid eye disease (TED) is an immune mediated infiltration and inflammation of the orbital and periorbital soft tissues which leads to disfiguring, and potentially blinding periorbital changes. Teprotumumab was FDA approved in 2020 for the treatment of TED. It inhibits insulin-like growth factor-1 receptor resulting in significant improvements in proptosis and diplopia. We are reporting Teprotumumab real world outcomes and side effects data from University of Pittsburgh Multidisciplinary TED Clinic.

**Methods:** We completed a retrospective chart review on all the patients who received Teprotumumab at University of Pittsburgh Multidisciplinary TED Clinic since its approval in January 2020. Clinical outcomes such as treatment completion rate, proptosis response, resolution of diplopia, and change in clinical activity score were analyzed. Data on adverse events were extracted from providers documentation and medication administration records.

**Results:** Total of 46 patients received Teprotumumab therapy for the treatment of TED from January 2020 to December 2023 in our clinic. Mean age of the study population was 56 years. Out of 46 patients, 36 (78.2%) completed the 8-infusion course. Proptosis improved by 2mm or more in 76% of patients (35/46). Disease inactivation occurred in 96% of patients (44/46) with average clinical activity score reduction of 3.4 points. Reduction in diplopia was seen in 82.6% of patients (38/46). Adverse Effects occurred in 60.8% of patients (28/46), none of them had any serious adverse events. The most common type of AEs was musculoskeletal (21.7%

[10/46]), ear and labyrinth (21.7% [10/46]), followed by metabolic (Hyperglycemia) (17.3% [8/46]), and gastrointestinal (10.8% [5/46]).

**Discussion/Conclusion:** University of Pittsburgh Multidisciplinary TED Clinic real world data shows Teprotumumab is an effective treatment in decreasing proptosis, resolution of diplopia and causing disease inactivation. Side effects profile of our cohort was similar to data reported in RCT. No serious AE, sepsis, or DKA were reported. Based on our analysis, we recommend baseline A1C screening and to consider early audiology/ENT involvement in patients with hearing impairments.

### Poster 0300

*Thyroid Cancer, Case Study, Poster*

#### **Malignant Struma Ovarii: A Rare Malignancy**

*Sahana Parthasarathy\*, Esra Karslioglu French, UPMC, USA*

**Introduction:** Malignant struma ovarii (MSO) is an extremely rare condition. So far less than 200 cases have been reported. The management of MSO cases remains a subject of controversy. Given the similarities with the thyroid cancer, cytoreductive surgery followed by with or without radioactive ablation therapy has been proposed. This report details a case of MSO with a detected RAS mutation.

**Description of the case:** 57-year-old female patient with right ovarian mass discovered incidentally during the evaluation of elective sigmoid resection for recurrent diverticulitis. Patient had a history of total thyroidectomy for Graves' disease at the age of 41 and she had been on levothyroxine replacement therapy since then. She had hysterectomy and left salpingo-oophorectomy at the age of 40 for fibroids/pelvic adhesions. Pre-operative studies showed normal thyroid function tests. Patient underwent laparoscopic sigmoidectomy with colorectal anastomosis and right salpingo-oophorectomy. Intra operative findings included enlarged right ovary which was not adherent to surrounding structures. Final pathology revealed MSO with papillary thyroid carcinoma, 2 cm in size, follicular and tall cell variants, confined to the ovary with a background of benign serous cystadenoma of 4 cm. There was no lymphovascular invasion seen. Post op evaluation included: Molecular study of the surgical specimen showing N-RAS mutation. Thyroid USG showed no abnormal tissue in the thyroid fossa. No suspicious or FDG avid lesions were seen on PET/CT. Thyroglobulin was < 0.5 ng/mL with Tg Ab < 0.4 U/mL. Patient was risk stratified to low-risk group with FIGO stage 1A and will be monitored annually with Tg panel and TSH goal of < 2 uIU/mL.

**Discussion:** MSO is a rare malignancy with variable treatment algorithms based on staging. Cases may benefit from risk stratification by pathological features similar to the ATA guidelines for thyroid cancer and multidisciplinary discussion for RAI utilization based on risk. In general, for early stage and low risk histopathology tumors, RAI can be safely omitted. Whereas the thyroid targeted therapy is warranted for high-risk histopathology and advanced disease. Molecular studies can help with risk stratification.

### Poster 0301

*Autoimmunity, Clinical, Poster*

#### **Clinical characteristics of serum IgG4 elevated Hashimoto's thyroiditis**

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**Background:** The aim of this study is to explore the clinical characteristics of elevated serum IgG4 ( $\geq 135$ mg/dl) in HT and the predictive value of serum IgG4 for the progression of HT to hypothyroidism.

**Methods:** Clinical data of HT outpatients with stored serum samples in our hospital were collected from April 2016 to September 2016, and a total of 200 HT patients were followed up during January 2021 to January 2022. The clinical data of HT patients with different serum IgG4 levels at initial enrollment and follow-up were compared, and the related risk factors for HT disease progression were further analyzed by Cox regression model.

**Results:** Only 11(5.5%) HT patients were diagnosed with serum elevated IgG4 HT in the 200 HT patients. There were no significant differences between elevated serum IgG4 HT and non-elevated serum IgG4 HT in age, gender, initial thyroid function status, TgAb and TPOAb levels, thyroid echography, and thyroid nodules. The follow-up time of 200 HT patients was 59 (20-68) months. After the follow-up, no significant differences were found in thyroid function status, L-T4 treatment, positive changes of TgAb and TPOAb, and disease progression between elevated serum IgG4 and non-elevated serum IgG4 HT groups. The incidence of initial hypothyroidism was higher (73.7% vs. 36.4%,  $P < 0.001$ ) and hypoechoogenicity was more likely to occur on thyroid ultrasound images (8.8% vs. 2.3%,  $P=0.038$ ) in the disease progression group than the non-progression group. There were no significant differences in age, gender, TgAb and TPOAb levels, serum IgG4 levels, grid-like echo characteristics and thyroid nodules between the two groups. Further analysis of risk factors for HT progression showed that the initial state of hypothyroidism is an independent risk factor for the progression of HT (HR: 2.19, 95%CI: 1.142 ~ 4.182,  $P=0.018$ ).

**Conclusions:** When serum IgG4 was measured by immunoturbidimetry, the incidence of elevated serum IgG4 HT was 5.5%. No unique clinical, ultrasonic characteristics or a tendency to disease progression were found in serum IgG4-elevated HT patients. Serum IgG4 may not be a good predictor of HT disease progression.

## Poster 0302

*Autoimmunity, Basic, Poster*

### LDHA Mediated Glycolysis Promotes Fibrosis in IgG4 Hashimoto's thyroiditis Through Facilitating Epithelial-Mesenchymal Transition

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**Background:** Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism. IgG4 HT, a special type of HT, is characterized by a shorter disease course, a more severe degree of interstitial fibrosis, and a higher tendency to progress into hypothyroidism. It is reported in the literature that glycolysis is enhanced in the epithelial-mesenchymal transition (EMT) of cardiac and hepatic cells, thus participating in the occurrence and development of fibrosis. This study aims to clarify the role and mechanism of lactate dehydrogenase A (LDHA) in the EMT and fibrosis of thyrocytes from the perspective of glycolysis, providing new ideas for the clinical treatment of thyroid fibrosis.

**Methods:** Proteomic analysis was applied to investigate the differential proteins in the glycolysis pathway between IgG4 HT and non-IgG4 HT, and the proteomic results were verified through immunohistochemistry. PCR and Western blot were used to detect changes in the expression of key glycolytic enzymes and EMT marker molecules (FN,  $\alpha$ -SMA, and E-Cadherin) in the thyroid cells. Furthermore, siRNA was used to knock down LDHA in the Nthy-ori 3-1 cells, and the expression changes of EMT in thyrocytes were examined. RNA sequencing was performed to compare the transcriptomes of control and TGF- $\beta$ 1 treated thyrocytes.

**Results:** Proteomic GSEA revealed glycolysis pathway was upregulated in thyroid tissues from IgG4 HT compared with non IgG4 HT. Increased expression of LDHA, FN,  $\alpha$ -SMA, and decreased expression of E-Cadherin were detected in IgG4 HT. TGF- $\beta$ 1 induced the EMT process by increasing the glycolysis relative gene LDHA. Moreover, knockdown of Nupr1 reduced the LDHA expression.

**Conclusions:** LDHA triggers the EMT of thyrocytes by driving abnormal glycolysis and may therefore become a potential therapeutic target for IgG4 HT.

## Poster 0303

*Autoimmunity, Clinical*

### Prognostic Factors and Outcomes of Intravenous Glucocorticoid Pulse Therapy in Moderate-to-Severe Thyroid Eye Disease

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**Objectives:** This retrospective cohort study aimed to identify prognostic factors associated with treatment success in patients with active moderate-to-severe Thyroid Eye Disease (TED) undergoing intravenous glucocorticoid (ivGC) therapy, defined as the absence of the necessity for additional rehabilitative surgery. Additional objectives included assessing changes in ophthalmological parameters and thyroid-specific markers correlated with TED development and severity post-treatment, aiming to optimize disease management strategies by predicting treatment outcomes and identifying potentially responsive individuals.

**Methods:** At Charité – University Hospital of Berlin (2014-2021), 146 patients underwent standard ivGC pulse therapy between 2014 and 2021 per ATA/EUGOGO guidelines for 12 weeks. Ophthalmological assessments, including visual field examinations, assessments of visual acuity, diplopia, Clinical Activity Score (CAS) and proptosis, were conducted before and after treatment alongside regular blood examinations evaluating thyroid hormone and antibody levels. Appropriate tests were implemented to assess differences in ophthalmological and thyroid parameters before and after treatment, as well as regression models to determine predictive factors associated with treatment outcomes.

**Results:** Current smoking (Odds Ratio, OR=3.243,  $p=0.010$ ), rather than smoking history, emerged as a significant predictor of the need for additional surgery following ivGC treatment. Similarly, baseline diplopia (OR=2.971,  $p=0.049$ ) was also identified as a significant predictor. Antithyroid drug (ATD) treatment showed marginal significance (OR=0.388,  $p=0.077$ ), indicating a potential predictive role in the requirement for rehabilitative surgery. Following treatment completion, only the CAS and diplopia exhibited statistically significant reductions ( $p<0.001$  for both), while other ophthalmic parameters did not demonstrate significant changes. Although there was a notable trend towards reduction in Thyrotropin Receptor Antibodies (TRAbs), it did not reach statistical significance.

**Conclusions:** Our study underscores the significant ophthalmological improvements achieved with ivGC treatment, reflected in the CAS and the reduction of diplopia, a prominent feature impacting the quality of life in Thyroid Eye Disease, which could partially be mediated through reductions, albeit non-significant, in TRAbs. Identifying predictors of treatment efficacy with immunosuppressive therapy, including smoking and baseline diplopia, emphasizes the need for personalized intervention strategies. Moreover, the marginal significance of ATD underscores the importance of maintaining euthyroidism to prevent exacerbation and optimize outcomes during ivGC treatment.

**Poster 0304***Autoimmunity, Clinical, Poster***Subcutaneous Efgartigimod PH20 for the Treatment of Thyroid Eye Disease in Adults (UplighTED): Study Design for Two Identical, Parallel, Phase 3, Randomized, Placebo-Controlled Studies**

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**Objective:** Preclinical/clinical studies support that thyroid-stimulating hormone receptor (TSHR) autoantibodies may drive thyroid eye disease (TED) pathogenesis. Efgartigimod, a human immunoglobulin G (IgG)1 Fc fragment, blocks the neonatal Fc receptor, selectively decreasing IgG levels, including pathogenic IgG autoantibodies. Efgartigimod could potentially reduce TED clinical manifestations. Two identical, parallel trials (UplighTED) will assess the efficacy, safety/tolerability, PK/PD, and immunogenicity of subcutaneous (SC) efgartigimod PH20 (co-formulated with recombinant human hyaluronidase PH20) administered by prefilled syringe in adults with TED.

**Methods:** These phase 3, randomized, double-masked, placebo-controlled, multicenter studies will each enroll ~108 participants with active, moderate-to-severe TED associated with autoimmune thyroid pathology (Graves' disease or Hashimoto's thyroiditis). Participants will be randomized 2:1 to receive efgartigimod PH20 SC (n=72) or placebo PH20 SC (n=36) once weekly during a 24-week, double-blinded treatment period (DBTP). Following the DBTP, proptosis responders will enter a 52-week, follow-up observational period to assess the safety/tolerability, and durability of efgartigimod PH20 SC while off therapy. Proptosis nonresponders at DBTP Week 24, and participants who have proptosis relapse during the observational period, will receive open-label, weekly efgartigimod PH20 SC for up to 24 weeks, from DBTP Week 24 or time of relapse, respectively.

**Results:** Primary endpoint is percentage of participants who are proptosis responders ( $\geq 2$  mm reduction from baseline in proptosis in the study eye [most severely affected eye at baseline] and without deterioration [ $\geq 2$  mm increase] of proptosis in the nonstudy eye) at DBTP Week 24. Key secondary endpoints include changes from baseline in proptosis measurement (study eye) and total Graves' Orbitopathy Quality of Life (QoL) questionnaire score, and percentage of participants with resolution of diplopia (baseline Gorman score of diplopia  $>0$ , with an improved score of 0 [no diplopia]), at DBTP Week 24.

Multiple secondary endpoints will assess speed of response onset, changes in diplopia Gorman score and clinical activity score, adverse events, PK parameters, development of antibodies against efgartigimod PH20 SC, effect on total binding TSHR autoantibodies, and participant-reported QoL and treatment satisfaction.

**Conclusion:** These phase 3 studies will assess the efficacy, safety/tolerability, PK/PD, and immunogenicity of efgartigimod PH20 SC in adults with TED.

**Poster 0305***Autoimmunity, Clinical, Poster***Clinical Outcomes in Pediatric Graves' Disease Treated with Anti-thyroid Drugs and Radioactive Iodine**

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**Background:** Graves' disease (GD) is the most common cause of hyperthyroidism in children and adolescents. It is an autoimmune disorder that causes the thyroid gland to increase thyroid hormone (TH) synthesis and secretion. THs play a crucial role in regulating metabolism, growth, and development. Excess THs levels can significantly impact a child's health. The current therapeutic approaches for pediatric GD include anti-thyroid drugs (ATD), radioactive iodine therapy (RAI), or surgery. There is a low disease remission rate with ATD use in this group, meaning that most children who take ATDs will eventually experience disease relapse.

**Objective:** To describe the clinical outcomes of young patients, under 19 years old, with GD treated with ATD and RAI. To critically assess the treatment's success rate and identify factors that might influence disease relapse.

**Methods:** Retrospective observational study, through evaluation of medical records of patients younger than 19 years of age with confirmed GD, from a tertiary hospital in Brasilia, Brazil. Exclusion criteria included incomplete medical records and patients with less than one year of follow-up.

**Results:** Twenty-one patients were included, predominantly females (15/21), 71.4%, (p=0.049). Mean age at diagnosis was  $9.6 \pm 3.5$  years, slightly prevailing prepubertal individuals (12/21). Mean free T4 (fT4) at diagnosis was  $5.27 \pm 2.04$  ng/dL and mean duration of methimazole treatment was  $3.1 \pm 2.0$  years. Sixteen patients underwent RAI, with a mean RAI dose of  $13.18 \pm 4.24$  mCi, and a recurrence rate of 25%. Notably, patients with fT4 greater than 5 ng/dL at diagnosis were more likely to be referred for RAI (p=0.016). Those who experienced recurrence after RAI were older ( $> 10$  years of age) at the time of diagnosis (p=0.032).

**Discussion/Conclusion:** The study suggests that a fT4 level above 5 ng/dL at diagnosis serves as a relevant indicator of a low remission rate with ATD and, consequently, progression to definitive therapy - RAI. Furthermore, we observed an elevated frequency of GD diagnosis in pre-pubertal individuals, suggesting that this autoimmunity dysregulation is manifesting earlier in the studied population. The recurrence rate after RAI did not differ significantly from other cohorts.

**Poster 0306***Thyroid Cancer, Clinical, Poster***Characteristics and Outcomes of Pediatric Differentiated Thyroid Carcinoma: A Single-Center Experience**

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**Introduction:** Pediatric differentiated thyroid cancer (DTC) is increasing among children and adolescents in recent years, and diagnosing DTC in this population can be challenging because it often presents with few or no symptoms and yet, with locoregional or distant metastasis. Papillary thyroid carcinoma (PTC) is the most common type of DTC in children. Genetic background, clinical presentation, and histopathology findings are different from adult DTC.

**Objective:** The study aimed to describe a pediatric cohort according to their clinical and histopathology findings and their outcomes.

**Methods:** Restrospective observational study with pediatric patients aged 5-21 years old, with DTC of at least one year follow-up, in a tertiary hospital in Brasilia, Brazil. Data were collected from medical records, such as histopathology findings, risk stratification, radioactive iodine therapy (RAI), and surgery.

**Results:** There were fourteen DTC patients, predominantly females 78.5% (11/14). The mean age at diagnosis was 16 years old

( $\pm$  2.9 SDS). According to DTC classification TNM, seventy percent had intermediate to high-risk stratification. The median tumor size was 2.7 cm (IQR= 1.48), with a slightly higher frequency of multifocal distribution (57%). The most frequent DTC type was papillary thyroid cancer (92,8%), with 8/14 from classic subtype. Four patients had aggressive histopathology findings, 02 diffuse sclerosing, 01 tall cell and 01 columnar cell subtypes. Most patients (64,2%) developed locoregional or distant metastasis, being 6/14 with pulmonary metastasis. Following high-risk disease stratification, the most frequent surgery performed was total thyroidectomy with ipsi or bilateral central/lateral lymphadenectomy 9/14. The RAI median dose was 100 mCi (IQR= 50). Only 3/14 patients had persistent disease with high levels of thyroglobulin. In this cohort, 1 patient had a pathogenic variant c.2804 duplication from Adenomatous Polyposis Coli - APC gene.

**Conclusions:** While the presence of intermediate to high-risk stratification and multifocal tumors suggests an aggressive presentation in this cohort, the good response to treatment, with only 3 patients showing persistent disease, indicates the potential effectiveness of current treatment strategies and good response in the pediatric population.

### Poster 0307

*Autoimmunity, Clinical, Poster*

#### **Subcutaneous Administration of VRDN-003, a Next-Generation Full Antagonist Antibody to IGF-1R, in Patients With Thyroid Eye Disease (TED): Two Randomized Placebo-Controlled Clinical Studies (REVEAL-1 and REVEAL-2)**

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**Objective:** VRDN-001 and VRDN-003 are full antagonist antibodies to the IGF-1 receptor (IGF-1R). These antibodies have the same binding domain but VRDN-003 contains half-life extension modifications. Prior phase 2 proof-of-concept data for VRDN-001 showed clinically meaningful improvements in TED signs and symptoms after 2 intravenous (IV) infusions administered every 3 weeks (Q3W). Phase 1 data for VRDN-003 in healthy volunteers showed that its half-life is 4-5 times that of VRDN-001, potentially enabling low-volume subcutaneous dosing as infrequently as Q8W, while achieving exposures in the range of those observed with VRDN-001 IV dosing Q3W. The safety and efficacy of subcutaneous administration of VRDN-003 are planned to be evaluated in two randomized placebo-controlled clinical studies in patients with moderate-to-severe active TED (REVEAL-1) and chronic TED (REVEAL-2).

**Methods:** The proposed study designs are currently pending regulatory alignment. They aim to evaluate VRDN-003 vs placebo administered as a subcutaneous injection in at least 1 of 3 dosing regimens: Q2W, Q4W, and Q8W. For REVEAL-1, patients must have a clinical activity score (CAS) of  $\geq 3$  and onset of signs/symptoms within 15 months of enrollment and for REVEAL-2, patients can have any CAS and must have onset of signs/symptoms at least 15 months prior to enrollment. Efficacy assessments will include measures of proptosis, diplopia, CAS, eyelid retraction, and quality of life. Safety and tolerability will be assessed through the full study period. An open-label study is planned for patients who are nonresponders at the end of the treatment phase to have the option to receive a full course of 5 injections of VRDN-003.

**Discussion/Conclusion:** VRDN-003 is in development as a subcutaneous treatment for TED with the goal of reducing the treatment

burden currently associated with IV infusions. The REVEAL-1 and REVEAL-2 randomized, double-masked, placebo-controlled trials will be the first to assess subcutaneous VRDN-003 in patients with TED.

### Poster 0308

*Disorders of Thyroid Function, Clinical, Poster*

#### **Comparative Efficacy of Corticosteroids and Teprotumumab in Thyroid Eye Disease Management**

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**Objective:** This study compares the need for additional therapeutic interventions in TED (Thyroid Eye Disease) patients treated with corticosteroids versus teprotumumab.

**Methods:** A retrospective cohort study identified TED patients (ICD-10 code E05.0) from the TriNetX Analytics EHR database. Excluding patients requiring high-dose steroids for other illnesses, two groups were formed: Group 1 received  $\geq 125$  mg IV methylprednisolone (IVMP) across at least four infusions, and Group 2 received  $\geq 10$  mg/kg teprotumumab in at least two infusions. A six-month washout period preceded outcome measurements to mitigate confounders. Outcomes included TED-related surgeries and further medical therapies, tracked over six, 12, and 18 months; IVMP group was additionally monitored for three years. Propensity Score Matching (PSM) was employed to adjust for baseline differences like sleep apnea and prior thyroidectomy, ensuring comparability. Data collection concluded on March 29, 2024, with t-tests analyzing group differences.

**Results:** The study included 497 IVMP and 318 teprotumumab patients, with 297 in each PSM cohort. Significant racial differences emerged with more Caucasians in the teprotumumab group and more African Americans in the IVMP group (75% vs. 65% and 24% vs. 9%,  $p < 0.005$ , respectively). The teprotumumab cohort needed fewer biologics and steroids but underwent more TED-related surgeries (ORs 3.8, 4.3, and 0.41; all  $p < 0.01$ ). Surgery rates in the IVMP cohort slightly rose over three years but were not significant. About 40% of each group required additional treatments, primarily repeating initial therapies (49.3% IVMP, 70.8% teprotumumab of those requiring additional treatment). Surgeries were more common post-teprotumumab, and corticosteroid therapies post-IVMP, with a lower reoperation rate in the teprotumumab group (23.8% vs. 50.0%).

**Conclusion:** TED patients treated with teprotumumab required fewer additional medical interventions yet more surgeries over the study period compared to those treated with IVMP. These findings suggest teprotumumab may stabilize the disease sufficiently for earlier surgical interventions, warranting further research to determine if teprotumumab directly impacts surgical needs or facilitates earlier rehabilitation through effective disease control.

### Poster 0309

*Disorders of Thyroid Function, Poster*

#### **Restoration of Bone Health in Hyperthyroid-Induced Osteoporosis: Insights from a Postmenopausal Case Study**

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Osteoporosis is a feature of untreated thyrotoxicosis secondary to an accelerated rate of bone turnover. Numerous reports describe a

consistent decrease in bone mineral density (BMD) and increase in fracture risk in overt hyperthyroidism. A TSH level of  $<0.1$  uIU/mL has been associated with a 4.5-fold risk of vertebral fracture. However, antithyroid treatment and achieving a euthyroid state can reverse osteoporosis caused by hyperthyroidism.

We present a 59-year-old woman who presented with weight loss, atrial fibrillation, and congestive heart failure in 2020, and was diagnosed with Graves' disease. On admission, her TSH was undetectable, with fT4 level of 7 ng/dL (0.93-1.7 ng/dL); serum calcium was 9.7 mg/dL, and vitamin D 34 ng/dL. Given hyperthyroidism and postmenopausal status, she underwent a dual-energy X-ray absorptiometry (DXA) scan in 10/20. The results indicated T scores of -2.7 at the lumbar spine (LS) and -2.4 at the femoral neck (FN) with Z scores of -1.9 and -1.4 respectively. Subsequently, an elevated fractionated bone alkaline phosphatase of 249 U/L (0- 55 U/L) was noted. She started on treatment with Methimazole and achieved euthyroidism within 6 months. She also followed recommendations for daily calcium and vitamin D supplementation.

A follow-up DXA scan in 12/21, conducted on the same GE Lunar Prodigy machine, demonstrated marked improvements with persistent euthyroidism: a T score of -1.4 at the FN and -0.7 at the LS with Z scores of -0.3 and 0.2 respectively, corresponding to a 28% increase in BMD at both sites. This was confirmed in 2023: FN T score -0.9. (6.7% further increase) and LS T score -0.2 (6% increase). Her current laboratory results indicate normal levels of bone-fractionated alkaline phosphatase.

This patient achieved complete normalization of bone density; however, there is currently no consensus on the optimal timing for conducting DXA scans, nor are there well-defined treatment strategies for managing osteoporosis in hyperthyroid patients. Specifically, the debate continues over whether to treat with antithyroid drugs alone or in combination with bisphosphonates, particularly in postmenopausal women. Improvements in our patient suggest that immediate implementation of osteoporosis drug therapy might be premature, but appropriate guidelines are wanted.

### Poster 0310

*Disorders of Thyroid Function, Clinical, Poster*

#### Barriers and Facilitators to Evidence-based Use of Levothyroxine

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**Objective:** Levothyroxine (LT4) is the second most prescribed drug in the United States (25 million users). There is clear evidence of substantial LT4 overuse, which is wasteful and harmful. Factors hindering the evidence-based use of LT4 are not well understood. We aimed to explore multi-level barriers and facilitators to evidence-based use of LT4, hypothesizing involvement from patients, clinicians, and the healthcare system.

**Methods:** Between September 2021 and October 2023, we conducted semi-structured in-depth interviews with a convenience sample of key Central Arkansas Veterans Healthcare System stakeholders to identify barriers and facilitators to implementing evidence-based use of LT4. The Consolidated Framework for Implementation Research (CFIR) 2.0 guided our formative evaluation, adapting interview guides for each stakeholder group. Data collection continued until saturation, with rapid qualitative analysis done within groups.

**Results:** We interviewed 10 primary care clinicians, three executive leaders in Primary Care, Pharmacy, and Informatics, and 45 patients with mild subclinical hypothyroidism treated with LT4. Barriers to evidence-based use of LT4 were grouped into four CFIR 2.0 domains: 1) lack of informed discussion about LT4 initiation between patients and clinicians (Implementation process), 2) lack of clinicians knowledgeable about updated clinical practice guidelines, prescriber comfort, clinical inertia, clinicians perceived benefits of LT4, patient anxiety/fear of losing any potential benefit, expectations for LT4 delivery (Individuals), 3) care coordination, waste of resources, time constraints, peer pressure (Inner setting), and 4) patient pressure (Outer setting). Hypothetical facilitators for evidence-based use of LT4 were grouped into four CFIR 2.0 domains: 1) electronic medical records decision support tools with built-in data, pharmacy alerts, clinical reminders, audit and feedback (Implementation process), 2) physician engagement, patient/provider education, patient satisfaction, patient-clinician trust (Individuals), 3) leadership support, access to specialists, access to patient labs prior to encounters, encounters dedicated to discuss LT4 initiation (Inner setting), and 4) organizational performance metrics (Outer setting).

**Discussion/Conclusion:** We identified multiple barriers and facilitators to implementation of current guidelines for LT4 use from the perspective of key stakeholders. Our findings can inform the development of a feasible and acceptable multi-level and multi-component strategy package to address LT4 overuse and support evidence-based LT4 prescriptions.

### Poster 0311

*Disorders of Thyroid Function, Clinical, Poster*

#### FLT3 polymorphisms and FLT3 ligand levels in thyroid irAEs

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**Objective:** Thyroid immune related adverse events (irAEs) are a frequent complication of immune checkpoint inhibitor (ICI) treatment. Clinical presentation and course of thyroid irAEs are similar to sporadic thyroiditis in patients with autoimmune thyroid disease (AITD) not receiving ICI-treatment. Autoimmune thyroiditis is highly heritable, and rs76428106-C single nucleotide polymorphism in fms-related tyrosine kinase 3 (FLT3) gene have recently been strongly associated with susceptibility to AITD.

**Methods:** Case control study of adult patients undergoing ICI-treatment for melanoma. Germline FLT3 rs76428106-C SNP data was determined from patient blood samples with known thyroid irAE outcomes.

**Results:** 482 patients were included, of whom 52% experienced a thyroid irAE. Allelic frequency of FLT3 rs76428106-C was low (1.9%). Two patients demonstrated homozygosity for the FLT3 rs76428106-C variant, both of whom developed a thyroid irAE. Fourteen patients demonstrated heterozygosity for the FLT3 rs76428106-C variant, of whom 8 (57%) developed a thyroid irAE. The remaining 466 patients were wild type for FLT3, of whom 224 (48%) developed a thyroid irAE.

**Discussion/Conclusion:** Our pilot study tested whether a recently discovered AITD susceptibility variant in FLT3 gene (rs76428106-C) was associated with the development of thyroid irAEs. GWAS data from 482 patients showed that thyroid irAE prevalence was highest in homozygotes (100%), intermediate in heterozygotes (57%), and lowest in wild type patients (48%). Due to our small sample size and the low allelic frequency of FLT3 rs76428106-C,

our study was underpowered to test statistical association with thyroid irAEs. However, our results showed a strong trend towards increased irAE susceptibility in association with FLT3 rs76428106-C SNPs. Our results suggest that FLT3 rs76428106-C warrants further investigation as a susceptibility marker for thyroid irAEs and supports a possible shared pathogenic mechanism between thyroid irAEs and other non-ICI mediated AITDs.

### Poster 0312

*Disorders of Thyroid Function, Clinical, Poster*

#### Outcome of radioactive iodine therapy for Graves' disease using pretreatment with either potassium iodide or methimazole

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**Objective:** To investigate the utility of inorganic iodine as a pretreatment before radioactive iodine therapy (RIT) for Graves' disease (GD) and the optimal withdrawal period of inorganic iodine before RIT.

**Methods:** We retrospectively reviewed the outcomes of RIT for GD patients pretreated with methimazole (MMI) or potassium iodide (KI) in our clinic. The subjects were 717 patients with thyroid volumes of 10.0-59.9 ml. <sup>131</sup>I was administered at a fixed dose of 481 MBq. MMI was transiently discontinued for 2 days (MMI, n=402), and KI was discontinued 3 days (KI3, n=149) or 5 days (KI5, n=166) before RIT. MMI and KI were resumed 2 days after <sup>131</sup>I administration to control hyperthyroidism and were continued in appropriate doses until hyperthyroxinemia had abated. Patients who did not receive MMI or KI were defined as being in remission.

**Results:** In MMI, KI3, and KI5 patients, the median pre-RIT thyroid volumes were 31.0 (IQR 23.7-41.8) ml, 25.9 (19.9-39.7) ml, and 28.3 (20.3-39.6) ml, respectively, and the overall remission rates at 1 year after RIT were 85.5%, 93.3% and 91.1%. Remission rates decreased as the pre-RIT thyroid volume increased. The remission rates classified by thyroid volumes were largely equivalent between MMI, KI3, and KI5 patients, but KI3 patients with a thyroid volume of <30.0 ml had lower remission rates (KI3, 91.9%; KI5, 100%; MMI, 97.3%). KI3 and KI5 patients with a thyroid volume of <50.0 ml had lower thyroidal <sup>99m</sup>Tc uptake rates on the day of RIT than MMI-patients. In addition, KI3 patients with a thyroid volume of <30.0 ml had lower thyroidal <sup>99m</sup>Tc uptake rates than KI5 patients.

**Discussion and Conclusion:** In RIT using a fixed 481 MBq of <sup>131</sup>I, KI-pretreatment did not negatively affect the outcomes of RIT in comparison to MMI-pretreatment, except in patients with a small goiter with a short KI discontinuation period. KI can be discontinued 3 days before RIT when severe hyperthyroidism needs to be avoided around RIT. KI should be discontinued at least 5 days before RIT in patients with mild hyperthyroidism to enhance the avidity of thyroidal <sup>131</sup>I uptake.

### Poster 0313

*Disorders of Thyroid Function, Clinical, Poster*

#### Unilateral Grave's Disease, A Poorly Understood Entity

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Unilateral Graves' disease (UGD) it's an exceedingly rare disease with roughly 25 cases reported thus far, in the medical literature.

**Objective:** Herein, we describe the clinical, biochemical, and imaging-test characteristics of patients with UGD.

**Methods:** Retrospective analysis of patients with UGD, who attended the "Thyroid Clinic of the National Institute of Health Sciences and Nutrition" in Mexico City, Mexico, between 2010 and 2024.

**Results:** We identified 10 patients with UGD, with a median age at diagnosis of 43.5 years (range, 15-52), and a stark female predominance (80%). The right thyroid lobe showed unilateral increased radioiodine (RAI) uptake more frequently (66%; 6/9, N=9), but color flow doppler ultrasound was not increased overall (N=9). However, in 33% of cases, it predominated in the high-uptake lobe (3/9, N=9), with all cases having ultrasonographic hypoechogenicity (9/9, N=9). Thyroid-stimulating immunoglobulin was positive in 86% (6/7, N=7), whilst concomitant thyroid antibody-positivity was encountered in 44% (4/5 N=9); over half of cases had thyroid eye disease (55%, 5/9, N=9). All patients were treated with thiamazole (block and replace strategy), with 3 having subsequent RAI treatment. Over an 8-year median follow-up (range, 2-15), 50% (5/10) of patients were euthyroid; and in remission, for a median of 5.5 years (range, 0-9).

**Discussion:** UGD is an unusual clinical subgroup of Graves' disease. However, patients present with identical symptoms as those with bilateral disease and should likely be treated similarly. UGD must be distinguished from hyperfunctioning thyroid nodules and thyroid hemiagenesis with hyperthyroidism. Although the pathophysiology of UGD is unclear, several hypotheses exist, such as side-to-side differences in function and/or structure of thyroid stimulating hormone (TSH) receptor, discrepancies in thyroid tissue antigen expression, differentially expressed sodium/iodide symporters, or from previously acquired conditions such as viral thyroid inflammation in a quiescent lobe, amongst others.

**Conclusion:** UGD remains a pathophysiologically poorly characterized entity, that albeit rare, should be considered in the differential diagnosis of thyrotoxicosis, in patients with unilateral increased in thyroid uptake.

### Poster 0314

*Disorders of Thyroid Function, Clinical, Poster*

#### Hypo Versus Hyperthyroidism in Heart Failure: A Retrospective Population-Based Study to Assess In-Hospital Outcomes

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**Objectives:** To compare the in-hospital mortality rates between patients admitted for heart failure with hyperthyroidism and those with hypothyroidism.

To assess and compare the average length of stay and hospitalization costs for patients admitted for heart failure with hyperthyroidism versus those with hypothyroidism.

To examine and compare the risk of atrial fibrillation among patients admitted for heart failure with hyperthyroidism and those with hypothyroidism.

**Methods:** A retrospective cohort study was conducted using the National Inpatient Sample (NIS) 2020 database. Patients with HF were identified using ICD-10 codes, and those with concurrent hyperthyroidism or hypothyroidism were divided into two cohorts: HF with Hyperthyroidism (HFHYPER) and HF with Hypothyroidism (HFHYPO). Appropriate statistical tests were applied to analyze the data.

**Results:** Out of 1,003,140 patients admitted with HF, 12,155 (1.2%) had HFHYPER, and 181,975 (18%) had HFHYPO.

In-hospital mortality rates were 2.4% for HFHYPER and 2.6% for HFHYPO. While HFHYPO exhibited 3% lower odds of mortality, this difference was statistically insignificant ( $p=0.856$ ).

The average length of stay was 5.54 days for HFHYPER and 5.62 days for HFHYPO. Multivariate analysis indicated a significant 74% reduction in length of stay for HFHYPO ( $p=0.028$ ).

The average cost of hospitalization was \$64,437 for HFHYPER and \$58,541 for HFHYPO, with a statistically insignificant \$84 decrease in costs for HFHYPO ( $p=0.978$ ).

HFHYPO patients had 35% increased odds of AF compared to HFHYPER ( $p=0.00$ ), along with increased odds of Dyslipidemia (19%,  $p=0.00$ ), Obesity (42%,  $p=0.00$ ), and Obstructive Sleep Apnea (16%,  $p=0.02$ ).

No significant differences were observed in the odds of Coronary Artery Disease, Peripheral Vascular Disease, Acute Kidney Injury, smoking, or hypertension between the groups.

**Discussion:** Hyperthyroidism elevates heart failure risk through tachycardia-induced cardiomyopathy and valvular disease, contrary to the previous belief of high-output heart failure [1]. Hypothyroidism diminishes cardiac contractility, causing diastolic dysfunction and impacting cardiac gene expressions [1]. Both conditions are known to influence in-hospital mortality in heart failure patients, yet our study found no significant difference between them, stressing equal treatment importance. While atrial fibrillation is often associated with hyperthyroidism alone, our research reveals increased odds of AF in HFHYPO compared to HFHYPER. Hypothyroidism could increase risk of atrial fibrillation indirectly by increasing risk of Obstructive sleep apnea however, the concrete mechanism underlying hypothyroidism's association with AF remains poorly understood.

### Poster 0315

*Disorders of Thyroid Function, Clinical, Poster*

#### **Methimazole Can Be Administered on a Weekly Basis**

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**Objective:** Graves' disease is an autoimmune thyroid gland disorder and the most common cause of hyperthyroidism in developed countries. Methimazole is an effective therapy in treating this condition. It has a half-life of 3-5 hours, and physicians frequently prescribe it as BID or even TID. However, despite its fast serum clearance, methimazole maintains thyroid gland concentration for over 20 hours, exerting a more sustained suppression. On the other hand, some physicians prescribe it on a weekly basis, ranging from 6 days to 3 days per week. Weekly dosing facilitates a smoother stepwise dose escalation and tapering. In this study, we aimed to assess the efficacy of weekly versus daily methimazole dosing in achieving euthyroidism (defined by a normal-range TSH) in patients with Graves' disease.

**Methods:** A retrospective cohort analysis encompassed 155 Graves' disease patients with 1,223 dose adjustments under the care of an academic outpatient endocrinology practice in the US. Patients received either daily or weekly methimazole dosing, with treatment responses categorized into five tiers: at goal (TSH 0.4 – 4.2 mCu/mL, free T4 0.6 – 1.5 ng/dL, and total T3 89 – 179 ng/dL), mild hypothyroidism (TSH 4.3 – 9.9 mCu/mL, free T4 0.3 – 0.5 ng/dL, and/or total T3 45 – 88 ng/dL), severe hypothyroidism (TSH  $\geq 10$  mCu/mL, free T4  $\leq 0.2$  ng/dL, and/or total T3  $\leq 44$  ng/dL), mild hyperthyroidism (TSH 0.1 – 0.3 mCu/mL, free T4 1.6 – 2.9 ng/dL, and/or total T3 180 – 359 ng/dL), and severe hyperthyroidism (TSH  $< 0.01$  mCu/mL, free T4  $\geq 3.0$  ng/dL, and/or total T3  $\geq 360$  ng/dL). Descriptive and inferential statistical tests were utilized.

**Results:** Daily methimazole dosing achieved 70.1% optimal levels (at goal), whereas weekly dosing attained 78.6%,  $p=0.002$ . Daily dosing exhibited 3.2% significant hypothyroidism and 0.4% significant hyperthyroidism. Conversely, weekly dosing showcased 1.3% and 0%, respectively,  $p=0.003$ .

**Conclusion:** Our findings suggest that treatment with weekly methimazole is as effective, or even more effective than daily methimazole, in managing patients with Graves' disease. Weekly dosing allows improved fine-tuning of its dose adjustments.

### Poster 0316

*Disorders of Thyroid Function, Clinical, Poster*

#### **Transient Thyrotoxicosis and Hypothyroidism after Combination Therapy with PD-1 and CTLA-4 Inhibitors for Cervical Cancer**

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**Introduction:** Mono or combination therapy with immune checkpoint inhibitors for malignancies causes thyroid dysfunction in the form of overt or subclinical hypothyroidism, or thyrotoxicosis. Thyrotoxicosis phase is often transient and in some cases so short that it cannot be diagnosed in time and the patient is examined late when hypothyroidism is confirmed. We describe a case of Cervical Cancer woman who developed transient thyrotoxicosis and later hypothyroidism after combination treatment with CTLA-4 and PD-1 inhibitors.

**Description:** A 60-year-old postmenopausal female developed transient thyrotoxicosis- TSH  $< 0.005$  (NR: 0.3-4.0 microIU/ml) and 2 weeks later Hypothyroidism TSH 220 microIU/ml 2 months after immunotherapy. The only complaints she had was palpitation and increased blood pressure. Her Anti-TPO was positive, but Anti-Tg and TRab were negative. Initial therapy for thyrotoxicosis was performed with propranolol and after the development of hypothyroidism L-thyroxine replacement therapy was started.

**Discussion:** Autoimmune thyroid dysfunction can be induced by immune checkpoint inhibitors treatment: anti-PD-1, anti-CTLA-4, and anti-PD-L1. An elevated level of clinical suspicion is required for the diagnosis of endocrinopathies due to an upward trend in endocrine disorders among cancer patients receiving immunotherapy. Early management of ICI-induced endocrinopathies improves the quality of oncopatients' life and continuity of anticancer treatment.

### Poster 0317

*Disorders of Thyroid Function, Clinical, Poster*

#### **Immune Checkpoint Inhibitor Related Thyroid Dysfunction: A Quality Improvement Project to Improve Access to Endocrine Care and Expedite Normalization of Thyroid Hormone Levels**

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**Objective:** Immune checkpoint inhibitors (ICIs) play a critical role in cancer treatment and have led to improved patient survival and quality of life. Immune-related adverse events (irAEs) are

common with up to 40% of patients developing thyroid dysfunction. The use of ICIs has significantly increased over the past decade resulting in a growing need for endocrine consultation. This quality improvement project focused on thyroid related immuno-oncology toxicity (IOTOX), the most prevalent endocrine irAE. Our objectives were to improve patient access to endocrine consultation and reduce the time to normalization of thyroid function tests.

**Methods:** Standardized quality improvement methodologies were used to identify barriers to accessing endocrine care and normalization of thyroid hormone levels. Two primary interventions were chosen: the creation of evidence-based algorithms for the treatment of thyroid related IOTOX and establishment of an APP (advanced-practice provider)-led IOTOX clinic with faculty support. The Plan-Do-Study-Act (PDSA) model was used to implement the interventions. The effectiveness of the clinic and treatment algorithms were repeatedly evaluated during team meetings, and improvements were enacted based on interdisciplinary feedback.

**Results:** We examined the medical records of 113 patients seen in consultation for thyroid related IOTOX. 67 were seen pre-implementation and 46 were seen post-implementation. The median consultation wait time improved significantly by 57%, decreasing from 21 to 9 days ( $p=.010$ ). Similarly, the median time to follow-up decreased by 68%, from 180 to 58 days ( $p<.001$ ). Notably, the median days to normalization of Free T4 and TSH levels showed marked reductions from 36 to 30 days ( $p=.078$ ) and from 102 to 38 days ( $p<.001$ ), respectively. During the PDSA cycles, clinic acceptance criteria were refined, screening for adrenal insufficiency was added, and clinic coverage during APP absences was addressed.

**Discussion:** The APP-led endocrine IOTOX clinic utilizing standardized treatment algorithms significantly improved patient access and time to normalization of thyroid function tests. Areas for further investigation include assessment of patient satisfaction and quality of life. Limitations include generalizability to institutions that lack experienced APPs or infrequently use ICIs. Future directions include applying this model to other irAEs.

