Who's Going to Manage the Thyroid Cancer?
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CD133 Expression in Medullary Thyroid Cancer Cells Identifies Patients with Poor Prognosis.
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CONTEXT: The identification of markers able to determine medullary thyroid cancer (MTC) patients at high-risk of disease progression is critical to improve their clinical management and outcome. Previous studies have suggested that expression of the stem cell marker CD133 is associated with MTC aggressiveness.

OBJECTIVE: To evaluate CD133 impact on disease progression in MTC and explore the regulatory mechanisms leading to the upregulation of this protein in aggressive tumors.

PATIENTS: We compiled a series of 74 MTCs with associated clinical data and characterized them for mutations in RET and RAS proto-oncogenes, presumed to be related with disease clinical behavior.

RESULTS: We found that CD133 immunohistochemical expression was associated with adverse clinicopathological features and predicted a reduction in time to disease progression even when only RET-mutated cases were considered in the analysis (log-rank test P < 0.003). Univariate analysis for progression-free survival revealed CD133 expression and presence of tumor emboli in peritumoral blood vessels as the most significant prognostic covariates among others such as age, gender, and prognostic stage. Multivariate analysis identified both variables as independent factors of poor prognosis (hazard ratio = 16.6 and 2; P = 0.001 and 0.010, respectively). Finally, we defined hsa-miR-30a-5p, a miRNA downregulated in aggressive MTCs, as a CD133 expression regulator. Ectopic expression of hsa-miR-30a-5p in MZ-CRC-1 (RETM918T) cells significantly reduced CD133 mRNA expression.

CONCLUSIONS: Our results suggest that CD133 expression may be a useful tool to identify MTC patients with poor prognosis, who may benefit from a more extensive primary surgical management and follow-up.

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Distant Metastasis in Pediatric and Adolescent Differentiated Thyroid Cancer: Clinical Outcomes and Risk Factor Analyses.
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CONTEXT: The specific characteristics of pediatric and adolescent differentiated thyroid cancer (DTC) is the more frequent occurrence of distant metastasis (DM) compared with adult DTC.

OBJECTIVE: To investigate the clinical outcomes of DM in this population and analyze risk factors related to DM.

DESIGN, SETTING, AND PARTICIPANTS: Medical records of 171 patients with DTC < 19 years old, who underwent initial surgery between 1979 and 2014 were retrospectively reviewed.

MAIN OUTCOME MEASURE: Clinical responses to radioiodine (RAI) therapy evaluated by the American Thyroid Association (ATA) guidelines for adult DTC and Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Risk factors related to distant-metastasis-free survival (DMFS).

RESULTS: DM was observed in 29 patients, and all were lung metastases. The pattern of lung metastasis was classified into 3 categories: macronodular, micronodular, and no apparent nodule (detected only by RAI scintigraphy). Patients with excellent responses according to the ATA guideline criteria or complete remission of the RECIST criteria were most frequently observed in those with no apparent nodule. Significant factors related to DMFS were sex, clinical lymph node metastasis (LNM), extrathyroidal extension, and number of LNM. Subjects were divided into 3 groups according to the number of risk factors: low risk (no risk factors); intermediate risk (1 risk factor); and high risk (≥2 risk factors). Twenty-year DMFS rates in the low-, intermediate-, and high-risk groups were 99.0%, 71.7%, and 28.6%, respectively.

CONCLUSION: To achieve the full efficacy of RAI therapy, early diagnosis of DM before apparent metastases appear is desirable. The selective approach would be preferable for pediatric and adolescent DTC.

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The Clinicopathological Results of Thyroid Cancer With BRAFV600E Mutation in the Young Population of Fukushima.

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BACKGROUND: Thyroid ultrasound screening for children aged 0 to 18 years was performed in Fukushima following the accident at the Fukushima Daiichi Nuclear Power Plant. As a result, many thyroid cancer cases were detected. To explore the carcinogenic mechanisms of these cancers, we analyzed their clinicopathological and genetic features.

METHODS: We analyzed 138 cases (52 males and 86 females) who had undergone surgery between 2013 and 2016 at Fukushima Medical University Hospital. Postoperative pathological diagnosis revealed 136 (98.6%) cases of papillary thyroid cancer (PTC).