### Poster 0318

*Disorders of Thyroid Function, Clinical, Poster*

#### Changes in Therapeutic Plasma Exchange in Hyperthyroidism Treatment Scenarios

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**Objective:** The application of therapeutic plasma exchange (TPE) in hyperthyroidism is no longer limited to patients with hyperthyroid crisis, but there is a lack of recommendations for the use of TPE in non-hyperthyroid crisis patients. To summarize the application scenarios of TPE in recent years and provide systematic references for its application in hyperthyroidism, we analyzed cases from our center and relevant literature.

**Methods:** Two cases from our hospital were combined, and a literature search of the PubMed database from 1970 to 2024 was conducted to identify relevant studies on the use of TPE for the treatment of hyperthyroidism. 75 articles were screened totally, comprising 287 patients with hyperthyroidism treated with TPE. A summary analysis was conducted on the indications for TPE, TPE implementation, outcomes, adverse reactions, and prognosis.

**Results:** Among the 289 patients included, indications for TPE for hyperthyroidism included hyperthyroid crisis ( $n=67$ ), ATD contraindications ( $n=144$ ), ineffective traditional medication ( $n=58$ ), preoperative preparation ( $n=5$ ), and others ( $n=28$ ). Over time, TPE indications shifted from primarily hyperthyroid crisis (22.19%) to diverse scenarios (1.66%–47.68%). Among the 200 patients for whom a specified replacement fluid was reported, 50% used plasma, 27.5% used albumin, and 21.5% used plasma combined with albumin. The median (range) number of TPE sessions and intervals were as follows: hyperthyroid crisis, 3(1-9)/1.32 days; ATD contraindications, 3(1-46) sessions/1.58 days; ineffective traditional medication, 3.5(1-10) sessions/1.4 days; preoperative preparation, 6(1-6) sessions/1.47 days; and other scenarios, 5(1-46) sessions/1.67 days. After a single TPE session, based on available data, TRAb, TT3, TT4, FT4, FT3, AST, and ALT decreased on average by 43.72%, 23.52%, 24.40%, 19.38%, 26.17%, 34.06%, and 34.96%, respectively. 122 patients underwent subsequent thyroidectomy, 12 received radioactive iodine therapy, 10 received ATD treatment, and 5 were followed up regularly, with no reports of hyperthyroid crisis recurrence. Only 5.6% (16 patients) reported inefficacy or death, all of which occurred when TPE was used for hyperthyroid crisis. 12.2% (35 patients) reported adverse reactions totally.

**Conclusion:** TPE is an effective and rapid unconventional treatment for hyperthyroidism, with indications extending beyond hyperthyroid crisis, and specific TPE strategies vary among different indications. In patients with non-hyperthyroid crisis hyperthyroidism, TPE seems to have a better prognosis than in those with hyperthyroid crisis.

### Poster 0319

*Disorders of Thyroid Function, Clinical, Poster*

#### Cost-effectiveness of different screening strategies for thyroid indicators during pregnancy based on a real-world cohort

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**OBJECTIVE:** Thyroid indicator screening is important for identifying thyroid dysfunction during pregnancy. There is still no consensus on strategies for screening thyroid indicators during pregnancy. This study aimed to evaluate the most cost-effective thyroid indicator screening strategy by establishing decision tree models based on a real-world cohort.

**METHODS:** We retrospectively collected medical records of 14,160 women who delivered or miscarried and were screened for thyroid function in early pregnancy at Peking University First Hospital from 2014 to 2016 and established decision tree models to compare the cost-effectiveness of different screening strategies. Strategies of no screening, high-risk screening and universal screening for TSH, FT4 and TPOAb were compared; further comparisons were made between a one-step approach to screening for the three indices and different combinations of stepwise screening pathways (prioritized TSH, TSH+TPOAb and TSH+FT4) under universal screening. Disease state transition probabilities in the model were derived from the aforementioned cohort or published literature, and the model outcome events were delivery or miscarriage.

**RESULTS:** Compared with that of no screening, the increased cost per additional quality-adjusted life years (QALYs) for high-risk screening was \$7448.16; compared with that for high-risk screening, the incremental cost-effectiveness ratio (ICER) of universal screening was \$16876.18/QALY, both of which were less than 3 times the GDP per capita of China in 2014-2016 (\$19378-22146). These

results indicated that universal screening was more cost-effective. However, a more cost-effective prerequisite for universal screening is that patient treatment compliance is greater than 82%. Compared with the stepwise approach of TSH screening, the ICERs of the one-step approach and stepwise approach for screening TSH+FT4 were \$59148.7/QALYs and \$107788.9/QALYs, respectively. In addition, the stepwise approach for screening TSH+TPOAb did not increase QALYs while incurring more costs, so the most cost-effective strategy is to first screen TSH using a stepwise approach.

**CONCLUSION:** A universal screening strategy for thyroid indicators during pregnancy is cost-effective for determining miscarriage outcomes, and the use of stepwise screening for TSH will maximize cost effectiveness.

### Poster 0320

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#### **Adverse Thyroid Reaction Caused by the Combination of Tyrosine Kinase Inhibitors and Immune Checkpoint Inhibitors: A Retrospective Study in Beijing**

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**Background:** Tyrosine kinase inhibitor (TKI) and immune checkpoint inhibitor (ICI) have been recognized to cause thyroid dysfunction (TD). However, the combination therapy-associated TD is still unclear.

**Objective:** We aimed to evaluate the clinical characteristics of TD in patients treated with TKI+ICI therapy.

**Methods:** This was a retrospective study of cancer patients treated with TKI+ICI between January 2020 and June 2023 at Peking University First Hospital. Patients who were pretreatment euthyroidism were divided into TD and non-TD group according to the occurrence of TD. Clinical features were analyzed in patients who developed TD.

**Results:** The cohort included 178 patients with a median age of 62.13 years and a median follow-up of 10.78 months, 119 (66.85%) were males, 100 (56.18%) were urologic neoplasms and 92 (51.69%) received second-generation TKI+anti-PD-1 antibody therapy. Among pretreatment euthyroid patients (n=132), 94 (71.21%) developed TD. TD occurred at a median of 7.29 (5.21–19.96) weeks after the start of TKI +ICI treatment. Multivariate logistic regression revealed that only baseline TSH level (OR 1.75, 95% CI: 1.10-2.77,  $P=0.017$ ) and females (OR 6.51, 95% CI: 1.38-30.56,  $P=0.018$ ) were significant risk factors for TKI +ICI treatment-related TD and did not show any difference in the risk of TD between patients with different cancer types or TKI+ICI regimen. The most common TD was subclinical hypothyroidism (65.96%), followed by overt hypothyroidism (22.34%), overt thyrotoxicosis (9.57%) and subclinical thyrotoxicosis (2.13%). Of the 83 patients initially diagnosed with subclinical and overt hypothyroidism, 20 (24.10%) progressed to euthyroid over the course of the disease, the median duration of hypothyroidism was 24.64 (8.61-34.89) weeks, and 63 (75.90%) sustained hypothyroidism. In the patients initially diagnosed with subclinical and overt thyrotoxicosis (n=11), 2 (18.19%) progressed to euthyroid, 9 (81.81%) converted to hypothyroidism, the median duration of thyrotoxicosis was 9.79 (8.07-14.14) weeks and without persistent hyperthyroidism. In 17 patients with pretreatment thyrotoxicosis, 9 (52.94%) converted to hypothyroidism. Of 29 patients with

pretreatment hypothyroidism, 18 (62.07%) converted to worsening hypothyroidism.

**Conclusions:** The main type of TD associated with combination therapy was hypothyroidism. Elevated baseline TSH level and females were risk factors for TD. More complex changes in thyroid function could occur in patients with pre-existing thyroid disease.

### Poster 0321

*Disorders of Thyroid Function, Clinical, Poster*

#### **In-Hospital Outcomes among Hospitalized Thyroid Storm Patients with Comorbid Heart Failure with reduced Ejection Fraction (HFrEF): A United States Population-Based Cohort Study**

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**OBJECTIVE:** Thyroid storm is a clinical condition that negatively impacts the hemodynamics of the cardiovascular system by means of its increased adrenergic activity. This is especially evident among those with pre-existing heart failure. There is paucity of data regarding the outcomes of hospitalized thyroid storm patients with comorbid heart failure with reduced ejection fraction (HFrEF). We aim to investigate the impact of HFrEF among thyroid storm patients based on in-hospital mortality, risk for acute respiratory failure and cardiogenic shock, and utilization of mechanical ventilation.

**METHODS:** We utilized the National Inpatient Sample (NIS) to identify patients with HFrEF who were hospitalized for thyroid storm during the index hospitalization using appropriate ICD-10 codes between 2018-2020. We investigated the impact of HFrEF among thyroid storm patients based on in-hospital mortality, risk for acute respiratory failure, cardiogenic shock, and utilization of mechanical ventilation. A multivariable logistic regression analysis was used to calculate adjusted odds ratios (ORs) for the outcomes of interest.

**RESULTS:** A total of 4,415 hospitalized patients with thyroid storm were identified, of which 18.80% (830/4,415) had concomitant HFrEF during the index hospitalization. The overall in-hospital mortality rate among hospitalized patients with thyroid storm was 9.74% (430/4,415). Among those with concomitant HFrEF, the in-hospital mortality rate was significantly elevated to 19.28% (160/830,  $p < 0.001$ ). After adjusting for possible confounders, concomitant HFrEF among hospitalized thyroid storm patients was not significantly associated with increased risk for in-hospital mortality (aOR 1.90; 95% CI, 0.92-3.92;  $p=0.083$ ), however, it was found to be an independent predictor of increased risk for acute respiratory failure (aOR 1.99; 95% CI, 1.23-3.22;  $p=0.005$ ), cardiogenic shock (aOR 7.63; 95% CI, 3.45-16.87;  $p < 0.001$ ), and utilization of mechanical ventilation (aOR 2.50; 95% CI, 1.46-4.31;  $p < 0.001$ ).

**DISCUSSION/CONCLUSION:** Our analysis showed that HFrEF among hospitalized thyroid storm patients was independently associated with increased adverse in-hospital outcomes. This is due to the adrenergic surge seen during a thyroid storm which impacts the hemodynamics of patients with known heart failure with systolic dysfunction. These warrants early detection of at-risk patients with HFrEF in order to mitigate the negative impact of a thyroid crisis in this population.

**Poster 0322***Disorders of Thyroid Function, Clinical, Poster***Risk for Cardiac Arrhythmia Development among Hospitalized Thyroid Storm Patients with Comorbid Heart Failure: A United States Population-Based Cohort Study**

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**OBJECTIVE:** Previous studies suggested that the adrenergic surge seen during thyroid storm increases the risk for cardiac arrhythmia development in predisposed patients. Our study aims to investigate the impact of comorbid heart failure and the risk of cardiac arrhythmia development among hospitalized patients with thyroid storm.

**METHODS:** We utilized the National Inpatient Sample (NIS) to identify patients with heart failure who were hospitalized for thyroid storm and subsequently developed cardiac arrhythmias during the index hospitalization using appropriate ICD-10 codes between 2018-2020. We investigated the impact of heart failure among hospitalized thyroid storm patients based on its risk for cardiac arrhythmia development. A multivariable logistic regression analysis was used to calculate adjusted odds ratios (ORs) for the outcomes of interest.

**RESULTS:** A total of 4,415 hospitalized patients with thyroid storm were identified, of which 32.27% (1,425/4,415) had concomitant heart failure during the index hospitalization. The overall rate of cardiac arrhythmias among hospitalized patients with thyroid storm was 33.52% (1,480/4,415). Among those with concomitant heart failure, the cardiac arrhythmia rate was deemed to be significantly higher to 52.98% (784/1,480,  $p < 0.001$ ) compared to those who did not have heart failure. After adjusting for possible confounders, concomitant heart failure among hospitalized thyroid storm patients was found to be an independent predictor of increased risk for cardiac arrhythmias (aOR 2.41; 95% CI, 1.55-3.76;  $p < 0.001$ ), specifically atrial fibrillation (aOR 2.19; 95% CI, 1.35-3.55;  $p = 0.002$ ), but not ventricular tachycardia (aOR 1.89; 95% CI, 0.86-4.14;  $p = 0.110$ ), ventricular fibrillation (aOR 2.54; 95% CI, 0.54-11.92;  $p = 0.236$ ), or supraventricular tachycardia (aOR 1.08; 95% CI, 0.42-2.77;  $p = 0.874$ ).

**DISCUSSION/CONCLUSION:** Our analysis showed that heart failure among hospitalized thyroid storm patients was independently associated with increased risk for the development of cardiac arrhythmias, specifically, atrial fibrillation. This is likely due to the inherent risk for cardiac arrhythmia development among patients with pre-existing heart failure which is further aggravated by the adrenergic surge seen in thyroid storm. Therefore, efforts should be focused on evaluating and treating heart failure to mitigate its adverse impact among hospitalized patients with thyroid storm.

**Poster 0323***Disorders of Thyroid Function, Clinical, Poster***International Survey of Trends in the Management of Thyroid Eye Disease**Danilo Villagelin<sup>\*1</sup>, David Cooper<sup>2</sup>, Henry Burch<sup>3</sup>, <sup>1</sup>Pontificia Universidade Católica de Campinas, Brazil, <sup>2</sup>Division of Endocrinology, Diabetes, and Metabolism, The Johns Hopkins University School of Medicine, USA, <sup>3</sup>National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, USA

**Objective:** To evaluate current practices in the management of Graves Disease (GD) and thyroid eye disease (TED).

**Methods:** We used an online global survey of endocrinologists to assess aspects of the diagnosis and treatments in a typical patient with GD and TED.

**Results:** A total of 1438 respondents from 82 countries completed the survey. For 66% of the participants, antithyroid drugs (ATDs) were the primary treatment for GD with TED, varying from 79% in Asian respondents to 55% respondents from Oceania. There were no differences regarding respondents' age or sex. Smoking cessation (96%), lubricating eye drops (86%), and consultation with an ophthalmologist with expertise in TED (91%) would be recommended by most respondents.

Sodium selenite would be prescribed by European respondents (66%) almost twice as often compared to those from other regions of the world (38%) ( $p < 0.0001$ ). Also, respondents younger than age 45 and those who see more than ten new cases of GD per month were more likely to prescribe sodium selenite ( $p < 0.005$ ).

Ophthalmologists would be responsible for prescribing medical therapy for TED in North America (75%) and Oceania (68%), compared to endocrinologists having primary responsibility in the other regions of the globe (Europe (63%), Latin America (63%), Asia (62%)). Considering only respondents from North America, teprotumumab would be almost twice as frequently prescribed as glucocorticoids (42% vs. 23%). There were no differences regarding sex, age, the number of new patients with GD per month, and the likelihood of prescribing teprotumumab.

**Discussion/Conclusion:** ATDs are the cornerstone of GD treatment in patients with TED. General supportive measures are used by most respondents. European patients are twice as likely to be treated with selenium compared to patients living in other parts of the world. Teprotumumab is the first choice of therapy for TED in North America (the only region in which teprotumumab was approved in the survey period). This survey highlights important similarities and differences in GD and TED management around the globe.

**Poster 0324***Disorders of Thyroid Function, Clinical, Poster***Treatment of Subclinical Hypothyroidism and its Impact on Lipid Metabolism**

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**Introduction:** Although subclinical hypothyroidism (SCH) is a common condition in the general population, there is no firm consensus whether treating patients with TSH levels below 10 mIU/L. While both overt and subclinical hypothyroidism are associated with hypercholesterolemia and increased cardiovascular risk, studies have shown that thyroid replacement therapy does not completely reverse the risk. One possible explanation is that levothyroxine (LT4), by lowering TSH, would suppress the residual endogenous production of T3, paradoxically worsening the hypothyroid state.

**Objective:** To determine the impact of LT4 therapy on serum lipids in patients with SCH followed in an academic medical center.

**Methods:** We performed a retrospective cohort study on patients with diagnosis of SCH seen in the outpatient clinics over a period of 12 months. Data were extracted from the electronic medical records and compared between initial and last observations. The primary endpoints were changes in serum TSH levels and in lipid panel parameters after treatment or observation. Inclusion criteria were a baseline TSH  $>4.5 < 10$  mIU/L, and availability of two lipid profiles. Statistical analysis was performed by paired (within group) and unpaired (between groups) t-test.

**Results:** Among 70 (38F/32M, age  $61.1 \pm 13.7$  years) patients with SCH, 21 received LT4 therapy ( $66.7 \pm 41.1$  mcg), while 59 remained untreated. The time between observations ranged from 2 months to

10 years. Baseline TSH was higher in the treated group ( $6.7 \pm 1.4$  vs.  $5.9 \pm 1.1$  mIU/L,  $p < 0.02$ ), while no differences between groups were observed at the last observation ( $4.6 \pm 2.8$  vs.  $4.9 \pm 2.0$  mIU/L,  $p = 0.617$ ). LT4 treated patients had a significant decrease in TSH (mean  $-2.1 \pm 3.1$  mIU/mL,  $P < 0.01$ ) and LDL cholesterol (mean  $-13.1 \pm 20.7$  mg/dL,  $P < 0.01$ ), and a non-significant decrease in total cholesterol. The untreated group had a significant decrease in TSH (mean  $-1.0 \pm 2.2$  mIU/mL,  $p < 0.01$ ) and a non-significant decrease in total and LDL cholesterol.

**Discussion/Conclusion:** In this dataset, LT4 treatment is associated with a reduction in LDL cholesterol, suggesting that replacement therapy is effective even in SCH. The reduction in TSH observed in the untreated group supports the recommendation of confirming abnormal values before initiating therapy. Further studies are necessary to expand this database, and to identify predictors of response to LT4 therapy.

### Poster 0325

*Disorders of Thyroid Function, Clinical, Poster*

#### Uncontrolled Hypothyroidism in Pregnancy Increases Risk of Preeclampsia

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**Objectives:** American Thyroid Association practice guidelines for thyroid disease in pregnancy report a clear association between overt hypothyroidism and adverse obstetric outcomes. Studies have demonstrated an increased risk of preeclampsia in overt and subclinical hypothyroidism in early pregnancy. This study aims to determine whether the degree of control of hypothyroidism by gestational week 28 affects risk for maternal outcomes.

**Methods:** A retrospective cohort study of singleton pregnancies being treated with levothyroxine at a large, tertiary, safety-net hospital from January 2015 to December 2023 was performed. Thyroid-stimulating hormone (TSH) levels were obtained throughout pregnancy. Hypothyroidism control was determined by TSH ranges:  $< 2.5$ ,  $2.5-4$ ,  $4-10$ ,  $10-20$ , and  $> 20$  mIU/L. Obstetrical outcomes were analyzed in relation to hypothyroidism status at gestational week 28 using chi-square analysis.

**Results:** 242 pregnancies were included in the analysis. Most women were Hispanic/Latino (82.3%), multiparous (79.3%), and mean age was 32.2 years (SD 6.6). At initial presentation, median gestational age was 9 weeks. Median gestational age at delivery was 38 weeks. 39.26%, 14.05%, 30.58%, 7.44%, and 8.68% of women had a TSH level of  $< 2.5$ ,  $2.5-4$ ,  $4-10$ ,  $10-20$ , and  $> 20$  mIU/L, respectively.

At gestational week 28, most patients' hypothyroidism was controlled with 72.05% of patients with TSH  $< 2.5$  mIU/L. Women with TSH  $> 2.5$  mIU/L had a higher incidence of preeclampsia compared to those with TSH  $< 2.5$  mIU/L at gestational week 28 (20.31% vs. 9.05%;  $p = 0.02$ ).

**Conclusion:** In a single-center retrospective cohort study of pregnant women with hypothyroidism treated with levothyroxine, there was an increased association with preeclampsia with uncontrolled TSH at gestational week 28. Maintaining a TSH level of  $< 2.5$  mIU/L at gestational week 28 may reduce risk of preeclampsia during pregnancy.

### Poster 0326

*Disorders of Thyroid Function, Clinical, Poster*

#### Prevalence and the Clinical Features of the Postpartum Thyrotoxicosis in the Patients with Graves' Disease, a Retrospective Single-Center Study in Japan

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**Objective:** This study aimed to investigate the prevalence of postpartum thyrotoxicosis in patients with Graves' disease (GD), which includes postpartum thyroiditis (PPT) and relapse of GD. It also aimed to investigate the clinical features of these patients.

**Methods:** This retrospective study enrolled 5,563 patients diagnosed with GD who had 7,248 deliveries between January 2004 and August 2022. Patients who underwent curative treatments for GD before pregnancy were excluded. 1742 deliveries that required medication throughout the pregnancy were also excluded. Differentiation of the postpartum thyrotoxicosis was made based on the clinical course of thyroid function.

**Results:** Among 5,506 deliveries, 2,989 cases (54.3%) developed postpartum thyrotoxicosis. Of these, 1,086 cases (19.7%) developed PPT, and 1,903 cases (34.6%) experienced a relapse of GD. The median time to event was 5.1 months in the GD relapse group and 3.0 months in the PPT group. Median levels of free-triiodothyronine (FT3), free-thyroxine (FT4), and the FT3/FT4 ratio at the onset of postpartum thyrotoxicosis were significantly higher in the GD relapse group compared to the PPT group (FT3: 9.8 pg/mL vs. 6.6 pg/mL,  $p < 0.0001$ ; FT4: 3.06 ng/dL vs. 2.54 ng/dL,  $p < 0.0001$ ; FT3/FT4 ratio: 3.08 vs. 2.63,  $p < 0.0001$ ). The positive ratio of thyroid receptor antibodies (TRAb) was 85.4% in the GD relapse group and 14.5% in the PPT group. The positive ratio of thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPOAb) was significantly higher in the PPT group compared to the group without postpartum thyroid dysfunction (TgAb: 67.8% vs. 58.2%,  $p < 0.0001$ ; TPOAb: 66.8% vs. 60.7%,  $p = 0.0014$ ); however, these differences were not observed between the GD relapse group and the group without postpartum thyroid dysfunction. Additionally, the positive ratio of TgAb and TPOAb was significantly higher in the PPT group than in the GD relapse group (TgAb: 67.8% vs. 57.8%,  $p < 0.0001$ ; TPOAb: 66.8% vs. 60.5%,  $p = 0.0015$ ).

**Conclusion:** Among patients with GD, the prevalence rates of postpartum thyrotoxicosis, PPT, and GD relapse were 54.3%, 19.7%, and 34.6%, respectively. PPT was more likely to occur in patients who tested positive for TgAb and TPOAb.

### Poster 0327

*Disorders of Thyroid Function, Clinical, Poster*

#### Spuriously High Free T3 in Clinically and Biochemically Euthyroid Patients

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#### Introduction

Despite being a frequently ordered laboratory test, the reliability and utility of the free triiodothyronine (FT3) is questionable, and its interpretation can be inaccurate. We present a case series of eighteen clinically and biochemically euthyroid patients who were found to have elevated levels of FT3 on routine screening lab tests.

#### Description of the Cases

All patients' data were reviewed retrospectively for this descriptive study. The utilized FT3 assay is a quantitative Electrochemiluminescent immunoassay. We used the Shapiro-Wilk test to assess normality.

Normally distributed data is presented as mean  $\pm$  standard deviation and skewed as median [interquartile range]. Age was 50.3 $\pm$ 14.4. Most were white (n=15), and three patients were black. The serum thyrotropin stimulating hormone (TSH) 1.18 [0.74-2.6] mIU/mL (reference range (ref) 0.4-4.2), free thyroxine (FT4) 0.88 $\pm$ 0.14 ng/dL (ref 0.6-1.5), and total triiodothyronine (TT3) 112 $\pm$ 18.5 (ref 82-179). They were all within the normal range. The FT3 was 3.95 [3.70-4.40] pg/mL (ref 1.5-3.5). All FT3 values for this cohort were falsely elevated.

#### Discussion

FT3 is the biologically active thyroid hormone. Although it should theoretically be the best reflection of active thyroid hormone level, its frequent unreliability is becoming more apparent. This is likely secondary to its inherent low serum concentration and affinity. Thus, the blind measurement of FT3 may be of limited utility and can be a pitfall, especially when the results are incongruent with the clinical picture and other thyroid hormone levels. Total T3 may be a better assay currently to assess T3 levels when warranted till the FT3 assay becomes more reliable.

#### Poster 0328

*Disorders of Thyroid Function, Clinical, Poster*

##### Drug Administration as A Factor Affecting Levothyroxine Therapy – Results of the CONTROL Surveillance II Study

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**Objective:** The primary objective was to quantify the number of patients taking levothyroxine outside of the administration guidance found in FDA-approved labelling. This includes the timing of administration ( $\geq$  30 minutes before breakfast) and coadministration with foods, beverages, and medications known to interfere with levothyroxine absorption. Secondary objectives included assessment of information given by prescribers relative to levothyroxine administration.

**Methods:** Online survey of 1,000 hypothyroid patients. Participants were selected randomly, were between 19-90 years old and not pregnant. Qualified subjects had been taking levothyroxine monotherapy for  $\geq$  1 year. The survey was initiated in December 2023 and completed in January 2024.

**Results:** Participants were predominantly female (74%). Non-Hispanic whites represented 84%; Hispanic/black non-Hispanics represented 14%. The median age was 62.

Many patients (29%) administer levothyroxine outside of FDA-approved labelling. This includes 18% who take levothyroxine  $\leq$ 30 minutes before eating, 2% while eating and 9%  $\leq$  1 hour after eating. Use of vitamins/supplements known to interfere with levothyroxine is high: calcium (30%), and iron (15%). Many patients (39%) take proton pump inhibitors (PPIs) which are classified as “interfering drugs” in FDA-approved levothyroxine labelling.

Most patients recall physician instructions to take levothyroxine in the morning  $\geq$  30 minutes before breakfast with water (72%). However, 55% do not recall instructions regarding consumption of interfering vitamins/supplements; 60% don't recall instructions regarding the use of PPIs or certain prescription medications. Patients managed by a primary care physician (PCP), versus those managed by a specialist, are more likely to take their medication after eating (18% vs 10%;  $p \leq 0.05$ ). Patients who report difficulty adhering to administration guidance are more likely to report that their hypothyroidism has reduced their quality of life (31% vs 18%;  $p < 0.05$ ) and more likely to report stopping their prescribed medication for  $\geq$  1 month (25% vs 10%;  $p < 0.05$ ). Many patients (53%) are

willing to consider liquid levothyroxine formulations which may be taken closer to mealtime or without regard to the presence of PPIs.

**Discussion/Conclusion:** Many patients are not following levothyroxine administration guidance as found in FDA-approved labelling. Improved physician-patient communication may better levothyroxine administration adherence and help patients reach their treatment goals.

#### Poster 0329

*Disorders of Thyroid Function, Clinical, Poster*

##### Hypokalemic Periodic Paralysis Precipitated by Levothyroxine Replacement in a Patient with Hashimoto's Hypothyroidism

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Periodic paralysis (PP) is a rare skeletal muscle channelopathy leading to recurrent episodes of muscle weakness. Hypokalemic PP is the most common form of PP and may be hereditary or acquired. Acquired hypokalemic PP is sometimes associated with thyrotoxicosis, in a condition called thyrotoxic periodic paralysis (TPP). We present a case of hypokalemic PP in a hypothyroid patient after starting levothyroxine replacement.

A 21-year-old asymptomatic female underwent routine labs with TSH  $>$  150 mIU/L (0.40-4.50 mIU/L) and FT4 0.4 ng/dL (0.8 - 1.8 ng/dL). She was diagnosed with hypothyroidism and was started on levothyroxine 25 mcg daily. One week into treatment, she noticed increased fatigue and muscle weakness. She presented to the emergency department (ED) where she was noted to have a potassium of 2.6 mmol/L. Repeat TSH was 21 mIU/L and thyroid peroxidase antibody level was  $>$  1000 IU/ml ( $<$  9 IU/mL). She was treated with IV and oral potassium and discharged on potassium chloride 10 mEq twice daily. The patient self-discontinued levothyroxine but continued to experience muscle weakness and returned to the ED twice over the following week for potassium repletion. Levothyroxine 25 mcg daily was resumed and she was discharged on a potassium regimen of 40 mEq three times daily, which she weaned to 10 mEq twice daily over the next month. Repeat TSH was 8.7 mIU/L and levothyroxine was increased to 50 mcg with precautions to increase potassium if experiencing muscle weakness. TSH normalized and potassium was discontinued without recurrence of symptoms.

The occurrence of hypokalemic PP in a hypothyroid patient after the initiation of levothyroxine suggests a pathophysiology similar to TPP. In TPP, hypokalemia is caused by intracellular potassium shift due to thyroid hormone sensitization of sodium-potassium ATPase. We hypothesize that in this patient with hypothyroidism, the initiation of levothyroxine may have unmasked an underlying channelopathy and led to similar intracellular potassium shift and hypokalemia. The onset of acute muscle weakness after levothyroxine initiation should prompt consideration of hypokalemic PP and levothyroxine replacement should be managed cautiously with adequate potassium replacement and electrolyte monitoring.

#### Poster 0330

*Disorders of Thyroid Function, Clinical, Poster*

##### The Association Between Hypothyroidism and Cognitive Function Change in Women Across the Menopause Transition: The Study of Women's Health Across the Nation (SWAN)

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**Objective:** Patients treated for hypothyroidism with levothyroxine (LT4) monotherapy may present with persistent hypothyroidism symptoms, including cognitive symptoms, despite having a normal thyroid stimulating hormone (TSH) level. It remains unclear whether LT4 monotherapy is adequate to normalize cognitive function outcomes over time.

**Methods:** This is a multi-site longitudinal study of a diverse group of women during mid-life representing 5 ethnic/racial groups from 7 enrollment sites across the US in the Study of Women's Health Across the Nation (SWAN). Women were screened for a history of thyroid disease and the use of LT4. The study consisted of two primary groups: women with LT4-treated hypothyroidism and control women without thyroid disease. Each participant completed up to 9 cognitive assessments over the study period testing perceptual speed, working memory, and episodic memory (immediate and delayed recall). Multivariable generalized linear mixed models of scores for each cognitive assessment were developed to determine the association between LT4-treated hypothyroidism and cognitive function trajectories. Covariates included sociodemographic, clinical characteristics, and menopausal status (pre/early peri-, late peri-, and surgical/post-). Sensitivity analyses were conducted to assess the impact of abnormal TSH levels and practice effects (i.e., improvements in scoring after repeated testing).

**Results:** Of the 2033 women who were included in the study, 227 (11.2%) met criteria for LT4-treated hypothyroidism. At baseline, both perceptual speed and working memory scores were higher in LT4-treated women (mean perceptual speed scores: 56.5 vs 54.4; p-value = 0.006; mean working memory scores: 6.8 vs 6.4; p-value = 0.018). However, when considering the effect of LT4-treated hypothyroidism over time, there were no significant differences in the rate of cognitive decline (in any measure) between the hypothyroidism and control groups with or without covariate adjustment. The results were similar when considering LT4-treated women with abnormal TSH levels or after minimizing practice effects.

**Conclusions:** We observed no difference in cognitive decline between women with LT4-treated hypothyroidism and women without thyroid disease. For similar-aged patients with cognitive complaints, if thyroid function testing is normal, clinicians should consider causes other than inadequate thyroid hormone treatment to explain these symptoms.

### Poster 0331

*Disorders of Thyroid Function, Clinical, Poster*

#### **Methimazole for Prevention of Iodinated Contrast Media Induced Exacerbation of Thyrotoxicosis in Susceptible Patients**

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**Introduction:** Iodinated contrast media (ICM) is widely used in a variety of radiologic examinations and procedures. In susceptible patients this exposure could lead to thyrotoxicosis or hypothyroidism. The role of prophylactic therapy for prevention of contrast-induced thyrotoxicosis is unclear. The aim of the current study was to investigate the efficacy of methimazole in prevention of thyrotoxicosis in patients undergoing ICM examinations or procedures.

**Methods:** Retrospective cohort study, performed at Rabin Medical Center (RMC), from inception to November 2022, included patients  $\geq 18$  years admitted to the emergency department or hospitalized, underwent ICM examination or procedure and received methimazole prior to exposure. The primary outcome was prevention of thyrotoxicosis after ICM exposure.

**Results:** One-hundred seventy nine patients with 202 hospitalizations were included. Average age at admission was  $72.3 \pm 13.5$  years, 64% were female. Nearly all patients (99%) had history of thyroid disease and 91% of the cohort were treated with methimazole prior to admission. Seventy-five patients had low TSH levels prior to ICM exposure. In this high-risk group, methimazole led to normalization of TSH after discharge in 19%, and 64% remained with low TSH levels after discharge but with a small median difference in FT4 levels of -0.5 (IQR -5.9 to 5.2). In the few patients with dose increase during hospitalization (8 patients), treatment with methimazole was beneficial with median FT4 decrease of -6.2 (IQR -9.2 to -1) and TSH increase of 0.2 (IQR 0.02 to 0.7). In 110 patients with normal TSH levels before admission, with methimazole treatment most (71%) remained euthyroid after discharge, 13% had low TSH and 9% had high TSH. In the few patients with high TSH levels prior to admission (15 patients), only two normalized TSH, 47% remained with high TSH with median TSH change of 3.1 (IQR 1.4 to 5.4), and 27% had low TSH after discharge.

**Conclusion:** In patients receiving methimazole before ICM exposure, thyroid functions remained stable without exacerbations of thyrotoxicosis. Furthermore, in patients with low TSH levels before admission, increasing dose of methimazole before iodine exposure led to improvement in thyroid functions after discharge.

### Poster 0332

*Thyroid Cancer, Clinical, Poster*

#### **Surgery for Papillary Thyroid Carcinoma with Microscopic Extra-Thyroid Extension – Is Lobectomy Enough?**

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**Introduction:** Microscopic or minimal extra-thyroid extension (mETE) is often detected after thyroid lobectomy for differentiated thyroid cancer (DTC). While most patients undergo completion thyroidectomy due to this pathologic finding, recent studies demonstrated mETE has little impact on the risk of recurrence, questioning the need for further treatment after initial surgery. However, little data is available on the risk of recurrence following lobectomy alone in patients with mETE.

**Methods:** A retrospective study was conducted on patients who underwent thyroid lobectomy at a single tertiary care center between January 2012 and December 2020. Only patients with DTC microscopic ETE were included. Data collected included demographics, laboratory, radiologic, and cytologic results, and surgical and pathological reports. Follow-up data included complications, need for completion surgery, recurrence-free survival, overall survival, and cause of death.

**Results:** Sixty-four patients had DTC with microscopic extension. Two of those (3.13%) had disease recurrence diagnosed at follow-up. Patients were divided into 22 (34.4%) having extension to the strap muscles, 28 (43.8%) to the perithyroidal fat, and 14 (21.9%) having an unknown site of extension. Tumors with posterior microscopic extension had a higher rate of tall cell variant than tumors with anterior microscopic ETE (6, 23.1% vs 2, 9.1%) and lower rates of positive surgical margins (6, 22.2% vs 9, 42.9%). Tumors with posterior mETE had a trend for higher recurrence with and lower recurrence-free survival compared to no recurrence in patients with anterior microscopic extension.

**Conclusion:** The risk for recurrence in patients undergoing lobectomy for DTC with mETE in our cohort was 3.13%, consistent with the low risk of recurrence category. The site of the microscopic extension might be important, with posterior extension

demonstrating a trend of a more aggressive tumor variant, higher recurrence rate, and a lower time to recurrence compared to tumors with anterior microscopic ETE.

### Poster 0333

*Disorders of Thyroid Function, Clinical, Poster*

#### **The First Robust Bioavailability/Bioequivalence (BA/BE) Study of Thyromimetic Tiratricol, a Treatment in Development for MCT8 Deficiency**

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**Background and Objectives:** MCT8 deficiency is a debilitating, ultra-rare, X-linked disorder resulting from dysfunctional thyroid hormone (TH) transport. A lack of TH in the brain results in profound neurodevelopmental delay while a co-existing excess of TH in tissues outside the brain leads to symptoms of chronic thyrotoxicosis. Tiratricol is a naturally occurring metabolite of triiodothyronine (T3) that clinical trials have shown can restore normal TH signalling. This study investigates the pharmacokinetics (PK) of tiratricol.

**Methods:** This novel Phase 1, randomized, five-period cross-over study was a hybrid combination of a two-period cross-over and a three-period balanced incomplete block design in healthy adult male subjects (N=30) with a washout of  $\geq 3$  days between periods. Single oral doses of tiratricol were administered.

The primary objective was to establish bioequivalence between 350 $\mu$ g tiratricol oblong tablets and 350 $\mu$ g tiratricol round tablets. The secondary objectives were to estimate the effect of food by comparing both 175 $\mu$ g and 1050 $\mu$ g tiratricol oblong tablet doses in fasted versus fed states, and to assess dose-proportionality of tiratricol oblong tablets in a fasted state. All subjects received the treatments for the critical assessment of bioequivalence and 3 additional ones. Serum tiratricol, standard PK parameters, and safety were assessed.

**Results:** Bioequivalence was established between 350 $\mu$ g tiratricol oblong and 350 $\mu$ g tiratricol round tablets in terms of AUC and C<sub>max</sub> with a serum half-life of approximately 13h for both administrations. Overall exposure (AUC) was comparable between the fasted and fed state. Absorption was rapid in the fasted state (median T<sub>max</sub> 0.5 hr) but slower in the fed state (median T<sub>max</sub> approximately 1.5 hr), with C<sub>max</sub> 67–70% lower. C<sub>max</sub> following treatment with the 175 $\mu$ g, 350 $\mu$ g, and 1050 $\mu$ g oblong tablet doses increased proportionally with increasing dose, whereas AUC increased in a slightly greater than proportional manner with increasing dose. Tiratricol was well tolerated in all doses and fasting states, with no serious adverse events recorded.

**Conclusions:** In this novel study, robust PK data for tiratricol was generated for the first time, establishing bioequivalence between the round tablet and the oblong tablet, and characterizing the effects of food and the PK properties of increased dosing.

### Poster 0334

*Disorders of Thyroid Function, Clinical, Poster*

#### **Association of serum calcium and glucocorticoid-induced hypertension in thyroid-associated ophthalmopathy patients treated with methylprednisolone**

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**Objective:** Hypertension is a common adverse event after extended courses or high doses of systemic glucocorticoid therapy. Prior studies suggested that blood pressure (BP) regulation was related to serum calcium level. However, whether serum calcium affects the risk of glucocorticoid-induced hypertension remains understudied.

**Methods:** We use data of consecutive thyroid-associated ophthalmopathy (TAO) patients who completed a course of intravenous methylprednisolone. Patients with high BP at baseline, documented history of hypertension, and missing data were excluded. Glucocorticoid-induced hypertension was defined as systolic BP (SBP)  $\geq 140$  mmHg or diastolic BP (DBP)  $\geq 90$  mmHg during follow-up. Multivariate logistic regression and generalized additive models were performed to investigate the association between serum calcium level and the risk of glucocorticoid-induced hypertension. After using multiple imputation and mean imputation to account for missing data, all analyses were repeated in the imputed cohort.

**Results:** Serum calcium level was negatively correlated with the risk of glucocorticoid-induced hypertension after adjusting for covariates with p-value  $< 0.1$  (including age, body mass index, baseline SBP, and DBP). For each 0.1 mmol/L increase in serum calcium, the OR (95% CI) was 0.61 (0.39, 0.95). Furthermore, a nonlinear relationship was observed with the inflection point at 2.10 mmol/L. After serum calcium level was converted to a categorical variable, hypocalcemia was positively associated with glucocorticoid-induced hypertension (OR = 3.26, 95% CI = 1.11-9.53). These results were almost stable in the processes of adjusting for other potential confounders and in the analyses of the imputation cohort.

**Conclusion:** Hypocalcemia was found to be associated with glucocorticoid-induced hypertension in TAO patients. Further research is needed to confirm this finding in larger populations and to investigate whether calcium supplementation before glucocorticoid therapy may reduce such risk.

### Poster 0335

*Disorders of Thyroid Function, Clinical, Poster*

#### **Thyroid Hormone resistance syndrome due to thyroid hormone receptor beta (THRB) gene**

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**Abstract:** We describe a case of 43-year-old male who presented for evaluation of abnormal thyroid function test (elevated serum free thyroid levels in absence of thyrotropin suppression) and was found to have mutation in *thyroid hormone receptor beta (THRB)* gene, which is a rare but clinically significant pathology that can present with variability in phenotypic manifestations.

**Case Presentation:** 43-year-old male with PMH of thyroid nodule who presented to Endocrine clinic for evaluation of abnormal thyroid function tests. Patient was noticed to have normal TSH and elevated free T4 and total T4 levels for past five years. He denied any tremors, palpitations, weight loss, diarrhea, heat intolerance,

worsening anxiety, insomnia or any compressive symptoms at the time. No thyromegaly, tremors or orbitopathy was noticed on physical exam. Free T4 by equilibrium dialysis confirmed high Free T4 levels excluding assay interference. Alpha subunit was normal. Thyroid stimulating antibodies were negative. Thyroglobulin antibodies and thyroid peroxidase antibodies were repeatedly positive. Thyroid US showed a 1.1 cm solid cystic hypoechoic nodule in the isthmus. Nuclear medicine thyroid scan showed normal uptake. Thyroid hormone resistance beta sequencing was obtained and The fluorescent sequence analysis showed a heterozygous mutation due to a single base change at c.1378G>A in exon 10 of the THR beta gene, resulting in abnormal TRHb protein (p.Glu469Lys). This pathogenic variant in THRB gene is known to be associated with autosomal dominant generalized thyroid hormone resistance.

**Discussion:** Thyroid hormone resistance syndrome (RTH) is a rare syndrome that manifests as a reduced target cell response to Thyroid hormone signaling. The severity of hormonal resistance varies among different tissues and features of TH deficiency and excess may co-exist which are due to differences in the relative expression of TR-beta and thyroid hormone receptor alpha (TR-alpha) in different tissues. Most patients with RTH-beta are clinically euthyroid since pituitary resistance results in hypersecretion of TSH, which compensates for thyroid hormone resistance in peripheral tissues. No specific therapy to fully correct the TR $\beta$  defect is currently available and management of TR $\beta$  is tailored to the individuals' symptoms resulting either from tissue TH excess or deprivation.

### Poster 0336

*Disorders of Thyroid Function, Clinical, Poster*

#### **Effect of Oral LT3 administration on Thyroid function Tests in Participants with Isolated Low T3 levels and Heart Failure: A Randomized, Placebo-controlled, Crossover Trial**

*Kristen Kobaly\*, Shanelle Mendes, Robert Gallop, Julio Chirinos, Thomas Cappola, Anne Cappola, University of Pennsylvania, USA*

**Objective:** To determine the effect of oral liothyronine (LT3) therapy on thyroid function tests (TFTs) in outpatients with isolated low T3 levels and heart failure.

**Methods:** 56 participants aged 18+ years were enrolled in a randomized, double-blind, placebo-controlled, parallel crossover trial of the safety and preliminary efficacy of oral LT3 in heart failure. Participants were prescribed LT3 or placebo for 8 weeks with a 2-week washout period. TSH, free T4, and total T3 levels were measured at the beginning and end of each treatment phase. Blood samples were collected 2 hours after the LT3 or placebo morning dose. The initial LT3 dose was 5 mcg three times per day, titrated weekly over 4 weeks to maintain total T3 levels below the upper limit of the reference range, to a maximum dose of 12.5 mcg three times per day.