RESULTS: The BRAFV600E mutation was detected using direct DNA sequencing in 96 (69.6%) of the thyroid cancer cases. In addition, oncogenic rearrangements were detected in 23 cases (16.7%). Regarding chromosomal rearrangements, 8 (5.8%) RET/PTC1, 6 (4.3%) ETV6(ex4)/NTRK3, 2 (1.4%) STRN/ALK, and 1 each of RET/PTC3, AFAP1L2/RET, PPFIBP/RET, KIAA1217/RET, ΔRFP/RET, SQSTM1/NTRK3 and TPR/NTRK1 were detected. Tumor size was smaller in the BRAFV600E mutation cases (12.8 ± 6.8 mm) than in wild-type BRAF cases (20.9 ± 10.5 mm). In the BRAFV600E mutation cases, 83 (86.5%) showed lymph node metastasis, whereas 26 (61.9%) of the wild-type BRAF cases showed lymph node metastasis.

CONCLUSIONS: The BRAFV600E mutation was mainly detected in residents of Fukushima, which was different from post-Chernobyl PTC cases with RET/PTC3 rearrangement. PTC with the BRAFV600E mutation was smaller but was shown in the high rate of central cervical lymph node metastasis than the wild-type BRAF PTC in the young population of Fukushima.

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BACKGROUND: Surgical removal of hyperfunctional parathyroid gland is the definitive treatment for primary hyperparathyroidism (pHPT). Postoperative follow-up shows variability in persistent/recurrent disease rate throughout different centers.

OBJECTIVE: To evaluate the incidence of redo surgery after targeted parathyroidectomy for pHPT.

METHODS: We performed a nationwide retrospective cohort study on the "Programme de Medicalisation des Systemes d'Information," the French administrative database that collects information on all healthcare facilities' discharges. We extracted data from 2009 to 2018 for all patients who underwent parathyroidectomy for pHPT between January 2011 to December 2016. The primary outcome was the reoperation rate within 2 years since first surgery. Patients who had a first attempt of surgery within the previous 24 months, familial hyperparathyroidism, multiglandular disease, and renal failure were excluded. Results were adjusted according to sex and the Elixhauser Comorbidity Index. Operative volume thresholds to define high-volume centers were achieved by the Chi-Squared Automatic Interaction Detector method.

RESULTS: In the study period, 13,247 patients (median age 63, F/M=3.6) had a focused parathyroidectomy by open (88.7%) or endoscopic approach. Need of remedial surgery was 2.8% at 2 years. In multivariate analysis, factors predicting redo surgery were: cardiac history (P=0.008), obesity (P=0.048), endoscopic approach (P=0.005), and low-volume center (P<0.001). We evaluated that an annual caseload of 31 parathyroidectomies was the best threshold to discriminate high-volume centers and carries the lowest morbidity/failure rate. CONCLUSION: Although focused parathyroidectomy represents a standardized operation, cure rate is strongly associated with annual hospital caseload, type of procedure (endoscopic), and patients' features (obesity, cardiac history). Patients with risk factors for redo surgery should be considered for an open surgery in a high-volume center.

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In the past decade, the field of cancer immunotherapy has been revolutionized by immune checkpoint blockade (ICB) technologies. Success across a broad spectrum of cancers has led to a paradigm shift in therapy for patients with advanced cancer. Early data are now accumulating in progressive thyroid cancers treated with single-agent ICB therapies and combination approaches that incorporate ICB technologies. This Review discusses our current knowledge of the immune response in thyroid cancers, the latest and ongoing immune-based approaches, and the future of immunotherapies in thyroid cancer. Physiologically relevant preclinical mouse models and human correlative research studies will inform development of the next stage of immune-based therapies for patients with advanced thyroid cancer.

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This Comment article provides a behind-the-scenes perspective and update of our 2016 Review, which discussed possible factors contributing to thyroid cancer incidence trends worldwide. We also highlight promising research directions that are improving the understanding of thyroid cancer aetiology.

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WeChat App in the follow up of thyroid cancer patients after thyroidectomy
during the COVID-19 pandemic.

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Quality of Life in Patients With Hypoparathyroidism After Treatment for Thyroid Cancer.
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PURPOSE: Surgical complications such as hypoparathyroidism (HPT) or vocal cord palsy are seldom assessed when the quality of life (QOL) in thyroid cancer
patients is investigated. The aim of this study was to measure the QOL difference in thyroid cancer survivors with and without HPT.

METHODS: Participants for this analysis were enrolled in 13 countries from a study that pilot-tested a thyroid cancer-specific QOL instrument. They were included if they had been diagnosed with thyroid cancer at least 9 months previously. QOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) and some items on HPT symptoms (e.g., tingling in fingers or toes). HPT status and other clinical data were extracted from the patients' medical charts. Comparisons of QOL domains between patients with and without HPT were performed using Mann-Whitney U test. The occurrence of HPT-related symptoms was compared using chi-square tests. Multiple ordinal regression analysis was performed to evaluate factors that might affect QOL.

RESULTS: Eighty-nine patients participated in this study, 17 of whom were considered to have HPT. Patients in the HPT group reported significantly reduced QOL in 9 of the 15 scales of the EORTC QLQ-C30 compared to patients without HPT. Regression analysis showed that HPT was independently negatively associated with various scales of the QLQ-C30. Both groups showed a high prevalence of typical HPT symptoms.

CONCLUSION: Thyroid cancer patients with HPT report significantly impaired QOL compared to thyroid cancer survivors without HPT. The assessment of HPT should be considered when measuring QOL in thyroid cancer patients.

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Ultrasonography for the Prediction of High-Volume Lymph Node Metastases in Papillary Thyroid Carcinoma: Should Surgeons Believe Ultrasound Results?

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BACKGROUND: Lymph node metastasis (LNM) often occurs in papillary thyroid carcinoma (PTC); the efficacy of ultrasound for predicting high-volume lymph node metastases (LNMs) in patients with PTC remains unexplored.

METHODS: The medical records of 2073 consecutive PTC patients were reviewed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to evaluate the efficacy of ultrasound. Risk factors for LNM/high-volume LNMs and lymph node involvement on ultrasound (usLNM) were identified by univariate and multivariate analyses.

RESULTS: Of all the patients, 936 (45.2%) patients had LNMs, and 254 (12.3%) patients had high-volume LNMs. The sensitivity of ultrasound for detecting LNM/high-volume LNMs was 27.9% and 63.8%, respectively; the specificity was 93.1% and 90.3%, respectively. The NPV for ultrasound in detecting high-volume LNMs was 94.7%. In multivariate analysis, male sex (OR = 2.108, p < 0.001), tumor diameter > 1.0 cm (OR = 2.304, p < 0.001) and usLNM (+) (OR = 12.553, p < 0.001) were independent clinical risk factors for high-volume LNMs. Tumor diameter > 1 cm (OR = 3.036, p < 0.001) and male sex (OR = 1.642, p < 0.001) were independent clinical risk factors for usLNM; a skilled sonographer (OR = 1.121, p = 0.358) was not significantly associated with usLNM.

CONCLUSIONS: Lymph node involvement found by ultrasound has great predictive value for high-volume LNMs; the NPV is very high for patients without lymph node involvement on ultrasound. The ultrasound results do not appear to be influenced by the experience of the sonographer.

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Inhibition of BRAF Sensitizes Thyroid Carcinoma to Immunotherapy by Enhancing TsMHC-II-mediated Immune Recognition.

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CONTEXT: Multiple mechanisms play roles in restricting the ability of T-cells to recognize and eliminate tumor cells.

OBJECTIVE: To identify immune escape mechanisms involved in papillary thyroid carcinoma (PTC) to optimize immunotherapy.

SETTING AND DESIGN: iTRAQ analysis was conducted to identify proteins differentially expressed in PTC samples with or without BRAFV600E mutation. Molecular mechanisms regulating tumor cell evasion were investigated by in vitro modulations of BRAF/MAPK and related pathways. The pathological significance of identified tumor-specific major histocompatibility complex class II (tsMHCII) molecules in mediating tumor cell immune escape and targeted immune therapy was further evaluated in a transgenic mouse model of spontaneous thyroid cancer.