**Results:** 48 participants had TFTs at all 4 timepoints. The mean LT3 dose was 0.31 mcg/kg/day. For the 23 participants in the placebo-first group, mean TSH, free T4, and total T3 values at baseline were 1.89 mIU/L, 1.28 ng/dL, and 0.96 ng/mL, remaining stable over the 8-week period (1.92 mIU/L, 1.20 ng/dL, and 0.96 ng/mL) and during the washout period (2.11 mIU/L, 1.20 ng/dL, and 0.98 ng/mL). Mean total T3 increased to 1.73 ng/mL after LT3 therapy, with a decrease in mean TSH to 1.02 mIU/L and free T4 to 0.73 ng/dL. For the 25 participants in the LT3-first group, mean total T3 increased from 0.83 to 1.72 ng/mL, TSH decreased from 1.64 to 0.50 mIU/L and free T4 decreased from 1.12 to 0.52 ng/dL. After washout, TFTs returned to baseline (TSH 1.81 mIU/L, free T4 1.03

ng/dL and total T3 0.74 ng/mL) and were maintained during the placebo phase (1.97 mIU/L, 1.12 ng/dL and 0.79 ng/mL). LT3 therapy was well tolerated.

**Conclusion:** In outpatients with heart failure and isolated low T3 levels, total T3 concentrations remained stably low over up to 10 weeks and returned to baseline after discontinuation of LT3 therapy, suggesting an altered setpoint rather than transient effects from non-thyroidal illness syndrome in these individuals.

### Poster 0337

*Disorders of Thyroid Function, Clinical, Poster*

#### **Sudden Onset T3 Thyrotoxicosis with Low Thyroxin**

*Mohammed Mahmoodurrahman\*, SASAN FAZELI, City of Hope, USA*

**Introduction:** Hyperthyroidism is a common condition, and graves' disease represents 60 to 80% of hyperthyroid cases. Triiodothyronine (T3)-toxicosis represents a variant and typically presents with elevated serum T3 and normal free and total thyroxine (FT4, TT4) levels. We present a case of T3 toxicosis with undetectable FT4 and TT4 levels.

**Case Description:** 46 YO female with history of breast cancer presented with abnormal thyroid function tests. Patient had a 4-month history of intermittent palpitations and insomnia. She was on exemestane and venlafaxine and not any herbal or other supplements. Initial set of labs showed, TSH <0.01 (0.35-5.5 mIU/L), FT4 <0.25 (0.54-1.24 ng/dL), TT4 <0.7 (6.09-12.23 mcg/dL), FT3 (FT3) 10.9 (2.3-4.2 pg/mL) and TT3 (TT3) was 4.48 (0.60-1.81 pg/mL). FT4 by equilibrium dialysis was 0.2 (1.1-2.4 ng/dL). TRAB, TSI and TPO antibody were negative and Thyroglobulin antibody was 24 (<0.4 U/mL).

US thyroid showed bilateral heterogenous thyroid gland without discrete nodule. A thyroid uptake scan showed generalized elevated 24-hour iodine uptake measuring 37.1% (10-35%), without focal hot nodule.

Patient was started on methimazole 10 mg daily, which up-titrated to 30 mg. After 5 months patient's free T3 normalized and TSH rose to 55.714. Methimazole was down titrated and eventually discontinued. Repeat labs 3 months after stopping methimazole revealed TT3 0.97 (0.60-1.81 pg/mL), FT4 0.83 (0.54-1.24 ng/dL) and TSH 2.332 (0.35-5.5 mIU/L). The patient's symptoms improved significantly.

**Discussion:** Our patient had undetectable FT4 and elevated T3 levels, an atypical form of T3 thyrotoxicosis. Tourkantonis<sup>1</sup> reported a case with similar biochemical findings. In that case, they had administered thyroxine to evaluate increased peripheral metabolism of thyroxine, and given pharmacologic doses of iodine to rule out iodine deficiency. Subsequently, these were ruled out as etiologies. It is unclear in our case as to what caused the free T4 levels to be undetectable. We speculate it could be due to undetectable TSH, in lieu of elevated T3 levels, and an abnormality in the conversion of T4 to T3.

### Poster 0338

*Disorders of Thyroid Function, Clinical,*

#### **Morphological and functional changes of the thyroid during pregnancy: Case of Pregnant Women in the District of Gbadolite/DR Congo**

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**Context and objective:** The occurrence of goiter at pregnant women limits the clinician's field of intervention, both for

diagnostics and for therapeutic management. Only non-invasive methods can be carried out under these conditions. The current study aimed to describe the clinical and ultrasound aspects of the thyroid and repercussions of goiter in Pregnancy.

**Methods:** This was a cross-sectional study of 60 pregnant women with goiters who were examined between June 2022 and June 2023 in the District Hospital of Gbadolite/DR Congo. Parameters of interest included age, marital status, parity, family history of goiter, thyroid hormones and TSH measurements as well as goiter ultrasound data. We used Pearson's and student's Chi-square tests to compare proportions and means.

**Results:** The mean age was 32.2 years. More than 60% of participants consulted in the first trimester of pregnancy. The study of thyroid function revealed the disturbance in 35% in the first trimester ( $p=0.02$ ). Ultrasound showed nodular or multinodular goiters in 85%. The prevalence of clinical hypothyroidism (high TSH and low T4) was 1%; subclinical hypothyroidism (high TSH & normal T4) was 4%. Hypothyroidism was found in 5% and accompanied by uncontrollable vomiting in 72% of cases. The majority of multiparous women experienced the occurrence of goiter from the third pregnancy in 76% of cases. 83% women had ioduria < 100 microgram/day. 81% of goiters were regressive in post-partum and 16% of goiters were persistent in post-partum.

**Conclusion:** The current study reveals that goiter occurs more frequently during the first trimester of pregnancy. Most of goiters are regressive in post-partum; however some cases persist and evolve to different degrees of goiter.

**Keywords:** Thyroid, thyroid ultrasound, dysfunction, DR Congo

### Poster 0339

*Disorders of Thyroid Function, Clinical,*

#### **Primary hypothyroidism and Ramadan**

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**Background:** Hypothyroidism is a common endocrinopathy, TSH is the essential parameter in order to adjust replacement therapy, an imbalance of TSH is often observed after Ramadan.

Objectives are to analyze certain parameters to determine the cause of the imbalance.

**Methods:** A prospective observational study of patients who consulted the first month after Ramadan, follow up TSH evaluation without therapeutic readjustment 8 weeks after for those with high TSH levels.

Inclusion criteria: Primary hypothyroidism.

Exclusion criteria: Age <18 years, Pregnancy or desire of pregnancy, thyroid cancer.

Note that: Iftar = Evening meal (after sunset) Suhoor = meal right before dawn

**Results:** the study grouped 96 patients with a mean age of 52 years old and a sex-ratio of 0.1, causes of hypothyroidism: 12% thyroidectomy, 88% other causes. Average dose of Levothyroxine 80 mic/day. average duration under stable dose 23 months. TSH before Ramadan: 2.509 mui/L, after Ramadan: 4.854 mui/L of which 23% had high TSH, 77% normal TSH and 0% low. Levothyroxine intake (18% at Iftar vs 82% at Suhoor). Elevated TSH levels compared with time of Levothyroxine intake (47% in Iftar group vs 18% in Suhoor group).

**Conclusions:** This study provides objective information regarding TSH levels imbalance during Ramadan, taking Levothyroxine at Suhoor can minimize the imbalance.

### Poster 0340

*Disorders of Thyroid Function, Case Study, Poster*

#### **A Case of Post-Aspiration Thyrotoxicosis and Hematoma in a 48-Year-Old Woman with a Thyroid Nodule**

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A 48-year-old woman with a history of benign thyroid nodule presented to the emergency department with neck pain, swelling, dysphagia following thyroid fine needle aspiration (FNA) 2 days prior to admission. A TSH 3 months prior to biopsy was 0.51 mIU/L. A thyroid ultrasound obtained prior to biopsy revealed a 2.0x1.4 cm cyst in the midpole of the right lobe and a 2.0x2.0 cm complex nodule at the lower pole of the right lobe (TR3). She was not taking any NSAIDs, antiplatelet agents, or antithyroid drugs. Both the complex nodule and the cyst were biopsied with 4 passes each, using a 25G needle. Cytology results were benign.

On physical exam, the patient was tachycardic and without signs of thyroid eye disease. She had an enlarged thyroid gland. A CT Angiogram of the neck with contrast showed a heterogeneous 5.3x4x5.8-cm right thyroid nodule with likely hemorrhage with leftward tracheal deviation and splaying of regional structures. There was no obvious active contrast extravasation to suggest active bleed. Laboratory values obtained <12 hours after iodinated contrast administration revealed a TSH <0.01 mIU/L; free T4 2.33 ng/dL and a total T3 of 339 ng/dL. TSH-Receptor antibody and thyroid-stimulating immunoglobulin were negative.

Over the course of her two-day admission, thyroid hematoma improved with compression. Patient represented to ED 1 week after discharge with exertional dyspnea. Laboratory tests revealed TSH <0.01 mIU/L, free T4 4.71 ng/dL, and total T3 345 ng/dL. Methimazole 20 mg daily was initiated. A thyroglobulin value of 4099.7 ng/dL resulted later. A CT Chest with contrast revealed bilateral segmental and subsegmental pulmonary emboli and anticoagulation was initiated. A Thyroid US showed a 5.1x4.6x3.6 cm almost completely solid, hypochoic thyroid nodule.

Post-aspiration hematoma is uncommon and could be explained by hemorrhage from one of the capsular vessels of the cyst during the procedure. Post-aspiration thyrotoxicosis is an extremely rare complication of thyroid FNA [1-3]. Trauma from aspiration coupled with leakage of cystic fluid contents into surrounding thyroid could lead to thyrotoxicosis [2]. This case supports this hypothesized mechanism and highlights the potential for rare but serious complications following FNA.

### Poster 0341

*Disorders of Thyroid Function, Case Study, Poster*

#### **A Case of Atrial Fibrillation with Rapid Ventricular Response in a 31-year-old Woman with Postpartum Thyrotoxicosis**

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A 31-year-old woman with no significant past medical history aside from cesarean section 4 months' prior presented to the emergency department with palpitations that began the day of presentation. She denied any associated neck pain, shortness of breath, or dizziness. She had no personal history of thyroid disease; her mother was recently diagnosed with hypothyroidism. On arrival, the patient was noted to be in atrial fibrillation with rapid ventricular response with rates up to 220s. Blood pressures were maintained throughout, but she was urgently cardioverted in this setting. Sinus rhythm was subsequently restored with heart rates in 110s. Physical exam

showed no goiter, no tenderness to palpation of the thyroid gland, and no thyroid eye disease. Laboratory workup revealed TSH <0.01 mIU/L, free T4 3.51 ng/dL, total T4 15.80 ng/dL, total T3 242.0 ng/dL. TSH level checked at 11 weeks' gestation was within-normal-limits at 1.27 mIU/L. A thyroid ultrasound was obtained, which showed a heterogeneous, mildly hypervascular thyroid gland. An echocardiogram demonstrated a structurally normal heart. She did not receive anticoagulation or intravenous contrast.

The patient was initially managed with beta-blockade and methimazole 20 mg daily, which was stopped after negative TSH-Receptor antibody and thyroid-stimulating-immunoglobulin resulted 3 days later. Heart rates downtrended to 80s-90s with beta blockade and she was discharged home. She was able to resume breastfeeding once home. Eighteen days after discharge, TSH remained <0.01 mIU/L, free T4 was 1.6 ng/dL, total T3 was 147 ng/dL, thyroglobulin was 37.6 ng/mL. Six weeks later, her TSH rose to 27.01 mIU/L, free T4 dropped to 0.7 ng/dL, and total T3 dropped to 97 ng/dL. An anti-TPO antibody was positive at >900 IU/mg.

Although hyperthyroidism is associated with supraventricular ectopic activity and arrhythmias, thyrotoxicosis-induced atrial fibrillation is rare in young patients with structurally normal hearts. To our knowledge, atrial fibrillation complicating postpartum thyroiditis has not been previously reported. Resolution of thyrotoxicosis from postpartum thyroiditis occurs over time and is managed symptomatically. This case should raise awareness for this unusual but serious complication.

#### Poster 0342

*Disorders of Thyroid Function, Case Study, Poster*

##### **A Unique Patient With Immune Checkpoint Inhibitor-Induced Thyroiditis: What's the Kidney Have to Do With It?**

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**Introduction:** Since FDA approval of the first immune checkpoint inhibitor (ICI) in 2011, utilization of ICIs in oncology has considerably increased. Thyroiditis is the most common endocrine immune-related adverse event (irAE) and large observational studies report its incidence as 42-53%. ICI related thyroiditis frequently results in the need for thyroid hormone replacement. We describe a patient for whom the weight-based full replacement dose of levothyroxine was inadequate due to an unusual cause.

**Case Description:** An 81 year-old female with clear cell uterine cancer reported tremor and weight loss two months after initiating treatment with lenvatinib and pembrolizumab. Thyroid function tests (TFTs) showed thyrotoxicosis [TSH=0.03 (0.27-4.20 mcunit/mL), FT4=5.06 (0.93-1.7 ng/dL), T3=419 (80-200 ng/dL)]. Her oncologist started propranolol for hypertension related to lenvatinib and referred her to endocrinology. ICI related thyroiditis was diagnosed and TFTs were monitored closely. Five weeks later, her FT4 and T3 normalized; nine weeks from the first abnormal TFTs she developed hypothyroidism [TSH=13.97, FT4=0.77, T3=60].

She was prescribed levothyroxine, and the dose was progressively increased. TSH remained elevated (21.28) despite normalization of FT4 on levothyroxine 150 mcg/kg (3mcg/kg, nearly double the expected weight-based dose). She reported taking levothyroxine in the proper manner. She had minimal diarrhea related to lenvatinib. Celiac disease was ruled out by antibody testing. However, a 24-hour urine collection revealed total protein of 3,294 mg/24 hr. Lenvatinib was held by oncology and 2 weeks later TFTs normalized [TSH=2.02, FT4=1.57]. After another week, urinary total protein decreased to 2,147 mg/24 hr and TFTs showed thyrotoxicosis

[TSH=0.18, FT4=1.95] requiring a decrease in the levothyroxine dose.

**Discussion:** A thorough evaluation is important when levothyroxine requirements exceed the calculated full weight-based dose. Consideration of medication side effects should be included (e.g., lenvatinib/proteinuria) in addition to drug-drug interactions. For this patient, it allowed early identification of a serious adverse reaction to lenvatinib. As ICIs are increasingly used in combination with other chemotherapeutic agents, this type of interaction may be seen more frequently. This also serves as a reminder that urinary loss of protein-bound thyroid hormone can result in increased levothyroxine requirements.

#### Poster 0343

*Disorders of Thyroid Function, Case Study, Poster*

##### **Asymmetric Periorbital Edema Due to Delayed Hypersensitivity Reaction to Thyroid Hormone Replacement: A Case Report**

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**Introduction:** Drug allergies often present with typical symptoms such as skin rash, pruritus, facial swelling, and wheezing. However, diagnosing allergic reactions can be challenging due to significant variability among individuals. While hypersensitivity reactions specifically to levothyroxine are rare, excipients like fillers, binders, and dyes in different formulations of levothyroxine can contribute to allergic responses in certain individuals. Here, we present a rare case of an unusual delayed hypersensitivity reaction characterized by isolated asymmetric periorbital edema in a patient receiving thyroid hormone replacement therapy with various levothyroxine formulations.

**Description of the Case:** A 77-year-old woman with postoperative hypothyroidism had been taking levothyroxine 50 mcg daily for several years, with intermittent interruptions. She recently developed asymmetric periorbital edema (primarily affecting her right eye) without conjunctivitis, eye discharge, skin rash, or pruritus after one month of using generic levothyroxine. Stopping the generic levothyroxine resolved her symptoms. Subsequently, she was switched to brand name Synthroid 50 mcg, which again resulted in the recurrence of periorbital edema after one month of use, resolving upon discontinuation. Despite the isolated and asymmetric nature of her eyelid swelling, suggesting a less typical allergy presentation, the clear timing of symptoms led us to suspect a drug allergy. Given the rarity of allergy to the active ingredient levothyroxine and the absence of dyes in the 50mcg tablets, we suspected an inactive ingredient, such as fillers, as the likely culprit. Transitioning the patient to Tirosint 50 mcg, a levothyroxine capsule with minimal inactive ingredients (gelatin, glycerin, water), was well-tolerated and supported our suspicion.

**Discussion:** This case highlights a rare and unusual presentation of a delayed hypersensitivity reaction to inactive ingredients in levothyroxine formulations. The occurrence of asymmetric periorbital edema without concurrent rash or pruritus poses a diagnostic challenge, requiring healthcare providers to remain vigilant for potential drug hypersensitivity reactions. Considering Tirosint capsules, which contain minimal excipients, may be advantageous for patients with allergies to various forms of levothyroxine tablets.

**Poster 0344***Disorders of Thyroid Function, Case Study, Poster***Thyroid Dysfunction Associated with Lenalidomide Therapy: A Case-Series***Hawra Kamal\*, Wayne State University, USA*

**Introduction:** Lenalidomide, an immunomodulatory drug employed in the treatment of relapsed/refractory multiple myeloma and various malignancies, has been linked to thyroid dysfunction, encompassing both hypo- and hyperthyroidism. Numerous case series have documented the emergence of thyroid disorders in individuals undergoing lenalidomide therapy. Notably, these abnormalities can manifest in patients previously undiagnosed as well as those with pre-existing thyroid conditions. Symptoms of thyroid dysfunction, such as fatigue, constipation, and cold intolerance, may overlap with adverse effects attributed to lenalidomide.

**Case description:** We present an analysis of three cases of thyroid dysfunction associated with lenalidomide treatment for multiple myeloma. None of these individuals had prior diagnoses of thyroid dysfunction. All three patients were female, with a median age at diagnosis of 60 years. Each was diagnosed with hyperthyroidism characterized by suppressed TSH levels and high FT4 except one patient exhibited normal FT4 levels, suggestive of subclinical hyperthyroidism. The median time from initiation of lenalidomide to the detection of abnormal thyroid function test was 12 months. Treatment with methimazole was initiated in all cases, yielding favorable responses. Notably, one patient underwent thyroidectomy. Furthermore, two patients had high titers of TSH receptor antibodies, hinting at underlying autoimmune thyroid pathology. Ultimately, adverse events necessitated discontinuation of lenalidomide in all cases.

**Discussion:** Lenalidomide therapy can lead to overt hyperthyroidism, emphasizing the importance of vigilant monitoring of thyroid function during treatment and its substantial impact on patient care, as highlighted by these cases. Thyroid abnormalities, such as hypo- and hyperthyroidism, affect about 5%-10% of lenalidomide-treated patients, typically manifesting as mild conditions. To enhance treatment outcomes, regular assessment of thyroid function is vital both before initiating lenalidomide and throughout the treatment course, especially in individuals with preexisting thyroid conditions.

**Poster 0345***Iodine Uptake and Metabolism, Case Study, Poster***Beyond the Thyroid: Iododerma as a Rare Dermatological Complication of Radioactive Iodine Ablation in Thyroid Disease***Hawra Kamal\*, Julie Samantray, Wayne State University, USA*

**Introduction:** Radioactive iodine ablation is a widely utilized method for managing thyroid diseases, particularly differentiated thyroid cancer. Despite its efficacy, this therapeutic modality entails inherent risks and potential complications. One such complication, iododerma, a rare dermatological condition triggered by iodine exposure, has been sporadically documented in association with radioactive iodine therapy for thyroid diseases. We present a case of iododerma following radioactive iodine ablation for thyroid disease, highlighting the clinical presentation and diagnostic challenges posed by this unusual adverse effect.

**Case:** A 71-year-old male was diagnosed with bilateral lung nodules, indicative of metastatic follicular thyroid cancer upon histopathological examination. Additionally, he presented with an FDG-avid right thyroid nodule, prompting the recommendation for a total thyroidectomy. Following the procedure, pathology results revealed

a benign hyperplastic nodule with extensive cystic degeneration. Subsequent evaluation via a bone scan revealed no evidence of disease (NED). Following this, the patient underwent thyroxine withdrawal I-131 therapy with 175mCi for pulmonary metastasis from follicular thyroid cancer. Approximately one week post-therapy, he developed a non-tender, non-pruritic skin rash affecting both upper and lower extremities, as well as the anterior abdomen area. Notably, the rash resolved spontaneously without the need for medication.

**Discussion:** Iododerma, characterized by inflammatory skin lesions typically appearing two to three weeks following iodine exposure, presents diagnostic challenges due to its rarity and diverse cutaneous manifestations. Although the exact pathophysiology remains unclear, hypotheses include hypersensitivity reactions to iodine and delayed clearance of iodine from the body. Histopathological findings of iododerma are nonspecific, emphasizing the reliance on clinical evaluation and exposure history for diagnosis. Management strategies vary based on lesion severity and may include topical and systemic steroids, as well as phototherapy modalities. Future research directions should focus on longitudinal studies to elucidate long-term outcomes and recurrence rates of iododerma post-ablation, facilitating improved understanding and management of this rare cutaneous complication in clinical practice.

**Poster 0346***Health Disparities/Health Equity, Clinical, Poster***Hispanic Race and Socioeconomic Status as Predictors of Pediatric Thyroid Cancer Presentation**

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**Objective:** Thyroid cancer has risen rapidly in the United States. As thyroid cancer becomes more prevalent in pediatric patients, more screening is necessary to detect these tumors. We seek to determine whether race and socioeconomic status (SES) affects how pediatric patients first present with thyroid cancer as later diagnosis may affect morbidity and outcomes.

**Methods:** We conducted a population-based study examining pediatric thyroid cancer patients using the NIH Surveillance, Epidemiology, and End Results (SEER) Census Tract Database. We stratified race as Hispanic and non-Hispanic. SES is stratified into quintiles using American Community Survey (ACS) census tract data. Group 1 is the lowest SES while group 5 is the highest. We included patients diagnosed with a thyroid malignancy from 2006-2020 aged 0-21 at time of diagnosis. Staging includes patients diagnosed from 2006-2015 using AJCC 6<sup>th</sup> edition criteria to avoid inconsistency in staging criteria. Group 5 was used as a reference group for statistical analysis using Chi-square tests with GraphPad Prism.

**Results:** Of 5,063 total patients, we analyzed 4,945 pediatric thyroid cancer patients who had an available SES quintile. There were 1,584 patients (32.0%) in group 5 and 667 patients (13.5%) in group 1. In group 1, 149 (36.3%) presented at T1 while 458 (45.1%) did in group 5 ( $p=0.0023$ ). The groups did not differ significantly in rate of nodal or distant metastasis. Among Hispanics, 286 (32.8%) presented at T1 vs. 1,068 (45.7%) of non-Hispanics ( $p<0.0001$ ). Also, 187 (21.4%) Hispanics presented at N1b compared to 371 (15.8%) non-Hispanics ( $p=0.0002$ ). Rate of distant metastasis was similar between groups. Total thyroidectomy was more common in Hispanics, with 1,222 (86.5%) undergoing this surgery opposed to 3,018 (82.7%) non-Hispanics ( $p=0.0010$ ).

**Discussion/Conclusion:** Lower SES and Hispanic race were found to be predictors of later stage at presentation. This presents the risk of increased mortality and morbidity. Despite the difference in presentation, the lowest SES had the lowest number of diagnoses. This could mean pediatric patients of lower SES have thyroid cancer that goes undiagnosed until later in life, further increasing risk. More studies are needed to determine if this difference is due to later detection or other exposures.

### Poster 0347

*Health Disparities/Health Equity, Clinical, Poster*

#### Using Artificial Intelligence To Aid Decision-Making And Improve Standards Of Care In Thyroid Surgery

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**Objective:** Outcomes for patients with thyroid disease requiring surgery vary across the U.S. and the world with multiple factors at play including surgeon expertise and use of dedicated endocrine-specific multidisciplinary teams. Lack of standardization can delay or prevent patients getting the care they need. Artificial intelligence (AI) tools have started to be used in attempts to improve patient care in various settings including AI-powered virtual tumor boards. This study aims to assess whether ChatGPT, a free and easily accessible AI-based tool could aid in standardizing approaches in thyroid surgery.

**Methods:** Fifteen questions were proposed to ChatGPT to assess if it can aid decision-making in complex clinical scenarios in the field of thyroid surgery. Questions included topics such as specific evaluation of indeterminate lesions, timing and indications for referral, and management and extent of surgery. The intention was to assess areas of dispute and investigate whether ChatGPT can be a useful and safe tool to aid in standardizing clinical decision making in areas in which universally accepted guidelines are either not currently available or are not widely utilized.

**Results:** Responses of ChatGPT to the posited questions were reviewed and compiled. They provided explanations and itemized relevant considerations often including a bulleted list format. Each answer contained pertinent information on the clinical scenario and potential management strategies were proposed. Data was included to support the compiled considerations in an easy-to-understand format. Answers were not always definitive, particularly to broader questions, but, rather, the risks and benefits of varying and complementary approaches were stated. Specific patient factors to be taken under consideration were mentioned. Emphasis was placed on shared decision making and multidisciplinary evaluations. The responses were independently researched to verify accuracy and were found to reflect medically accurate information. They were consistent with views from experienced endocrine surgeons and, at times, included insights that may be supplementary to such expert opinions.

**Conclusion:** Although AI is an inadequate replacement for expert clinical decision-making at this time, it can supplement healthcare professionals' approaches to complex thyroid surgery issues, aid in ensuring consistency and raise standards of care in the field.

### Poster 0348

*Pediatrics, Clinical, Poster*

#### Composition and Priorities of Pediatric Thyroid Programs: A Consensus Statement

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**Objective** The incidence of pediatric thyroid cancer has been increasing, and care varies due to socioeconomic disparities or differing practice patterns. Clinical guidelines call for care in multidisciplinary teams to minimize variance and provide protocols. Based on expert opinion, we hope to describe the form and function of such multidisciplinary teams for pediatric thyroid programs.

**Methods** A modified Delphi method to reach consensus statements over 2 rounds. Twenty-one experts with varying backgrounds responded to each statement on a 9-point Likert scale. Upon completion of the survey, the panel reviewed and shared the results and comments from participants, and modified the statements accordingly. This process was repeated such that statements reached consensus, were deemed no consensus, or had no change in the mean.

**Results** There was an 88% and 83% completion rate for Rounds 1 and 2, respectively. A consensus was observed that there is a distinct definable model of care for pediatric thyroid patients. No consensus was reached for the age range of patients, but programs should care for children with medullary thyroid cancer, differentiated thyroid cancer, and patients with genetic predisposition syndromes. A comprehensive team includes, but is not limited to, a thyroid surgeon, a pediatric endocrinologist, a high-volume fine-needle aspiration (FNA) proceduralist, an oncologist, a nuclear medicine physician, a pediatric pathologist, a pediatric radiologist, and a nurse coordinator. Necessary support services involve care coordination, access to a multidisciplinary tumor board, ability to perform ultrasound-guided FNA, and access to molecular testing. The panel emphasized cross-institutional collaborative research prioritizing guidelines development, disease-specific outcomes, treatment toxicity, and the molecular landscape of thyroid cancer.

**Discussion** These consensus statements can be beneficial in improving multidisciplinary care, by describing which elements of pediatric thyroid programs should be consistent across institutions. Overall, the panel agreed that pediatric thyroid centers should provide integrated care with defined team members, services, resources, and research priorities. This model has the potential to standardize various aspects of clinical care and enhance our ability to study patient outcomes, improve health care delivery, and increase scholarly collaboration.

### Poster 0349

*Pediatrics, Clinical, Poster*

#### Combined Levothyroxine and Propylthiouracil Treatment in Children with MCT8 Deficiency: A Retrospective Review of 11 Patients

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**Objective:** Allan Herndon Dudley Syndrome is an X-linked disorder caused by mutations in the *SLC16A2* gene encoding monocarboxylate transporter 8, MCT8. Subjects have neurodevelopmental impairment, muscular hypotonia, and movement disorders from infancy. The endocrine basis is impaired transport of thyroid hormone (TH) into the developing brain and elevated TH in peripheral tissue mainly due to increased generation of T3 by deiodination of T4 to T3. Currently, there are no standard treatments for the neurologic or metabolic sequelae of MCT8 deficiency. This study evaluated the efficacy of combined propylthiouracil (PTU) and levothyroxine (LT4) administration and determining the optimal therapeutic dosages. The goal of treatment was to maximize serum T4 levels while minimizing serum T3.

**Methods:** We performed a retrospective chart review of 11 male patients diagnosed with MCT8 deficiency, whose parents or

guardians consented to treatment with PTU and LT4 from January 2008 to February 2023. The study focused on the safety and outcomes of the treatment, analyzing baseline and last encounter metabolic, and anthropometric parameters. Statistical analyses included Wilcoxon Signed Ranks tests, Generalized Estimating Equations to assess effects on thyroid and metabolic markers, and Receiver Operating Characteristics curves to identify optimal dosing.

**Results:** Patients showed a significant reduction in serum total T3 (TT3) concentration and TT3/TT4 ratio, with increased serum TT4 and FT4 concentrations. The use of PTU effectively reduced TT3 concentration by 25% at an average dose of 6.8 mg/kg/day, while LT4 increased FT4 concentration by 40% from baseline at an average dose of 4.3 mg/kg/day. TSH concentration was undetectable on treatment. No statistical differences were observed in metabolic and physical parameters between baseline and subsequent encounter, except for an increase in weight (z-score) in 6 of the 7 subjects with available data. No adverse effects on liver function or granulocyte counts were observed throughout the study period.

**Discussion/Conclusion:** Combined treatment with PTU and LT4 effectively normalized serum T3, FT4, and TT4 levels in patients with MCT8 deficiency. Individualized dose adjustments were necessary for achieving therapeutic goals in terms of serum TH levels, underscoring the necessity for personalized treatment plans in these children.

### Poster 0350

*Pediatrics, Clinical, Poster*

#### **Safety and feasibility of transoral endoscopic thyroidectomy vestibular approach in pediatric populations**

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**Objective:** The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is increasingly being adopted worldwide because of its many advantages. However, there are few reports on the effectiveness and safety of TOETVA in children. In this study, we report the results of the application of TOETVA on 40 pediatric patients in Vietnam. To the best of our knowledge, this is also the largest sample size of the TOETVA technique performed by a single surgeon on pediatric patients worldwide.

**Methods:** From June 2020 to January 2024, we performed TOETVA on 40 pediatric patients ( $\leq 18$  years old). The outcomes of the procedure were retrospectively reviewed.

**Results:** Our study was conducted on 40 pediatric patients, of whom 36 were female (90%). The mean age was 16.1 (range 10-18). 25 patients had benign thyroid nodules with a mean nodule size of 33 (range 20-50mm), and 15 patients had papillary thyroid carcinoma with a mean nodule size of  $10.2 \pm 5.6$  (range 4-19mm). All 40 patients underwent successful TOETVA without any conversion to open surgery. The 25 patients with benign thyroid nodules had lobectomies with a mean operative time of 80 minutes (range 60-105 minutes). Among the 15 patients diagnosed with thyroid cancer, 13 had a lobectomy, isthmusectomy, and central neck dissection, with a mean operative time of 85 minutes (range 65-100 minutes). The other two underwent total thyroidectomy with central lymph node dissection with a mean operative time of 132.5 minutes. The mean hospital stay was 4.5 days (range 3-7 days). No patient had permanent complications, such as hypocalcemia, recurrent laryngeal nerve injury, or mental nerve injury. The rates of temporary recurrent laryngeal nerve injury and mental nerve injury were 5% (2/40)

and 10% (4/40) respectively. Median follow-up time was 21 months (3-43) months. No recurrence was recorded.

**Conclusions:** TOETVA may be a feasible and safe surgical method for children with thyroid disease. However, we recommend that only high-volume thyroid surgeons with experience in TOETVA should perform TOETVA on the pediatric population.

### Poster 0351

*Surgery, Clinical, Poster*

#### **Transoral endoscopic thyroidectomy vestibular approach: Experience from a single institution with 900 patients**

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**Objective:** The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a scarless thyroid surgery used as an alternative to open conventional surgery. In this study, we will evaluate the safety and outcomes of TOETVA in a single institution in Vietnam.

**Methods:** A retrospective analysis on 900 patients performed TOETVA at Vietnam National Cancer Hospital from March 2018 to January 2024. The data were analyzed with regard to complications, surgery time and long-term oncological outcomes.

**Results:** The average age was 30.2 years. Majority of patients were female (95,0%). A tumor located in the right lobe accounted for 53% and in the left lobe contribute to 47%. 163 patients (18.1%) had benign thyroid nodules and 737 patients (81.9%) had papillary thyroid carcinoma. For benign patients, 163 patients underwent hemithyroidectomy with 70,3 minutes for the mean operative time. For cancer patients, 685 cases were pT1a stage (92,9%), 52 cases were pT1b (7.1%). 702 patients underwent hemithyroidectomy, isthmectomy plus unilateral central neck dissection with 80,4 minutes for the mean operative time. While 35 patients had total thyroidectomy plus bilateral central neck dissection with 115,5 minutes for the mean operative time. The number of retrieved lymph nodes was  $4.5 \pm 2.3$ . The mean hospital stay was  $3,9 \pm 0,7$  days. There was no case with conversion to open surgery. No patient had permanent complications, such as hypocalcemia, recurrent laryngeal nerve injury, or mental nerve injury. The rates of temporary recurrent laryngeal nerve injury, temporary hypoparathyroidism and mental nerve injury were 3.9%, 6.7 and 7.8% respectively. There were five cases of infection (0.56%). The mean follow-up period lasted for 32 months (ranged 3-67 months), during which no other complications or tumor recurrence were observed.

**Conclusion:** We conclude that TOETVA is feasible and safe for the treatment of patients with benign thyroid nodules and selected well-differential thyroid cancer. For selected patients, this technique is a viable alternative to conventional thyroidectomy.

### Poster 0352

*Pediatrics, Clinical, Poster*

#### **Surgical Outcomes of Endoscopic Thyroidectomies in Pediatric Patient for Thyroid Tumors: Single Surgeon's Experience from India**

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**Introduction:** Thyroid nodules are rare in children. However, thyroid nodules in children have a higher malignancy risk than in adults. The endoscopic thyroidectomy is being rapidly adopted

worldwide because of its many advantages. However, there is limited literature on the effectiveness and safety of children.

**Objective:** We report a single surgeon's experiences and surgical outcomes of 25 Endoscopic Thyroidectomy cases in Children.

**Methods:** This study included and analysed twenty-six patients who underwent endoscopic Thyroidectomies from July 2018 to June 2023 in pediatric patients (<18 years). All patients were diagnosed with thyroid tumours, including solitary thyroid nodules, multinodular goitre, Grave's Disease and thyroid cancers. All patients underwent endoscopic thyroidectomies via bilateral axillary and breast approach (BABA) & Trans oral thyroidectomy via vestibular approach (TOETVA). Central compartment lymph node dissections were also performed in all cases diagnosed with PTC.

**Results:** This Study Includes 24 Female Patients (92%) and 02 Male patients (08%). The mean age is 16.24(±1.62) years, Tumour size 4.94(±1.14) cm. the mean duration of goitre was 21.64 (±24.50) Months.

The commonest FNAC includes BETHESDA II (72%), BETHESDA III (08%) and BETHESDA IV (12%). In two patients, FNAC was not done. The endoscopic surgical approach was BABA 64% & TOETVA 36%. The extent of surgery includes Hemithyroidectomy, Total thyroidectomy (TT), and completion total thyroidectomy were applied in 20 cases (80%), 03 cases (12%) and 1 Case (4%), respectively one patient was converted to open thyroidectomy. The mean operative time was 148.96 (±55.73) minutes. The mean hospital stay was 3 (±1.22) days. There were 05 patients (20%) diagnosed with thyroid cancer and 20 patients (80%) diagnosed with benign tumour based on histopathology. There was no case of permanent hypocalcaemia, vocal cord palsy and numbness. One patient developed transient hypocalcaemia after TT and central neck dissection, which were managed with calcium and vitamin D. Focal transient numbness in the Neck and upper chest area was observed only in two patients, and all patients recovered fully after surgery.

**Conclusion:** Endoscopic Thyroidectomy is an effective and safe treatment option for paediatric patients in selected groups who do not want to have visible scars on their neck area post-thyroidectomy for thyroid tumours.

### Poster 0353

*Pregnancy and Development, Translational, Poster*

**Intraamniotic levothyroxine treatment of fetal goiter caused by synonymous mutation creating a cryptic splice site and nonsense mutation in thyroglobulin**

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**Introduction:** Nonimmune fetal goiter is a rare condition that can cause perinatal complications, such as polyhydramnios, fetal death, preterm delivery, labor dystocia, neonatal asphyxia, and long-term neurodevelopmental and growth delay. In regions without endemic iodine deficiency, genetic defects that impair thyroid hormonogenesis can cause fetal goiter. Prenatal treatment with intraamniotic levothyroxine can be used to reduce goiter size.

**Description of case:** We report a case of fetal goiter identified via ultrasound at 22-weeks gestation. Repeat ultrasound at 26-weeks demonstrated an increase in goiter size to 2.9(W)x 2.5(H)x2.4(AP) cm with complicating polyhydramnios. Maternal thyroid function tests (TFTs) and antibody testing were unremarkable. Intra-amniotic levothyroxine injections were given weekly during gestation weeks 27 through 34 with improvement of amniotic TSH levels. The fetal goiter decreased in size with subsequent improvement in polyhydramnios. The patient was born at 35-weeks due to preterm labor.

Congenital hypervascular goiter was present at birth without respiratory compromise, with right lobe 1.6x1.4x3.3 cm, volume 3.6 mL, and left lobe of 1.6x1.6x2.6cm, volume 3.2 mL measured by ultrasound. At 48-hours of life TSH was elevated at 37.1 uIU/mL (1.23 - 27.20) with FT4 of 1.27 ng/dL (0.8–2.6 for preterm infants during 1<sup>st</sup> week of life), TT3 124 ng/dL (80 – 195) and TG 6.7 ng/mL (<33), antibody negative. The newborn was started on L-T4 37.5 mcg daily. TFTs at 4 months showed normal TSH 3.4 uIU/mL (1.03 - 6.80) and TT3 213 ng/dL with undetectable TG by radioimmunoassay. Genetic testing using commercial WES identified three rare mutations in the thyroglobulin *TG* gene not previously reported to cause congenital hypothyroidism: an early termination, c.886C>T: p.R296\*, a missense mutation c.7157G>A:p.R2386H, and a synonymous nucleotide change c.1029G>T:p.Gly343 predicted to create a cryptic splice site. Segregation of the *TG* mutations in the family demonstrated that the nonsense and missense mutations were inherited from the mother and the synonymous mutation predicted to affect splicing, from the father.

**Discussion:** Genetic defects causing dysmorphogenesis can manifest with fetal goiter and congenital hypothyroidism. Treatment in utero with intraamniotic levothyroxine can prevent perinatal complications. Genetic testing can determine the underlying mechanism, guide treatment, and assist in familial genetic counseling.

### Poster 0354

*Pregnancy and Development, Clinical, Poster*

**The association of gestational thyroid function and thyroid autoimmunity with offspring neurodevelopment: an individual participant meta-analysis**

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**Objective:** Adequate thyroid hormone availability during pregnancy is essential for fetal neurodevelopment, and recent studies suggested an inverse U-shaped association of gestational thyroid function with IQ-measurements. Our aim was to investigate the association of gestational thyroid function with offspring IQ scores, if there is a critical window in pregnancy and the persistence into adulthood.

**Methods:** We performed a systematic search for prospective cohort studies and issued open invitations to authors to participate in the current study. Exposures were maternal thyroid function and autoimmunity, and clinical disease entities calculated according to current guidelines. The primary outcome was IQ-scores. We performed mixed regression models accounting for repeated measurements, adjusting for maternal age, maternal education, ethnicity, body mass index, smoking status, parity, gestational age at blood sampling, fetal sex and child age of IQ assessment. We used multilevel multiple imputation for missing covariate data and inverse probability weighting to account for attrition.

**Results:** The final study population comprised 14767 participants from 11 cohorts with 22099 IQ measurements (median age of measurement 6.1 years, interquartile range [IQR] 3.1-8.7 years). There was an inverted U-shaped association of FT4 with child IQ-scores ( $P=0.00048$ ), which corresponded for low and high FT4 with a mean difference in IQ-scores of -5.5 to -6.5 in the full range and -1.0 to -1.5 in the euthyroid range. The association diminished for higher child age with no association between FT4 and child IQ-scores present at >10 years of age. After stratification for gestational age at blood sampling (median 13.2 weeks, IQR 11.6-17.5), there was no

association between FT4 and child IQ-scores after 25 weeks of gestation, although data were limited in this period. There was no statistically significant association of TSH, thyroid autoimmunity or clinical disease entities with child IQ scores.

**Conclusions:** Both low and high maternal FT4, but not TSH, in pregnancy are associated with lower child IQ scores. This is the first multicenter study to replicate these findings and add important data on time dependency and persistency of the effect in adolescence. These results emphasize that caution should be exercised when supplementing thyroxine in pregnancy at the risk of overtreatment and possible detrimental effects on offspring neurodevelopment.

### Poster 0355

*Pregnancy and Development, Clinical, Poster*

#### **The association of gestational thyroid function with gestational diabetes mellitus: a systematic review and individual participant meta-analysis**

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**Objective:** Gestational thyroid dysfunction and gestational diabetes mellitus (GDM) are common complications in pregnancy and frequently coincide. Since thyroid hormones have multiple effects on glucose metabolism, our aim was to study if and to what extent maternal thyroid function is associated with glucose metabolism and GDM.

**Methods:** We performed a systematic search for prospective cohort studies and issued open invitations to authors to participate in this study. Exposures were maternal thyroid function, thyroid autoimmunity and clinical disease entities calculated according to current guidelines. The primary outcome was GDM, secondary outcomes were glucose and insulin measurements. Individual-participant data were analyzed using mixed-effects regression models adjusting for maternal age, body mass index, smoking, parity, ethnicity, fetal sex and gestational age at blood sampling.

**Results:** From 468 published articles, 36 cohorts were invited and 25 cohorts were included after agreeing to participate, including 63548 participants after exclusions. There were 1687 (3.2%) women with subclinical hypothyroidism, 1153 (2.2%) with isolated hypothyroxinemia and 2958 (4.7%, range 0.5-42.3%) cases of GDM. Isolated hypothyroxinemia was associated with a higher risk of GDM as compared to euthyroid women (absolute risk 6.5% vs 3.5%; odds ratio 1.5, 95%CI 1.2-2.0;  $P=0.0017$ ). In continuous analyses, low FT4 was nonlinearly associated with a higher risk of GDM ( $p<0.001$ ). Similarly, low FT4 was associated with higher glucose measurements during the oral glucose tolerance test after 1 and 2 hours (+0.8 and +0.6 mmol/L, respectively, for lowest FT4 values compared to mid-range values;  $p<0.001$ ). There was an L-shaped association of FT4 and fasting insulin concentrations, with doubling of fasting insulin concentrations for the lowest FT4 values ( $p<0.001$ ). There was no association of thyroid stimulating hormone, thyroid autoimmunity and other disease entities with GDM.