RESULTS: Proteomic analysis showed that tsMHCII level was significantly lower in BRAFV600E-associated PTCs and negatively correlated with BRAF mutation status. Constitutive activation of BRAF decreased tsMHCII surface expression on tumor cells, which inhibited activation of CD4+ T-cells and led to immune escape. Pathway analysis indicated that the TGF-β1/SMAD3-mediated repression of tsMHCII, which could be reversed by BRAF inhibition (BRAFi). Targeting this pathway with a combined therapy of BRAF inhibitor PLX4032 and anti-PD-1 antibody efficiently blocked tumor growth by increasing CD4+ T-cell infiltration in a transgenic PTC mouse model.

CONCLUSIONS: Our results suggest that BRAFV600E mutation in PTC impairs the expression of tsMHCII through the TGF-β1/SMAD3 pathway to enhance immune escape. Combined treatment with PLX4032 and anti-PD-1 antibody promotes recognition and elimination of PTC by the immune system in a pre-clinical mouse model, and therefore offers an effective therapeutic strategy for patients with advanced PTC.

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METHOD: Data on patients with stage pT1-3 papillary thyroid cancer, who underwent TT with or without CLND between 1 July 2004 and 30 June 2014 were retrieved from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery. Drug use was ascertained by cross-linking with the Swedish Prescribed Drug Register. Permanent hypoparathyroidism was defined as treatment with active D vitamin or oral calcium drugs for more than 6 months after surgery. Data were analysed separately for all patients and those who underwent TT + CLND. Univariable and multivariable logistic regression analyses were done, yielding odds ratios (ORs) with 95 per cent confidence intervals.

RESULTS: A total of 722 patients were included in the study. Permanent hypoparathyroidism was more common in the TT + CLND group than the TT group: 30 of 265 patients (6·6 per cent) versus six of 457 (2·3 per cent) (P = 0·011). In multivariable logistic regression analysis, CLND was a risk factor for permanent hypoparathyroidism (OR 3·74, 95 per cent c.i. 1·46 to 9·59, based on use of combined therapy 6 months after surgery). In patients who had TT + CLND, node negativity was associated with a risk of permanent hypoparathyroidism (OR 3·08, 1·31 to 7·25).

CONCLUSION: CLND is an independent risk factor for permanent hypoparathyroidism. Node negativity is associated with a higher risk of permanent hypoparathyroidism.

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The Oncocytic Variant of Poorly Differentiated Thyroid Carcinoma Shows a Specific Immune-Related Gene Expression Profile.
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BACKGROUND: Poorly differentiated thyroid cancer (PDTC) is a rare, follicular cell-derived neoplasm with an unfavorable prognosis. The oncocytic variant of PDTC may be associated with even more adverse outcome than classical PDTC cases,
but its specific molecular features are largely unknown. Our aim was to explore
the immune-related gene expression profile of oncocytic and classical PDTC, in
correlation with clinical and pathological characteristics (including programmed
death ligand 1 [PD-L1] expression) and outcome, and in comparison with a control
group of well-differentiated follicular carcinomas (WDFCs), including
conventional follicular carcinomas (FTCs) and Hürthle cell carcinomas (HCCs).

METHODS: A retrospective series of 48 PDTCs and 24 WDFCs was analyzed by means
of NanoString technology employing the nCounter PanCancer Immune Profiling
panel. Gene expression data were validated using quantitative real-time
polymerase chain reaction.

RESULTS: Oncocytic PDTCs showed a specific immune-related gene expression
profile, with higher expression of LAIR2, CD274, DEFB1, IRAK1, CAMP, LCN2, LY96,
and APOE, and lower expression of NOD1, as compared to conventional PDTCs. This
molecular signature was associated with increased intratumoral lymphocytic
infiltration, PD-L1 expression, and adverse outcome. Three of these genes,
CD274, DEFB1, and IRAK1, as well as PD-L1 expression, were also the hallmarks of
HCCs as compared to FTCs. By contrast, the panel of genes differentially
regulated in PDTCs as compared to WDFCs was unrelated to the oncocytic
phenotype.

CONCLUSIONS: Our results revealed a distinctive immune-related gene expression
profile of oncocytic PDTC and confirmed a more aggressive outcome in this cancer
subtype. These findings may provide guidance when exploring novel
immunotherapeutic options for oncocytic PDTC patients.

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European multicentre study on outcome of surgery for sporadic primary
hyperparathyroidism.
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BACKGROUND: International multicentre outcome studies of surgery for primary
hyperparathyroidism (pHPT), especially for rate of conversion to bilateral neck
surgery and persistent hypercalcaemia, are scarce.

METHODS: Eurocrine® is a European database for endocrine surgery. Data are
entered according to predefined data fields. Outcomes for patients who underwent
first surgery for sporadic pHPT were analysed. Multivariable analysis was
performed to identify risk factors for adverse outcome using Cox regression with
constant follow-up.

RESULTS: A total of 5861 patients were registered between 2015 and 2018.
Preoperative localization procedures were used in most patients, with moderate sensitivity. Intraoperative parathyroid hormone (ioPTH) measurement was used in three-quarters of patients. Bilateral surgery was performed in 1574 patients (26·9 per cent). Among 4683 patients (79·7 per cent) for whom unilateral or focused operation was planned, the procedure was converted to bilateral surgery in 396 (8·5 per cent). The risk of conversion decreased with the use of ioPTH monitoring (relative risk (RR) 0·77). Persistent hypercalcaemia was registered in 253 patients (4·3 per cent), and was less likely with the use of two (RR 0·55) or three (RR 0·44) localization procedures. In patients with a concordant localized single lesion, the rate of persistent hypercalcaemia was 2·5 per cent. The risk of persistent hypercalcaemia decreased with the use of ioPTH measurement, but was increased in patients with negative localization procedures and conversion to bilateral surgery.

CONCLUSION: The use of ioPTH measurement decreased the risk of conversion and persistent hypercalcaemia. The use of two or three localization procedures decreased the risk of persistent hypercalcaemia; in patients with a concordant single lesion, the risk of persistent hypercalcaemia was low.

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Erratum for

The article "Clinical Assessment of Pediatric Patients with Differentiated Thyroid Carcinoma: A 30-Year Experience at a Single Institution", written by Kim et al., was originally published electronically on the publisher's internet portal (currently SpringerLink) on May 21, 2020, with open access. With the authors' decision to step back from Open Choice, the copyright of the article changed on September 14, 2020 to © Société Internationale de Chirurgie 2020 and the article is forthwith distributed under the terms of copyright. The original article has been corrected.
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The treatment of patients with progressive metastatic follicular cell-derived and medullary thyroid cancers that do not respond to standard therapeutic modalities presents a therapeutic challenge. As a deeper understanding of the molecular drivers for these tumors has occurred and more potent and specific compounds are developed, the number of FDA-approved treatments for thyroid cancer has expanded. In addition, with the advent of disease-agnostic target-directed FDA approvals an ever-broadening number of therapeutic options are available for clinicians and patients. However, to date, complete remissions are rare, the average durations of response are relatively modest, and toxicities are common. These factors accentuate the need for further understanding of the mechanisms of resistance that result in treatment failures, the development of biomarkers that can improve patient selection for treatment earlier the disease process, and the continued need for new therapeutic strategies. In this New Horizons brief review, recent approvals relevant to thyroid cancer will be discussed along with selected new potential avenues that might be exploited for future therapies.

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hyperparathyroidism (PHPT).

METHODS: We performed a retrospective cohort study of patients undergoing parathyroidectomy for PHPT at a single center (1997-2015). Patients were classified by self-identified race, as African-American or White. The primary outcome was disease severity at referral. The secondary outcome was completeness of preoperative evaluation. Operative success and surgical cure were evaluated.

RESULTS: A total of 2392 patients were included. The majority of patients (87.6%) were White. African-American patients had higher rates of comorbid disease as well as higher preoperative calcium (10.9 vs. 10.8 mg/dl, p < 0.001) and PTH levels (122 vs. 97 pg/ml, p < 0.001). White patients were more likely to have history of bone loss documented by DXA and nephrolithiasis. African-American patients had lower rates of complete preoperative evaluation including DXA scan. Operatively, African-American patients had larger glands by size (1.7 vs. 1.5 cm, p < 0.001) and mass (573 vs. 364 mg, p < 0.001). We observed similar operative success (98.9 vs. 98.0%, p = 0.355) and cure rates (98.3 vs. 97.0%, p = 0.756).