**Conclusions:** Among pregnant women, low FT4 and isolated hypothyroxinemia were significantly associated with a higher risk of GDM and unfavorable changes in glucose metabolism. Physicians should anticipate potentially relevant changes in insulin sensitivity after correction of low FT4 in patients, which could be of particular significance for patients treated with insulin. Future research should assess whether modifying maternal thyroid dysfunction results in reduced risk of GDM.

### Poster 0356

*Pregnancy and Development, Clinical, Poster*

#### **Changes in Thyroid Function during Pregnancy: A Prospective Observational Study to Determine Trimester-specific Reference Intervals**

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**Background:** Thyroid function test (TFT) reference ranges vary across ethnicities and pregnancy trimesters, underscoring the importance of utilizing population-based reference intervals for accurate thyroid disorder diagnosis.

**Methods:** We designed a prospective study to establish trimester-specific reference ranges for TFTs in Taiwan. From March 2019 to March 2023, 209 pregnant women in their first trimester at Taipei Veterans General Hospital were enrolled. Anti-thyroid antibodies and TFTs were assessed in each trimester. The trimester-specific TFT reference ranges were determined based on the 2.5th and 97.5th percentiles of the women ( $n=123$ ) who did not have thyroid disorder, tested negative on all thyroid autoantibodies, and had complete follow-up through all three trimesters.

**Results:** The mean age of the cohort was 33.9 years, with 61.0% experiencing their first pregnancy. The median value and trimester-specific reference ranges for TFTs in the first, second and third trimester were: TSH (1.00 [0.007-3.08], 1.46 [0.33-4.55], 1.52 [0.29-4.64]  $\mu$ IU/mL), free T4 (1.29 [0.96-2.44], 0.97 [0.74-1.24], 0.94 [0.72-1.18] ng/dL), total T4 (9.9 [6.4-17.2], 9.4 [6.5-13.2], 9.4 [6.7-12.7]  $\mu$ g/dL), free T3 (3.0 [2.2-5.1], 2.5 [1.9-3.2], 2.4 [1.8-2.9] pg/mL), and total T3 (135 [89-214], 141 [92-203], 140 [85-194] ng/dL), respectively. Notably, TSH increased significantly between the first and second trimesters, while free T4 and free T3 gradually decreased throughout pregnancy. The percentage of patients with positive thyroid antibodies in the first, second and third trimester were 7.2%, 3.3%, and 2.9% for aTPO and 7.2%, 6.7%, and 5.7% for aTG, respectively. For those whose thyroid antibodies were persistently positive ( $n=13$  for aTPO,  $n=7$  for aTG) through pregnancy, significant decrease in aTPO levels between the first and second trimesters was observed (first, second and third trimester levels for aTPO: 1036.9  $\pm$  1323.1 IU/mL, 749.6  $\pm$  760.3 IU/mL, and 691.1  $\pm$  791.9 IU/mL; aTG: 516.1  $\pm$  534.9 IU/mL, 292.2  $\pm$  290.2 IU/mL, and 213.1  $\pm$  209.4 IU/mL, respectively).

**Conclusions:** Our study represents the first comprehensive investigation of ethnicity-based and trimester-specific reference intervals for TFT in Taiwan.

### Poster 0357

*Pregnancy and Development, Clinical, Poster*

#### **Iodine and Selenium Nutritional Status: a cross-sectional analysis in women with unexplained infertility**

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**Objective:** Adequate Iodine (I) and Selenium (Se) nutritional status are essential for conception and pregnancy. Little is known about I/Se status among women with infertility, especially in Latin American populations. We aimed to analyze I/Se status in women with unexplained infertility (UI) screened in Brazil.

**Methods:** Socio-demographic, health and reproductive data from 90 UI women were obtained. Iodine (UIC) and selenium (USEC) spot urinary concentrations were measured by ICP-MS and analyses were performed in duplicate. Thyroid function (TSH, freeT4, free T3, thyroid autoantibodies), FSH, Estradiol and anti-Mullerian hormone (AMH) were measured. Mann-Whitney tests for quantitative analysis, Chi-squared tests for nonparametric qualitative analyses, and Kruskal Wallis for group comparisons were employed (Phyton<sup>®</sup> 3.12.3 statistical package).

**Results:** The median (IQR) age was 37 (34-40) years with 55/90 (61%) <40 yr. Low income was reported by 17/90 (19%) and 33/90 (37%) had comorbidities. The median BMI was 25.7kg/m<sup>2</sup> (23.2-29.4) and 24/90 (26%) were obese. The median time attempting to conceive was 5 (3-7) years and 30/90 (33%) had a history of pregnancy loss. Median UIC was 190.2µg/L (IQR, 113.2-289µg/L) indicating iodine adequacy by World Health Organization standards. However, UIC <100 µg/L was seen in 19/90 (21%) and UIC >199 µg/L in 41/90 (45%). Elevated UIC levels were more frequent in women under age 35 vs. individuals age 35-39 and >40 [66% vs. 18% vs. 15%, respectively, p=0.03]. Median USEC was 34.44 µg/L (IQR, 23.98-50.28 µg/L), indicating Se adequacy (SA) (reference range: 10-110 µg/L). Median (IQR) values were: TSH 1.35 (0.94-1.89) µIU/mL; fT4 0.95 (0.89 - 0.99) ng/dl; fT3 0.87 (0.8 - 0.99) ng/dl; FSH4.76 (3.42-6.46) µIU/mL; estradiol 90 (43.5-141.75) pg/mL; and AMH 1.36 (0.56-2.37) ng/ml. AMH <1.2 ng/ml was found in 45%, indicating low ovarian reserve. Thyroid antibody positivity was seen in 24/90 (26%). No association between other socio-demographic, health, reproductive or biochemistry results and I/Se was observed.

**Conclusion:** Median UIC and USEC demonstrate I/Se sufficiency in Brazilian UI women, but possible iodine excess was observed in a subgroup of the youngest and most obese. A better understanding of factors associated with I/Se status in these women is needed.

### Poster 0358

*Pregnancy and Development, Clinical, Poster*

#### **Selenium deficiency is associated with high-risk pregnancy in selenium-rich Brazilian pregnant women population**

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**Objective:** To analyze the Se nutritional status in pregnant women (PW) screened in a public maternity hospital in Brazil.

**Methods:** In This cross-sectional study, 330 PW were investigated for Urinary Selenium Concentration (USEC) using the inductively coupled plasma mass spectrometry (ICP-MS) method. Socio-demographic, anthropometric data were collected, and gestational risk was classified according to the Ministry of Health.

**Results:** 330 PW [median age: 29 (range 15-46) years] were divided into: (i) 226 HRPW and (ii) 104 Low risk pregnancy women (LRPW). The overall median USEC (MUSEC) was 25 µg/L (25th-75th percentile, 17-35.8 µg/L) and the mean was 28.4 ± 6.79 µg/L, indicating Se adequacy (SA). Low USEC (<15 µg/L) was detected in 20% of PW. MUSEC levels were significantly lower in HRPW vs. LRPW [MUSEC: 24 (15.3- 33.8) vs. 29.1 (20.2-40.6) µg/L, p=0.0035]. SeD rate was more prevalent in HRPW vs. LRPW [24.3% vs 10.6%, p=0.0037] [OR: 2.71; CI 1,4-5,7; P=0.0048]. The odds ratio (OR) of HRP being associated with SeD was 3.38 (95% CI: 1.56 - 8.06, p = 0.003) after confounder adjustment in a multivariate logistic regression.

**Conclusion:** In the hitherto largest number of HRPW studied, we demonstrate an association between low USEC and high-risk pregnancy in Brazil, suggesting need of nutritional monitoring of HRPW. The question of causality could be addressed in a randomized prospective intervention study

### Poster 0359

*Disorders of Thyroid Function, Clinical, Poster*

#### **Genomic Ancestry as a Risk Factor for Thyroid Dysfunction: Data from 9372 Individuals Analysed at ELSA-Brasil Longitudinal Study**

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**Introduction:** Previous data from Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study showed that self-reported brown and black ethnicities were protective for overt hypothyroidism (OH). Brazilians form one of the most heterogeneous populations in the world and the investigation of genomic profiles that distinguish biogeographical ancestry may be a tool to evaluate the association between ethnicity and thyroid function.

**Objective:** To investigate the genomic ancestry as a risk factor for OH and subclinical hypothyroidism (SCH) at ELSA-Brasil population.

**Methods:** 9372 ELSA-Brasil participants were genotyped. Global genetic ancestry was determined by purified DNA, using QIAamp DNA Mini-kit1, QuantstudioTM platform and ADMIXTURE program. TSH and FT<sub>4</sub> serum levels were determined by a third-generation immunoenzymatic assay. Cut-off values for TSH were <0.4 mIU/L for hyperthyroidism and >4.0 mIU/L for hypothyroidism and for FT<sub>4</sub> they were >1.9 ng/dL and <0.8 ng/dL, respectively. Kruskal-Wallis and Dunn's tests were performed for all variables. Logistic regression models with mixed effects were used to calculate odds ratios (ORs) between exposure variables and the main outcome.

**Results:** The median age of participants was 51 years, 53.8% being women; 7769 had normal thyroid function, 847 had SCH, 669 had OH and 87 had subclinical or overt hyperthyroidism. Thyroid dysfunction was predominant in women compared to men (p < 0.0001), specially in OH (82.5%) and hyperthyroidism (65.5%).

Concerning to genomic ancestry, European (>50%) was predominant, followed by African and Native American (medians of 69.9%, 13% and 4.6%, respectively) with multi-ancestry at 12.6%. European ancestry displayed a significant correlation with both SCH and OH (9.9% and 7.9%, respectively)( $p < 0,0001$ ); conversely, African ancestry was associated with hyperthyroidism (1.7%) and multi-ancestry (9%) exhibited a higher prevalence of SCH ( $p < 0,001$ ). TSH demonstrated a directly proportional relationship with European ancestry ( $p < 0.01$ ) and an inversely proportional relationship with African ancestry ( $p < 0.01$ ), as well as with free T4 ( $p < 0.01$ ).

**Conclusion:** Genomic European ancestry was predominant in ELSA-Brasil participants and displayed a significant correlation with both SCH and OH. Genomic African ancestry was protective for hypothyroidism compared with European ancestry. Our results demonstrate important influences of genomic ancestry on the diagnosis of thyroid disorders.

### Poster 0360

*Thyroid Hormone Action, Metabolism and Regulation, Case Study, Poster*

#### Third Time is the Charm: Persistent Thyroid Stimulating Immunoglobulin Elevation After Two Thyroidectomies

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#### Introduction

Total thyroidectomy is considered a definitive treatment for Graves' disease. Thyroid Stimulating Immunoglobulins (TSI) gradually decline following total thyroidectomy, generally reaching a nadir 6 months post-surgery. We present a case of persistent TSI elevation following total thyroidectomy and subsequent anterior neck mass resection.

#### Description of the Case

A 30-year-old female underwent total thyroidectomy for Graves' disease in 2012. Following thyroidectomy, she was started on Synthroid 150 mcg. Six years later, she developed a right anterior neck mass. Neck ultrasound noted a hypervascular soft tissue nodule. Cytology from fine needle aspiration was consistent with thyroid tissue. She later developed thyroid eye disease with mild left exophthalmos and bilateral upper eyelid retraction. The patient was referred to endocrinology for further evaluation. Her TSH was  $< 0.01$  IU/mL on Synthroid 100 mcg daily. TSI were elevated at 50.7 IU/mL. In September 2023, she was referred to ENT for excision of the anterior neck mass. Surgical pathology demonstrated thyroid tissue with previously treated Graves' disease. Two months following surgery, her TSI level decreased to 38.2 IU/mL. Six months following surgery, her TSI increased to 51.6 IU/mL, raising concern for residual thyroid tissue. A thyroglobulin level was obtained and resulted as 11.4 ng/dL. An I-123 whole body scan was then performed. Given the patient had post-procedural hypothyroidism requiring Synthroid, 2 doses of Thyrogen were administered in the days preceding the scan. 24 hours following administration of 2.04 mCi of I-123, planar whole body images were performed in addition to SPECT-CT images of the neck and chest. Imaging findings included a 2.1 cm hyperattenuating soft tissue nodule with associated intense iodine uptake in the right thyroid surgical bed and a 0.6 cm x 0.4 cm small hyperattenuating soft tissue nodule in the left surgical bed consistent with residual thyroid tissue. A third neck surgery is planned to resect the residual thyroid tissue with the goal to normalize TSI.

#### Discussion

Persistent elevation of TSI following total thyroidectomy should raise suspicion for residual thyroid tissue. In patients with post-thyroidectomy hypothyroidism, I-123 whole body scan with Thyrogen can serve as an imaging modality to locate residual thyroid tissue.

### Poster 0361

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

#### Vital Signs Among Patients With Hypothyroidism Treated for up to 48 Weeks With Armour Thyroid or Synthetic Levothyroxine: ARCH Phase 2 Randomized Double-Blind Study

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**Objective:** This analysis examined vital signs among patients with hypothyroidism treated with Armour Thyroid or synthetic levothyroxine (LT4) in the phase 2 ARCH study.

**Methods:** ARCH was a phase 2, multicenter, double-blind, randomized, dose-conversion study. Adults (age, 18–75 years) with primary hypothyroidism who had an in-range thyroid stimulating hormone value (0.45–4.12 mIU/L) at screening and were treated with LT4 for  $\geq 12$  months were eligible. Participants were randomized to receive up to 48 weeks of treatment with their same dose of LT4 or an approximately matching dose of Armour Thyroid (calculated using the USP Drug Information 2000 dose conversion chart). Patients with a sitting systolic blood pressure (BP)  $\geq 140$  mmHg or  $\leq 90$  mmHg or diastolic BP  $\geq 90$  mmHg or  $\leq 50$  mmHg observed during screening were excluded. Vital sign assessments were prespecified as part of the ARCH study safety evaluation and were described here without formal comparisons.

**Results:** In the safety analysis dataset (all participants receiving  $\geq 1$  study drug dose), 141 and 143 patients received Armour Thyroid and LT4, respectively. In the prespecified analysis of potentially clinically meaningful criteria, 11.6% of Armour Thyroid patients and 15.2% of LT4 patients experienced a systolic BP  $\geq 140$  mmHg and increase  $\geq 20$  mmHg; 4.3% of Armour Thyroid patients and 7.2% of LT4 patients experienced a diastolic BP  $\geq 90$  mmHg and increase  $\geq 15$  mmHg; and 0.7% of Armour Thyroid patients and 3.6% of LT4 patients experienced a pulse rate  $\geq 100$  bpm and increase  $\geq 15$  bpm. By study end, clinically modest changes in mean systolic BP were reported in both arms (Armour Thyroid, 2.8 mmHg [median 2.0 mmHg]; LT4, 1.7 mmHg [median 2.0 mmHg]) and minimal changes in mean diastolic BP (Armour Thyroid, 0.8 mmHg [median 0.0 mmHg]; LT4, -0.9 mmHg [median -1.0 mmHg]) and pulse rate (Armour Thyroid, 0.5 bpm [median 0.0 bpm]; LT4, 0.7 bpm [median 1.0]) were reported.

**Discussion/Conclusion:** Overall, the use of Armour Thyroid for up to 48 months was safe and well tolerated in the Phase 2 ARCH study. When examining SBP, DBP, and pulse rate as part of the safety evaluation, Armour Thyroid and LT4 treatment yielded clinically similar findings.

### Poster 0362

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

#### Exploring the Clinical and Genetic Characteristics of Resistance to Thyroid Hormone $\beta$ Patients: A Tertiary Center Experience

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**Objective:** Resistance to thyroid hormone  $\beta$  (RTH $\beta$ ) results from mutations in the *THRB* gene, which encodes the thyroid hormone receptor  $\beta$  (TR $\beta$ ). The clinical phenotype varies and can mimic other conditions, potentially leading to misdiagnosis. Our objective was to delineate the clinical and genetic profiles of patients diagnosed with RTH $\beta$  at a tertiary center for thyroid diseases in Thailand.

**Methods:** Clinical and biochemical details of 10 patients with genetically confirmed RTH $\beta$  from seven families were retrospectively reviewed. A molecular analysis of exon 7-10 of the *THRB* gene was performed by Sanger sequencing.

**Results:** Six children and four adults with genetically confirmed RTH $\beta$  were included. The main presentations were diffuse goiter (70%) and tachycardia (80%). Two adults presented with atrial fibrillation, prompting thyroid function testing. Genetic studies were conducted in one asymptomatic adult as part of a family study. Elevated FT3 and FT4 alongside non-suppressed TSH concentrations were observed in all patients. Seven patients (six children and one adult) were misdiagnosed with Graves' disease and treated with antithyroid drugs (ATD), resulting in fluctuating thyroid hormone and increased TSH levels. One girl exhibited pituitary hyperplasia due to ATD-induced primary hypothyroidism, which regressed after ATD discontinuation. Persistently elevated FT4 with non-suppressed TSH levels during levothyroxine treatment and positive thyroid autoantibodies led to the considering of coexisting RTH $\beta$  and Hashimoto thyroiditis in this girl. TSH-secreting pituitary adenomas were misdiagnosed in two adults, with one undergoing unnecessary pituitary surgery. Molecular analysis confirmed the diagnosis of RTH $\beta$  in all patients. Seven heterozygous missense mutations (R243W, R338W, L341V, I353V, H435R, P453T, and L456F) were identified, all located in three CpG-rich hotspots in the ligand-binding domain of TR $\beta$ . The presence of goiter and severity of tachycardia varied among family members carrying similar mutations.

**Conclusion:** We present the largest series of RTH $\beta$  patients from Thailand. Consistent with other RTH $\beta$  cohorts, our patients are susceptible to misdiagnosis, leading to unnecessary treatment. Key diagnostic features include diffuse goiter, tachycardia, and elevated thyroid hormones with non-suppressed TSH levels. Mutation analysis provides a definitive diagnosis of RTH $\beta$ , offering avoidance of misdiagnosis and inappropriate treatment.

### Poster 0363

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

**Effect of bariatric surgery on TSH levels and levothyroxine dosage in patients with thyroid disease: Sleeve gastrectomy vs Roux-en-Y Gastric bypass**

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**Objective:** Some evidence indicates how bariatric surgery impacts the thyroid function test and, in hypothyroid patients, the dose of levothyroxine (LT4), but data are not univocal. To examine, in a single center retrospective analysis, the relationship between change in body weight, plasma levels of TSH and dosage of LT4 in patients with thyroid disease undergoing bariatric surgery and to compare the effects of Roux-en-Y gastric bypass (RYGB) vs sleeve gastrectomy (SG).

**Methods:** The data was collected from medical records of hospitalization of 235 patients (104 SG and 131 RYGB) who underwent pre-surgical work-up and from outpatient medical records of the same patients at 45 days, 3–6 months and 1-year visits after surgery. In the final analysis we included 69 patients on LT4 therapy (43 Tr-RYGB and 26 Tr-SG) and 85 patients without thyroid diseases with normal thyroid function (48 Ct-RYGB and 37 Ct-SG), who served as matched controls.

**Results:** The mean body weight reduction for all cohort was in 31.4±0.7% after 1 year from the surgery. In the two Ct groups, TSH levels remained stable throughout the observation period, without differences for type of surgery and without relationship with body weight. Free-T3 levels, decreased significantly at all follow-ups, in both Ct groups and in Tr-RYGB ( $p < 0.01$ ). After bariatric surgery, the patients treated with LT-4, belonging to both Tr-RYGB and Tr-SG, needed to increase the dosage per body weight to achieve stable TSH. At 1 year, the increase of LT4/kg/die was higher in the Tr-RYGB group than Tr-SG group (0.44 vs 0.30 mcg/kg/die,  $p = 0.032$ ).

**Conclusion:** In patients with severe obesity with normal thyroid function, TSH levels are not related with body weight change. Patients treated with LT4, after bariatric surgery need to increase the dosage pro kg of body weight of the LT4 and the increase is higher after surgery with malabsorptive component (RYGB) compared to restrictive surgery (SG). These data support a major role of the impaired drug absorption consequence of bariatric surgery rather than of the new body weight in determining the subsequent LT4 dosage. The results should be confirmed on a larger sample.

### Poster 0364

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

**The associations between thyroid hormone state and psychiatric symptoms in hospitalized patients with bipolar disorder or depression**

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**Objective:** Thyroid hormones were reported to play a crucial role in regulating mood, and cognitive function. However, the influences of thyroid function state on psychiatric symptoms are still unclear. This study aimed to examine the association between psychiatric symptoms and thyroid hormone state in patients with bipolar disorder and depression.

**Methods:** In this retrospective cross-sectional study, we enrolled patients with bipolar disorder or depression, who were admitted to Department of Psychiatry at our hospital from April 2014 to March 2023. We examined the associations between thyroid function state at admission and psychiatric symptoms, which were evaluated by Global Assessment of Functioning (GAF) score.

**Results:** 238 patients with bipolar disorder (female 161, mean age: 56±15 years) and 263 patients with depression (female 165, mean age: 63±16 years) were enrolled in this study. In patients with bipolar disorder, mean free T3 was 3.15±0.52 pg/ml, free T4 was

1.04±0.26 ng/ml, and TSH was 1.54±1.41 μIU/ml. In patients with depression, mean free T3 was 2.68±0.49 pg/ml, free T4 was 1.00 ± 0.26 ng/ml, and TSH was 1.53±1.73 μIU/ml. 160 patients with bipolar disorder (67.2%) and 161 patients with depression (61.2%) had normal thyroid hormone state. Hypothyroidism was observed in 51 patients with bipolar disorder (19.4%), and 35 patients with depression (14.7%). In patients with bipolar disorder, GAF score had a negative correlation with free T4 ( $r=-0.238$ ,  $p<0.001$ ) and positive correlation with TSH ( $r=-0.238$ ,  $p<0.001$ ). In patients with depression, there were a weak but significant negative correlation between GAF score and free T4 ( $r=-0.162$ ,  $p=0.010$ ).

**Discussion/Conclusion:** The rate of patients with thyroid dysfunction was higher in patients with bipolar disorder or depression, compared with that reported in general population. Moreover, the negative correlations between GAF score and free T4 suggested the associations between elevated thyroid hormone levels and exacerbated psychiatric symptoms. Our study presented the possible associations between thyroid hormone state and psychiatric symptoms.

### Poster 0365

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

#### Liquid L-T4 Formulation in Hypothyroid Patients with Celiac Diseases or Non-Celiac Gluten Sensitivity

Francesca Ragusa<sup>1</sup>, Giusy Elia<sup>1</sup>, Armando Patrizio<sup>2</sup>, Chiara Botrini<sup>1</sup>, Valeria Mazzi<sup>1</sup>, Eugenia Balestri<sup>1</sup>, Licia Rugani<sup>1</sup>, Oriana Fabrizio<sup>1</sup>, Roberta Pitzus<sup>1</sup>, Enke Baldini<sup>3</sup>, Mario Miccoli<sup>4</sup>, Concettina La Motta<sup>5</sup>, Gabriella Cavallini<sup>6</sup>, Silvia Martina Ferrari<sup>4</sup>, Alessandro Antonelli<sup>1</sup>, Poupak Fallahi<sup>\*6</sup>, <sup>1</sup>University of Pisa, Department of Surgical, Medical and Molecular Pathology and Critical Area, Italy, <sup>2</sup>Azienda Ospedaliero-Universitaria Pisana, Department of Emergency Medicine, Italy, <sup>3</sup>"Sapienza" University of Rome, Department of Experimental Medicine, Italy, <sup>4</sup>University of Pisa, Department of Clinical and Experimental Medicine, Italy, <sup>5</sup>University of Pisa, Department of Pharmacy, Italy, <sup>6</sup>University of Pisa, Department of Translational Research and New Technologies in Medicine and Surgery, Italy

**Objective:** Considering the damage to the gastro-intestinal mucosa and villi observed in celiac disease (CD), the absorption of many drugs taken orally is impaired, and these include levothyroxine (L-T4), the cornerstone therapy for any form of hypothyroidism.

**Methods:** The stability of TSH in hypothyroid patients with CD or non-celiac gluten sensitivity (NCGS), is reported in this observational and retrospective study, which compares patients in treatment with liquid LT4 (L-LT4 26; 22 females, 85%; 4 males, 15%) with those in treatment with tablet LT4 (T-LT4 21; 19 females, 90%; 2 males, 10%). Both groups are similar for gender distribution, mean age, body weight, the type of enteric disease (17 CD or GS), the treatment with proton-pump inhibitors (33% in the T-LT4, vs 23% in the L-LT4) and the mean L-T4 dosage ( $p>0.05$ , for all comparison).

**Results:** At the basal evaluation, in the T-LT4 group, the prevalence of patients with TSH>3.5 mIU/mL was 38%, whereas in the L-LT4 group was 42% ( $p>0.05$ ). In a total period ranging from 23 to 34 months, and after the dosage of the L-T4 therapy was adjusted, the patients were re-evaluated in an interval range of 4-8 months, for 4 times, during which the therapy was adjusted if needed on the base of TSH, FT4, and FT3 levels. At the first re-evaluation the prevalence of patients with a TSH>3.5 mIU/mL was 25% in the T-LT4 group, compared to 23% in the L-LT4 group ( $p>0.05$ ); at the second re-evaluation, the prevalence of patients with a TSH>3.5 mIU/mL was 27.8% in the T-LT4 group, vs, 16.7% in the L-LT4 ( $p>0.05$ ); at the third re-evaluation the prevalence of patients with a

TSH>3.5 mIU/mL was 47% in the T-LT4 group, vs, 9% in the L-LT4 (Chi-square=0.0071); at the fourth and last re-evaluation, the prevalence of patients with a TSH>3.5 mIU/mL was respectively of 38.8% in the T-LT4 group, vs, 9.0% in the L-LT4 group (Chi-square=0.0248).

**Conclusions:** To conclude, our data demonstrate a better control of TSH values in hypothyroid patients with celiac disease, or non-celiac gluten sensitivity in treatment with liquid L-T4, compared to L-T4 tablets.

### Poster 0366

*Thyroid Hormone Action, Metabolism and Regulation, Clinical, Poster*

#### Treatment with Soft Gel Capsule L-T4 in Hypothyroid Patients with Gastric Diseases Associated with L-T4 Malabsorption

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**Objective:** Levothyroxine (L-T4) is used to treat any form of hypothyroidism. Endogenous (i.e. gastric diseases) or exogenous factors (i.e. some drugs) can reduce the absorption of L-T4, by altering the acidic environment of the stomach. The aim of this study was to evaluate the stability of TSH and thyroid hormone levels in hypothyroid patients with gastric disease treated with different formulations of L-T4, soft gel capsule or tablet.

**Methods:** In this observational and retrospective study, we evaluated the potential difference of L-T4 formulations in reaching normal and stable TSH values over time, in patients who suffer from hypothyroidism and gastric diseases, subdivided in two matched arms: one group of patients on soft capsule (S-LT4; 32 patients) and the other on L-T4 tablets (T-LT4; 100 patients). In both L-T4 groups, no significant difference was reported in gender, age distribution, types of gastric disease (chronic gastritis; gastrectomy; gastroplics), prevalence of patients chronically treated with proton-pump inhibitors, frequency of Helicobacter Pylori infection and the mean of L-T4 dosage.

**Results:** At the basal evaluation the prevalence of patients with a TSH > 3.5 mIU/mL in the T-LT4 group was 16%, vs, 28.1% in the S-LT4 (Chi-square;  $p=0.1$ ). After the basal evaluation, the L-T4 dose was adjusted (if needed), after re-evaluating patients in an interval range of 4-8 months, for 4 times, during an overall period ranging from 20 to 24 months, on the base of TSH, FT4, and FT3 levels. The prevalence of patients with a TSH > 3.5 mIU/mL was: 1) at the first re-evaluation, 13.2% in the T-LT4 group, vs, 6.6% in the S-LT4 group (Chi-square;  $p=0.32$ ); 2) at the second re-evaluation, 25.2% in the T-LT4 group, vs, 3% in the S-LT4 group (Chi square;  $p=0.0052$ ); 3) at the third re-evaluation, 18.8% in the T-LT4 group, vs, 4% in the S-LT4 group (Chi-square;  $p=0.06$ ); 4) at the last re-

evaluation, 17.39% in the T-LT4 group, vs 11.1% in the S-LT4 group (Chi-square;  $p=0.43$ ).

**Conclusion:** To conclude our data demonstrate a better control of TSH values in hypothyroidism gastropathic patients in treatment with soft gel capsule L-T4 formulation, compared to L-T4 in tablets.

### Poster 0367

*Thyroid Hormone Action, Metabolism and Regulation, Basic, Poster*  
**ScRNA-seq Analysis Reveals Drastic Epithelial Population Transformation at the Climax of Xenopus Metamorphosis**  
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**Abstract:** Adult organ/tissue maturation occurs during postembryonic development in vertebrates. This often involves the formation of adult tissue-specific stem cells that play critical roles for organ homeostasis as well as tissue repair and regeneration. However, it has been difficult to study the maturation of adult organs and tissues in mammals due to the difficulty to access uterus-enclosed late-stage embryos. The T3-dependent *Xenopus* metamorphosis is a process mimicking the postembryonic development in mammals and transforms essentially all tissues, including larval tissue degeneration, de novo adult tissue formation, and remodeling of larval tissues to the adult type. Of particular interest is intestinal metamorphosis, which involves apoptotic degeneration of the larval epithelium, de novo formation of adult stem cells and their subsequent proliferation and differentiation into the adult epithelium. This makes intestine a unique organ for studying adult stem cell development. Toward understanding the cell transformations in the intestinal epithelium during metamorphosis, we perform single cell RNA sequencing (ScRNA-seq) analysis on intestinal epithelial cells isolated from stage 56 (the larval stage) and 61 (the climax of metamorphosis) tadpoles. Our data indicated that the epithelial cells at the stage 61 had very different transcriptome compare to that at stage 56. In addition, we identified the stem cell-like cells and cells likely undergoing epithelial-mesenchymal transition cells at the climax of metamorphosis. Further analyses of the transcriptome changes and the cell types present at the climax of metamorphosis should help to reveal how the molecular mechanism underlying T3-induction of adult epithelial stem cell development.

**Acknowledgements:** This work was supported by the Intramural Research Program of NICHD, NIH.

### Poster 0368

*Thyroid Cancer, Case Study, Poster*

#### **Tall Cell Variant Papillary Thyroid Cancer with Unexplained TSH and Thyroglobulin Elevation**

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**Introduction:** Papillary thyroid cancer has an excellent prognosis, however, 20-30% of patients develop recurrent disease. It is challenging to predict disease prognosis despite advancements and changes in treatment of thyroid cancer.

**Description of the case:** We present a 44-year-old woman diagnosed with papillary thyroid carcinoma (PTC) in 2018. She underwent total thyroidectomy with a central and bilateral neck dissection. Pathology revealed a 2.1 cm tall cell variant PTC with a positive margin, 6/6 right central neck, 1/7 right lateral neck, and 2/8 left lateral neck lymph nodes (LN) were positive. The largest LN was 1.4 cm, with extranodal extension present. She received 125 mCi adjuvant I-131. Post-treatment scan showed uptake in the thyroid bed. Over the next 5 years thyroglobulin (Tg) ranged from <0.2-0.4 with appropriately suppressed TSH (0.02-0.23). In October 2023, she presented with a TSH > 100 and Tg 64, despite reported compliance with Levothyroxine (137 mcg daily). Cytomel 25 mcg was added, but TSH remained >100 with undetectable FT4 and T3; Tg rose to 108 in November 2023. She was severely symptomatic with generalized edema. Neck ultrasound demonstrated a 5 mm left thyroid bed nodule, thought unlikely to be the cause of her high Tg. CT scan of her chest was negative. She underwent an additional 130 mCi I-131 in December 2023 with thyrogen stimulation. Stimulated Tg was 118, and the post-treatment scan showed no evidence of malignancy. One month after I-131 treatment, her TSH (0.66) and Tg (1.7) had significantly improved. She resumed taking Levothyroxine alone (137 mcg). Four months after I-131, Tg was 0.4 with TSH 0.11.

**Discussion:** We present a patient with tall cell variant PTC, initially treated with surgery and adjuvant I-131. Five years later she experienced a rapid rise of Tg (>100), unexplained elevation of TSH levels (>100), and no imaging consistent with significant structural recurrence. Repeat I-131 administration resulted in a rapid decrease in Tg, with levels dropping in a month. A prolonged stimulation of TSH >100 for two months may enhance radioactive iodine effect in recurrent PTC relative to short term elevation of TSH.

# Saturday, November 2, 2024

## Poster 0369

*Pregnancy and Development, Case Study, Poster*

### Delayed Recovery From Gestational Transient Thyrotoxicosis Causing Clinical Hypothyroidism in a Twin Pregnancy

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**Introduction:** B-hCG shares an alpha-subunit with TSH and can cause transient elevation in T4 and suppression of TSH. This phenomenon is particularly pronounced in twin pregnancies. TSH gradually returns to preconception levels as pregnancy progresses.<sup>1,2</sup> We present a patient who presented with decreased TSH and elevated FT4 in the first trimester of her twin-pregnancy consistent with gestational transient thyrotoxicosis (GTT) that failed to recover and led to clinical hypothyroidism. To the best of our knowledge, this has not been described in the literature.

**Case:** A 30yo G2P1 woman with no history of thyroid or autoimmune disease, and no family history of thyroid disorders presented at gestational week (GW) 11 of a monochorionic diamniotic pregnancy with a TSH level <0.01 uIU/mL (0.27–4.20) and a FT4 level of 1.77 ng/dL (0.93–1.70). Her vitals were within normal range. She had a mild tremor, thyroid gland was two times normal, but no ophthalmopathy. Thyroid peroxidase antibody and thyroid-stimulating immunoglobulin antibody were not elevated. At GW 21, TSH level remained low at 0.14 uIU/mL (0.27–4.20), FT4 dropped to 0.69 ng/dL (0.93–1.70), Total T4 6.5 mcg/dL (6.75–17.55) and FT4Index 3.25 mcg/dL (4.50–11.70). Patient was started on LT4 75mcg daily and dose was titrated up to LT4 125mcg daily. At GW 26, TSH 0.04 uIU/mL (0.27–4.20), FT4 1.08 ng/dL (0.93–1.70), and TT4 10.1 mcg/dL (6.75–17.55). Total T4 and FT4I remained in the normal range for the remainder of the pregnancy, while TSH remained low. FT4 briefly increased to normal range before becoming and remaining low from GW30 onwards. Patient delivered at GW 37 without complication. At 2 months post-partum and one-month off thyroid medication, thyroid function tests (TFTS) normalized to TSH of 0.49 uIU/mL (0.27–4.20) and a FT4 of 0.99 ng/dL (0.93–1.70).

**Discussion:** In the setting of twin pregnancy, normalization of TSH suppression due to high levels of B-hCG may “lag” resulting in decreased thyroid hormone production that may warrant treatment. This case emphasizes the importance of continued monitoring of abnormal TFTs throughout pregnancy.

## Poster 0370

*Surgery, Clinical, Poster*

### Intraoperative Assessment of Gross Extrathyroidal Extension to Strap Muscle in Differentiated Thyroid Carcinoma: Factors Influencing Accuracy and Association with Recurrence

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**Objective:** According to the 8th edition of the AJCC staging system, differentiated thyroid carcinomas with extrathyroidal extension (ETE) into the strap muscles are designated as T3b. Unlike other cancer types, thyroid cancer is assessed intraoperatively by surgeons to determine the T3b, based on visual inspection for

muscle invasion. This study aimed to investigate whether the evaluation of muscle invasion in thyroid cancer during surgery is accurately performed compared to actual pathological findings, and to examine the recurrence and prognosis of cases that were inaccurately assessed.

**Methods:** A retrospective analysis of 4987 patients who underwent thyroidectomy at Seoul St. Mary's Hospital between 2017 and 2022 was conducted. Patients were categorized into three groups: Group A with confirmed muscle invasion on final pathology with intraoperative gross ETE, Group B with no muscle invasion on final pathology despite intraoperative gross ETE, and Group C with misclassified intraoperative gross ETE (no gross ETE identified intraoperatively but muscle invasion confirmed on final pathology). Patient characteristics, recurrence rates, and factors influencing misclassification of gross ETE were compared between groups.

**Results:** Among the 4987 patients, 179 (3.6%) had gross ETE. Group A, Group B, and Group C comprised 141 (2.8%), 38 (0.7%), and 33 (0.6%) patients, respectively. Recurrence rates were not significantly different among the groups (6.4% in Group A, 2.6% in Group B, and 3.0% in Group C). There were no significant differences in patient characteristics between the groups except for lymphatic invasion and tumor size. Multivariate analysis revealed that age (OR 0.961, 95% CI 0.932-0.990, p=0.009), tumor location (OR 0.182, 95% CI 0.056-0.591, p=0.005) and lymphatic invasion (OR 0.292, 95% CI 0.118-0.719, p=0.007) were independent predictors of misclassified gross ETE.

**Discussion/Conclusion:** In this study, among the 179 patients assessed as having gross ETE, 38 (21.2%) had no muscle invasion on pathology. Although there was no difference in recurrence among the three groups. However, considering that the recurrence rate of group A was relatively lower than that of group C, which also had pathology-positive results, it is thought that the surgeon's judgment on whether or not it is T3b is important for prognosis. Long-term follow-up is needed to confirm this difference.

## Poster 0371

*Surgery, Clinical, Poster*

### Pre-operative Calcium and Vitamin D Supplement Can Prevent Postoperative Hypocalcemia Following Total Thyroidectomy: A Randomized Controlled Trial

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**Background:** Hypocalcemia following total thyroidectomy is an undesired complication. We postulated that pre-operative calcium and vitamin-D supplement would be another intervention to prevent post-thyroidectomy hypocalcemia required treatment and longer hospital stay.

**Objectives:** To study incidence of post-thyroidectomy hypocalcemia in patients underwent total thyroidectomy comparing between patients who received pre-operative calcium and vitamin-D and those who did not

To study optimal dosages of calcium and vitamin-D supplement in correction post-thyroidectomy hypocalcemia.

**Methods:** A randomized-controlled trial (RCT) was conducted in patients who underwent total or completion thyroidectomy at Siriraj Hospital, Thailand. Total 64 patients were randomized into two groups: Group-A received calcium carbonate (2 gm/day) and

alfacalcidol (1 µg/day) consecutively for 14 days prior to surgery and Group-B did not receive these drugs. Baseline serum calcium (sCa), vitamin-D and parathyroid hormone (PTH) levels were recorded before commencing interventions. Postoperatively, hypocalcemia was monitored using both clinical signs and symptoms. Also, sCa and PTH level were measured at 3, 6, 24 hours and 7-14 days. Calcium and vitamin-D supplement was administered only when either patients developed symptomatic hypocalcemia or sCa <7.5 mg/dl (asymptomatic).

**Results:** Patients in Group-A had significantly lower incidence of symptomatic hypocalcemia compared to those in Group-B (21.9% vs 59.4%,  $p=0.002$ ). Percentages of patients who required calcium and vitamin-D supplement were 28.1 in Group-A and 62.5 in Group-B, respectively ( $p=0.006$ ). In correction of post-thyroidectomy hypocalcemia, the optimal dosages for calcium carbonate and alfacalcidol were 7.5-9 gm. and 2 µg. per day. Moreover, the percentages of patients received intravenous calcium replacement were significantly lower in Group-A (6.3 vs 15.6). In monitoring post-operative PTH level, the study demonstrated significantly lower percentages of permanent hypoparathyroidism in Group-A (6.3 vs 40;  $p=0.003$ ). In addition, we found that the cut off point for 3-hour and 6-hour PTH levels which significantly correlated with symptomatic hypocalcemia were <10.00 and <11.5 pg/ml, respectively, considerably being the predictor tool used for projection of developed post-operative hypocalcemia necessitated treatment.

**Conclusions:** Our RCT study emphasized the benefits of pre-operative calcium and vitamin-D supplement consecutively 14 days before surgery in order to prevent or at least to minimize hypocalcemia and hypoparathyroidism following total thyroidectomy.

### Poster 0372

*Thyroid Cancer, Case Study, Poster*

#### **No Surgical Resection: Successful Resensitization of Recurrent BRAF Mutated Iodine-Refractory Thyroid Cancer Involving Trachea/Thyroid Cartilage with Dabrafenib and Trametinib**

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#### **Introduction**

Recurrent Iodine-refractory thyroid cancer (IRTC) involving trachea/thyroid cartilage remains a formidable clinical challenge. Surgical resection often results in significant impairment of quality of life. Tyrosine kinase inhibitors (TKIs) have become a standard treatment for advanced IRTC. Moreover, targeting BRAF with dabrafenib and trametinib has shown some promise in resensitizing IRTC to radioactive iodine (RAI), thereby potentially expanding treatment options and improving patient outcomes.

#### **Cases**

**Case 1:** a 72-year-old male with BRAF positive papillary thyroid cancer presented one year after initial therapy with IRTC involving left tracheoesophageal groove and lung metastasis, requiring tracheal and esophageal resection. He received dabrafenib/trametinib for 16 months, achieving radiographic complete remission and successful RAI ablation. He has now been off treatment without progression of disease for 15 months.

**Case 2:** a 48-year-old Native American male with BRAF mutated papillary thyroid cancer developed IRTC with extensive cervical and mediastinal lymph node metastases 1 year after initial treatment.

He experienced multiple episodes of hemoptysis due to tracheal invasion. The patient was treated with dabrafenib/trametinib. His hemoptysis resolved in 2 weeks and had a near-complete response 6 months later. He received successful RAI therapy with discontinuation of TKIs. He has been progression free for 8 months.

**Case 3:** a 66-year-old male presented with recurrent BRAF positive IRTC 6 years after initial treatment. Despite a successful central neck dissection removing multiple lymph nodes, total laryngectomy was required for 1-cm metastasis involving thyroid cartilage. Treatment with dabrafenib/trametinib for 7 months was complicated by severe hyponatremia, confusion, and muscle spasm, requiring dose reduction of dabrafenib. With successful resensitization and RAI, he has been treatment-free and event-free for 12 months.

#### **Discussion**

To our knowledge, this is the first report that dabrafenib/trametinib combination therapy was used successfully to treat BRAF mutated IRTC recurrence involving trachea or thyroid cartilage without surgical resection. All three patients continue to enjoy event-free survival with great quality of life. This unique strategy highlights the therapeutic efficacy of TKIs in disease control as well as overcoming iodine refractoriness in this challenging clinical scenario. Further research is warranted to address this unmet clinical need.

### Poster 0373

*Thyroid Cancer, Clinical, Poster*

#### **Leukemia Threats Following Radioactive Ablation Iodine for Thyroid Cancer**

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**Background:** Radioactive iodine (RAI) therapy is a common minimally invasive treatment for patients diagnosed with differentiated thyroid cancer (DTC). Although previous studies have identified a link between RAI and the mortality from secondary solid cancers, the connection between RAI and leukemia remains under-researched. This study investigates the differential risk of leukemia and its subtypes in DTC patients following RAI treatment.

**Methods:** DTC patients from the Surveillance, Epidemiology, and End Results (SEER) Registry 17 (2000-2019) were analyzed. The Standard Incidence Ratio (SIR) and Excess Risk (ER) compared to the reference population were calculated.