CONCLUSIONS: At the time of surgical referral, African-American patients with PHPT have more biochemically severe disease and higher rates of incomplete evaluation. Operative success and cure rates are comparable.

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CONTEXT: US papillary thyroid carcinoma (PTC) incidence recently declined for the first time in decades, for reasons that remain unclear.
OBJECTIVE: This work aims to evaluate PTC incidence trends, including by histologic subtype and size, and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).
RESULTS: During 2000 to 2015, PTC incidence increased an average 7.3% per year, (95% CI, 6.9% to 7.8%) during 2000 to 2009, and 3.7% per year (95% CI, 0.2% to 7.3%) during 2009 to 2012, before stabilizing in 2012 to 2015 (annual percentage change [APC] = 1.4% per year, 95% CI, -1.8% to 4.7%) and declining in 2015 to 2017 (APC = -4.6% per year, 95% CI, -7.6% to -1.4%). The recent declines were observed for all sizes of PTC at diagnosis. Incidence of follicular variant of
PTC (FVPTC) sharply declined in 2015 to 2017, overall (APC = -21.1% per year; 95% CI, -26.5% to -15.2%) and for all tumor sizes. Observed increases in encapsulated papillary carcinoma (classical PTC subtype) and NIFTP each accounted for 10% of the decline in FVPTC. Classical PTC incidence continuously increased (2000-2009, APC = 8.7% per year, 95% CI, 8.1% to 9.4%; 2009-2017, APC = 1.0% per year, 95% CI, 0.4% to 1.5%), overall and for all sizes except smaller than 1 cm, as did incidence of other PTC variants combined (2000-2017, APC = 5.9% per year, 95% CI, 4.0% to 7.9%).

CONCLUSION: The reasons underlying PTC incidence trends were multifactorial. Sharp declines in FVPTC incidence during 2015 to 2017 coincided with clinical practice and diagnostic coding changes, including reclassification of noninvasive encapsulated FVPTC from a malignant to in situ neoplasm (NIFTP). Observed increases in NIFTP accounted for 10% of the decline in FVPTC.

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Immune Co-inhibitory Receptors PD-1, CTLA-4, TIM-3, LAG-3 and TIGIT in Medullary Thyroid Cancers: A Large Cohort Study.
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CONTEXT: PD-1, CTLA-4, TIM-3, LAG-3 and TIGIT are considered as major immune co-inhibitory receptors (CIRs) and most promising immunotherapeutic targets in cancer treatment, but they are largely unexplored in medullary thyroid carcinoma (MTC).

OBJECTIVE: We aimed to provide first evidence regarding the expression profiles and clinical significance of CIRs in a large cohort of MTCs.

DESIGN AND PATIENTS: In total, 200 MTCs who received initial surgery in our hospital were included. Immunohistochemistry was performed to evaluate CIR expressions in tissue microarrays (TMA). Combined with the results of our previous PD-L1 study, clinicopathologic and prognostic correlations of these proteins were retrospectively analyzed.

RESULTS: TIM-3, PD-1, CTLA-4, LAG-3 and TIGIT positivity was detected in 96 (48.0%), 27 (13.5%), 25 (12.5%), 6 (3.0%) and 6 (3.0%) patients, respectively, in which TIM-3, PD-1 and CTLA-4 expressions were positively correlated. Both log-rank tests and multivariate Cox analyses indicated that TIM-3, CTLA-4 expression and PD-1/PD-L1 coexpression were associated with worse structural recurrence-free survival. In addition, among 20 patients who developed advanced
disease during follow-up, 12 (60%) showed TIM-3 positivity, wherein 6 cases also had concurrent moderate to strong PD-1, PD-L1 or CTLA-4 expression.

CONCLUSIONS: Using the currently largest TMA cohort of this rare cancer, we delineated the CIR expression profiles in MTC, and identified TIM-3, CTLA-4 expression and PD-1/PD-L1 coexpression as promising biomarkers for tumor recurrence. Furthermore, a subset of advanced MTCs are probably immunogenic, for whom single or combined immunotherapy including TIM-3, PD-1, PD-L1 or CTLA-4 blockade may be potential therapeutic approaches in the future.