**Results:** Out of 196,569 DTC patients, 1,381 patients developed various types of hematological malignancies. Leukemia was diagnosed in 508 of these patients and had the highest risk among the malignancies studied, with SIR of 1.74 (95%CI: 1.59-1.9). The RAI group had an SIR of 2.12 (95%CI: 1.87-2.39) while the non-RAI group had an SIR was 1.45 (95%CI: 1.37-1.52) ( $p<0.001$ ). Those diagnosed before the age of 55 years had a conspicuously elevated risk (SIR 2.74) compared to those diagnosed at 55 years or older (SIR 1.53). American Indian/Alaska Native survivors manifest a pronounced leukemia risk with an SIR of 7.63 (CI: 2.46-17.8). RAI treatment increased the risk of leukemia as adjuvant therapy in surgical patients (SIR 2.12) and sole treatment in non-surgical patients (SIR 2.80).

**Conclusions:** There exists a significant association between RAI treatment in DTC patients and the incidence of leukemia. This susceptibility seems to be modulated by factors including time since diagnosis, age, gender, and racial background.

**Poster 0374***Thyroid Cancer, Clinical, Poster***Initial versus Staged Thyroidectomy for Differentiated Thyroid Cancer: A Retrospective Multi-Dimensional Cohort Analysis of Effectiveness and Safety**Yaser Bashumeel<sup>\*1</sup>, Ahmed Abdelmaksoud<sup>1,2</sup>, eman Toraih<sup>1</sup>, Mohammed Hussain<sup>1</sup>, Abdulrahman Ghaleb<sup>1</sup>, Emad kandil<sup>1</sup>.<sup>1</sup>Tulane University, USA, <sup>2</sup>University of California, Riverside, USA

**Background:** Differentiated thyroid cancer is often initially treated with lobectomy, but completion thyroidectomy may be indicated for aggressive features on pathology. However, the risks of staging completion thyroidectomy versus upfront total thyroidectomy remain debatable. We assessed whether an initial thyroidectomy or staged completion thyroidectomy is associated with greater risk of complications in cases of differentiated thyroid cancer.

**Study Design:** Post-operative complications following thyroidectomy were analyzed from four sources: (1) Institutional series of 148 patients; (2) National Surgical Quality Improvement Program (NSQIP) database of 39,992 cases; (3) TriNetX repository of over 30,000 patients; (4) Systematic literature review of 10 studies encompassing 6,015 thyroidectomies.

**Results:** Institutional data revealed a higher complication rate with total thyroidectomy (18.3%) versus completion thyroidectomy (6.8%), driven by increased temporary hypocalcemia (10% vs 0%,  $p=0.004$ ). Analysis of NSQIP cohort demonstrated comparable findings, with total thyroidectomy having a 72% increased risk of transient hypocalcemia ( $p<0.001$ ) and 25% higher permanent hypocalcemia ( $p<0.001$ ). TriNetX data supported this, with obesity and concurrent lymphadenectomy escalating hypocalcemia risks further. Pooled meta-analysis found total thyroidectomy increased transient and permanent hypocalcemia risks (RR=1.63 and 1.23;  $p<0.001$ ). When examining completion thyroidectomy timing, the institutional and TriNetX data indicated lowest permanent complication rates at 1-6 months versus after 6 months.

**Conclusions:** For differentiated thyroid cancer, total thyroidectomy carries slightly higher transient and permanent hypocalcemia risks compared to staged completion thyroidectomy. However, timing completion between 1-6 months after initial lobectomy may mitigate permanent complications versus later intervals. Careful consideration of these nuances can guide individualized management.

**Poster 0375***Thyroid Cancer, Clinical, Poster***Body Mass Index and Sporadic Medullary Thyroid Cancer: insights from a large series of patients**Alessandro Prete<sup>\*1</sup>, Antonio Matrone<sup>1</sup>, Carla Gambale<sup>1</sup>, Elisa Minaldi<sup>1</sup>, Gabriele Materazzi<sup>2</sup>, Liborio Torregrossa<sup>3</sup>, Ferruccio Santini<sup>1</sup>, Alessio Basolo<sup>1</sup>, Rossella Elisei<sup>1</sup>, <sup>1</sup>Unit of Endocrinology, University of Pisa, Italy, <sup>2</sup>Unit of Endocrine Surgery, University of Pisa, Italy, <sup>3</sup>Unit of Pathology, University of Pisa, Italy

**Objective:** An increased Body Mass Index (BMI) has been associated with higher prevalence and, in some series, aggressive behaviour of differentiated thyroid cancer. However, scanty data have been reported about the potential association between BMI and sporadic medullary thyroid cancer (MTC). We aimed to evaluate potential influence of BMI at diagnosis on MTC clinical presentation and outcome.

**Methods:** We reviewed data of 444 consecutive sporadic MTC patients (2000-2019), surgically treated at the Endocrine Surgery

Unit and followed at the Endocrine Unit of the University Hospital of Pisa.

**Results:** At time of surgery, 92/444 (20.7%) patients had BMI  $\geq 30$  (Ob-group) and 352/444 (79.3%)  $< 30$  Kg/m<sup>2</sup> (control group). Ob-group was significantly older (median 59.5 vs 54.0 years,  $p<0.01$ ), without difference in gender (males: 44.6% vs 45.1%,  $p=ns$ ). Ob-group showed a significantly smaller tumor dimension compared with controls (median 1 vs 1.3 cm,  $p<0.01$ ). Particularly, tumors  $\leq 1$  cm were present in 50/92 (54.3%) and 136/352 (38.6%), 1-2.5 cm in 25/92 (27.2%) and 137/352 (38.9%), 2.5-4 cm in 16/92 (17.4%) and 52/352 (14.8%) and  $> 4$  cm in 1/92 (1.1%) and 27/352 (7.7%), in Ob-group and controls, respectively ( $p<0.01$ ). Ob-group showed MTCs with lower T and N stage compared with controls ( $p=0.019$  and 0.013, respectively) and lower levels of pre-operative calcitonin (median 67.2 vs 123.5 pg/mL,  $p=0.036$ ). After surgery, without difference in the median follow-up time (5.2 vs 6.3 years,  $p=ns$ ), Ob-group showed significantly lower rate of structural disease, compared with control group (13 vs 22.7%,  $p=0.036$ ).

**Conclusions:** In our series, at the time of surgery, about 21% of sporadic MTC patients were suffering from obesity, more than general population. These patients showed smaller tumors, less metastatic lymph node involvement and less structural disease at the end of the follow-up than controls. The most frequent medical evaluations experienced by these population, potentially leading to an early detection of MTC, cannot be overlooked. These data confirmed the clinical relevance of the early diagnosis of MTC.

**Poster 0376***Thyroid Cancer, Clinical, Poster***Dissecting the Preoperative Profiles of Oncocytic and Follicular Thyroid Carcinomas**Alicia Belaiche<sup>\*1</sup>, Grégoire Morand<sup>2,3,4</sup>, Sena Turkdogan<sup>5</sup>, Esther ShinHyun Kang<sup>1</sup>, Véronique-Isabelle Forest<sup>2</sup>, Marc Pusztaszeri<sup>6</sup>, Michael Hier<sup>2</sup>, Alex Mlynarek<sup>2</sup>, Keith Richardson<sup>5</sup>, Nader Sadeghi<sup>5</sup>, Marco Mascarella<sup>2,5</sup>, Sabrina Da Silva<sup>2</sup>, Richard Payne<sup>2,5</sup>, <sup>1</sup>Faculty of Medicine and Health Sciences, McGill University, Canada, <sup>2</sup>Department of Otolaryngology – Head and Neck Surgery, Jewish General Hospital, McGill University, Canada, <sup>3</sup>Department of Otorhinolaryngology – Head and Neck Surgery, University Hospital Zurich, Switzerland, <sup>4</sup>Faculty of Medicine, University of Zurich, Switzerland, <sup>5</sup>Department of Otolaryngology – Head and Neck Surgery, Royal Victoria Hospital, McGill University, Canada, <sup>6</sup>Department of Pathology, Jewish General Hospital, McGill University, Canada

**Objective:** Oncocytic thyroid carcinoma (OTC) was previously considered a variant of follicular thyroid carcinoma (FTC) but has recently been reclassified as a separate form of thyroid cancer by the World Health Organization. Due to this historical classification and the relative rarity of these tumors, research on the distinguishing features of OTC remains limited. This study aimed to characterize and contrast the preoperative profiles of FTC and OTC.

**Methods:** A retrospective chart review of patients with FTC and OTC operated at two McGill University Hospitals with available preoperative FNAB and molecular testing from January 2016 to September 2023 ( $n = 3219$ ) was conducted. Demographic factors, cytopathology, histopathology, and molecular testing results were analyzed.

**Results:** Fifty patients met the inclusion criteria. FTC was identified in 27 (54.0%) patients, and OTC in 23 (46.0%) patients. The cytopathology results were similarly distributed between FTC and OTC, with Bethesda IV (Oncocytic Follicular Neoplasm) not surprisingly being the most common category for both cancers (59.3% and 52.2% respectively). However, a distinction was observed in

Bethesda III and IV subcategories where OTC tumors showed a higher proportion of oncocyctic subtypes (85.0%) compared to FTC tumors (20.8%). The tumor size distributions for both neoplasms were similar with respective tumor mean sizes of 3.0 cm and 3.5 cm. Aggressive tumors were found in 39.1% (9/23) of OTCs compared to 11.1% (3/27) of FTCs ( $p=0.021$ ). Bethesda category did not predict tumor aggressiveness. Male patients represented 44.4% of OTC aggressive tumors versus 0.0% of FTC aggressive tumors. Additionally, patients with OTC were older (61.8 years) than FTC patients (51.2 years) ( $p=0.013$ ). OTC patients with a *TERT* alteration on molecular testing ( $n=4$ ) had a significantly higher mean age of 78.8 years. Conversely, patients with a *RAS* alteration +/- a *GEP* alteration ( $n=4$ ) had a younger average age of 47.3 years.

**Discussion/Conclusion:** Demographic and pathological factors set OTC apart clinically such as older age, oncocyctic Bethesda subcategory, and higher tumor aggressiveness, particularly in male patients. In our study, *TERT* alterations were associated with older age while *RAS* alterations were associated with younger age. It is important to further investigate molecular testing as a potential avenue to distinguish these neoplasms pre-operatively and offer a more tailored management approach for OTC patients.

### Poster 0377

*Thyroid Cancer, Clinical, Poster*

#### Systematic Review & Meta-Narrative of Unmet Care Needs in Adult Thyroid Cancer Survivors

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**Objective.** Thyroid cancer survivors make up 10% of all cancer survivors in the United States. While most patients with thyroid cancer have high survival rates, there are still several areas in which care needs remain unmet. Our objective was to summarize the unmet care needs of thyroid cancer survivors.

**Methods.** Systematic review and meta-narrative of studies evaluating the unmet care needs of adult thyroid cancer survivors. We included quantitative and qualitative reports without any language restrictions published between January 2000 - September 2023. Due to data heterogeneity, quantitative findings were summarized descriptively. Identified care needs were categorized according to the Supportive Care Framework for Cancer. Qualitative findings were summarized using meta-aggregation. Risk of bias was evaluated according to included study design.

**Results.** We identified 13 quantitative ( $N=8736$ ) and 9 qualitative studies ( $N=166$ ). Overall, studies were at moderate to high risk of bias. Most studies conducted a single-time assessment of unmet care needs, and most participants were women diagnosed with papillary thyroid cancer.

Amongst the quantitative studies, 3 studies utilized validated questionnaires to assess unmet needs across multiple domains with unmet psychological needs being the most reported by participants (50-70%). Physical and daily living needs were also significant, with 25-50% reporting unmet needs in each of these domains. Informational needs were frequently assessed using both validated and non-validated instruments, but the extent to which they were considered unmet varied among participants, ranging from 2% to 63%.

Through meta-aggregation of qualitative studies, four synthesized findings were derived: (1) thyroid cancer "good cancer" label driving unmet needs, (2) unmet informational needs through the survivorship process (e.g., diagnosis, treatment, recovery, re-integration), (3) unmet emotional support needs from: family, peers, medical professionals, and co-workers, and (4) unmet practical needs that hinder daily living (e.g. diet, medication management).

**Conclusion.** Evaluation of quantitative and qualitative data demonstrates that thyroid cancer survivors commonly expressed unmet psychological and emotional support needs that might be driven by the label of "good cancer", with variability in unmet informational needs. These findings can inform the development of targeted interventions to improve the care of thyroid cancer survivors.

### Poster 0378

*Thyroid Cancer, Clinical, Poster*

#### Development and Validation of the Thyroid Cancer Modified Anxiety Scale (TC-Max)

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**Objective:** Develop and validate the Thyroid Cancer Modified Anxiety Scale (TC-MAX) to facilitate the assessment of thyroid cancer-related distress.

**Methods:** This multiphase prospective study characterized an 18-question scale (TC-MAX) to measure distress specific to thyroid cancer. Three distinct subscales were developed: a Thyroid Cancer Anxiety Subscale, a Ultrasound Anxiety Subscale, and a Fear of Recurrence Subscale. Development entailed (1) conceptualization (systemic literature review, expert MD panel ( $n=4$ ), and patient focus groups ( $n=5$ )), qualitative refinement (pilot testing ( $n=59$ ) and debriefing interviews), and psychometric validation ( $n=158$ ) with thyroid cancer patients along the management spectrum. Internal consistency, test-retest reliability, exploratory factor analysis, and construct validity (NCCN Distress Thermometer, FACT-G, and HADS) were evaluated. The minimal clinically important difference (MCID) was determined by a distribution-based method at 0.5 of the standard deviation.

**Results:** Analysis of TC-MAX revealed a high degree of internal consistency (Cronbach  $\alpha =0.93$ ), excellent test-retest reliability (ICC 0.86 [95% CI 0.79-0.90]), and moderate to strong construct validity (Spearman rank correlation coefficient 0.56 (NCCN Distress Thermometer,  $p<0.001$ ), 0.52 (HADS,  $p<0.001$ ), and -0.50 (FACT-G,  $p<0.001$ )). Exploratory factor analysis demonstrated higher than expected loadings for the 3 subscales, supporting that the 18-question/3 subscale format was parsimonious. The MCID for the overall score was found to be 5.8.

**Discussion/Conclusion:** TC-MAX represents the first validated, reliable measure of anxiety in patients with thyroid cancer. It passes multiple psychometric criteria that substantiate its utility in a vulnerable patient population, accounting for viewpoints on cancer, ultrasound monitoring, and fear of recurrence. The scale may serve as an effective tool to counsel patients, including determining fit for active surveillance or surgery.

### Poster 0379

*Thyroid Cancer, Clinical, Poster*

#### Superior Re-differentiation of BRAF-Mutated Radioactive Iodine Refractory Differentiated Thyroid Cancer with Longer Duration of Dabrafenib and Trametinib

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**Background:** Iodine refractory differentiated thyroid cancer (DTC) carries a poor prognosis. BRAF/MEK/MAPK pathway activation is associated with loss of expression of iodine-metabolizing genes in thyroid cancer, resulting in iodine refractoriness. BRAF, MEK inhibitors have previously been shown to resensitize iodine refractory DTC in small clinical trials, however, the optimal drug/drug combination and duration of resensitization remain to be elucidated.

**Methods:** This is a single-center, retrospective study of resensitization of BRAF-mutated iodine-refractory DTC using both dabrafenib and trametinib (DT) between January 2020 and April 2024. Successful resensitization was defined as significant uptake of <sup>131</sup>I on the posttreatment whole body scan (WBS); median duration of response was calculated from initiation of RAI treatment. Duration of resensitization, thyroglobulin levels were also collected.

**Results:** A total of 28 patients were identified, including 6 patients currently receiving DT; 1 patient died from lung cancer; 2 patients discontinued DT due to treatment-related heart failure. 19 patients were included in the final analysis, with median age of 66 years, 53% (10/19) females, and 58% (11/19) Caucasian, 32% (6/19) Hispanic and 10% (2/19) Native American. All patients were confirmed to have BRAF V600E mutation; 84% (16/19) had distant metastasis; 84% (16/19) had baseline WBS with iodine uptake; 16% (3/19) had progression of disease 3 months after the previous RAI ablation. At median duration of 6 months (range 3-16); 90% (17/19) of patients achieved successful resensitization. Of note, 4 patients failed to resensitize at 6 to 12 weeks but reached the goal after 6 months. Interestingly, for patients without baseline thyroglobulin antibody, marked elevation of thyroglobulin level correlated very well with successful resensitization in 80% (12/15) of patients. At median follow-up of 10 months (range 1-33), no patients with successful resensitization had progression of disease. Combination of DT was well tolerated, two patients developed congestive heart failure and were excluded from the study analysis. 5 patients developed severe confusion, renal failure and hyponatremia, requiring dose reduction of dabrafenib but were able to complete the treatment.

**Conclusions:** Longer duration of dabrafenib and trametinib appears to be safe and effective on resensitization of BRAF-mutated iodine refractory DTC. This approach merits further prospective investigation.

### Poster 0380

*Thyroid Cancer, Clinical, Poster*

**Reliability of serum thyroglobulin post-total thyroidectomy for detecting structural disease in thyroid cancer patients without radioactive iodine therapy, A prospective trial with median follow up of 7 years**

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**Objective:** To determine the diagnostic reliability of post-operative serum thyroglobulin (Tg) cut-off value for evaluating the likelihood of structural disease (SD) in patients with differentiated thyroid cancer (DTC) following a total thyroidectomy without radioactive iodine therapy (RAI).

**Material and Methods:** We prospectively followed-up patients with histopathology confirmed DTC who underwent total thyroidectomy without receiving RAI therapy at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia, from 2000 to 2020. We

compared the diagnostic reliability of using a Tg level of  $\leq 0.2$  ng/mL with Tg level of  $\leq 1.0$  ng/mL.

**Result:** Of 184 included patients, 163 (88.6%) were females. The mean age was 46.0 years and the mean duration of follow-up was 7 years. Overall, 23 patients (12.5%) had structural disease. Structural disease was seen in 4 of 122 patients (2.2%) with Tg  $\leq 0.2$  ng/mL, and in 6/163 (3.3%) patients who had Tg level of  $\leq 1.0$  ng/mL. Tg level of  $\leq 1.0$  ng/mL showed a diagnostic sensitivity of 73.9%, specificity of 96.3%, positive predictive value of 73.9%, negative predictive value of 96.3%, and diagnostic accuracy of 93.5% comparable with Tg level of  $\leq 0.2$  ng/mL.

**Conclusion:** This study suggests that a non-stimulated Tg cut-off value of  $\leq 1$  ng/mL has a comparable diagnostic reliability with a Tg level of  $\leq 0.2$  ng/mL to indicate structural disease recurrence in DTC patients 3 to 6 months following total thyroidectomy who have not received RAI therapy.

This cut-off level demonstrates high diagnostic reliability comparable to the established Tg levels of  $\leq 0.2$  ng/mL. Large sampled studies are needed to consider higher Tg cut-off level in low to intermediate risk DTC post total thyroidectomy with no RAI in monitoring disease recurrence.

### Poster 0381

*Thyroid Cancer, Basic, Poster*

**Exploration of Potential Biomarkers in Papillary Thyroid Cancer via RNA-seq Analysis**

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Papillary thyroid cancer (PTC) has experienced an increase in incidence in recent decades. Despite advances in PTC research, challenges such as understanding the molecular mechanisms persist. Thus, increased knowledge on the molecular basis of thyroid neoplasia allows for an improved approach to diagnosis through subclassification of indeterminate thyroid nodules, prognosis and therapeutics by identifying potential new therapeutic targets. Objective. The aim of this study was to identify differentially expressed genes (DEGs) in PTC and their involvement in biological processes. Methods. Six RNA-seq transcriptomic datasets (GSE197443, GSE201365, GSE171011, GSE87410, GSE153659, and GSE165724) from PTC and adjacent normal tissue obtained from NCBI's Gene Expression Omnibus public repository were analyzed. Identification of DEGs was performed with the DESeq2 package in RStudio. Genes with an adjusted p value  $< 0.05$  were considered significant and with a log<sub>2</sub> fold change value  $> 2$  and  $< -2$  were considered overexpressed and underexpressed, respectively. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed using ClusterProfiler package in Rstudio. Protein-protein interaction (PPI) network analysis was performed in STRING platform, molecular networks were retrieved in Cytoscape software to identify hub genes and 10 hub genes were screened according to the Maximal Clique Centrality (MCC) score. Finally, 2 genes were selected and their expression was analyzed by qPCR through mRNA isolated from FNA samples from patients with a diagnosis of PTC (Bethesda V and VI) (n=37), benign thyroid disease (Bethesda II) (n=32) and indeterminate cytological diagnosis (Bethesda IV)

(n=17). Results. A total of 131 DEGs were identified among the 6 datasets, 3 down-regulated and 128 up-regulated. Among the biological processes in which DEGs participate are skin development, epidermis development, tissue development, wound healing, epithelium development, cell adhesion, animal organ development, and growth development regulation. They were shown to be involved in cellular components at cell-cell junction, basal part of cell, plasma membrane region, integral component of plasma membrane and apical junction complex. The 10 hub genes screened were *FNI*, *MET*, *KRT19*, *DPP4*, *CLDN1*, *ITGA2*, *ERBB3*, *TGFA*, *CDH3*, and *SERPINA1*. *CLDN1* and *KRT19* were selected for testing by qPCR and both were found to be significantly overexpressed in Bethesda VI (*CLDN1*=5.26±4.1 and *KRT19*=4.11±3.2) compared to Bethesda II (p<0.05). Conclusions. These findings suggest that these DEGs could serve as potential biomarkers for the diagnosis and prognosis of PTC. Furthermore, understanding the molecular mechanisms underlying thyroid neoplasia could facilitate the development of new targeted therapeutic strategies.

### Poster 0382

*Thyroid Cancer, Clinical, Poster*

#### Unveiling the issues about sporadic apparently non-invasive medullary thyroid cancer

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**Background:** Medullary thyroid cancer (MTC) is a malignant tumor producing calcitonin (CTN). Most of the MTC are sporadic and can metastasize to lymph nodes and distant sites. High pre-operative CTN values and larger tumor dimension are usually associated with metastatic disease. However, anecdotal cases of large sporadic MTC with high pre-operative CTN values, without lymph nodes metastases, and completely cured after surgery have been described configuring a picture of non-invasive MTC (niMTC).

**Aim:** We aimed to unveil the issues about these niMTC in a large series of sporadic MTC followed at the Unit of Endocrinology of the University of Pisa (2000-2020).

**Results:** From a prospectively maintained database 674 sporadic MTC patients were evaluated. We excluded patients with lymph nodes and distant metastases at diagnosis, those with tumor diameter <2 cm and without controls after surgery. Then, 63 cases were included. Median age at diagnosis was 53 years. Pre-operative median CTN values were 730 ng/L (IQR 349-1890) with median tumor dimension of 3 cm. All patients were pN0 (median removed lymph nodes: 8). At first post-operative evaluation (median 4 months), most of patients (58/63-92%) were cured, conversely 5 (8%) showed detectable CTN values but negative imaging. After a median follow-up of 74 months, 77.8% (n=49) remained cured. Conversely, 9 (14.3%) had biochemical disease, 3 (4.8%) had metastatic lymph nodes and 2 (3.2%) distant metastases. After a median of 100 months (IQR 64-181) of follow-up, two patients died for the disease. No differences were highlighted in age at diagnosis, pre-operative CTN values and tumor dimension between cured and not cured patients. However, in not cured patients histologic desmoplasia (p=0.03) (but not Ki-67 or mitosis) was more frequently detected.

**Conclusions:** In our series, prevalence of sporadic niMTC was 9.3%. Despite high pre-operative CTN levels and large tumors, most of these patients are early cured after surgery. However, few cases

can develop metastatic disease also after several years. Therefore, follow-up should be careful pursued over time, particularly in those cases with presence of desmoplasia at histology.

### Poster 0383

*Thyroid Cancer, Clinical, Poster*

#### Preoperative Thyroglobulin Antibody Status Predicts Histopathological Aggressiveness of Differentiated Thyroid Cancer

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**Objective:** Autoimmune thyroid disease is associated with increased occurrence of differentiated thyroid cancer (DTC) (1) but its link with DTC histopathological aggressiveness and prognosis is conflicting in studies. Additionally, positive thyroglobulin antibody (TgAb) postoperatively can make risk stratification and follow-up complicated. Preoperative assessment of anti-thyroid antibodies and thyroglobulin (Tg) is not clinically performed in most cases. Hence, we aimed to identify the link between preoperative serum levels of Tg, TgAb, and TPOAb with histopathological status of DTC.

**Methods:** We conducted a cohort study of 98 adults with DTC consented in the Thyroid Cancer and Tumor Collaborative Registry (2) with stored sera available in which we measured levels of Tg, TgAb, and TPOAb. We collected clinical and pathological information from medical records. These patients were managed according to clinical guidelines, as we retrospectively tested the stored sera for research.

**Results:** Median age was 48.5 y; 74.5% females; 95% papillary. AJCC stage was 1 in 84.7%, 2 in 13.3%, and 3 in 2%. ATA risk was low in 55.1%, intermediate in 22.5%, and high in 22.4%. Distant metastasis was present in only 1 case. Most patients (78.6%) had excellent response to treatment. TgAb was elevated in 10/98 (10.2%), TPOAb was elevated in 34/47 (72.3%). Higher preoperative TgAb level was associated with lower T category (p=0.03) after adjusting for age and sex and TgAb positivity (>20 IU/mL) with lower neck lymph nodes involved ratio (p=0.01). There were no significant associations with preoperative TPOAb levels due to 52% unavailable data and mild elevations. Higher preoperative Tg level was associated with higher AJCC stage (p=0.008) after adjusting for age and sex.

**Conclusions:** Preoperative thyroid autoimmunity is associated with more favorable while thyroglobulin level with less favorable histopathological status in differentiated thyroid cancer. After validation in a larger dataset, these could be additional biomarkers of differentiated thyroid cancer prognosis.

### Poster 0384

*Thyroid Cancer, Clinical, Poster*

#### Changes in survival in patients with metastatic thyroid cancer in the era of tyrosine kinase inhibitors

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**Objective:** Tyrosine kinase inhibitors (TKI) have activity in the treatment of advanced thyroid cancer. Six agents have received Food and Drug Administration (FDA) approval since 2011 for the treatment of either advanced differentiated, medullary, or anaplastic thyroid cancers, with off label use as early as 2004. Most studies have demonstrated an improvement in progression-free survival but not necessarily overall survival because of cross-over design. The aim of this study was to evaluate overall survival benefit for patients with these cancers before and after the availability of TKIs.

**Methods:** Using the Surveillance, Epidemiology and End Results Program (SEER) database, the number of patients with thyroid cancer and distant disease was evaluated for the years 1992 – 2003 and compared to 2010-2017. Survival in months was retrieved for patients whose data was known and median survival was calculated for the following histologies: Medullary; Papillary; Follicular and Oncocytic. The median overall survivals (OS) for each histology were compared between the two groups.

**Results:** The results for the two cohorts patients are listed below: 1992-2003

Papillary number of patients (N): 273 OS 10 months (mo) Confidence Interval (CI) 6.8 - 13.2 mo,

Medullary N 50, OS 8 mo, CI 12.7 – 22.4 mo;

Follicular N 111 OS 11 mo CI 5.6 – 16.4 mo;

Oncocytic N 26 OS 5.5 mo CI 2.6 – 10.4 mo.

2010 – 2017

Papillary N 2155 OS 60 mo CI 58.4 – 61.6 mo; (p<0.001)

Medullary N 226 OS 31 mo CI 26-3 – 35.6 mo; (p=0.004)

Follicular N 299 OS 44 mo CI 40.1 – 47.9 mo; (p<0.001)

Oncocytic N 85 OS 46 mo CI 38.8 – 53.2 mo. (p=0.5)

**Conclusions:** Though our study is limited by potential inconsistencies in the coding of distant disease and the reliability of follow-up information, there was an improvement in survival for patients with metastatic papillary, follicular, and medullary thyroid cancers following the introduction of TKIs for advanced thyroid cancer.

### Poster 0385

*Thyroid Cancer, Clinical, Poster*

#### Impact of Physical Activity and its Maintenance in the Efficacy and Safety of Tyrosine Kinase Inhibitors in Advanced Thyroid Carcinoma Patients

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**Objectives:** Tyrosine kinase inhibitors (TKIs) display high efficacy in the treatment of advanced thyroid cancer (TC), though are burdened by multiple adverse events (AEs). Only one non-peer-reviewed article on the role of prehabilitation is available for advanced TC patients treated with TKIs. This preliminary study aims to evaluate the impact of physical activity and its maintenance on the safety and efficacy of TKIs in advanced TC.

**Methods:** We enrolled 18 patients: 10 Differentiated TC, 3 Poorly Differentiated TC, 5 Medullary TC, treated for an average time of 45 months (range 6-180) with Lenvatinib (n=12), Vandetanib (n=4), and Cabozantinib (n=2). Three modified long-form International Physical Activity Questionnaires (IPAQ) were administered for each patient at different time points (T0, before TKI treatment; T1, intermediate; T2, at last follow-up). Metabolic equivalents (METS) were calculated at each time point. Quality of Life

Questionnaire-Core 30 (QLQ-C30) and QLQ-Thyroid Cancer Module (QLQ-THY34) were also administered. Basal Eastern Cooperative Oncology Group Performance Status (ECOG PS) was assessed, and AEs were graded according to the CTCAE v5.0. Tumour response was evaluated according to RECIST v 1.1.

**Results:** A significant reduction in METS during treatment [from T0 to T1 ( $P=0.04$ ) and T0 to T2 ( $P=0.02$ )] was associated with AEs of grade  $\geq 3$ . Among all AEs, fatigue (of grade  $< 3$ ) mostly limited patients' activity status during TKI treatment. Maintaining high METS levels at T2 correlated statistically with higher QLQ-C30 functional state points ( $P=0.05$ ,  $r=0.49$ ). Moreover, being physically active at T2 was associated with fewer AEs compared to sedentary patients (40 vs. 82%,  $P=0.09$ ). Patients with an active lifestyle before TKI start (T0) experienced fewer TKI interruptions (43 vs. 82%,  $P=0.09$ ) and TKI dose reductions (20 vs. 64%,  $P=0.1$ ). Progressive disease (PD) occurred less frequently in patients maintaining a high level of physical activity, although not statistically significant (12 vs. 38%,  $P=0.2$ ).

**Discussion:** Physical activity and its maintenance seem associated with milder AEs, potentially reducing the need for TKI reduction/discontinuation and offering a benefit in terms of PFS. This preliminary study gives the opportunity for wider and prospective research on the impact of prehabilitation in TKI treatment for advanced TC.

### Poster 0386

*Thyroid Cancer, Clinical, Poster*

#### Variation in Episode Spending for Thyroidectomy in Thyroid Cancer

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**Objective:** Thyroidectomy is the primary treatment for patients with thyroid cancer. With rising healthcare costs, it is essential to understand variation in spending for this common procedure to identify opportunities for optimizing value. Therefore, we aimed to evaluate variation in 90-day episode spending for thyroidectomy and identify factors associated with increased spending.

**Methods:** This retrospective cohort study analyzed data from a risk-adjusted, price-standardized statewide claims registry from 2015-2022 and included patients who underwent thyroidectomy for lower-risk thyroid cancer (ICD-10 C73) defined as those who did not receive radioactive iodine. The primary outcome was mean 90-day spending across extent of surgery (thyroid lobectomy, total thyroidectomy, and lobectomy followed by completion thyroidectomy). Mixed linear model with facility as a random effect identified patient- and facility-level factors associated with spending variability.

**Results:** 2,469 patients underwent thyroidectomy at 79 facilities. Risk-adjusted 90-day episode spending varied widely across facilities from \$4,892 to \$24,286 (median \$9,344). Spending was lowest for lobectomy (median \$8,063; IQR \$7,193-\$9,359), then total thyroidectomy (median \$9,682; IQR \$8,855-\$11,083), and highest for lobectomy+completion thyroidectomy (median \$13,500; IQR \$12,466-\$14,326). Patients undergoing lobectomy compared to those who received total thyroidectomy had significantly shorter lengths of stay (60.6% same day discharge versus 19.0%, respectively;  $p<0.001$ ) and lower readmission rates (0.8% versus 3.1%;  $p=0.001$ ).

In the mixed model, patient factors significantly associated with increased spending were age (\$61 per year older [95%CI \$28-\$94],  $p<0.001$ ) and post-operative length of stay exceeding 2 nights

(\$14,630 [95%CI \$12,879-\$16,382],  $p < 0.001$ ). Compared to lobectomy alone, greater extent of surgery was associated with increased spending: total thyroidectomy (\$1,229 [95%CI \$321-\$2,138];  $p = 0.008$ ) and lobectomy+completion thyroidectomy (\$5,680 [95%CI \$3,384-\$7,975];  $p < 0.001$ ). Patients requiring readmission within 30 days had dramatically higher spending (\$17,885 [95%CI \$15,362-\$20,408];  $p < 0.001$ ). Factors not significantly associated with spending variation included patient insurance, case volume, bed size, and teaching status.

**Conclusion:** Significant variation exists in 90-day episode spending for thyroidectomy in thyroid cancer. Key factors that drive this variation include extent of surgery, length of stay, and readmission. Reducing length of stay and readmission through surgeon and patient education may represent opportunities to enhance the value of thyroidectomy for patients with lower-risk thyroid cancer.

### Poster 0387

*Thyroid Cancer, Clinical, Poster*

#### **A Revised Perspective on the AJCC Staging System for Medullary Thyroid Cancer: Results from a Chinese Nationwide Multicenter Cohort and the US SEER Database**

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**Background:** The current TNM Staging System for medullary thyroid cancer (MTC) by the American Joint Committee on Cancer (AJCC), which was largely extrapolated from that used for differentiated thyroid cancer, had considerable deficiencies. However, the scarcity of clinical data on this rare disease limited a deeper understanding, thus hindering improvements to the staging system.

**Methods:** This population-based retrospective study utilized two nationwide cohorts. The first cohort included 1,051 MTC patients from 18 Chinese referral centers (1998-2023). The second cohort, used for external validation, included 1,518 MTC patients from the Surveillance, Epidemiology, and End Results (SEER) database (2004-2015).

**Results:** Upper mediastinal (level VII) lymph node metastasis (LNM) occurred in 14.9% of patients from our multicentric cohort, most of whom were accompanied by lateral cervical (levels I-V) LNM. Additionally, we found that MTC patients with upper mediastinum LNM experienced worse outcomes than those with LNM in other cervical regions, prompting us to up-classify 'level VII metastases' from N1a to a new category named N1c. Upon updating, we regrouped four TNM stages based on recursive partitioning analysis for overall survival: stage I (T1-2N0-1aM0), stage II (T1-3N1bM0, T3N0-1aM0), stage III (T4N0-1bM0, T1-3N1cM0), and stage IV (T4N1cM0, T1-4N0-1cM1). We demonstrated a significant superiority in prognostic discrimination, with hazard ratios of 8.789 (95% CI, 2.937-26.303) for stage II, 18.182 (95%CI, 6.114-54.073) for stage III, and 70.862 (95%CI, 24.345-206.262) for stage IV (stage I as reference). Furthermore, higher C-index, lower Akaike information criterion, and significant improvement in Net Reclassification Index collectively affirmed the exceptional predictive power of our modified staging system.

**Conclusions:** We uncovered for the first time that the upper mediastinum represented the most critical site for cervical LNM in MTC. Adjustments to the N category and TNM staging system in this study might better stratify risk and guide treatment strategies for MTC patients.

### Poster 0388

*Thyroid Cancer, Clinical, Poster*

#### **Identifying Prognostic Thresholds for Lymph Node Metastasis in Medullary Thyroid Cancer**

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**Objectives:** Whereas the current AJCC medullary thyroid cancer (MTC) staging system stratifies positive lymph node (LN) status qualitatively (based on involved LN compartments), extant ATA guidelines for MTC management note that quantitative assessment of LN metastases is "an important prognostic classifier that should be incorporated into the AJCC staging system." Several studies have challenged the current staging system, with some proposing a positive LN ratio (LNR) of 10-50% and others proposing  $\geq 10$  positive LNs as potential prognostic parameters. We a) assess whether there are prognostically significant thresholds for number of positive LNs and LNR associated with MTC-specific mortality and b) estimate the association of LN factors on MTC-specific mortality.

**Methods:** Patients with MTC were abstracted from the SEER database (2004-20). Cox proportional hazards models with restricted cubic splines were used to assess the functional relationship of LNR and number of positive LNs with MTC-specific mortality. Threshold values were estimated using a Markov Chain Monte Carlo procedure and bootstrapping. Multivariable models were used to estimate the association of the identified thresholds with MTC-specific mortality.

**Results:** There were 2709 patients; 2098 (77.4%) had LNs examined. Mean patient age was 54.1 years, 59.1% were female, and 69.6% were non-Hispanic White. Mean tumor size was 23.5 mm; 52.7% of patients with LNs examined had  $\geq 1$  positive LN. The 5-year MTC-specific survival was 93.3%. There was a non-linear association (ie thresholds exist) between LN factors and MTC-specific mortality; threshold values of 7.8 positive LNs and an LNR of 13.8% were identified ( $p < 0.001$  for both). Adjusted analyses showed that  $\geq 8$  positive LNs was associated with a 53% increase in risk of MTC-specific mortality (hazard ratio (HR):1.53, 95% confidence interval (CI):1.10-2.12,  $p = 0.008$ , model AUC 86.7%); a positive LNR  $\geq 14\%$  was associated with a 346% increased mortality risk (HR: 3.46, 95% CI: 2.20-5.44,  $p < 0.001$ , model AUC: 87.9%).

**Conclusion:** Using population-level data, we identified robust LN thresholds associated with MTC-specific mortality which could aid the refinement of the current staging system for MTC. As compared to a threshold of 8 positive LNs, an LNR threshold  $\geq 14\%$  was associated with a larger difference in risk of MTC-specific mortality.

### Poster 0389

*Thyroid Cancer, Clinical, Poster*

#### **Increased Exposure to Medical Radiation from CT Scans and Other Imaging Procedures in Relation to Increased Risk of Thyroid Cancer**

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**OBJECTIVE:** The rapid rise in thyroid cancer in the U.S. and other developed countries during recent decades has been well-documented. While the causes of the rise remain unidentified, emerging literature suggests that increased exposure to ionizing radiation due to increased use of medical imaging procedures such as CT scans in recent decades may be contributing to the rise in thyroid cancer. Thyroid tissues, especially papillary cells, are known to be among the tissue cells most sensitive to the impacts of radiation. It is also well-known that early life (childhood and young adulthood) is

the period most susceptible to the impacts of radiation exposure on the risk of thyroid cancer. We conducted a large-scale matched case-control study to investigate the hypothesis that increased exposure to radiation from CT scans and other medical imaging procedures is contributing to the rapid rise in thyroid cancer in recent decades.

**METHOD:** Thyroid cases (N=898) were identified through our Cancer Registry. We also randomly selected 7,624 controls without thyroid cancer from all eligible controls matched to cases on age-, sex- and enrollment status. Exposure to imaging procedures was ascertained from our EHR databases. Conditional logistic regression was used. To avoid possible reverse causality, all imaging procedures within **24 months prior** to the initial diagnosis of thyroid cancer were excluded.

**RESULTS:** After controlling for confounders including follow-up duration, exposure to CT scans was associated with **10-fold** risk of thyroid cancer compared to those without medical imaging procedures: adjusted odd ratio (aOR)=**10.0**, 95% confidence interval (CI): 5.6-17.9. The association showed a dose-response relationship: aOR=9.8 (95% CI: 5.5-17.6) for one CT scan and aOR=**10.6** (5.8-19.4) for 2+ CT scans. Similar, but slightly weaker, associations were observed for non-CT scan imaging procedures which generate lower levels of radiation than CT scans on average. Sensitivity analysis by further excluding imaging procedures up to 36 months prior to the initial diagnosis of thyroid cancer showed similar results, confirming that reverse causality is not a factor for the associations.

**DISCUSSION/CONCLUSION:** Exposure to CT scans and other medical imaging procedures was associated with 10-fold increased risk of thyroid cancer characterized by a dose-response relationship.

### Poster 0390

*Thyroid Cancer, Clinical, Poster*

#### **Germline PPMID Variant Association with Aggressive Oncocytic Thyroid Carcinoma**

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**Objective:** Oncocytic thyroid carcinoma (OTC) is a rare form of thyroid cancer (TC) characterized by a unique molecular landscape. Somatic pathogenic variants in *PPMID* gene have not been reported in OTC. Germline pathogenic *PPMID* variants cause Jansen de Vries syndrome (JdVS) associated with characteristic physical features, neurodevelopmental abnormalities, and cardiac defects. We describe a novel association between germline *PPMID* variant and OTC.

**Methods:** We performed phenotyping and genotyping of the participant of a TC cohort study (clinicaltrials.gov ID NCT00001160). We analyzed the prevalence of somatic mutations in *PPMID* using the whole exome sequencing data derived from 1620 TC patients from TCGA and 70 OTC patients from COSMIC database. We performed disease-free survival (DFS) analysis using Kaplan-Meier curves.

**Results:** We identified a 67-year-old man with germline *PPMID* variant (p.Thr483Lysfs\*4), who presented with progressive metastatic OTC. Tumor tissue, apart from *PPMID* variant, harbored somatic pathogenic variants in *ARID1A*, *CDKN1A* and had a high expression of PD-L1. After thyroidectomy, radioiodine-therapy, repeated neck dissections and radiation therapy for loco-regional recurrences, the patient presented with progressive distant metastases affecting skeleton, lungs, adrenal gland, and the posterior wall of the right eye globe. Targeted therapy with tyrosine kinase inhibitors (lenvatinib and cabozantinib), MEK inhibitor, immunotherapy, as well as radiation to the spine, hip and ocular lesion failed to control the disease.

Other clinical features included short stature, broad forehead, broad mouth with thin upper lip, and first-degree relatives with short stature and neuro-developmental disorders (epilepsy and learning disability), suggestive of JdVS. While p.Thr483Lysfs\*4 variant has uncertain significance as a cause of JdVS, we found it as a rare (0.18%) somatic pathogenic driver in TC (3/1620 TCGA). Different *PPMID* pathogenic variants are observed in 1.3% (21/1620) of papillary TC and 1.4% (1/70) of OTC. DFS is significantly lower in TC patients harboring pathogenic *PPMID* mutations as compared with patients with non-pathogenic variants (p=0.006).

**Discussion/Conclusion:** We discovered a novel association between germline *PPMID* variant and OTC. Shorter DFS in patients with *PPMID*-mutation positive TC as well as published pre-clinical studies indicating TC growth-stimulatory effect of *PPMID*, suggest that *PPMID* might be one of the drivers of aggressive OTC.

### Poster 0391

*Thyroid Cancer, Clinical, Poster*

#### **The Role of Molecular Testing for Bethesda V Thyroid Nodule: Clarity or Controversy?**

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**Background:** The 2023 Bethesda System update introduced molecular testing as a management option for Bethesda V cytology nodules, aiming to guide surgical decision-making. This study investigates the correlation between molecular profiling and malignancy aggressiveness to evaluate the utility of genetics in Bethesda V management.

**Methods:** We conducted a retrospective multicenter study involving patients with Bethesda V cytology and confirmed malignant pathology who underwent molecular profiling between 2018-2021. Demographic data, definitive pathology results, and genetic variants were analyzed. Malignancy aggressiveness was assessed based on histopathological features following 2015 ATA guidelines. Molecular profiling results were stratified according to the molecular risk group

**Results:** Overall, 156 patients were included. Genetic stratification revealed No-mutation in 39.7% (n=56), Low-risk (n=49, 31.4%), and Intermediate-risk variants (n=45, 28.8%). Only one patient had a high-risk variant. Patients in the Intermediate-molecular risk group have a 6 fold risk for aggressive disease compared to those with the low-molecular risk group (49% vs. 8.2%, P<0.001). *RAS* mutations were the most common among the low-risk group (87%) and *BRAF V600E* predominated in the Intermediate-risk group (91.8%). Lymph node metastasis was the most common aggressive feature among both the low- and - intermediate molecular risk groups.

**Conclusion:** Our findings suggest that molecular profiling offers insights into risk stratification for Bethesda V thyroid lesions, demonstrating a very low incidence of aggressive pathology in the low-risk molecular group. These findings can be used in preoperative risk assessment and guide surgical decisions, as recommended by the latest Bethesda system update.

### Poster 0392

*Thyroid Cancer, Clinical, Poster*

#### **Serum Anti-thyroglobulin Antibody Levels Following Total Thyroidectomy Are Related To The Recurrence Of Papillary Thyroid Carcinoma**

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**Objective:** Thyroid cancer, particularly papillary thyroid carcinoma (PTC), is globally on the rise, driven by increased incidental findings. PTC treatment boasts a commendable 93% 10-year survival rate, yet up to 28% of patients experience locoregional recurrences. Serum thyroglobulin (Tg) serves as a vital marker in post-operative surveillance for differentiated thyroid cancer (DTC). Anti-thyroglobulin antibodies (TgAb) play a crucial role in Tg interpretation, with their interference requiring reliable detection as per American Thyroid Association guidelines. Elevated TgAb levels, more prevalent in recent DTC cases, correlate with increased risks of persistence or recurrence, forming the focus of this study's analysis.

**Methods:** This retrospective study included 15,620 patients from Gangnam Severance Hospital Thyroid Cancer Center who underwent bilateral thyroidectomy for thyroid cancer from March 2004 to December 2022. After exclusions for missing postoperative TgAb results and other carcinoma types, 4434 cases of papillary thyroid carcinoma (PTC) were retrospectively reviewed. Preoperative evaluations involved thyroid ultrasound and fine needle aspiration biopsy for suspicious nodules. TgAb tests, initiated 2 days post-surgery and repeated annually, were stratified into quartiles, and logistic regression analysis revealed a significant association between TgAb levels and PTC recurrence.

**Results:** The study group comprised 4434 thyroid cancer patients, with 775 males and 3659 females, and a median age of  $46 \pm 11.68$ . In Group 1 (TgAb level less than 20), consisting of 3640 patients, 81.2% were female. Tumor size and cancer recurrence rates increased significantly with higher TgAb levels in each group ( $P < 0.001$ ). The proportion of females was consistently higher across all TgAb groups. Extrathyroidal extension did not exhibit a similar trend. The correlation analysis illustrated a consistent pattern: increasing TgAb levels corresponded to elevated odds ratios and probabilities of papillary thyroid carcinoma recurrence.

**Conclusion:** In patients who underwent total thyroidectomy for papillary thyroid cancer, serum TgAb levels may be useful in predicting patient recurrence. Taking advantage of the fact that the higher the serum TgAb level, the higher the recurrence rate, this value alone can be used as a new prognostic indicator regardless of the timing of the TgAb test after surgery.

### Poster 0393

*Thyroid Cancer, Clinical, Poster*

#### **Therapeutic Outcomes and Safety of Radiofrequency Ablation for Primary Papillary Thyroid Carcinoma: Meta-analysis**

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**Objective:** Radiofrequency ablation (RFA) is an emerging treatment option for small, low-risk papillary thyroid carcinoma (PTC). This systematic review and meta-analysis aimed to evaluate and compare the efficacy and safety profiles of RFA for primary T1a vs. T1b PTC.

**Methods:** PubMed, Web of Science, Embase, Google Scholar, and ScienceDirect databases were searched from inception to February 14, 2024 for studies reporting outcomes of RFA for T1a vs. T1b PTC with no known nodal or distant metastasis. The primary outcomes assessed were pooled proportions of tumor disappearance, volume reduction, complications, and recurrence.

**Results:** Twenty studies with 6,613 RFA-treated PTC nodules were included. The median age was 44 years, and the average follow-up was 36.4 months. The mean tumor volume and diameter were  $168.9 \text{ mm}^3$  and 0.69 cm, respectively. The pooled tumor disappearance rate was 94.3% for all tumors, with rates of 96.1% for T1a and 76.7% for T1b lesions ( $p=0.05$ ). The disappearance rate

increased from 61.8% at 12 months to 91.5% at 48 months post-RFA. The overall volume reduction rate (VRR) was 99.4% for both T1a and T1b tumors, increasing from 36.8% at 1 month to 99.6% at 48 months. Tumor progression occurred in only 1.33% of the cases overall, with low recurrence rates in both T1a (1.11%) and T1b (4.21%) lesions. New cancer foci and lymph node metastases were rare, observed in 0.81% and 0.20% of cases, respectively. The overall complication rate was 1.71%, with transient voice change (0.44%) and neck pain (0.30%) being the most common.

**Conclusions:** RFA is a safe and effective minimally invasive treatment option for both T1a and T1b PTC, with high tumor disappearance and volume reduction rates and low complication and recurrence rates. The low progression rates in both tumor sizes suggest that RFA is a promising alternative to surgery for selected low-risk PTC patients. Prospective studies with standardized protocols are warranted to validate these findings.

### Poster 0394

*Thyroid Cancer, Clinical, Poster*

#### **Current status of repeated 100 mCi radioiodine therapy for differentiated thyroid cancer: 86 cases in Japan**

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**Objective:** To evaluate the effectiveness of radioiodine therapy (RIT) using 100 mCi: typically, in Japan.

**Background:** In Japan, RIT exceeding 30 mCi requires hospitalization in an isolation facility, but there is a shortage of hospital beds, and patients must wait six months to a year before RIT. Furthermore, the dose per treatment is limited (commonly, maximum single dose: 100 mCi), and repeated treatments are often required. At our institution, this accounts for 18% (86/489) of cases and 37% (240/871) of all treatments for differentiated thyroid cancer.

**Methods:** We retrospectively evaluated the epidemiological, clinical, and pathological data of 86 patients [34 men (40%) and 52 women (60%)] with DTC, referred to NHO Okayama medical center between May 2003 and March 2023.

**Results:** Median age: 56 (21~88). Pathology: papillary: 69, follicular: 16, poorly: 1. 2 times RIT: 48 patients, 3 times: 20, 4 times 7, 5 times: 8 and 6 times: 3. Patients with increasing TG without tumor localization are 29% (25/86) and the remaining 71% (61/86) of patients had distant metastasis [bone:19 (22%), lung:47 (55%), lymph-node:19 (22%)]. The iodine uptake rate at 2<sup>nd</sup> RIT is 71% (5/7), 29% (6/21) and 8% (1/12), respectively. For bone, all cases are positive from the 3<sup>rd</sup> RIT.

**Discussion:** The reason why the bone uptake rate was high after 2 to 6 doses was thought to be due to an insufficient single dose (100 mCi). Most cases of lung uptake were resolved by the third time. The lymph node accumulation rate was low, and repeated cases were rare.

**Conclusion:** Relaxing the upper limit on radiation doses used will contribute to reducing the number of treatments required, especially for cases of bone and lung metastases, and will help ease supply and demand.

### Poster 0395

*Thyroid Cancer, Clinical, Poster*

#### **A Case of a Devious Diffuse Large B-Cell Lymphoma of the Thyroid Gland**

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**Introduction**

Primary thyroid lymphoma is a rare entity, representing less than 5% of thyroid malignancies and less than 2% of all lymphomas occurring outside the lymph nodes.

**Case Description**

A 58-year-old male was admitted with hypercalcemia, AKI, and significant thyromegaly. He had a two month history of new hypothyroidism with rapidly enlarging goiter, leading to progressive dysphagia and a 25 pound weight loss. His labs showed hypercalcemia of 11.5 (8.7-10.5 mg/dL), PTH <6 (16-77 pg/mL), 25-OH Vitamin D 22 (30-100 ng/mL), 1, 25 dihydroxy vitamin D 142 (18-72 pg/mL). Patient received zoledronic acid and intravenous fluids. CT showed enlarged thyroid gland with superior mediastinal extension, completely encircling the trachea with mass effect on the esophagus. Thyroid ultrasound revealed a heterogeneous and hypervascular goiter without distinct thyroid nodules or abnormal lymphadenopathy.

FNA and two core biopsies showed atypical lymphoid infiltration, however due to having a limited sample with necrosis, definitive diagnosis was unable to be made. He subsequently had an excision of the thyroid isthmus and was diagnosed with diffuse aggressive B-cell non-Hodgkin lymphoma.

Molecular testing was positive for C-MYC gene rearrangement (82/200, 41% of nuclei). PET/CT showed substantial enhancement of the thyroid gland without evidence of FDG-avid metastatic lesions. Patient received 5 cycles of chemotherapy with R-CHOP. He had a significant clinical response after cycle one, with improvement in dysphagia and hypercalcemia. Vitamin D 1,25 OH level was used as a tumor marker and normalized to 26 (18-72 pg/mL) at the end of the treatment. PET scan after last chemotherapy cycle showed resolution of the goiter and there was no evidence for FDG avid residual malignancy. Thyroid function tests were monitored and levothyroxine dose adjusted during the duration of treatment.

**Discussion**

This is a case of a thyroid lymphoma that took three different tissue sampling modalities to establish the diagnosis. Though primary thyroid lymphoma is rare, the index of suspicion should remain high in patients who have a rapidly enlarging goiter and 1,25-dihydroxy Vitamin D mediated hypercalcemia. If core biopsy results are equivocal, excisional biopsy might be needed.

**Poster 0396**

*Thyroid Cancer, Clinical, Poster*

**The Prognostic Value of RAS Mutations in Thyroid Cancer: A Meta-Analysis**

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**Background:** Mutational testing provides insights into malignancy risk in thyroid cancer (TC). We aimed to evaluate RAS mutations as predictors of metastatic potential and prognosis in TC.

**Methods:** A systematic meta-analysis was conducted, comparing postoperative outcomes between RAS mutation-positive and -negative cohorts. Outcomes included distant metastasis, lymph node involvement, extrathyroidal extension, recurrence, and mortality.

**Results:** The meta-analysis included 17 articles and 2,552 patients. Of these, there were **946** RAS-mutated TC patients. RAS mutations were detected in 36% of TC patients. RAS-positive patients showed a rate of distant metastasis of 0.25 (95% CI, 0.10–0.41) while the rate of distant metastasis in RAS-negative patients was 0.11 (95% CI, 0.01–0.20). RAS positivity is an independent risk factor for distant metastasis (RR 3.23), lymph node metastasis (RR

1.93), extrathyroidal extension (RR 1.69), recurrence (RR 1.78), and mortality (RR 4.36).

**Conclusions:** RAS mutation positivity in TC patients confers a significantly increased risk of aggressive disease and adverse postoperative outcomes. RAS testing provides clinically valuable prognostic information to guide personalized treatment decisions and follow-up strategies.

**Poster 0397**

WITHDRAWN

**Poster 0398**

*Thyroid Cancer, Clinical, Poster*

**Pemetrexed-Carboplatin Salvage Therapy in Advanced Thyroid Cancers**

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**Background/Objective:** The overall survival (OS) of patients with advanced thyroid cancers that have progressed following lenvatinib and/or targeted therapies is limited, indicating a strong need for salvage treatments. Pemetrexed, an antifolate therapy targeting DNA replication, has shown efficacy in patients with advanced thyroid cancers in phase I clinical trials. Unpublished observations from our endocrine oncology practice also showed the efficacy of pemetrexed-carboplatin (PC) in several patients treated for lung cancer and mesothelioma with synchronous thyroid cancer. This led to our off-label use of PC as salvage therapy in patients with life-threatening thyroid cancers that progressed following multiple prior systemic treatments. We now summarize our single center experience and demonstrate PC as a potentially important salvage therapy for such patients.

**Methods:** We retrospectively analyzed all patients with advanced thyroid cancer treated with PC at Mayo Clinic Rochester since 2019.

**Results:** Eleven patients, 3 with anaplastic thyroid cancer (ATC), 7 with differentiated thyroid cancer (DTC)/poorly differentiated thyroid cancer (PDTC) and 1 with oncocytic carcinoma of the thyroid (OCT), were treated with PC after progression on a median two lines of prior systemic therapy. Patients with DTC (n=7) had durable responses with a median progression-free survival (PFS) of 29 months. Median % change in thyroglobulin (Tg) level at 3 months was -39.8%. One responder included a patient with ATC whose disease progressed following lenvatinib and dabrafenib/trametinib. On this 3<sup>rd</sup> line treatment, the patient remains on therapy to date, over 12 months after initial response. Four of the 6 patients with BRAF mutant disease responded to therapy. Grade 3 or 4 toxicities occurred in 4 patients, all with somatic CDKN2A or MTAP gene alterations.

**Conclusions:** This single-institution case series reinforces prior published phase I clinical trial data and shows that pemetrexed can have potent efficacy in the treatment of the most advanced thyroid cancers. However, this study is limited by the small number of patients and its retrospective approach. A prospective phase II clinical trial is needed to objectively assess treatment effect and identify biomarkers associated with both disease response and toxicity.

### Poster 0399

*Thyroid Cancer, Clinical, Poster*

#### **RAS Mutations as Predictors of Malignancy Status of Thyroid Nodules - a Retrospective Review**

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**Background and Objective:** Ultrasound guided fine needle aspiration (USFNA) of thyroid nodules is an important diagnostic tool. A limitation of USFNA is that approximately 25% of results end up as indeterminate, providing clinicians with a low to intermediate risk of malignancy. As such, molecular testing of these thyroid nodules has gained in popularity. Among the mutations prevalent in thyroid cancers are NRAS, HRAS and KRAS. While these RAS mutations tend to show more indolent behaving tumors, differentiating the outcomes of isoforms is limited. The study aims to investigate the differences between isoforms, with respect to malignancy rates, aggressiveness, and outcomes.

**Methods:** A retrospective chart review was conducted on thyroid surgery patients at McGill University Health Network from Jan 2017 to Nov 2023. Included patients had pathology analysis and molecular testing showing either no mutations or RAS isoform mutations in thyroid nodules. Patients with non-RAS mutations or multiple mutations were excluded. Univariate regression analyses examined the relationship between RAS isoforms and malignancy

rates. Fisher exact testing assessed the association between RAS isoforms and aggressive pathological features (such as extra-thyroid extension, lymph node metastasis, or high-risk variants like columnar, tall cell, or hobnail) and recurrence of malignancy at the latest follow-up.

**Results:** The study involved 121 patients, analyzing malignancy rates among those with no mutations (52.5%, n=80), NRAS (60%, n=25), HRAS (50%, n=12), and KRAS mutations (50%, n=4), finding no significant differences ( $P \geq 0.423$ ). Aggressive pathological features were seen in confirmed malignancies: NRAS (12.5%, n=8), HRAS (33%, n=3), KRAS (0%, n=2), with no significant differences in aggressiveness ( $P \geq 0.491$ ). Recurrence at the latest follow-up was 0% for NRAS (n=8), 33% for HRAS (n=3), and 0% for KRAS (n=2), with no significant differences between groups ( $P=1$ ).

**Conclusion:** This represents an analysis of malignancy rates and outcomes for NRAS, HRAS, and KRAS isoforms mutations. The preliminary analysis suggests that individual isoforms mutations do not affect malignancy rates, nor do individual isoforms show a difference in aggressivity features or recurrence rate. The use of individual isoforms as prognostic factors for thyroid malignancy is not supported by this current analysis. However, the sample size of this preliminary analysis is small, such that the results could differ significantly when further analysis is done on the complete dataset. Additionally, we aim to investigate whether specific copy number alterations or gene expression profiling of RAS isoform mutations have any impact on malignancy outcomes.

### Poster 0400

*Thyroid Cancer, Clinical, Poster*

#### **Papillary Thyroid Microcarcinoma: Large Case Series and Outcomes Over Up to 45 Years of Follow-Up**

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A significant increase in the incidence of papillary thyroid cancer, especially papillary thyroid microcarcinoma (mPTC), has been reported worldwide. Due to its indolent nature, excellent clinical outcomes have been reported for mPTC patients.

**Objectives:** To evaluate the clinical characteristics and follow up of patients with a diagnosis of mPTC treated at a University Hospital over 45 years, correlating clinical and evolution data.

**Methods:** From a database of 1,500 patients with thyroid carcinoma, 220 with mPTC were selected for analysis between 1978-2020. The <sup>V600E</sup>BRAF mutation analysis in cytological samples was introduced 16 years ago and was evaluated in 80 (36.4%) patients.

**Results:** 220 patients were selected (Female=85.4%; Male=14.6%) with a median age of 48 years (15-78). At presentation, 41.8% (N=92) had an initial diagnosis of multinodular goiter, 43.2% (N=95) of unimodular goiter, 2.3% (N=5) came due cervical adenomegaly and in 3.6% (N=8) and 0.9% (N=2) of cases, mPTC was found in the surgical specimens of patients operated on due Grave's disease and hyperparathyroidism, respectively. 36 were <sup>V600E</sup>BRAF positive and 44 <sup>V600E</sup>BRAF negative. 193 (87.7%) were submitted to total thyroidectomy, 26 (11.8%) to total thyroidectomy with neck dissection and 1 patients to hemithyroidectomy. The mean tumor size was 0.6 cm (0.1-1.0 cm); 74 patients (33.6%) had multifocal tumor; subtypes identified were: 49.1% classical, 38.6% follicular, 2.7% oncocytic, 3.2% sclerosing, 0.9% trabecular and 5.5% mixed; 3.2% (N=7) with vascular invasion; 15.5% (N=34) with lymph node metastasis at biopsy. 51.4% were treated with <sup>131</sup>I. The median follow-up was 8.9 years (1.2-41.4

years). Lymph node metastasis was observed in 7/36 (21.9%) <sup>V600E</sup>BRAF positive tumors and in 8/44 (18.2%) <sup>V600E</sup>BRAF negative tumors. 23 (16.4%) without BRAF analysis presented lymph node metastases. Recurrence was observed in 10 patients [lung (N=2), cervical nodal (N=7) and thyroid bed (N=1)] of which 3 were <sup>V600E</sup>BRAF positive, 4 <sup>V600E</sup>BRAF negative, and 3 in which genetic analysis was not performed (P=1.0). 21 patients died, all from unrelated causes. 7.3% developed definitive postoperative hypoparathyroidism.

**Conclusions:** In most cases, mPTC is a frequent finding in goiter surgery and it has an excellent prognosis. In our series, only 10 (4.5%) presented recurrences, 4 of them presenting nodal metastasis at initial diagnosis. Recurrence occurred despite total thyroidectomy and radioiodine therapy. Notably, multicentricity of the tumor was a prevalent feature in biopsy results, accounting for 33.6% of cases. Importantly, no fatalities were recorded due to the disease. In this series, <sup>V600E</sup>BRAF was not associated with worse prognosis.

### Poster 0401

*Thyroid Cancer, Clinical, Poster*

#### **The development of a thyroid cancer cohort and biospecimen biorepository at Mount Sinai Hospital: DIRECT-P cohort**

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**Objective:** To assess potential thyroid cancer novel risk factors with a focus is on environmental exposures including endocrine-disruptive chemicals, we have developed a cohort that combines demographic and clinical information with exposure questionnaires, pathologic thyroid samples and exposure profiles based on dried blood spot metabolomics. Here we aim to 1) describe the development of the Database Investigating Risk Factors and the Environment in Thyroid Cancer; a prospective study (DIRECT-P) and 2) provide descriptive statistics of the cohort enrolled to date.

**Methods:** Starting January 2022, thyroid cancer patients with Bethesda III-VI are asked to participate in DIRECT-P. Before surgery, patients provide a dried blood sample using a minimally invasive microsampling device, which is stored in a -80°C freezer. Patients are asked to fill out an exposure and risk factor questionnaire. Demographic and clinical data is extracted from the medical records and safely stored in a REDCap database. Following enrollment, patients are contacted on a yearly basis for a follow-up blood sample collection and exposure/thyroid cancer questionnaire over a 5-year study period. In collaboration with the Department of Pathology, fresh frozen thyroid tissue samples are collected after thyroid surgery and stored in a -80°C freezer.

**Results:** As of today, 73 patients consented to participate in our study; 8 patients requested to discontinue their participation due to unknown reasons. Of the 65 patients currently enrolled, 51 (78%) are female, age ranges: 26-87 years, with a mean age of 53 years; 33 patients (51%) filled out the baseline questionnaire. Of the 41 patients due for their year 1 follow-up blood sample, 10 provided a sample (24%); 8 patients (20%) agreed to follow-up but samples are still pending. Of the 18 patients who received a follow-up questionnaire invitation, 6 (33%) submitted their responses. In total, 23 fresh frozen thyroid tissue samples have been collected after surgery.

**Discussion/Conclusion:** This cohort is an important resource for future studies on the link between environmental exposures and the development of more aggressive forms of thyroid cancer.

### Poster 0402

*Thyroid Cancer, Clinical, Poster*

#### **Consolidative radiotherapy for oligometastatic and oligoprogressive anaplastic thyroid carcinoma: the potential utility of local therapy for limited distant sites**

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**Objective:** Local consolidative radiotherapy (LCRT) can improve outcomes for various malignancies involving a limited number of oligometastatic ( $\leq 5$ -total) or oligoprogressive ( $\leq 5$ -growing) distant sites, but this paradigm has yet to be formally evaluated for metastatic anaplastic thyroid carcinoma (mATC)

**Methods:** Forty-three mATC patients (22 oligometastatic and 21 oligoprogressive) were treated from 2016-2024 with 56 LCRT courses for 77-sites: thorax (60%), bone (12%), brain (15.5%), abdomen (6.5%), and head/neck (6.5%). LCRT was delivered via stereotactic (high-dose;  $\leq 5$ -fxs) or hypofractionated regimens for definitive control. Progression was defined via RECISTv1.1, and outcomes evaluated via Kaplan-Meier (associations via Cox proportional hazards).

**Results:** First LCRT occurred a median 11-months (IQR:4-20) after ATC diagnosis, with follow-up thereafter of 13-months (IQR:6-21). Median age was 69-years and primary disease was initially treated for all with resection (93%) and/or neck RT (79%; 60% post-operatively; 53% with chemotherapy). Molecular profiling revealed the following mutations: BRAF-V600E (40%), TERT-promoter (33%), NF (33%), TP53 (40%), and RAS (19%). Most (63%) were on systemic therapy (ST) prior to first LCRT, with each course treating 1-4 sites, averaging total 2 (range:1-6) per patient. Following LCRT, 84% resumed/started ST (53% same as pre-CRT): dual-kinase inhibitor (12%), immunotherapy (19%), or multidrug combination of both (53%). Median OS from LCRT was 15.4-months (95%CI:11-20) with 2-year estimate of 38% (SE $\pm$ 8.5%), while Median PFS was 10.2-months (95%CI:2-19). TERT-mutation was associated with worse outcomes for OS (HR3.96,95%CI:2-9, p=0.001) and PFS (HR3.25,95%CI:2-7, p=0.002). No associations were observed with other mutations (including BRAF-status), type of ST, disease at presentation (oligometastatic vs. oligoprogressive), timing of LCRT, or number of treated sites. Local (in-field) recurrence was the next site of failure for 8% of irradiated lesions. Grade 2 toxicities attributable to LCRT were observed among 16%, but no Grade 3-5 events. By last follow-up (median 13.4-months), 12 patients (28%) remained alive without progression, with most (92%) continuing ST

**Conclusions:** LCRT imparts durable local control with acceptable toxicity, in the setting of ongoing ST, and may benefit select mATC patients with limited distant sites. Definitive RT can be considered within a multimodality approach for these patients, and investigation is warranted into novel combinations with modern ST regimens

### Poster 0403

*Thyroid Cancer, Clinical, Poster*

#### **Effect of 1 versus 2 week low-iodine diet on urinary iodine levels prior to RAI therapy**

*Nikhila Janakiram, Tracy Tylee, Mara Roth, Mayumi Endo\*, University of Washington, USA*

**Objective:** The optimal period of a low-iodine diet prior to treatment with radioactive iodine (RAI) for thyroid cancer is not well established. We conducted a retrospective analysis of patients who underwent RAI therapy at a single institution and compared spot urine iodine concentration in patients who followed a low iodine diet for one- versus two-weeks prior to RAI.

**Methods:** We performed a retrospective chart analysis in a single academic center with a diagnosis of differentiated thyroid cancers who underwent total thyroidectomy and RAI therapy between 2022 to 2024. Patients were excluded if they were younger than 18 years or if they did not have urinary iodine level. All patients followed a low-iodine diet for one or two weeks prior to recombinant TSH-stimulated RAI therapy. Patients followed a one vs two-week low iodine restriction based on the standard practice of the treating endocrinologist. Spot urine iodine/creatinine levels were obtained during the low iodine restriction on the day of the pre-therapy recombinant TSH injection and compared between the two groups.

**Results:** There were 72 patients who met the criteria for analysis. Of these, 53 patients underwent a 1-week and 19 patients underwent a 2-week low-iodine diet before RAI therapy. The median age of this cohort was 46 years old and 62.5% were female. Among the total patients evaluated, 42.3% had ATA high risk disease, 50.7% had ATA intermediate risk disease, and 7.0% had ATA low risk disease. The median value of urine iodine in 2 weeks-restriction was lower compared to 1 week (31 vs 47 mcg/L respectively), but not statistically significant ( $p=0.25$ ). There were no statistically significant differences in age, gender, renal function, thyroid stimulating hormone level, surgical pathology, TNM staging, American Thyroid Association risk category, and radioactive iodine dose between week one and two arms (all  $p>0.05$ ).

**Discussion/Conclusion:** Although the urine iodine level was lower following 2 weeks of low-iodine diet, there was no statistically significant difference between the two groups. Currently, there is no target urinary iodine level. Many small observational studies have evaluated 24 hour urinary iodine levels and have had mixed results following RAI uptake with dietary iodine restriction. A larger cohort evaluating 24 hour urine iodine levels is needed to validate these findings as well as potentially its effect on recurrence rates.

## Poster 0404

*Thyroid Cancer, Clinical, Poster*

### The Effect of Age at Diagnosis and Histological Subtype on Survival in Differentiated Thyroid Carcinoma:

#### An International Individual Participant Data Meta-Analysis

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**Background.** Disease-specific survival (DSS) for patients with differentiated thyroid cancer (DTC) can be estimated by the Tumor Node Metastasis (TNM) Staging system. The current edition incorporates a binary age cut-off at 55 years, which is unlikely to accurately represent tumor biology. Furthermore, although suggested in earlier literature, no distinction is made between papillary (PTC) and follicular thyroid carcinoma (FTC).

**Objective.** To study the association of age at diagnosis and histological subtype on DSS.

**Methods.** We included DTC patients from an international multi-institutional thyroid cancer collaboration including data from Europe, the Middle East, Asia and the Americas. Using individual participant data, we performed a survival analysis with cohort-stratified Cox regression models for disease-specific mortality. Non-linearity and interaction terms were tested for age at diagnosis and histological subtype.

**Results.** From 13 cohorts originating from 8 different countries, a total of 11,501 patients were included. Mean age at diagnosis was 47.2 ( $\pm 14.5$ ) years, and median follow-up time was 102 months (interquartile range: 53-142). In multivariable analysis, higher age at diagnosis (HR 1.08; 95%CI: 1.07-1.09) and FTC (HR 1.48; 95%CI: 1.14-1.90) were significantly associated with disease-specific mortality. A non-linear association was found for age at diagnosis with DSS in DTC, showing a stronger association in younger than older patients. Furthermore, in PTC the effect of higher age at diagnosis on disease-specific mortality was stronger, whereas in FTC the overall hazard of disease-specific mortality was higher compared with PTC.

**Conclusion.** To our knowledge, this is the first study to investigate the effect of age at diagnosis and histological subtype on DSS in a large international collaboration of clinician-collected cohorts. We were able to show that age at diagnosis was associated with DSS in a non-linear fashion, and that the effect of age on DSS differs between PTC and FTC. Our data suggest that a binary age cut-off is insufficient to represent the effect of age on survival in DTC patients. Also, our findings reinforce the concept that PTC and FTC are entities with different prognoses. Our results may fuel attempts to further optimize the TNM Staging system for patients with DTC.

## Poster 0405

*Thyroid Cancer, Clinical, Poster*

### The treatment and prognosis in locally advanced and metastatic thyroid cancer: a single center experience of 279 patients

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**Objective:** To investigate the clinical features, gene alterations, treatment options and survival in locally advanced and metastatic thyroid cancer in China based on an institutional database.

**Methods:** The clinical database of locally advanced and metastatic thyroid cancer in Fudan University Shanghai Cancer Center was reviewed. All patients were evaluated and treated by a thyroid cancer multidisciplinary treatment (MDT) panel. Gene test was performed using institutional thyroid cancer panels with next generation sequencing.

**Results:** A total of 297 patients treated between Aug 2019 and Feb 2023 were included into analysis. According to the primary pathology type, 132 were differentiated thyroid cancer (DTC), 34

were poor-differentiated thyroid cancer (PDTC), 61 were anaplastic thyroid cancer (ATC), 55 were medullary thyroid cancer (MTC), and 15 were other rare thyroid cancer. 176 (59.3%) patients were staged T4, 240 (80.8%) were N1 and 171 (57.6%) were M1. Up to 212 (71.4%) patients had prior treatment. 250 (84.2%) patients had gene test of cancer tissue. *BRAF* mutation (74.5%) and *TERT* promoter mutation (56.4%) were the top gene alterations in papillary thyroid cancer (PTC). *BRAF* mutation, *TERT* promoter mutation, and *TP53* mutation were the top gene alterations in PDTC and ATC. Up to 58.2% cases had *RET* mutations in MTC. Multi-kinase inhibitor (mTKI) was the major treatment option in DTC, while mTKI + PD1 inhibitor was the major treatment option in PDTC/ATC. 37.5% PDTC/ATC with *BRAF* mutations and 47.5% cancer with *RET* alterations received BRAF inhibitor and RET inhibitor, respectively. The median follow-up time was 18.0 months, and 103 deaths were observed during this period, among which 93 deaths were caused by thyroid cancer. The median overall survival (OS) for PDTC and ATC were 19.7 months and 9.5 months, respectively. The estimated 3-year OS rates in DTC, PDTC, ATC, MTC and other pathology group were 73.2%, 12.0%, 20.7%, 83.5%, and 65.5%, respectively ( $P < 0.001$ ). Survival analysis demonstrated that ATC and PDTC had similar OS ( $P = 0.478$ ), while DTC and MTC had similar OS ( $P = 0.207$ ).

**Conclusions:** Both PDTC and ATC had poor survival and similar gene mutation landscape, indicating more aggressive treatment modalities might be appropriate. DTC and MTC had better prognosis. Thus, balancing the risks and benefits of first-line treatment as well as exploring second-line treatment were important in these patients.

#### Poster 0406

*Thyroid Cancer, Clinical, Poster*

##### **Comparative Outcomes Of Synchronous Follicular And Papillary Thyroid Cancers: A Retrospective Analysis**

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**Objective:** The concurrent presence of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) within the same thyroid lobe is extremely rare, with only a few documented cases. This co-occurrence, involving two distinct follicular epithelial cell carcinomas, highlights the complexity of both diagnosis and treatment. The lack of established therapeutic guidelines for such cases presents significant challenges in surgical decision-making and postoperative management. Given the rarity and clinical uncertainty of these synchronous thyroid malignancies, a cautious and individualized approach to treatment is essential. These complexities underscore the need for further research to enhance treatment strategies for mixed thyroid cancers.

**Method:** This retrospective study reviewed 258 patients from the Gangnam Severance Hospital Thyroid Cancer Center who underwent thyroidectomy for thyroid cancer between March 2003 and December 2021. We analyzed data from 44 patients diagnosed with synchronous FTC with PTC and 214 patients diagnosed with FTC post-surgery. Clinical and pathological characteristics were obtained from electronic medical records.

**Results:** The study included forty-four synchronous FTC with PTC patients and 214 single FTC patients. A higher percentage of females was noted in synchronous FTC with PTC group (84.1%) compared to the FTC group (74.6%). The total thyroidectomy rates in the synchronous FTC with PTC group and FTC group were 34 (77.3%) and 86 (40.4%) with a statistically significant difference ( $P < 0.001$ ). In both groups, lateral neck dissection was performed in

4 (9.1%) and 2 (0.9%) cases, respectively, with a significant difference ( $p = 0.008$ ). The extrathyroidal extension (ETE) rate was 47 (22.1%) in the FTC group and 19 (43.2%) in the synchronous FTC with PTC group ( $P = 0.006$ ). Additionally, there were 8 recurrences of cancer in the FTC group only. The overall survival time was 92.7 months for the synchronous FTC+PTC group and 72.3 months for the only FTC group. There was no difference in tumor size distribution between the two groups.

**Conclusion:** The synchronous FTC with PTC group had a high total thyroidectomy and lateral neck dissection ratio, but the recur ratio was significantly lower than that of FTC group. So, careful surgical extent setting will be necessary during surgery for the synchronous FTC with PTC group.

#### Poster 0407

*Thyroid Cancer, Clinical, Poster*

##### **Health-related quality of life analysis in a phase 2 study of encorafenib + binimetinib for patients with unresectable or metastatic BRAF V600-mutated thyroid cancer**

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**Objective:** A phase 2 study of encorafenib (ENC) in combination with binimetinib (BIN) in patients with unresectable BRAF V600E-mutated thyroid cancer showed a centrally assessed objective response rate of 54.5% (95% CI, 32.2–75.6), which met the pre-specified statistical hypothesis, and a manageable toxicity profile (Thyroid. 2024 Apr;34(4):467-476.). Here, we report the results of a health-related quality of life (HR-QoL) analysis as a secondary endpoint of this study.

**Methods:** This study was conducted at 10 sites in Japan involving patients with unresectable locally advanced or metastatic BRAF V600-mutated thyroid cancer who were refractory to or intolerant of multi-targeted kinase inhibitors (MKIs) (Clinical trial registry: jRCT 2011200018). Patients completed the HR-QoL questionnaires, including EORTC QLQ-C30 and thyroid cancer module (QLQ-THY34), at baseline and follow-up times. Mean changes from baseline were assessed for each HR-QoL score, with a minimally important change (MIC) from baseline defined as 10 points.

**Results:** Twenty-two BRAF V600E-mutated thyroid cancer patients (12 males; median age, 68.0 [range, 50-77]) were enrolled. Seventeen patients had differentiated thyroid cancer (DTC) and 5 had anaplastic thyroid cancer (ATC). Fourteen of the DTC patients (82.4%) received radioactive iodine therapy and 20 of the total patients (90.9%) received one or more MKIs. With a median follow-up period of 11.5 months, mean changes from baseline were generally maintained with regard to global health status and functional scales for QLQ-C30. Among QOL scores for QLQ-THY34, mean change from baseline for most items was maintained. However, a multi-item scale of support from others consecutively improved over the MIC while a single item scale of joint pain deteriorated over the MIC of 10 points. Furthermore, for ATC patients, improvement over the MIC of 10 points in swallowing and body image in QLQ-

THY34 was observed at early time points. In contrast, for DTC patients, most HR-QoL scores tended to be maintained from baseline.

**Conclusion:** Treatment with ENC/BIN was generally associated with the maintenance of HR-QoL in patients with unresectable locally advanced or metastatic BRAF V600E-mutated thyroid cancer. These results further support the use of ENC/BIN for patients with unresectable locally advanced or metastatic BRAF V600E-mutated thyroid cancer.

#### Poster 0408

*Thyroid Cancer, Clinical, Poster*

##### **The Role of Artificial Intelligence in Predicting the Future Burden of Thyroid Cancer in Missouri. A Comparative Analysis**

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**Introduction:** As artificial intelligence (AI) develops predictive analysis capabilities, the ability to perform complex projections of future disease burden is expected. Although there are statistical models that have demonstrated a rising incidence and disability-adjusted life years for thyroid cancer globally, there have been no studies on the role of AI in predicting future disease burden due to thyroid cancer. The objective of this study is to present 10-year projections for the United States of America (US) and Missouri (MO) determined by AI for future thyroid cancer burden.

**Methods:** Data for this study was extracted from the Global Burden of Disease (GBD) study between the years 1990-2019. The focus was on years of life lost (YLL) rates due to thyroid cancer in Missouri and the US. YLL represents the number of deaths multiplied by the standard life expectancy. Julius AI was used to describe trend data, conduct a linear regression, and perform a 10-year predictive analysis. The primary outcome evaluated was rates of YLL predicted from 2020-2029.

**Results:** Overall rising YLL rates are seen on trend data as demonstrated by Figure 1. Linear regression models completed by Julius AI demonstrate a MO slope of 0.1553 and a US slope of 0.1479. R-squared for MO is 0.985 and US is 0.984, indicating a very high level of fit. Pearson correlation coefficient for MO is 0.9922 and for US is 0.9927. Mean Standard Error is 0.03 for MO and 0.02 for US. MO is projected to reach YLL rates of 16.7 compared to 16.1 for the US overall by 2029 as seen in Table 1. Residuals are observably scattered around the zero line without pattern suggesting no bias in this study as seen on Figure 2.

**Conclusion:** Julius AI was able to predict a strong statistical prediction of rising YLL rates due to thyroid cancer in MO and US. MO was found to have a slightly higher disease burden than the US. Despite an overall good prognosis and overdetection, AI predicts that thyroid cancer will continue to impact YLL rates in the next few years. This study is limited by the lack of statistical validation for the analysis completed by AI. However, future studies should determine the validity and usability of AI for predicting future thyroid cancer burden.

#### Poster 0409

*Thyroid Cancer, Clinical, Poster*

##### **Programmed Death-Ligand 1 Expression is Associated with Local Invasion and Distant Metastases in Differentiated Thyroid Cancer: a Systematic Review and Meta-Analysis**

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**Objective:** Programmed death-ligand 1 (PD-L1) contributes to tumor evasion from the host's immune system. Studies have reported the association between tumoral expression of PD-L1 and clinico-pathologic features of differentiated thyroid cancer (DTC), but unlike that in anaplastic thyroid cancer, the data have not clearly identified a link. This systematic review and meta-analysis aims to investigate the link between tumoral PD-L1 positivity and DTC features.

**Methods:** We searched the Cochrane, EMBASE, MEDLINE OVID, and PubMed databases up to January 23<sup>rd</sup>, 2023 for terms 'thyroid cancer' OR 'thyroid' AND 'programmed death 1 receptor' OR 'PD-1' OR 'programmed cell death protein' OR 'programmed cell death 1' OR 'programmed death ligand' OR 'PD-L1', which yielded 1,333 studies in any language. Studies without DTC and without PD-L1 expression and any clinical or pathologic outcomes were excluded. After screening titles and abstracts, 102 were assessed for a second exclusion criteria which evaluated pathological and clinical outcomes. Finally, 12 studies were included in the meta-analysis to compare tissue PD-L1 positivity amongst clinico-pathologic variables by weighted pooled odds ratio (OR) or with recurrence risk by pooled hazard ratio (HR). Data extraction and quality assessment were performed independently by two reviewers, with discrepancies addressed by a 3<sup>rd</sup> reviewer. Modified Newcastle-Ottawa tool was used for quality assessment;  $I^2$  statistic was calculated to determine total between-study variation due to heterogeneity (25% low, 50% moderate, 75% high). All values are 2-tailed and  $p < 0.05$  was set as the threshold for statistical significance.

**Results:** All 12 studies were retrospective observational, being of moderate quality. Tumoral PD-L1 positivity was lower in DTC without lymphovascular invasion (LVI) (OR=0.24; 95% CI 0.1, 0.6;  $p=0.002$ ,  $I^2=41%$ ) and without extrathyroidal extension (ETE) (OR=0.6; 95% CI 0.4, 0.9;  $p=0.007$ ;  $I^2=36%$ ). Tumoral PD-L1 positivity was lower in DTC without distant metastasis (OR=0.2, 95% CI 0.1, 0.6;  $p=0.005$ ;  $I^2=0%$ ). Tumoral PD-L1 positivity was not significantly associated with tumor size, multifocality, lymph node involvement, DTC stage, mortality, and recurrence risk, but the studies reporting these variables showed moderate to high heterogeneity.

**Discussion:** Tumoral PD-L1 expression is associated with higher risk of local invasion (LVI, ETI) and distant metastases, as shown in studies with low to moderate heterogeneity, suggesting that PD-L1 expression contributes to DTC progression. The lack of association with tumor stage, mortality, and recurrence could be due to the overall favorable prognosis of DTC. Future research should be focused on prospective study designs and additional tumor microenvironment impacts on DTC prognosis.

#### Poster 0410

*Thyroid Cancer, Clinical, Poster*

##### **Ultrasound-guided treatment of cervical metastases from thyroid carcinoma: a prospective clinical trial with cryoablation, laser or radiofrequency ablation**

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**PURPOSE** To evaluate safety and efficacy of thermal ablation of cervical metastases from thyroid carcinoma; best response to thermal ablation defined as lymph node reduction or volume stability; tumor marker response; complications, side effects and tolerability among laser (LA), radiofrequency (RF) or cryoablation (CA).

**MATERIALS AND METHODS** This prospective clinical trial obtained IRB approval. All patients provided informed consent, including those with differentiated or medullary thyroid carcinoma confirmed by fine-needle aspiration biopsy. Ablation techniques (LA, RF or CA) were randomly assigned to participants. Eligible subjects presented with up to six concurrent lesions larger than 0.8 cm diameter. US examinations were conducted at baseline, 6, 12, and 24-months post-treatment. Data was collected in a web-based tool. Evaluation criteria included changes in tumor volume, rates of technical success, complications, tumor marker response and need for additional surgery.

**RESULTS** Seventy-two patients (n=145 tumors) were evaluated. Mean age was 67.8±15.1 years, 54 (75%) being females. Technical success rate reached 100%. Baseline mean and standard deviation lymph node volumes (cc) for each ablation group were as follows: LA, 0.83±1.14 (range: 0.15-4.34); RF, 2.49±6.9 (range: 0.1-25.6); CA, 1.28±2.12 (range: 0.12-8.08). Significant lymph node volume reduction was observed at 6, 12, and 24 months up to 97.9% of volume reduction ratio (all P < 0.001). No instances of volume regrowth were detected. Absolute decrease of tumor markers was noted. Major complication rate was 1.4% (n=1): one vocal cord palsy, leading to bronchopneumonia, prolonged hospitalization and eventual fatality. Minor complications rates were 9.2% (n=7): 1.4% (n=1) of cutaneous fistulae with brief spontaneous resolution, and 7.9% (n=6) of transient vocal cord palsy with complete recovery after one month. Only 2.6% (n=2) patients were treated twice for residual tumor. None of the patients required additional neck surgery due to ablation failure over time. All patients with new recurrent cervical metastases (n= 18, 25%) underwent additional ablation.

**CONCLUSION** Both thermal ablation modalities (LA, RF, CA) were feasible, effective and safe in well selected patients with cervical metastases from thyroid carcinoma. No significant difference among the thermal ablation methods in terms of complications, side effects and tolerability were observed.