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Pediatric Primary Hyperparathyroidism: Experience in a Tertiary Care Referral Center in a Developing Country Over Three Decades.
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BACKGROUND: There is limited experience in managing pediatric primary hyperparathyroidism (PHPT). The aim of this study was to analyze the clinical presentation and outcome of surgery in children with PHPT managed at a tertiary referral center.

METHODS: This retrospective study (September 1989-August 2019) consisted of 35 pediatric PHPT patients (<18 years) who underwent parathyroidectomy. Clinico-pathologic profile and outcome were noted.

RESULTS: The mean age of cohort was 15.2±2.9 years and girls outnumbered boys (M:F = 1:1.9). Familial and symptomatic disease was noted in 8.5 and 94.3% cases, respectively. Skeletal manifestations (83%) were the commonest followed by renal (29%). Fifty-four percent children had skeletal fractures, and 23% were bed-ridden. Among rare manifestations, hypercalcemic crisis, recurrent pancreatitis and stigmata of rickets were observed in 2.8, 11.4 and 14.2% children, respectively. Mean calcium concentration was 12.1 ± 2.0 mg/dl and PTH 91.8 ± 66.5 pmol/L. The sensitivity of preoperative imaging in parathyroid localization was 91.4%. Minimally invasive parathyroidectomy (MIP) was performed in 40% cases. Parathyroid adenoma was observed in 91.4% patients, whereas remaining had hyperplasia. Thirty-four percent suffered from Hungry bone syndrome in postoperative period. The cure rate following primary surgery was 97%. One child with persistent PHPT had successful re-operation. Median follow-up was 5 (1-17) years, and no recurrence or familial disease was revealed during this period.
CONCLUSION: Majority of pediatric patients present with symptomatic PHPT. Despite relatively high incidence of familial disease select pediatric patients can undergo successful MIP.

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Delta Neutrophil Index and Neutrophil-to-Lymphocyte Ratio in the Differentiation of Thyroid Malignancy and Nodular Goiter.
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BACKGROUND: It was aimed to evaluate the relationship between delta neutrophil index (DNI) and neutrophil-to-lymphocyte ratio (NLR) in the preoperative differentiation of nodular goiter and thyroid malignancy.

METHODS: Patients over the age of 18 who underwent thyroid surgery between November 2014 and November 2019 were evaluated in this retrospective cohort study. Patients were divided into two groups according to their pathology results: malignant (Group M) and benign (Group B) thyroid disorders. White blood cell (WBC) count, neutrophil count, lymphocyte count, IG count and DNI were measured using an automated hematological analyzer from blood samples obtained at the preoperative period and postoperative 6th month of the follow-up. Neutrophil-to-lymphocyte ratio (NLR) values were manually calculated. Numerical data are expressed as means ± standard deviations (minimum-maximum values) or medians (minimum-maximum values) according to the normal distribution. Categorical values are expressed as percentages (%).

RESULTS: A total of 243 patients (190 patients in Group B and 53 patients in Group M) who met the inclusion criteria were evaluated. The male/female ratio was 49/194. A statistically significant difference between Group M and Group B in terms of preoperative NLR, DNI and IG count was observed (p = 0.001, < 0.001 and < 0.001, respectively). No statistically significant difference was observed between the groups in terms of the control values performed in the postoperative period in terms of the NLR, DNI and IG count (p = 0.711, 0.333 and 0.714, respectively). A significant decrease was observed in the preoperative and postoperative DNIs, IG counts and NLRs in Group M (p = 0.009, < 0.001 and < 0.001, respectively). For the diagnosis of malignant thyroid diseases, the cut-off value of DNIs was ≥0.35%, and DNI sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 79.2%, 78.9%, 79.2% and 77.9%, respectively [area under the curve (AUC): 0.847; confidence interval [CI]: 0.784-0.911]. The cut-off value of the IG count was ≥25/mm3, and
its sensitivity, specificity, PPV and NPV were 83%, 72.1%, 83%, and 72.1%, respectively (AUC: 0.847; CI: 0.784-0.911).