#### Poster 0411

*Thyroid Cancer, Clinical, Poster*

##### **Back pain masquerading as metastatic papillary thyroid carcinoma**

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**Introduction:** Papillary thyroid carcinoma (PTC) is the most common histological subtype of thyroid cancer, representing approximately 80% of cases. While PTC typically exhibits an indolent course with an excellent prognosis, metastatic cases can present in uncommon ways. Here we present a diagnostically challenging case of metastatic PTC and our therapeutic considerations.

**Case presentation:** A 71-year-old female presented to the emergency department with lower back pain for one month. On physical examination, vital signs were normal. Systemic examination was remarkable for right costovertebral angle and point tenderness over lower thoracic vertebral area.

CT abdomen showed complex cystic lesions within the right kidney, and a 4 cm x 3 cm soft tissue mass medial to the right kidney, lytic lesion in the T12 vertebra with osseous destruction of the vertebral body, pedicle and right 12<sup>th</sup> rib. Further evaluation with MRI showed more lytic lesions in the cervical vertebrae, initially suggesting a primary renal neoplasm with metastatic spread to the vertebrae.

Excision biopsy of the soft tissue mass however revealed the tall cell variant of papillary thyroid carcinoma, with extensive necrosis, hemorrhage and areas of psammomatous calcification. CT soft tissue neck obtained afterwards, showed a heterogenous mass in the right thyroid.

The patient underwent total thyroidectomy that confirmed papillary thyroid carcinoma, with pathology revealing a diffuse follicular variant with focal oncocyctic features. Molecular testing demonstrated mutations in NRAS and TERT genes, indicative of high-risk thyroid cancer with potential for early distant metastasis. Immunohistochemistry was positive for HBME-1, thyroglobulin, TTF-1 and CK-19 also consistent with papillary thyroid carcinoma.

Her postoperative course was uneventful. Long-term management plans included consideration of targeted therapy, and optimization of bone health.

**Conclusion:** The case of metastatic papillary thyroid carcinoma in our patient highlights the diagnostic and therapeutic challenges associated with atypical presentations of thyroid cancer. Multidisciplinary collaboration is essential for optimizing patient care and outcomes. Advances in molecular profiling and targeted therapies offer new avenues for the treatment of metastatic PTC, but further research is needed to elucidate optimal treatment strategies and improve long-term outcomes.

#### Poster 0412

*Thyroid Cancer, Clinical, Poster*

##### **Response to therapy in ATA high risk of recurrence differentiated thyroid cancer patients treated with adjuvant high-dose radioactive iodine**

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**Objective:** The ATA guidelines suggest treating ATA high-risk of recurrence differentiated thyroid cancer (DTC) patients with high-dose (<sup>3</sup>100 mCi) postoperative radioactive iodine (RAI). In the absence of known macroscopic residual disease, the intent of such “adjuvant treatment” is to reduce the risk of recurrence and improve survival. This study evaluated the response to therapy of high-risk DTC patients treated with adjuvant RAI after initial surgery.

**Methods:** Using our institutional prospective thyroid cancer database, we identified ATA high-risk DTC patients, who were administered adjuvant RAI (doses (<sup>3</sup>100 mCi) postoperatively between 2017-2022, with a minimum follow-up of one year. We excluded patients who received “treatment” RAI for known macroscopic disease. The primary objective was to determine the worst response to therapy during follow-up and the secondary objective was to define the disease management of patients exhibiting a structural incomplete response (SIR) to therapy.

**Results:** Among 763 database patients, we included 84 DTC patients with median age at diagnosis of 46 years (range 14-76), 57% female, and 76% papillary histology. Initial treatment included: total thyroidectomy (n=84, 100%), central neck dissection (n=57, 69%), lateral neck dissection (n=49, 58%), and adjuvant external beam radiotherapy (n=4, 5%). The initial postoperative RAI dose was: 100 mCi (n=77, 92%) or 150 mCi (n=7, 8%), and intent of RAI was considered adjuvant treatment in all cases.

The rate of SIR during a median 44 months of follow-up was 42% (n=35 patients; 25 had locoregional disease and 13 had distant metastases). Site of distant metastases included: lung n=13 and bone n=2. Twenty-three patients (27%) required additional treatment after initial surgery and adjuvant RAI, which included: observation

(n=12, 34%), additional surgery (n=13, 57%), additional RAI (n=7, 30%), and systemic therapy (n=7, 30%).

**Conclusion:** The intent of adjuvant RAI is destruction of microscopic disease after primary surgical resection, resulting in improved survival. We showed a high rate (42%) of SIR despite high-dose ( $^{131}\text{I}$  100 mCi) postoperative RAI for adjuvant treatment. Nearly one-third of all patients required additional treatment (surgery, RAI, or systemic therapy) for disease progression. Our results illustrate the need for more efficacious treatment, beyond RAI alone, in high-risk patients.

### Poster 0413

*Thyroid Cancer, Clinical, Poster*

#### **A novel online medullary thyroid cancer (MTC) educational resource: How patients find it, use it, and what they learn**

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**Objective:** Rare cancer populations, such as those with medullary thyroid cancer (MTC), experience clinical vulnerability due to limited expert clinicians, treatment options, and accessible information. In a prior study, MTC patients, caregivers, and physicians indicated a need for readily available educational materials and strategies for conveying patient priorities to clinicians. As such, we developed and launched MTCeducate.org, an online educational resource for the MTC community. In this report, we analyze how people accessed and used the website along with its usability and acceptability.

**Methods:** MTCeducate.org was deployed in April 2023. Strategic promotion occurred through patient support organizations (PSO), social media platforms, the American Thyroid Association (ATA), national conferences, and a robust MTC Collaborative Registry (MTCCoRe) listserv. Site metrics were assessed via Google Analytics, and site usability and acceptability were evaluated via a confidential, online survey.

**Results:** Since its launch, MTCeducate.org has attracted 2,077 unique visitors. Among them, 64% accessed the site using a mobile device and 36% used a desktop computer or tablet. The site had visitors from 69 countries with the majority (70%) from the United States. Over half of all visitors (52%) accessed the site via direct links including those found in MTCCoRe newsletters and emails, PSO and ATA websites, or Twitter (X) whereas 45% accessed the site by a patient-managed MTC Facebook page. Visitors spent an average of 157 seconds on the website with most time spent on “Frequently Asked Questions” (253 sec) and “Patient Stories” (202 sec). Seventy-six visitors completed the site usability and acceptability survey, and most correctly answered MTC knowledge-based questions about tumor markers (96%), lymph node dissection (94%), and FDA-approved medications (71%). Most found the site easy to use (88%) and well-integrated (84%). Further, most could learn to use MTCeducate.org quickly (86%) and confidently (81%) and indicated they would use the site frequently (81%).

**Conclusion:** MTCeducate.org, a new online educational platform for MTC patients, has achieved international reach through various advertising methods and has been positively received by the MTC community. Future efforts should focus on identifying ways to encourage extended and more consistent engagement with online educational content.

### Poster 0414

*Thyroid Cancer, Clinical, Poster*

#### **Association between Environmental Air Pollution and Thyroid Cancer and Nodules: A Systematic Review**

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**Objective:** The global incidence of thyroid cancer has increased over the past several decades. While this increase is partially due to increased detection, environmental pollutants have also emerged as a possible contributing factor. Our goal was to perform a systematic review to assess the relationship between environmental air pollution and thyroid cancer.

**Methods:** After registration in PROSPERO, we performed a systematic literature search using PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases, searching for original articles published in English prior to March 2024 investigating outdoor air pollution and thyroid cancer/nodules. Inclusion criteria included quantitative reporting of pollutant levels and effect size. Specific EPA criteria pollutants included ozone (O<sub>3</sub>), particulate matter less than 2.5 microns in diameter (PM<sub>2.5</sub>), PM less than 10 microns in diameter (PM<sub>10</sub>), sulfur dioxide (SO<sub>2</sub>), nitric oxides (NO<sub>x</sub>), carbon monoxide (CO), and polyaromatic hydrocarbons (PAHs). Study design, sample size, methods of pollution assessment, covariates, and strength/direction of associations between pollutants and thyroid cancer/nodule detection were extracted.

**Results:** Of 1,294 studies identified in the literature search, 11 met inclusion criteria for analysis. Over six million patients from regions including China, United States, Brazil, and Iran were represented across studies. Pollutants studied included O<sub>3</sub> in 5 studies, PM<sub>2.5</sub> in 3 studies, PM<sub>10</sub> in 3 studies, unspecified PM in 2 studies, SO<sub>2</sub> in 3 studies, NO<sub>x</sub> in 3 studies, and CO in 2 studies, and PAHs in 1 study. The primary outcome was thyroid cancer diagnosis among 9 studies and thyroid nodule detection in 2. Across 9 cancer studies, only 1 identified a subtype (papillary thyroid cancer). All 3 studies examining NO<sub>x</sub> and all 5 studies examining O<sub>3</sub> pollutants demonstrated positive associations with both thyroid cancer/nodules. Of the 2 studies assessing PM<sub>2.5</sub> and thyroid cancer, both demonstrated a positive association. Inconsistent results were observed for levels of CO, PM<sub>10</sub>, and SO<sub>2</sub>.

**Discussion/Conclusion:** In an emerging body of literature, air pollution was associated with thyroid cancer and thyroid nodule diagnosis across diverse geographic regions. These findings underscore the potential for environmental risk factors of thyroid cancer and warrant further investigation of the mechanism underlying the observed associations.

### Poster 0415

*Thyroid Cancer, Clinical, Poster*

#### **Clinicopathologic Characteristics and Outcomes in Early Versus Later-Onset Advanced Thyroid Carcinoma**

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**Objective:** Early-onset cancers, defined as cancers diagnosed in people <50 years, have increased in prevalence in recent decades. This study aimed to evaluate differences in clinicopathologic features and treatment outcomes among patients with early compared to later-onset advanced thyroid carcinoma.

**Methods:** A retrospective review was conducted on patients with advanced (defined as unresectable or metastatic) thyroid cancer seen at Princess Margaret Cancer Center between 2007 and 2022. Medical records were reviewed to obtain next-generation sequencing, clinicopathologic, and treatment data for all patients. Patients were categorized into early-onset (age at diagnosis <50 years) and later-onset (age at diagnosis ≥50 years) groups. Clinicopathologic and molecular features were compared between both cohorts. Overall survival (OS) was determined using the Kaplan-Meier method and the time from initial medical oncology consultation to last follow-up date or date of death.

**Results:** Among 248 patients with advanced thyroid cancer, 82 (33%) were <50 and 166 (67%) were ≥50 years at diagnosis. Medullary carcinomas were more common in early-onset patients (28 vs 9%,  $p < 0.001$ ). The early-onset cohort had more *RET* mutations (27% vs 8%,  $p < 0.001$ ), while later-onset patients had more *RAS/RAF* pathway (74% vs 52%,  $p = 0.001$ ), *TP53* (10 vs 2%,  $p = 0.04$ ), and *TERT* promoter (34 vs 18%,  $p = 0.02$ ) mutations. There was no difference in the proportion of patients receiving systemic therapy (61 vs 60%,  $p = 0.95$ ). Multikinase inhibitors were the most common first-line treatment in both cohorts. The median duration of first-line treatment was longer in early-onset patients (21.0 vs 9.1 months,  $p = 0.006$ ). OS was 134.9 months (77.6 – NA) in early-onset compared to 73.6 months (47.0-126.4) in later-onset patients ( $p = 0.005$ ). In univariable analysis, later-onset (HR 2.03,  $p = 0.006$ ), ECOG 3 (HR 9.63,  $p = 0.002$ ), local recurrence (HR 1.82,  $p = 0.008$ ), lung metastases (HR 1.85,  $p = 0.02$ ) and pleural metastases (HR 4.40,  $p < 0.001$ ) were poor prognostic factors for OS. Later-onset (HR 5.26,  $p = 0.03$ ) and lung metastases (HR 6.61,  $p = 0.003$ ) remained poor prognostic factors in multivariable analyses.

**Conclusion:** This study represents one of the largest cohort studies comprehensively comparing early vs later-onset thyroid carcinoma patients receiving contemporary treatments. Later-onset patients had significantly worse prognosis. Further studies are warranted to elucidate the reasons for this phenomenon.

## Poster 0416

*Thyroid Cancer, Clinical,*

### Study on association Between human plasma Polybrominated Diphenyl Ethers and Thyroid carcinoma

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**Objective:** Polybrominated diphenyl ethers (PBDEs) are a class of persistent organic pollutants (POPs) that have been reported to have endocrine-disrupting and tumor-promoting activity. However, evidence regarding the association of PBDE exposure with thyroid health in humans remains limited. This study aims to examine the potential association between environmental exposure to PBDEs and the risk of thyroid cancer.

**Methods:** A total of 53 patients who underwent thyroid surgery at the Shanghai Sixth People's Hospital from February to July 2022 were recruited. PBDEs concentrations were measured in plasma using gas chromatography/mass spectrometry. The Spearman rank correlation coefficient was used to evaluate the correlation between PBDE congeners. A multiple linear regression model was used to explore the relationship between PBDEs and thyroid function. The Point-Biserial correlation coefficient was used to evaluate the relationship between plasma PBDEs, clinicopathologic and molecular characteristics of thyroid cancer. The Bayesian kernel machine regression (BKMR) model was used to explore the association between PBDE congeners and thyroid cancer risk.

**Results:** BDE-209 was found to be the highest PBDE congeners (median, 11.36 ng/g lipid) in the plasma. BDE-100 was positively associated with free triiodothyronine (FT3), suggesting that levels of BDE-100 were related to an increased risk of hyperthyroidism. Exposure to PBDE congeners (BDE-28, -47, -99, -100) increased the risk of aggressive PTC subtypes (tall cell subtype and hobnail subtype), and BDE-154 were significantly positive associations with extranodal extension. No significant correlation between PBDEs and *BRAF* or *RAS* mutations in PTC patients, which suggest that PBDEs may not directly induce the tumorigenesis of thyroid cancer MAPK signal way. The BKMR model show that higher concentrations of BDE-47 and BDE-99 were observed to have correlation with the risk of thyroid cancer. However, this result was not statistically significant.

**Conclusion:** The present study not only contributes to the growing evidence regarding the impact of PBDEs on thyroid function but also provides new insights into the association between exposure to certain PBDE congeners and the aggressive pathological characteristics of thyroid cancer. Large-scale prospective studies are still needed to support our findings and further explore the association between PBDEs exposure and thyroid cancer.

## Poster 0417

*Thyroid Cancer, Clinical, Poster*

### Reappraisal of *BRAF*<sup>K601E</sup>-positive Thyroid Tumors in the NIFTP Era

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**Objective:** *BRAF*<sup>K601E</sup> is a rare mutation found in low-risk follicular-patterned thyroid tumors. Previous studies on *BRAF*<sup>K601E</sup>-positive thyroid tumors were conducted prior to the clinical implementation of the non-invasive follicular neoplasm with papillary-like nuclear features (NIFTP) diagnosis. The aim of this study was to characterize *BRAF*<sup>K601E</sup>-positive tumors and evaluate changes in diagnosis and management of these tumors at a single institution after introduction of NIFTP.

**Methods:** We evaluated 25 thyroid tumors at the University of Pittsburgh Medical Center (UPMC) that were positive for *BRAF*<sup>K601E</sup> on ThyroSeqv3 genomic classifier testing from 2018-2023. Clinicopathologic characteristics and recurrence rates of these tumors were compared to 29 *BRAF*<sup>K601E</sup>-positive tumors reported at

UPMC prior to the 2016 implementation of NIFTP.  $BRAF^{V600E}$ -RAS score (BRS) and thyroid differentiation score (TDS) were calculated based on RNA-sequencing data from representative  $BRAF^{K601E}$ -positive tumors (n=10).

**Results:** Three quarters (18/25) of  $BRAF^{K601E}$ -positive tumors in the current study were diagnosed as non-invasive tumors on resection, including 12 (48%) NIFTP, 4 (15%) papillary thyroid carcinomas (PTC), and 2 (8%) follicular adenomas. Invasive tumors comprised 5 (20%) encapsulated follicular variant PTC (EFVPTC), 1 (4%) oncocytic carcinoma and 1 (4%) anaplastic carcinoma - the only case with a concurrent *TERT* promoter mutation.  $BRAF^{K601E}$ -positive tumors exhibited a RAS-like gene expression profile with BRS and TDS distinct from  $BRAF^{V600E}$ -positive tumors ( $P<0.001$ ). Compared to  $BRAF^{K601E}$ -positive tumors diagnosed prior to 2016, the current cohort revealed a lower proportion of PTC (93% vs 36%,  $P<0.001$ ), particularly EFVPTC (66% vs 24%,  $P=0.003$ ). Since 2018, patients with  $BRAF^{K601E}$ -positive tumors less frequently underwent total thyroidectomy (100% vs 41%,  $P<0.001$ ) and received radioiodine (75% vs 7%,  $P<0.001$ ). None of the tumors positive for an isolated  $BRAF^{K601E}$  mutation from the current (1.9 years median follow-up) or 2016 (7 years) studies showed recurrences.

**Conclusions:** Our study demonstrates that the majority of  $BRAF^{K601E}$ -positive tumors are low risk, RAS-like tumors, which are now diagnosed as NIFTP in half of all cases. Further, since 2018, patients with  $BRAF^{K601E}$ -positive nodules receive less aggressive treatment. Although longer-term follow-up is necessary, the risk of recurrence of  $BRAF^{K601E}$ -positive tumors appears to be low, and lobectomy without radioiodine is likely sufficient treatment for these patients.

## Poster 0418

*Thyroid Cancer, Basic, Poster*

### The Role of CREB3L1 in Thyroid Carcinoma Dedifferentiation and Prognosis: Insights from Murine Models and Clinical Specimens

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**Objective:** Dedifferentiation is recognized as an adverse prognostic factor in thyroid carcinoma. In our previous research, our group identified *CREB3L1* as a potential transcription factor involved in the process of thyroid cancer dedifferentiation. However, the mechanisms by which *CREB3L1* promotes tumor progression and enhances invasiveness remain elusive. We aimed to investigate the role of *CREB3L1* in thyroid cancer progression and dedifferentiation, in order to identify potential approaches for diagnosing and treating dedifferentiated thyroid carcinoma.

**Methods:** We employed genetic engineering to establish a conditionally inducible murine model of anaplastic thyroid carcinoma (ATC) on a C57BL/6 background (TBP group). Using this model, we generated mice with a specific knockout of *CREB3L1* in the thyroid epithelium (TBPC group) for detailed analysis. We validated the role of *CREB3L1* in both groups through survival analysis, tumor kinetics, single-cell transcriptomic, and spatial transcriptomic analyses. Additionally, we collected over 300 postoperative specimens from patients with differentiated thyroid carcinoma (DTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC), assessing *CREB3L1* expression in tumors via immunohistochemistry. Furthermore, we obtained 5 ml peripheral blood samples from 91 patients to quantify circulating tumor cells (CTCs) and evaluate *CREB3L1* expression in these cells.

**Results:** Survival analysis revealed that TBPC group mice, with a *CREB3L1*-specific knockout, exhibited a significantly improved prognosis, with a median survival of 225 days compared to 160 days in the TBP group. The *CREB3L1* knockout extended the median lifespan by 65 days, roughly equivalent to 7 human years. Moreover, spatial as well as single-cell transcriptomic analysis and molecular characterization indicated that tumors with *CREB3L1* knockout demonstrated better differentiation. Furthermore, *CREB3L1* expression in epithelial CTCs showed a strong correlation with extrathyroidal extension.

**Discussion/Conclusion:** This study demonstrates that *CREB3L1* plays a critical role in thyroid carcinoma dedifferentiation. Notably, the specific knockout of the *CREB3L1* substantially prolongs the survival of mice and suppresses tumor dedifferentiation. These findings provide valuable insights into the mechanisms underlying thyroid cancer development, thereby presenting promising therapeutic avenues for further exploration.

## Poster 0419

*Thyroid Cancer, Clinical, Poster*

### Combined detection of preoperative serum calcitonin and carcinoembryonic antigen for the diagnosis and prognosis prediction of medullary thyroid cancer: a retrospective multicenter cohort study

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**Objectives:** Preoperative serum calcitonin (Ctn) testing are known to contribute to the diagnosis and management of medullary thyroid cancer (MTC). However, the clinical value of combined detection of Ctn and carcinoembryonic antigen (CEA) in diagnosing MTC and predicting lymph node metastasis and prognosis remains to be further explored.

**Methods:** Our retrospective multicenter cohort study involved 9941 patients with thyroid nodules who underwent preoperative testing for both Ctn and CEA and had definite pathological diagnosis from 6 centers between 2013 to 2023. Receiver operating characteristic curves were constructed to compare the diagnostic efficacy of MTC and cervical lymph node metastasis between Ctn or CEA alone and their combination. Kaplan-Meier method was used to estimate recurrence-free survival (RFS) of MTC patients with or without elevated Ctn or CEA.

**Results:** In total, 104 patients with MTC, 7986 with differentiated thyroid cancer and 1843 with benign thyroid nodules were analyzed. The sensitivity, specificity, positive predictive value, negative predictive value, and the area under the curve (AUC) of Ctn, CEA detection alone and their combination for the diagnosis of MTC were 95%, 99%, 56%, 100%, 0.991; 91%, 98%, 30%, 100%, 0.986; and 98%, 99%, 47%, 100%, 0.998, respectively. The AUCs of Ctn, CEA alone, and combined detection in predicting cervical lymph node metastasis were 0.530, 0.511, and 0.503, respectively. The sensitivity of combined detection was 86%, which was higher than that of Ctn (24%) and CEA (57%) alone, while the specificity of combined detection was 12%, lower than that of Ctn (80%) and CEA (42%) alone. Among the 90 MTC patients with elevated Ctn and CEA, 16 of them experienced recurrence, while none of patients with no elevation or elevated Ctn or CEA alone had recurrence. The survival curve showed a trend of poorer RFS in MTC patients with elevated levels of both Ctn and CEA ( $p$ -value=0.17).

**Conclusions:** Combined detection of preoperative Ctn and CEA doesn't show a significant improvement in the diagnosis of MTC or prediction of lymph node metastasis compared with Ctn detection

alone. The necessity of preoperative CEA testing in patients with thyroid nodules should be carefully considered.

### Poster 0420

*Thyroid Cancer, Clinical, Poster*

#### **Role of Ultrasound Surveillance for Thyroid Cancer in Setting of Negative Thyroglobulin**

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**Objective:** Given the high sensitivity of serum thyroglobulin (Tg), the added value of routine neck ultrasound (US) becomes unclear in post-treatment papillary thyroid cancer (PTC) patients with undetectable Tg. We aimed to assess the utility of US surveillance in PTC patients who underwent thyroidectomy with undetectable Tg and Tg antibodies (Tg Ab).

**Methods:** We performed a retrospective analysis of TxNxM0 PTC patients who underwent total thyroidectomy at our institution from 2010-2023. We identified patients who then had US-guided fine needle aspiration (FNA) biopsy during their surveillance period. Patients were categorized based on lab status prior to the US: Negative Tg (if undetectable Tg and Tg Ab), Positive Tg (if positive Tg and undetectable Tg Ab), and Positive Tg Ab. We calculated the positive predictive value (PPV) of US by defining "true positive" as FNA biopsy consistent with PTC and "false positive" as FNA biopsy with benign or other findings.

**Results:** Of a total of 1,654 subjects, 144 (9%) underwent US-guided FNA biopsy during their postoperative surveillance: 27 (19%) had Negative Tg, 89 (62%) Positive Tg, and 28 (19%) Positive Tg Ab prior to the US. Median follow-up was 7.2 years. Negative Tg patients were older (median age 48 years vs 43 years [Positive Tg] vs 37 years [Positive Tg Ab],  $p=0.003$ ) and had lower rates of American Thyroid Association (ATA)-high recurrence risk pathology (7% vs 33% [Positive Tg] vs 32% [Positive Tg Ab],  $p=0.025$ ). The PPV of US in the setting of Negative Tg was 1 of 27 (3.7%) while it was 43 of 89 (48.3%) in Positive Tg and 15 of 28 (53.6%) in Positive Tg Ab ( $p<0.001$ ). The one patient with Negative Tg who recurred had an initial ATA-intermediate risk pathology in which the recurrence was detected on routine 6-month postoperative US.

**Conclusion:** When Tg is undetectable, the PPV of US drops significantly from 50% to 3.7%. We should consider reducing the frequency of US surveillance in this patient cohort as it incurs a high rate of false positive results, and ultimately increased healthcare costs, patient anxiety, and iatrogenic injuries.

### Poster 0421

*Thyroid Cancer, Clinical, Poster*

#### **Clinical Characteristics and Prognostic Evaluation of Calcitonin-Negative Medullary Thyroid Carcinoma in a Multicenter Cohort of 1018 Patients**

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**Objectives:** Calcitonin (Ctn) levels below the upper reference threshold reliably exclude medullary thyroid carcinoma (MTC) with high accuracy. However, instances of MTC without elevated preoperative calcitonin levels have been rarely reported. This study sought to explore the prognostic and clinical distinctions between Ctn-negative patients and those with elevated Ctn levels.

**Methods:** This nationwide multicenter cohort from 18 Chinese centers collected data on 1018 MTC patients diagnosed from 1998 to 2024. Long-term follow-up was meticulously and comprehensively documented. All patients underwent surgical treatment, with specimens retained for further Immunohistochemical (IHC) staining and genetic testing. Patients whose preoperative calcitonin levels fell within the reference level were classified as Ctn-negative patients. Structural recurrence-free survival (SRFS) was our main outcome.

**Results:** Clinical characteristics of 40 Ctn-negative patients in our cohort exhibited a tendency towards less invasiveness when compared to Ctn-elevated patients. These patients presented at an earlier stage according to AJCC 8th edition staging ( $P < 0.001$ ) with smaller tumor sizes (0.80cm, IQR[0.58, 1.70],  $P < 0.001$ ), and a reduced incidence of lymph node metastases, especially in advanced locations like the lateral or upper mediastinum ( $P = 0.001$ ). The proportion of KRAS mutations in Ctn-negative patients was higher than Ctn-elevated patients (10.0% vs 2.9%  $P=0.002$ ). Kaplan-Meier survival curves showed a markedly improved prognosis in patients with negative Ctn levels ( $P=0.019$ ). Based on Cox regression analysis, low Ctn levels (HR 0.292  $P=0.038$  in univariate; HR 1.00  $P=0.995$  in multivariate) did not adversely affect prognosis. Additionally, by further dividing subgroups in Ctn-negative patients, we found that patients with undetectable serum calcitonin had a worse prognosis than those within the reference level (Log-rank  $P=0.004$ ), and observed no significant difference between immunohistochemical (IHC) Ctn staining negative and positive patients (Log-rank  $P=0.203$ ).

**Conclusions:** Clinical characteristics of Ctn-negative patients exhibited a tendency toward less invasiveness. Low Ctn levels did not adversely affect prognosis. Analyses subdividing Ctn-negative patients revealed those with undetectable serum calcitonin levels had a worse prognosis than those within reference level, and no significant prognosis differences were found between IHC Ctn staining negative and positive patients.

### Poster 0422

*Thyroid Cancer, Clinical, Poster*

#### **Cancer Recurrence in a Cohort of Patients With Differentiated Thyroid Cancer Diagnosed 5 or More Years Ago in Northwest Mexico**

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**Objective:** To relate time of illness since diagnosis of differentiated thyroid cancer (DTC) and its recurrence in adult patients diagnosed  $\geq 5$  years ago.

**Methods:** This retrospective, observational, descriptive, cross-sectional study in which clinical records of patients older than 18 years with DTC diagnosed 5 or more years ago, in northwestern Mexico. They had to meet the study entry criteria, including having a diagnosis of DTC evidenced in a histopathological report and maintain follow-up for at least 5 years.

**Results:** We identified 77 adult patients (18-69 years,  $\bar{x}=43$ ), 68 females (88%) and 9 males (12%), with DTC followed for a median of 10.9 years (5.03-30.9 years) after total thyroidectomy ( $n=62$ ) or thyroidectomy in two surgical stages ( $n=15$ ). Treated with iodine I-131 at different doses. Patients were initially stratified according to ATA risk system into: low 63(81.8%), intermediate 11(14.3%) and high 3(3.9%). All patients received TSH suppressive therapy and clinical data obtained during follow up (Tg and imaging studies) were used to identify recurrence, which was found in 28 patients (34%), evidenced from 0.94 to 22.7 years ( $\bar{x}=6.06$ ). The relationship

was evaluated from two correlational approaches. We used Spearman's rho to investigate whether there is a relationship between the number of days from diagnosis to recurrence of DTC and the number of days with the disease, showing a direct and significant correlation of a moderate type, according to  $\rho(28)=.49$ ,  $p=.008$ , between both variables. And a qualitative approach using chi-square, categorizing variables; using the median illness time to assess whether DTC recurrence was found after 10.9 years and as the second variable dividing time of recurrence in two groups: 1-5 years or >5 years. Results also revealed a significant association between the two groups ( $\chi^2(1)=5.32$ ;  $p=.021$ ).

**Conclusion:** Observing that the group of patients with  $\geq 10.9$  years of disease had greater recurrence compared to <10.9 years, suggest that, the longer the duration of DTC, the risk of recurrence may increase and that after 5 years from initial diagnosis, recurrence may appear and increases in patients with  $\geq 10.9$  years of disease. Furthermore, it was found that the greatest number of cases with recurrence after 5 years was in patients with a low initial ATA risk. This suggests that follow-up of DTC for only 5 years may not be enough despite having an excellent response; however, individualizing each case should be a priority.

### Poster 0423

*Thyroid Cancer, Case Study, Poster*

#### **Thyroid Collision Tumor: Incidental Detection of Synchronous Medullary Thyroid Carcinoma and Papillary Thyroid Microcarcinoma- A Case Study**

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**Introduction:** An increase in thyroid cancer (TC) incidence is widely attributed to frequent detection of Papillary Thyroid Microcarcinoma (PTMC), more so than Medullary Thyroid Carcinoma (MTC). While *PTMC* and *MTC* vary in their clinical and histological findings, overlapping sonographic features prompts the use of confirmatory tests to rule out aggressive *TC*, especially in unusual cases of synchronous *PTC/MTC* on the same thyroid lobe.

**Clinical Case:** A 37-year-old female with a history of *TC* and total thyroidectomy presented to the outpatient clinic with complaints of insomnia, palpitations, and tremor. She denied exposure to head/neck radiation and family history of *TC*. Preoperative thyroid u/s revealed a solid micronodule 5 x 3 mm in diameter with irregular contours and microcalcifications on the left thyroid isthmus junction (TIRADS 5). Post-surgical pathology reports were consistent with *PTMC* along with extrathyroidal extension and angio/lymphatic invasion on the left lobe. Incidentally, amorphous, eosinophilic ovoid and fusiform cells with mild atypia were also observed, suggestive of *MTC*. Follow-up immunohistochemical analysis was performed. Positive results for calcitonin and neuroendocrine markers (PCK, synaptophysin, chromogranin) were consistent with morphological findings which confirmed the presence of *MTC* on the left lobe. The same lobe had been previously diagnosed with *PTMC* by a pathology report. Meanwhile, postoperative serum TSH was 19.70  $\mu\text{UI/mL}$  (0.27-4.20) while free T4 was 0.75 ng/dL (0.93-1.71). Serum tumor marker levels were the following: thyroglobulin 3.25 ng/mL (0-78), antithyroglobulin antibody 41.90 UI/mL (0-115), calcitonin <2 pg/mL (<5), CEA 0.5 ng/mL (<5.0). RET gene analysis was unavailable. Active surveillance with laboratory tests and neck u/s in the past two years suggested low risk *PTMC* with indeterminate response, and stage 1 *MTC* with excellent response.

**Discussion:** The etiology of mixed medullary-papillary carcinoma remains ambiguous, though often associated with RET mutations. Without available genetic testing for this proto-oncogene, pinpointing this tumor's origin is challenging. Consequently, discerning its sporadic nature or potential link to MEN2 Syndrome remains unclear. Therefore, regular screening for pheochromocytoma and primary hyperparathyroidism is advised.

### Poster 0424

*Thyroid Cancer, Clinical, Poster*

#### **Use of Natural Language Processing to automate risk of recurrence in patients with papillary thyroid cancer using surgical pathology reports**

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**Objective:** To assess the pathology features and risk of cancer recurrence among patients diagnosed with papillary thyroid cancer (PTC) across a national multicenter health system, we employed ThyroPath. This Natural Language Processing (NLP) pipeline, developed earlier, extracts key information from structured surgical pathology reports, aiding in estimating the likelihood of recurrence.

**Methods:** We identified 10,358 adult patients who underwent initial thyroid ultrasonography at the three Mayo Clinic main sites and their health care systems between January 2019 and December 2022. Among these, 703 received either partial or total thyroidectomy, with 288 diagnosed with papillary thyroid carcinoma (PTC). For each case, we utilized ThyroPath, an NLP pipeline that extracts 18 PTC pathology features from the pathology report with 95% accuracy. The system classifies cases into very low, low, intermediate, and high recurrence risk categories, following a modified 2015 American Thyroid Association (ATA) classification, also with 95% accuracy. We presented the extracted pathology features and ATA risk classification using descriptive methods.

**Results:** In a cohort of 288 papillary thyroid carcinoma (PTC) cases, key findings included: 42.36% (n=122) underwent total thyroidectomy, with 65.62% (n=189) being unifocal and 63.19% (n=182) classified as classic variants. Follicular variants accounted for 23.61% (n=17) of cases. Negative resection margins were observed in 55.55% (n=160) of cases. Additionally, angioinvasion, lymphatic invasion, extrathyroidal extension, and extranodal extension were noted in 4.16% (n=12), 9.02% (n=26), 4.16% (n=12), and 12.84% (n=37) of cases, respectively. Predominant pathological stages were T1a (23.61%, n=68), Nx (10.41%, n=30), and Mx (4.51%, n=13). The automated model's risk stratification resulted in the following distribution: 27.62% very low risk (n=79), 32.52% low risk (n=93), 22.03% intermediate risk (n=63), 9.09% high risk (n=26), and 8.74% no risk (n=25).

**Conclusions:** ThyroPath exhibits promise by effectively identifying and extracting pathology features related to thyroid cancer, enabling the classification of recurrence risk within large pathology report databases. This capability addresses the labor-intensive yet crucial process of manual pathology report review. It represents a significant stride towards establishing comprehensive digital registries for thyroid cancer. However, before integration, ThyroPath necessitates further external validation.

**Poster 0425***Thyroid Cancer, Clinical, Poster***Exploring Participant Demographics in Studies Addressing Unmet Care Needs of Thyroid Cancer Survivors: A Systematic Review**

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**Objective:** Social determinants of health and patient demographics greatly affect the frequency, evaluation, prognosis, and outcomes of thyroid cancer patients. This systematic review aims to analyze participant demographics in studies on unmet care needs among thyroid cancer survivors, identifying groups with poorly understood unmet care needs.

**Methods:** We conducted a systematic review of qualitative and quantitative studies published between 2000 and November 2023 addressing unmet care needs among adult thyroid cancer survivors. Participant demographics in each study were analyzed using the PROGRESS-Plus framework, which includes social disadvantage variables, aiding in assessing population diversity. The frequency of reporting each PROGRESS-Plus component was summarized through descriptive statistics. Additionally, we identified the most common participant responses, provided that they were reported by at least 30% of the studies.

**Results:** We identified 23 studies on unmet needs among thyroid cancer survivors (N=9188). Demographics were reported in all studies, with age and gender the most common (100% and 95%, respectively), followed by education (65%), social capital (69%), occupation (52%), and language (39%). Race/ethnicity (30%), income (17%), place of residence (22%), insurance status (17%), and religion (4%) were the least frequently reported. Across studies reporting gender, 7742 out of 9124 participants (75%) were female. Regarding age, 2300 out of 3869 participants (60%) were 40 years or older. College or higher education was present in 67% (1152 of 1728) of participants. Marital status data showed that 72% (1718 of 2398) were married or in a stable relationship, full time or part-time employed represented 639 out of 1196 (53%). English was the dominant language, comprehended by 1815 out of 1915 participants (95%). White participants accounted for 2578 out of 3078 (84%) participants reporting their race.

**Conclusion:** Our review reveals that the studies addressing unmet needs among adult thyroid cancer survivors predominantly include female, white, well-educated, employed, and married English-speaking participants. Information on key demographics such as race or ethnicity as well as insurance status that can significantly influence care experiences and outcomes are often overlooked, limiting our understanding of the study participants.

**Poster 0426***Thyroid Cancer, Clinical, Poster***Characteristics Assessment Of YouTube Videos On Radioactive Iodine Therapy For Thyroid Cancer For Patient Education**

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**Objective:** YouTube is one of the most popular websites on the internet, serving as a common platform to obtain health information. Young adults who encompass a great proportion of patients with

thyroid cancer, frequently utilize YouTube to gain or share health related information. However, there are concerns regarding the quality of videos and the dissemination of potentially inaccurate information on the platform. This study aims to assess the characteristics, reliability, and content of YouTube videos on radioactive iodine (RAI) therapy for thyroid cancer.

**Methods:** The first 50 videos across four different YouTube searches, using terms related to RAI for thyroid cancer, were identified by rank ordering the retrieved videos and applying pre-determined exclusion criteria. A previously validated video assessment tool was utilized to evaluate the videos. Two independent reviewers assessed a random sample of 10 videos, while the remaining 40 videos were evaluated by one reviewer due to minimal discrepancies in coding.

**Results:** Just over half of the videos (52%) were published within the past 3 years, with a median video length of 4 minutes and 53 seconds. The most common publisher affiliations were non-profits (30%), personal accounts (24%) and healthcare organizations (22%). Most of the videos originated in the United States (62%), featured physician presenters (76%), used an interview style format (76%), and were targeted towards patients (78%). Seven major themes were identified, with an average of 2.52 themes covered in each video. The major theme, RAI therapy, identified “Side effects and risks” (56%) and “RAI Overview” (54%) as highly covered sub-themes. Modified DISCERN scores varied by publisher affiliation and presenter type.

**Conclusion:** This study outlines the landscape of YouTube videos on RAI therapy for thyroid cancer, underscoring both strengths and limitations in the available online content. There was a lack of coverage of some of the eight identified RAI therapy sub-themes within the videos, which might contribute to potential knowledge gaps. The results are valuable for informing the development of new high-quality YouTube videos allowing patients to receive the most current and comprehensive information on RAI therapy supporting health education and patient care.

**Poster 0427***Thyroid Cancer, Clinical, Poster***Characterization of RAS-mutant Anaplastic Thyroid Carcinoma (ATC)**

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**Background:** RAS-mutant ATCs have the worst overall survival (OS). We aimed to describe their genotypic/phenotypic landscape.

**Methods:** Retrospective chart review of RAS-mutated ATC identified on targeted gene panels between 5/2016-6/2023. Survival was assessed by Kaplan-Meier; association between tumor characteristics and survival by Cox proportional hazards model.

**Results:** Seventy-one patients with RAS-driven ATC were included. 40/71(56%) were women; median age at diagnosis was 63 (range,30-80); 50/71(70%) had stage IVC disease. 23% had history of thyroid nodules; median time from nodule to ATC diagnosis was 13.5years (range,2-38). RAS mutation distribution: 51(72%) NRAS, 11(15%) HRAS, 11(15%) KRAS. Most were at residue Q61x (56/73,77%). Most common additional mutations were in tumor suppressor genes (TP53 64%, NF1 7%, RB1 4%), TERT promoter (61%) and PI3K pathway (PTEN 10%, PIK3CA 4%). 41/43(95%) evaluable specimens had a PD-L1 ≥1%. 9/21(43%) patients with

stage IVB disease developed distant metastases (DM), all within 1 year (median time to DM=5 months). Most frequent sites of DM were lungs(92%), bones(49%) and liver(29%). 17/69(25%) patients with brain imaging had brain metastases. 47/71(66%) had surgical resection of their primary tumor, 57/71(80%) had radiation therapy (RT) to the neck. First-line systemic therapy in patients with DM included cobimetinib+atezolizumab (n=12), lenvatinib+pembrolizumab (n=12), lenvatinib (n=3), pembrolizumab (n=3), cytotoxic chemotherapy (n=2), and others (n=3). In patients with localized disease, systemics included adjuvant pembrolizumab (n=12), and neoadjuvant cobimetinib+atezolizumab (n=1). 23/71(32%) received no systemic therapy. After a median follow-up of 36months, median OS was 7.0months (95%CI,3.3-10.7). Multivariate Cox regression analysis showed that earlier stage(HR=0.24), surgery(HR=0.31) and neck RT(HR=0.50) were positive predictors for survival. Median OS was significantly longer in patients with stage IVB disease compared to stage IVC (56.0vs4.0 months; p<0.001). In patients with DM, OS was 8.0 months(95%CI,2.0-14.0) with cobimetinib+atezolizumab, 9.0 months(95%CI,0-30.2) with lenvatinib+pembrolizumab and 1.0 month(95%CI,0.9 -1.15) with other therapies.

**Conclusion:** Based on this large cohort of 71 patients, RAS-mutant ATC exhibit an aggressive clinical course, with a high propensity for DM, including the brain. Current treatments are limited, and prognosis remains reserved despite expert multidisciplinary care, highlighting the need for better therapeutic options. Most RAS-mutant ATCs harbor Q61x mutations, for which targeted therapies are being studied.

#### Poster 0428

*Thyroid Cancer, Clinical, Poster*

##### **Evaluating How Patients With Thyroid Cancer Use Online Resources And Social Media to Access Health Information**

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**Objective:** Thyroid cancer is the most common cancer diagnosis in individuals aged 15-29. Given the near-universal use of the internet and social media among this population, many patients use these platforms to obtain health information. This study evaluates how thyroid cancer patients utilize online resources, with a focus on social media platforms like YouTube and their resultant impact.

**Methods:** Between June-December 2023, thyroid cancer patients under care at a tertiary cancer center were invited to participate in a survey regarding their internet and social media usage. Surveys were distributed both in hard copy and an online version, with 55 out of the 102 surveys returned (54%). The survey comprised of 37 open and closed-ended questions exploring demographics, internet and social media habits, and the utility of these platforms. A mixed-method analysis was employed, utilizing descriptive statistics for quantitative data and a grounded theory approach for qualitative insights.

**Results:** Almost all participants (98%) reported using the internet, with 91% utilizing it to obtain information on thyroid cancer. Less than half (38%) of the participants used social media sites for acquiring thyroid cancer information. YouTube was the most popular site (95%), followed by Facebook (38%). The most common topics searched were personal experiences with thyroid cancer (62%) and radioactive iodine therapy (58%). YouTube was found to be easier to understand (61%) and easier to use (50%) compared to other

internet resources. Only 17% of participants informed their healthcare providers that they use social media for thyroid cancer information. Social media users expressed it was useful (88%), increased their understanding of thyroid cancer (76%), and informed treatment decision making (39%).

**Conclusion:** Social media platforms, particularly YouTube, are becoming increasingly popular for accessing health information. Overall, patients perceive social media to be a beneficial tool that enhances their understanding of thyroid cancer and influences decision-making. Most patients do not inform their healthcare providers about their use of social media sites. Healthcare providers should be encouraged to inquire about their thyroid cancer patients' use of social media and online resource to offer guidance on selecting sources and address any knowledge gaps unmet by these platforms.

#### Poster 0429

*Thyroid Cancer, Clinical, Poster*

##### **Efficacy and Safety of Selective RET Inhibitors in Hereditary Medullary Thyroid Carcinoma**

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**Background:** Two selective RET inhibitors (RETi) are effective in RET-altered medullary thyroid carcinoma (MTC), but prior phase I/II trials did not delineate hereditary MTC (hMTC) from sporadic (sMTC) cases. We aimed to review our single-center experience using a RETi to treat advanced hMTC.

**Methods:** Retrospective review of all patients with metastatic hMTC treated with a selective RETi at a tertiary referral center. Primary outcome was objective response rate using RECIST1.1. Secondary endpoints included overall survival (OS), progression-free survival (PFS), biochemical response rate, and safety. Survival outcomes were calculated by Kaplan-Meier method. Data cut-off was 1/15/2024.

**Results:** Twenty-three patients (61% female) were included: 15 MEN2A; 8 MEN2B. Median age at start of RETi was 51 years (range,15-79). All patients had distant metastases and 52% (12/23) had received prior systemic therapy (median=1, range 0-3). Patients were treated with selpercatinib[S](n=13) or pralsetinib[P](n=10), 56% (13/23) within a clinical trial. Median duration of RETi was 25 months (range,3-72) with 11/23(48%) patients remaining on drug at data cut-off. Reasons for drug discontinuation included: disease progression (n=5), death (n=3), treatment-related toxicity (n=3) and drug holiday in an excellent responder (n=1). Median duration of follow-up was 49 months (range, 9-72). All patients had clinical benefit: best radiographic response was partial response in 18 (78%) and stable disease in 5 (22%) patients. Median OS was 51.0 months (95%CI, 40.5-61.3) while median PFS was not reached. Most common adverse events (AEs) were increased ALT (48%) [S:54%; P:40%] and AST (26%) [S:31%; P:20%], dry mouth (39%), fatigue (35%) and hypertension (26%) [S:15%; P:40%]. AEs led to treatment interruptions and dose reductions in 8 (35%) and 8 patients (35%), respectively. While the germline nature of the RET pathogenic variant in hMTC could hypothetically result in increased drug-induced toxicity, the incidence of AEs was comparable to what was reported in the phase I/II trials.

**Conclusion:** Selective RETi appear safe with no apparent increased toxicity in hMTC, similar to the clinical trial cohorts, which mostly comprised sMTC. Response rates and survival

outcomes were also comparable to the clinical trials. Whether or not the duration of response is different from sMTC requires longer follow-up.

### Poster 0430

*Thyroid Cancer, Clinical, Poster*

#### Clinicopathological Features of Advanced, RAS-driven Differentiated Thyroid Carcinoma (DTC)

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**Background:** RAS is the second most frequent oncogenic driver in DTC, yet little is known about the clinicopathological characteristics of RAS-mutant DTCs. As several drugs with potential efficacy against RAS are under investigation, better understanding of these tumors is warranted.

**Methods:** Retrospective chart review of patients with RAS-mutant DTC identified on targeted gene panels, prior to systemic therapy initiation, between 6/2016-6/2023. Survival was assessed by Kaplan-Meier method.

**Results:** 120 patients were identified [48% women; median age at diagnosis 61 years (range, 27-85)]. DTC subtypes: follicular thyroid cancer (n=46, 38%), papillary thyroid cancer (n=31, 26%), poorly differentiated thyroid cancer (n=32, 27%). RAS mutation distribution: NRAS in 83(69%), HRAS in 23(19%) and KRAS in 14(12%). RAS mutations were in residue Q61 in 114(95%) cases. Most patients had distant metastases (DM) at diagnosis (64%) or later during disease course (31%) justifying molecular testing. Median time to detection of DM was 4 years (range, 0.3-45). DM most frequently involved lungs (87%), bones (79%), mediastinum (54%) and liver (25%). 16/83(19%) patients with brain imaging had brain metastases. Almost all of the cohort underwent surgery (98%) and radioactive iodine (RAI) treatment (93%) [median cumulative activity 200mCi (range,30-1046)]. After a median follow-up of 8 years, median overall survival (OS) was 16 years (95%CI, 9.5-22.5). Age at diagnosis <55 or ≥55 was not associated with OS differences (15 vs. 16 years, p=0.566). 59/120(49%) patients received at least one line of systemic therapy (ST), most commonly lenvatinib (47/59, 80%). Median time to starting ST was 3.5 years from diagnosis, and median OS from start of drug was 6 years (95%CI, 4.8-7.2).

**Conclusion:** In this large cohort of RAS-mutated DTC enriched with advanced disease, 95% of patients had a mutation in residue Q61, NRAS being the most frequently mutated. DM most commonly affected the lungs, bones and liver, while brain metastases were also seen frequently. In patients treated with systemic therapy, OS from time of drug start was 6 years. While no specific drugs targeting RAS are approved for thyroid cancer, pan-RAF inhibitors are currently under investigation for tumors harboring a NRASQ61X mutation, which was the most frequent mutation encountered in our cohort.

### Poster 0431

*Thyroid Cancer, Clinical, Poster*

#### Medullary Thyroid Cancer with Novel Gene Alteration and Novel Management

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### Introduction

Medullary thyroid carcinoma (MTC) is one of the potentially aggressive forms of thyroid cancer, with a 5-year survival for stage IV as low as 28%.

### Case description

A 43-year-old gentleman presented with a left neck mass for six months. No self or family history of thyroid disorders or malignancy. Examination showed thyroid nodules with cervical lymphadenopathy. Investigations showed TSH=2.2mIU/L, and neck ultrasound showed a left thyroid nodule of 2.2 cm (TR4) and Left cervical suspicious lymph nodes (LN). FNA from the thyroid nodule: Bethesda 6 (malignant). Core biopsy from Left cervical LN: MTC. CT neck showed Left thyroid nodules, with suspicious left cervical lymphadenopathy, the largest is 3.6 cm at level III. No invasion of surrounding tissue. RET oncogene: negative. Calcitonin: 243 ng/L. CT chest showed lung metastasis, and MRI liver showed multiple liver metastatic lesions, the largest 1.3cm. Patient underwent total thyroidectomy with central and Left lateral neck dissection.

Histopathology: Unifocal MTC at the left lobe 3.4 x 2 x 2 cm. Mitotic figures <1/2 mm<sup>2</sup>. Negative margins and no extrathyroidal extension. Malignant LN (4/37) on the Left side, largest (4 cm), with extranodal extension. Three months postoperatively, Calcitonin: 45 ng/L, CEA 19.7. PET scan: Left humeral head and acetabulum metastasis. Known lung metastases were stable. Liver metastasis progressed, reaching 2.7 cm at segment 3, and 3 cm at segment 6. Patient declined medical therapy. He underwent external beam radiation to the affected bone lesions, and also Denosumab was started. Eight months later, there was further progression in the liver and bone. Calcitonin level increased to 251, and CEA 756.

Tumor genetic testing showed SCG-3 ALK-fusion. Therefore, the patient was commenced on Alectinib. Three months later, subsequent images showed a dramatic reduction in the size and number of liver lesions, significant response in the lung lesions, and stability in the bone lesions. Calcitonin level dropped to an undetectable level.

### Discussion

This is an entirely new gene fusion that has never been reported in thyroid cancer or any other cancer listed in the COSMIC or cBioportal database. Advances in genetic testing have transformed the management of thyroid cancer.

### Poster 0432

*Thyroid Nodules and Goiter, Clinical, Poster*

#### Diagnostic Accuracy of Thyroid Nodules with Indeterminate Cytology when Combined with Ultrasonographic Risk

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**BACKGROUND AND OBJECTIVES:** The most common tools for assessing thyroid nodules are ultrasound (US) and Fine-needle aspiration cytology (FNAC). However, 25% of FNAC are indeterminate and remain without a definite answer till after surgery. In this study, we aim to evaluate whether US features can improve the prediction of malignancy in thyroid nodules with indeterminate FNAC.

**METHODS:** This retrospective chart-review study was conducted at King Abdul-Aziz University Hospital in Jeddah, Saudi Arabia. The study analyzed thyroid nodules in adult patients undergoing total or hemithyroidectomy from 2016 to 2023, focusing on histopathology, US risk stratification based on the 2015 American Thyroid Association (ATA) guidelines, and FNAC based on the Bethesda classification system. The malignancy rate was calculated in each US risk and each FNAC category. Indeterminate cytology

categories were follicular lesion of undetermined significance (FLUS), and follicular neoplasm (FN). We calculated sensitivity, specificity, and kappa twice using high-risk US features as suspicious for malignancy in patients with FLUS and FLUS plus FN. The primary outcome measure was the accurate assignment of malignancy among patients with indeterminate cytology.

**RESULTS:** We had a total of 290 patients. We found low-risk US to be the most common US feature in 114 (39%) patients and benign cytology as the most encountered FNAC feature in 78 (27%). The malignancy rate in the high-risk US in the entire cohort was 68 (72%). We had 118 patients with FLUS and FN. The malignancy rate was 38% and 52% in FLUS and FN, respectively. In cases with FLUS and FN, high-risk US features had sensitivity, specificity, and Kappa of 47%, 81%, and 29%, respectively, for predicting malignancy. The high US features improved the malignancy rates (PPV) in cases of FLUS from 38% to 61% (P 0.051).

**CONCLUSIONS:** In patients with indeterminate cytology, US features can aid management decision-making. Thus surgery should be favored in patients with high-risk US rather than repeating the FNAC or follow-up.

### Poster 0433

*Thyroid Cancer, Clinical, Poster*

#### **Recombinant Human Thyroid-stimulating Hormone versus Thyroid Hormone Withdrawal in Aiding Postoperative Dynamic Surveillance for Patients with Differentiated Thyroid Cancer**

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**Objectives** With a quite favorable outcome, dynamic long-term follow-up and active surveillance would apparently be the focus of post-operative or post-radioiodine-131 (<sup>131</sup>I) management in patients with differentiated thyroid cancer (DTC). This study assessed the efficacy and safety of a novel recombinant human thyroid-stimulating hormone (rhTSH, ZGrhTSH) as an alternative to thyroid hormone withdrawal (THW) in aiding postoperative dynamic surveillance of DTC patients, including imaging of radioiodine-131 (<sup>131</sup>I) -whole body scan (Dx-WBS) and measurements of serum stimulated thyroglobulin (Tg).

**Methods** This open-label, multicenter, self-controlled, phase 3 study, patients who had undergone total or near-total thyroidectomy with or without <sup>131</sup>I ablation were enrolled, with their suppressive Tg levels below 2 ng/mL. Dx-WBS and Tg measurements were performed during both phases for all patients. In the first phase, patients received two doses of ZGrhTSH while maintaining thyroid hormone therapy (ZGrhTSH-stimulated phase), and in the second phase, patients discontinued thyroid hormones (THW phase). Analyses were done in the full analysis set of patients with Dx-WBS available during both phases. The primary endpoint was the concordance of the scan results between two phases; secondary endpoints included the concordance of stimulated Tg in two phases, the diagnostic concordance of stimulated Tg combined with Dx-WBS, safety,

immunogenicity, and patient-reported quality of life (QoL). This study is registered with ClinicalTrials.gov, NCT04971473.

**Results** Overall, 201 patients were enrolled into the study, of which 195 patients had evaluable scans determined by the independent reviewers. Concordant scans between two phases were noticed in 88.2% (172/195; 95% CI, 83.7% to 92.7%) of the patients. The concordant stimulated Tg level with the cut-off of 1 ng/mL was noticed in 90.4% (169/187) of the patients. The concordance of scans combined with stimulated Tg was observed in 175 of 187 patients (93.6%, 95% CI: 90.1% to 97.1%). Out of 201 patients, 22 (10.9%) experienced ZGrhTSH-related adverse events, which were grade 1 or 2, and mostly mild and transient.

**Conclusion** The ZGrhTSH, resulted in noninferior radioiodine uptake and serum Tg levels, with better QoL over that observed in the same patients after thyroid hormone withdrawal, holds promise in aiding postoperative dynamic surveillance for patients with DTC.

### Poster 0434

*Thyroid Cancer, Case Study, Poster*

#### **A case of thyroid eye disease complicated with radioactive iodine refractory differentiated thyroid cancer under anlotinib therapy**

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#### **Introduction**

Thyroid eye disease (TED) is an autoimmune disease of the retro-orbital tissues. The cross-reaction of thyroid-stimulating hormone receptor antigen in thyroid and ocular fibroblasts is critical to TED pathogenesis. TED after radioactive iodine (RAI) therapy for differentiated thyroid cancer (DTC) is rare, particularly in metastatic patients. We describe a patient with RAI refractory DTC who developed TED after RAI therapy and anlotinib therapy.

#### **Description of the Case**

A 66-year-old female underwent three times of surgeries for papillary thyroid cancer and lymph node metastasis in 1996, 2011, and 2016 respectively, followed by two RAI therapies of 150 mCi. From August 2017 to June 2022, her suppressed thyroglobulin (Tg) level gradually grew from 0.96 to 248 ng/mL while the Tg antibody was negative. Additionally, her thyrotrophin receptor antibody (TRAb) level increased from negative to 33.43 (<2.5) IU/L. She then started anlotinib therapy for multiple unresectable cervical metastatic lymph nodes and lung metastases. She achieved partial response 6 weeks after anlotinib but soon began to complain of diplopia, periorbital edema, and proptosis. Her Tg level declined to 42.1 ng/mL, whereas TRAb stayed at 34.5 IU/L. Orbital magnetic resonance imaging and ophthalmologic examinations confirmed the diagnosis of TED. Considering the presence of multiple metastases, she received retrobulbar injections of triamcinolone under anlotinib instead of i.v. glucocorticoids. After 8 injections (20 mg per side q.m.), her symptoms were significantly improved, and TRAb dropped remarkably to 5.44 IU/L, therefore she ceased the monthly injections. By March 2024, she had sustained remission, with a Tg level of 5.68 ng/mL and TRAb of 3.07 IU/L.

#### **Discussion**

The inducement of TED after RAI therapy is regarded as thyroid antigen leakage caused by radiation injury. In our patient, TED symptoms occurred shortly after the initiation of anlotinib therapy, which may be further triggered by tumor destruction. While localized glucocorticoid therapy eased the symptoms, continuous

anlotinib therapy maintained the tumor burden at a relatively low level and led to the steady reduction of TRAb. In such case, a potent anticancer therapy is the key to treating both TED and disease progression.

### Poster 0435

*Thyroid Cancer, Clinical, Poster*

#### **Thyroid-Stimulating Hormone Suppression for Low-Risk Differentiated Thyroid Cancer: A Large-Scale Real-World Study of Over 10,000 Patients**

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**Objective:** Over 500,000 new cases are diagnosed with differentiated thyroid cancer (DTC) globally per year, of whom the vast majority are low-risk based on the American Thyroid Association risk stratification. Although thyroid-stimulating hormone (TSH) suppression is traditionally recommended for all postoperative DTCs, its necessity remains highly controversial in low-risk patients. Since current guideline recommendations are still empirical, we aim to provide a direct, large-scale real-world evidence.

**Methods:** Low-risk DTC patients who underwent initial surgery from January 2007 to June 2022 in a Chinese tertiary hospital were enrolled. The mean TSH level was calculated based on stable serum TSH values during follow-up. Propensity score matching (PSM) was used to adjust for confounders among groups. Kaplan-Meier and log-rank analysis were used for survival comparison. Multivariate analyses were performed with Cox proportional hazards models to identify the prognostic factors.

**Results:** A total of 10,271 consecutive patients with low-risk DTC were included with a median follow-up of 61 months. Based on the mean TSH level, we classified patients into  $\leq 0.5$  (n=1,355, 13.2%), (0.5-1] (n=4,280, 41.7%), (1-2] (n=4,140, 39.3%), (2-3] (n=476, 4.6%) and  $> 3$  (n=127, 1.2%) mU/L groups. These five groups revealed significant differences in preoperative TSH level (P<0.001), gender (P<0.001), N stage (P=0.004), multifocality (P<0.001), type of thyroid surgery (P<0.001) and the proportion of very low-risk disease (P=0.032). After PSM, Kaplan-Meier and multivariate Cox analyses revealed no significant difference in recurrence-free survival (RFS, Log-rank P=0.253, Cox P=0.874), locoregional recurrence-free survival (LRRFS, P=0.358, Cox P=0.462), distant metastasis-free survival (DMFS, P=0.752, Cox P=0.638) among the five groups. Subgroup analyses showed that TSH level did not impact tumor recurrence regardless of age, tumor size, lymph node metastasis, multifocality, pathologic type, surgery type, biochemical evidence, or whether it was very low-risk.

**Conclusion:** Deliberate TSH suppression may be exempted for low-risk DTC, as it confers no prognostic benefit, but may bring secondary complications. Maintaining a TSH level within the normal range is safe for these patients.

### Poster 0436

*Thyroid Cancer, Clinical, Poster*

#### **Hemithyroidectomy versus Total Thyroidectomy for Sporadic Medullary Thyroid Cancer: A Chinese Nationwide Multicenter Large-Scale Retrospective Study**

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**Objective:** Medullary thyroid cancer (MTC) is a rare thyroid neuroendocrine neoplasm, of which 70-80% are sporadic (sMTC). Total thyroidectomy (TT) is regarded to be mandatory for all sMTCs in current guidelines, although recently growing advocacy has been raised for reducing the extent of surgery. However, data are very scarce to compare hemithyroidectomy (HT) and TT due to the rarity of this disease. We aim to assemble the largest MTC cohort to date and address this important clinical controversy.

**Methods:** This is a Chinese nationwide multicenter study enrolling MTC patients from 18 referral centers. **All patients underwent genetic testing.** We comprehensively evaluated the safety of HT in sMTC from five aspects: (1) prevalence of occult bilateral foci; (2) prevalence of contralateral lobe recurrence during follow-up; (3) biochemical response; (4) structural recurrence-free survival (SRFS); and (5) overall survival (OS).

**Results:** 1018 MTC patients were enrolled with a median follow-up of 71 months, of whom 830 were genetically confirmed as sMTC (648 initially-treated, 182 re-operated). Of the 648 initially-treated sMTCs, HT was done in 232 patients (35.8%) with earlier AJCC staging (P<0.001) than those undergoing TT. In the TT group, bilateral foci were found in 34 patients (8.2%), but only 10 (2.4%) were sonographically occult, of whom only three (0.72%) had a maximal tumor  $\leq 2$ cm. For all initially-treated and re-operated patients whose initial surgery was HT, only 1.5% (5/329) had recurrence in the preserved lobe, of whom only one (0.3%) had a maximal tumor  $\leq 2$ cm. After propensity score matching, we found there was no significant difference in OS (Log-rank: P=0.370; Cox regression: P=0.340), SRFS (Log-rank: P=0.946; Cox regression: P=0.191) and biochemical response (Chi-square: P=0.819; Logistic regression: P=0.253) between the two groups. Subgroup analyses showed that HT still conferred comparable structural and biochemical outcomes with TT in small ( $\leq 2$ cm) sMTCs with high-risk factors including high preoperative calcitonin level, multifocal disease, lymph node metastases, *RET*<sup>M918T</sup> mutation and desmoplasia.

**Conclusion:** TT is not the best care for all sMTCs. For small unilateral sMTCs, HT is a safe and adequate alternative standard surgery that does not compromise prognosis while avoiding TT-related additional complications.

### Poster 0437

*Thyroid Cancer, Clinical, Poster*

#### **Heterogeneity of genetic characteristics in metastatic thyroid cancer**

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**Objective:** Differences in genetic characteristics are a crucial factor leading to heterogeneity in thyroid cancer, and with the advent of targeted therapy, the genetic heterogeneity has become a focus of clinical attention. This study aimed to explore the molecular heterogeneity of patients with thyroid cancer by comparing the genetic information across multiple samples.

**Methods:** Patients who underwent next-generation sequencing of a customized 26-gene panel (ThyroLead) with multiple samples of non-medullary thyroid cancer were retrospectively included. The concordances of sequencing results, including overall, paired

primary and metastatic lesions, and early- and late-stage samples were assessed using jaccard similarity index (JSI).

**Results:** A total of 203 samples from 91 patients were collected. The overall concordance rate is 57.1%. The concordance rate between paired primary and metastatic samples is 68.5%, and the corresponding data are higher than 85% for the recurrent genetic alterations; 71.2% of patients had at least one sample detected clinically actionable alteration, with a concordance rate of 87.7%. The consistency of synchronous samples is slightly higher than that of metachronous samples, with JSI values of  $0.73 \pm 0.37$  and  $0.64 \pm 0.43$ , respectively. In patients with discordant sequencing results, metastatic lesions and late-stage samples are more likely to detect late-hit events such as *TERT* promoter and *TP53* mutations. In terms of the relationship between genetic and clinical characteristics, male, elderly patients and those with distant metastasis are prone to detect late-hit events; *PIK3CA* mutations are more common in poorly differentiated thyroid cancer; *BRAF* and late-hit events are associated with metachronous distant metastasis; patients with *RAS* mutations are more likely to be involved in multiple-organ metastases.

**Conclusion:** Recurrent genetic alterations are highly concordant across multiple samples and are acceptable in clinical applications. For patients with genetic heterogeneity, it is necessary to be alert to dynamic changes of tumor aggressiveness and clinical progress, real-time genetic information should be used to guide clinical diagnosis and treatment when it allowed.

#### Poster 0438

*Thyroid Cancer, Clinical, Poster*

##### Prognosis and Risk Factors in Patients With Distant Metastatic Differentiated Thyroid Cancer

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**Objective:** Patients with distant metastatic differentiated thyroid cancer (DM-DTC) have notably diverse prognoses, identifying the prognostic factors will provide information for more precise management.

**Methods:** The demographic, clinicopathological, and genetic characteristics of DM-DTC patients were retrospectively included to analyze the correlation between each factor and overall survival, as well as radioactive iodine refractoriness (RAIR). Cox regression analysis is used to analyze the risk factors of RAIR after introducing the index of time to RAIR from DM (TTR).

**Results:** A total of 310 patients with DM-DTC were included, and 14 died at the end of follow-up. The 10-year survival rates from diagnosed as DTC, DM, and RAIR were 87.5%, 67.6%, and 35.0%, respectively. Compared to patients in survival group within 10 years from DM, patients in dead group exhibited a higher age at diagnosis ( $48.6 \pm 9.7$  years vs.  $33.1 \pm 13.5$  years,  $P=0.001$ ), a higher proportion of distant metastases beyond lung and bone (75.0% vs. 8.0%,  $P<0.001$ ), a higher proportion of RAIR (100.0% vs. 68.0%,  $P=0.036$ ), a shorter median TTR (129.5 months vs. 13.0 months,  $P=0.029$ ), and a higher prevalence of late-hit events (75.0% vs. 32.0%,  $P=0.032$ ), especially *TERT* promoter mutations (66.7% vs. 16.0%,  $P=0.007$ ). Univariate Cox regression analysis showed that age at diagnosis, histopathology, DM sites, DM synchronicity, RAI uptake patterns, *BRAF*, *TERT* promoter, *RET* fusions, genetic subtypes, early events classifications, late-hit events, and number of genetic alterations were all associated with the cumulative risk of RAIR. Multivariate analysis further suggests that poorly differentiated thyroid cancer

(HR=2.21; 95%CI: 1.03-4.74;  $P=0.041$ ), metachronous DM (HR=1.97; 95%CI: 1.45-2.67;  $P<0.001$ ), initially non-RAI-avid pattern (HR=7.07; 95%CI: 5.10-9.81;  $P<0.001$ ), and *BRAF*<sup>V600E</sup>-like genetic subtypes (HR=2.44; 95%CI: 1.60-3.73;  $P<0.001$ ) were independent risk factors for RAIR.

**Conclusion:** RAIR, TTR, late events, older age, distant metastases beyond lung and bone are associated with the survival of patients with DM-DTC. Histopathology, DM synchronicity, RAI uptake patterns, and genetic characteristics are independent predictors of RAIR. Incorporating genetic features can contribute to more precise prognostic stratification and management for patients with DM-DTC.

#### Poster 0439

*Thyroid Imaging, Clinical, Poster*

##### Evaluating the Completeness of Thyroid Nodule Ultrasounds Reporting Using Natural Language Processing

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**Objective:** Evaluation of thyroid nodule features via ultrasound is pivotal in patient care. This study assessed the completeness of ultrasound reporting on thyroid nodule features, utilizing a newly developed natural language processing (NLP) pipeline.

**Methods:** Retrospective evaluation of patients undergoing thyroid ultrasound at the University of Florida between 2013 and 2020. A recently developed high-performance NLP pipeline, was deployed to identify thyroid nodules and their characteristics on thyroid ultrasound reports: size, composition, echogenicity, shape, margins, echogenic foci and cervical lymph nodes.

Employing a rule-based approach, the information extracted by the NLP was utilized to categorize thyroid ultrasound reports as complete if all six aforementioned features of interest and lymph nodes were reported. Only nodules with a reported size measuring > 1 cm were included. A subgroup analysis of thyroid nodule ultrasound reporting completeness was conducted per year (ACR TIRADS implemented in 2017 in our practice) and for those > 2 cm (clinical relevance).

**Results:** Out of 8855 thyroid ultrasound reports examined, 5792 reported at least one thyroid nodule measuring > 1 cm. The total number of nodules was 9108 nodules across these reports. At the nodule level, the reporting of features was: 71% included composition, 50% echogenicity, 25% shape, 35% margins and 40% echogenic foci. Cervical lymph nodes were described in 67% of reports.

At the nodule level, 2084 out of 9108 nodules > 1 cm (22%) were considered complete and 827 out of 4312 nodules > 2 cm (19%) across the study period. There was an increasing proportion of completeness in thyroid nodule ultrasound reporting. This ranged from 0% in the years 2013 to 2017, 16% in 2018, 65% in 2019, and 73% in 2020 for nodules > 1 cm.

**Conclusion:** There was variability in the frequency of reported thyroid features that influence decision-making, with shape being less commonly reported. There was an increasing trend in the

completeness of thyroid nodule ultrasound reporting features following the implementation of ACR-TIRADS, reaching completeness for 7 out of 10 nodules after three years. The use of NLP holds promise for enabling low-cost and timely evaluation of thyroid ultrasound report completeness in practice.

#### Poster 0440

*Thyroid Imaging, Clinical,*

##### **Diagnostic Performance of AI Model for Thyroid Nodules with Initially Nondiagnostic Cytologic Results:**

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**Objective:** Artificial intelligence (AI) model for thyroid ultrasonography (US) seems to be a promising diagnostic tool for patients with thyroid nodules. Prior studies have shown high diagnostic performance of AI models for predicting malignant thyroid nodules. However, studies on the role of AI model for thyroid nodules with initially nondiagnostic cytologic results are presently lacking. This study aimed to evaluate the diagnostic performance of AI model in thyroid nodules with nondiagnostic results at previous fine-needle aspiration (FNA).

**Methods:** Between January 2019 and September 2023, 13,164 nodules underwent US-guided FNA at our institution. Among them, 413 nodules from 409 patients (121 men, 288 women) with a mean age of 51.3 years (age range, 18–81 years) with nondiagnostic results at previous FNA were reviewed retrospectively. AI-Thyroid, a deep learning model for identifying malignant thyroid nodules, was tested online (<http://us.cdss.co.kr/>). Model performance was compared against blinded expert radiologist performance using Thyroid Imaging Reporting and Data System (TIRADS) interpretation. Sonographic characteristics associated with false positive diagnosis were analyzed.

**Results:** A total of 413 thyroid nodules were analyzed, 102 (24.7%) comprising malignant nodules. Using AI-Thyroid, 318 nodules (77.0%, 318 of 413) had accurate diagnoses with high negative predictive value (92.9%, 234 of 252). The area under the receiver operative curve (AUROC), sensitivity, and specificity were 0.845, 82.4% (84 of 102), and 75.2% (234 of 311), respectively. The AUROC value was significantly higher for the AI-Thyroid, compared to the TIRADS-based classification (0.845 vs. 0.623,  $p < 0.001$ ). False positive diagnoses were significantly associated with presence of macrocalcifications and TIRADS category 4 and 5 (all  $p < 0.001$ , respectively).

**Conclusion:** AI-Thyroid demonstrates high rates of accurate diagnoses with high negative predictive value in patients for whom previous FNA results were nondiagnostic, thereby reducing the need for unnecessary diagnostic surgery or repetitive FNAs.

#### Poster 0441

*Thyroid Imaging, Clinical, Poster*

##### **A randomized controlled trial comparing non-selective vs selective cytology using EU-TIRADS - the Ultracyst study**

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**Objective:** Cervical ultrasound is the first line radiologic modality in the diagnostic work-up of thyroid nodules. During the last 15 years several ultrasound risk stratification systems have been developed. Both retrospective and prospective studies have demonstrated

the performance of these systems. This multicenter regional study aims to investigate the safety of using selective cytology using EU-TIRADS.

**Material and Methods:** This was a regional, multi-center (four units), interventional prospective randomized unblinded trial comparing selective and non-selective FNA of thyroid nodules in a thyroid cancer diagnostic programme in Western Sweden. Patients were randomized to either selective cytology according to EU-TIRADS criteria or non-selective cytology. All nodules were evaluated using the EU-TIRADS risk stratification system. Primary outcome was the frequency of Bethesda IV-VI and the secondary outcome was rate of malignancy.

**Results:** Some 195 patients were included, 93 in the non-selective group and 102 in the selective group. The frequency of nodules with category Bethesda IV-VI was higher in the selective group (8% versus 4%,  $p=0.006$ ). The rate of malignancy was similar in both groups (6% in the selective group versus 5% in the non-selective group).

**Conclusion:** This randomized controlled trial supports the use of EU-TIRADS as a means to correctly select neoplastic nodules for FNAC without missing thyroid cancer. However, the rate of patients where FNAC can be safely omitted using EU-TIRADS may have been exaggerated, indicating a need for further refinement of risk stratification systems for thyroid cancer diagnostics.

#### Poster 0442

*Thyroid Imaging, Clinical, Poster*

##### **The Role of Microvascular Patterns Combined with Greyscale Ultrasound in Diagnosis and Recommending Fine-Needle Aspiration Biopsy of Thyroid Nodules**

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**Objective** To explore the value of microvascular patterns on Superb Microvascular Imaging (SMI) combined with greyscale ultrasound in differentiating benign and malignant thyroid nodules and recommending Fine-Needle Aspiration Biopsy (FNAB).

**Methods** Adult patients with thyroid nodules in our center from May 2023 to February 2024 were prospectively recruited. The greyscale features of thyroid nodules were evaluated according to the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) and the American Thyroid Association Risk Stratification System (ATA RSS). The microvascular patterns on SMI were used to adjust the category of nodules. The diagnostic performance and FNAB recommendation of microvascular patterns combined with greyscale ultrasound were compared with greyscale ultrasound alone.

**Results** A total of 253 thyroid nodules (136 malignant nodules, 117 benign nodules) in 203 patients were included. The malignant microvascular patterns including the crab claw-like pattern and the root hair-like pattern were an independent risk factor for malignant thyroid nodule (odds ratio 62.71, 95% CI 16.33-240.84). The areas under the receiver operator characteristic curve (AUC) of the microvascular patterns combined with the ACR TI-RADS and the ATA RSS in differentiating benign and malignant thyroid nodules were higher than that of the ACR TI-RADS (0.883 vs 0.811,  $P<0.0001$ ) and the ATA RSS (0.891 vs 0.825,  $P=0.0001$ ) alone. Compared with the ACR TI-RADS and the ATA RSS alone, the microvascular patterns combined with the ACR TI-RADS and the ATA RSS reduced the unnecessary FNAB rate by 5.48% and 2.61% respectively.

**Conclusion** The microvascular patterns combined with greyscale ultrasound could enhance the diagnosis validity and reduce the unnecessary FNAB rate of the ACR TI-RADS and the ATA RSS for thyroid nodules.

#### Poster 0443

*Thyroid Imaging, Clinical, Poster*

##### **Predicting retreatment after radiofrequency of benign thyroid nodules: pre-treatment nodular growth rate and viable volume at 6 months follow-up are the most accurate factors**

Gilles RUSS\*, Adrien Ben Hamou, Sylvain Poiree, Jean-Guillaume Marchand, Camille Buffet, La Pitie-Salpetriere Hospital, France

**Objective:** Radiofrequency ablation (RF) is an alternative to surgery for the treatment of symptomatic benign thyroid nodules. However, the long-term efficacy of RF is a prerequisite for its acceptance. The literature shows a recurrence rate of approximately 20% at 5 years, but data on retreatment are scarce. Thus, the aim of our study was to determine the predictive factors for the risk of retreatment in the following 5 years.

**Materials and Methods:** A retrospective study of 145 nodules in 145 patients treated with RF between 2018 and 2023 was performed, comparing two groups: retreated and non-retreated nodules, and searching for retreatment criteria. Retreatment criteria included persistence/recurrence of symptoms and/or nodule regrowth >50%. Eleven pre-treatment, treatment and post-treatment variables were subjected to univariate, multivariate and ROC curve analysis.

**Results:** Retreatment was performed in 51 patients compared to 94 patients treated once during the same period. Median follow-up was 55 months. Variables were separated in 3 groups: pre- and post-treatment ones, for a total of 12. Six factors were identified as associated with retreatment by univariate analysis: initial volume, growth rate, delivered energy, volume reduction ratio, ablation ratio and viable volume. ROC curve analysis showed that viable volume measured six months after RF was the most significant criteria (AUC: 0.808), followed by post-treatment total volume (AUC: 0.802) and growth rate (0.750; cut-off 3.7 mm/year). Retreatment rates were 2%, 9% and 66% for viable volumes  $\leq 1$  cm<sup>3</sup>, between 1 and 5 cm<sup>3</sup> and > 5 cm<sup>3</sup>, respectively. Graphs and abacus were designed to give a direct indication of the risk of a second treatment at 5 years according to growth rate and viable volume.

**Discussion/Conclusion:** Pre-treatment measurement of nodular growth rate and of viable volume 6 months after RF of benign thyroid nodules are simple and effective criterion for predicting the risk of retreatment. Selecting nodules with a less than 2.4 mm growth rate per year and aiming for a post-treatment viable volume of less than 2 ml may help reducing the risk of retreatment to less than 10%.

#### Poster 0444

*Thyroid Imaging, Clinical, Poster*

##### **Cracking thyroid: report of the first case following radiofrequency ablation of a microcarcinoma**

Gilles RUSS\*, Adrien Ben Hamou, Sylvain Poiree, Jean-Guillaume Marchand, Camille Buffet, La Pitie-Salpetriere Hospital, France

**Introduction:** acute transient thyroid swelling, also named "cracking thyroid" is an extremely rare complication of fine-needle aspiration biopsy (FNAB). To our knowledge, this is the first report of a case following radiofrequency ablation of a microcarcinoma.

**Description of the case:** 52-year-old journalist, previously operated on for pT1aN0 microcarcinoma of the left lobe, with post-operative dysphonia. Diagnosis of a Bethesda 6 cytology proven new microcarcinoma in the right lobe 2 years after first operation. Patient wishes to minimize risk of voice surgery and try to maintain normal thyroid function. After local anaesthesia and hydrodissection, a 7mm active tip 18G RF electrode was inserted into the thyroid microcarcinoma under US guidance with no particular difficulties. The power was 30W and 2224J were deposited. An ablation volume of 785 mm<sup>3</sup> was achieved. The electrode was withdrawn. Immediately afterwards, the patient began to complain of moderate pain in the right cervical region. US examination allowed for the diagnosis of a cracking thyroid: postprocedural US showed an enlarged lobe with heterogeneous echotexture showing black lines corresponding to the cracks. Gentle manual pressure was applied for 10 minutes, which partially relieved the symptoms. Paracetamol was prescribed and advice to apply ice to the neck was given and the patient was completely pain free 3 days later. US follow-up at 3 months showed restitution ad integrum of normal thyroid parenchyma.

**Discussion:** acute transient thyroid swelling is an extremely rare complication of FNAB. Only 15 cases have been reported in 11 published articles so far in 2023. The mean time for a diffuse thyroid swelling to occur after FNAB is very short, thought to be around 10 min. Oedema along thyroid septa is thought to be associated with the lines. Being aware of the appearance may avoid unnecessary interventions and anxiety as the complication is self limiting and heals spontaneously. However, one case with Airway obstruction requiring tracheal intubation has been described. Thus, excluding airway obstruction and hemorrhage is essential. To our knowledge, this is the first reported case after thyroid RF ablation. Operators performing this treatment should be aware of its existence and management.

#### Poster 0445

*Thyroid Imaging, Clinical, Poster*

##### **Deciphering the Role of Pre-Ablation Diagnostic I-123 Iodine Scans in Patients with Differentiated Thyroid Cancer**

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**Objectives:** Traditionally, diagnostic Planar 123-Iodine scans (Dx 123-I scans) have been used in guiding Radioactive Iodine (RAI) therapy, providing valuable information on disease localization and metastatic spread. However, questions have arisen regarding their impact on treatment decisions. Allegheny Health Network routinely uses Dx 123-I scans before ablation therapy. Our study aims to assess the utility of Dx 123-I scans for risk stratification and RAI administration decisions in post-thyroidectomy patients with differentiated thyroid cancer (DTC).

**Methods:** A retrospective chart review was conducted in patients (>18 years old) diagnosed with DTC, post total/near total thyroidectomy and were sent for evaluation of RAI therapy at Allegheny General Hospital. Three blinded endocrinologists assessed risk stratification and determined whether to administer RAI and its dosage without viewing the Dx 123-I scans, actual RAI dose and post-therapy RAI scan. They used clinical and histopathology data including demographics, details of the surgery, tumor histopathology, TNM classification etc to decide on an empiric dose of RAI in those patients who may benefit from treatment based on recent ATA guidelines. The treatment decision were compared with the actual treatment decisions that utilized Dx 123-I scan data.

**Results:** Among 165 of 180 patients meeting inclusion criteria: 122 (73.9%) received RAI and 43 (26.1%) did not. The RAI doses for the 122 patients were distributed as follows 30 mCi for 46 (37.7%), 75 mCi for 26 (21.3%), 100 mCi for 37(30.3%), 125 mCi for 3 (2.5%), 150 mCi for 9 (7.4%) and 200 mCi for 1(0.8%). Endocrinologist interpretation classified 90(54.3%) patients as low-risk, 61 (37.2%) patients as intermediate-risk, and 14 (8.5%) high-risk patients. Notably, in 8 (4.8%) patients, the endocrinologist's decision whether to treat with RAI and the dose differed from the actual treatment that had utilized Dx 123-I scan data.

**Discussion:** In very few cases (<5%), endocrinologists' decisions on RAI treatment and dosage post-thyroid surgery differed from actual treatment based on Dx 123-I scans, resulting in minor management alterations. Therefore, routine scan use may not justify cost-effectiveness. Advanced risk stratification methods like high-quality neck ultrasounds and prognostic markers offer promising alternatives, potentially reducing dependency on diagnostic scans.

#### Poster 0446

*Disorders of Thyroid Function, Case Study, Poster*

##### **Pembrolizumab Watch: Spotting Early Red Flags**

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**Introduction:** Pembrolizumab is an immune checkpoint inhibitor that blocks the interaction between programmed death receptors and their ligands, enhancing T-cell-mediated antitumor immunity. However, through T-cell-mediated destruction, it carries a risk for several endocrinopathies, including thyroid dysfunction, diabetes mellitus, primary adrenal insufficiency, and hypophysitis, which can be fatal if left untreated.

**Description:** A 52-year-old woman with a past medical history of Graves' disease, migraines, and grade 3 triple-negative invasive ductal breast carcinoma. She recently began pembrolizumab-based chemotherapy, precipitating the onset of nonspecific symptoms within two weeks, including fatigue, constipation, rash, and depression. Laboratory findings confirmed hypothyroidism with TSH of 46.7 mIU/L (0.4-4.0 mIU/L), T3 of 32 ng/dL (80-200 ng/dL), T4 of 0.33 ng/dl (0.70-1.90ng/dL) and Thyroid Microsomal Abs 110 IU/ml (<40 IU/mL) prompting levothyroxine initiation. After her symptoms improved, pembrolizumab was resumed, and her levothyroxine dose was adjusted. Twelve weeks later, she underwent a mastectomy and experienced a recurrence of fatigue and depression accompanied by the onset of arthralgias, myalgia, weakness, and low blood pressure. Further evaluation was consistent with secondary adrenal insufficiency with AM cortisol of 0.2 mcg/dL (6-18.4 mcg/dL), ACTH of 5 pg/mL (10-48 pg/mL), and negative 21- Hydroxylase antibodies. She received a short course of methylprednisolone followed by ongoing maintenance with physiological doses of hydrocortisone. Further evaluation for hypophysitis, including FSH, LH, IGF-1, estradiol, and pituitary imaging, was recommended.

**Discussion:** The case of pembrolizumab triggering thyroiditis and possible hypophysitis emphasizes the importance of vigilant physician monitoring of endocrinopathies, especially in patients with

thyroid dysfunction and adrenal insufficiency. Given the distinct management required for Graves' disease and Hashimoto's thyroiditis, it is imperative to establish baseline TFT values and conduct follow-up assessments every 4-6 weeks. Symptoms may manifest as early as two weeks into treatment, necessitating earlier screening if clinically indicated. While routine monitoring for adrenal and reproductive hormones is not a standard, a comprehensive approach to symptom assessment and patient education is crucial. Nonspecific manifestations like fatigue should not be dismissed as chemotherapy-related, and further evaluation by an endocrinologist could be necessary to prevent life-threatening conditions such as myxedema coma, acute adrenal crisis, or diabetic ketoacidosis.

#### Poster 0447

*Thyroid Cancer, Clinical, Poster*

##### **Brain Metastases from Differentiated Thyroid Cancer in the Era of Targeted Therapies: A Multi-Center Retrospective Cohort**

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**Background:** With the emergence of tyrosine kinase inhibitors (TKIs) and targeted therapies for differentiated thyroid cancer (DTC), survival has improved even in the presence of metastatic disease. Although brain metastases (BM) originating from DTC are rare, they significantly reduce survival.

**Methods:** A retrospective review was conducted on the medical records of patients diagnosed with DTC and BM. Data on patient and disease characteristics, histopathological features, administered treatments, and outcomes were recorded. Kaplan-Meier survival estimates were utilized to assess the impact of various variables on survival.

**Results:** A total of 22 patients with BM from DTC were identified in the databases of Tel Aviv Sourasky Medical Center and Rabin Medical Center between 1985-2023. Among these patients, 14 (64%) had papillary thyroid carcinoma, 5 had follicular carcinoma, 2 had poorly differentiated carcinoma, and 1 had Hurtle cell thyroid carcinoma. All patients exhibited previous or synchronous distant metastases other than BM. The average interval between the diagnosis of DTC and BM was 9.2 years (range 0 – 32.8 years). Neurosurgery was performed on 8 patients, 14 received stereotactic radiosurgery (SRS), and 6 were treated with whole-brain radiotherapy. The overall median survival after a BM diagnosis was 17.13 months. Patients who had received TKIs or targeted systemic therapies before BM diagnosis had a better median survival (27.3 months vs. 9.4 months, P = 0.035). The site of BM (intracranial vs. extra-axial) or treatment with SRS did not impact survival, while patients who were not amenable to neurosurgery had worse survival (10 months vs. 72 months, P = 0.03).

**Conclusions:** Brain metastases from DTC are rare but are associated with a poor prognosis. TKIs and targeted systemic therapies seem to improve outcomes, even in the context of BM.