CONCLUSION: DNI and IG counts are cheap and easily accessible tests that can be automatically calculated from automated systems without additional cost in differentiation of thyroid malignancies from benign disorders in the preoperative period.

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OBJECTIVE: The aim of this study was to determine physician-reported use of and barriers to active surveillance for thyroid cancer.

SUMMARY BACKGROUND DATA: It is not clear whether active surveillance for thyroid cancer is widely used.

METHODS: Surgeons and endocrinologists identified by thyroid cancer patients from the Surveillance, Epidemiology, and End Results (SEER) registries of Georgia and Los Angeles County were surveyed between 2018 and 2019. Multivariable weighted logistic regression analyses were conducted to determine physician acceptance and use of active surveillance.

RESULTS: Of the 654 eligible physicians identified, 448 responded to the survey (69% response rate). The majority (76%) believed that active surveillance was an appropriate management option, but only 44% used it in their practice. Characteristics of physicians who stated that active surveillance was appropriate management, but did not report using it included more years in practice (reference group <10 years in practice): 10 to 19 years [odds ratio, OR 0.50 [95% confidence interval, CI 0.28-0.92]; 20 to 29 years[OR 0.31 (95% CI 0.15-0.62)]; ≥30 years [OR 0.30 [95% CI 0.15-0.61]] and higher patient volume 11 to 30 patients per year [OR 0.39 (95% CI 0.21-0.70)] and >50 patients per year [OR 0.33 [95% CI 0.16-0.71]] compared to ≤10, with no significant difference in those seeing 31 to 50 patients. Physicians reported multiple barriers to implementing active surveillance including patient does not want (80.3%), loss to follow-up concern (78.4%), more patient worry (57.6%), and malpractice lawsuit concern (50.9%).

CONCLUSION AND RELEVANCE: Despite most physicians considering active surveillance to be appropriate management, more than half are not using it. Addressing existing barriers is key to improving uptake.
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Papillary Thyroid Carcinoma in Children: Clinicopathological Profile and Outcomes of Management.
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BACKGROUND: We aim to analyze the clinicopathological profile and outcomes of management for children with papillary thyroid carcinoma (PTC).
METHODS: Relevant clinical data of children ≤ 18 years of age managed for PTC between January 2006 and July 2018 as well as details of their follow-up till December 2019 were retrospectively collected and analyzed.
RESULTS: There were 82 children with PTC that were managed during the study period. At presentation, 39 (47.6%) had cervical lymphadenopathy, while 9 (11%) had systemic metastasis. Majority of patients 39 (47.6%) underwent total thyroidectomy with a selective neck dissection, while total thyroidectomy alone was performed in 26 (31.7%). Following surgery, hypocalcemia was seen in 39 (47.6%): 28 (34.1%) were temporary, while 11 (13.4%) were permanent.
Twenty-eight (34%) developed persistent disease after surgery and 131I therapy. Significant risk factors for persistence and metastatic disease were metastatic cervical lymph node at presentation (p = 0.002) and tumor size (p = 0.014), respectively. The mean duration of follow-up was 60.3 (range 12-150) months with a mean overall disease-free survival of 60 months (95% CI 57.11, 77.95).
CONCLUSION: Children with papillary thyroid cancers present with aggressive disease, 47.6% with cervical nodal metastasis and 11% with distant metastasis in this cohort. The rate of post-thyroidectomy hypocalcemia in this study is substantial, and efforts to reduce it are actively being pursued. The presence of metastatic cervical lymph node at presentation (p = 0.002) and tumor size (p = 0.014) were the only significant risk factors for persistent and metastatic disease, respectively, in this study.
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Complications after medullary thyroid carcinoma surgery: multicentre study of the SQRTPA and EUROCRINE® databases.
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BACKGROUND: Surgery is the curative therapy for patients with medullary thyroid carcinoma (MTC). In determining the extent of surgery, the risk of complications should be considered. The aim of this study was to assess procedure-specific outcomes and risk factors for complications after surgery for MTC.

METHODS: Patients who underwent thyroid surgery for MTC were identified in two European prospective quality databases. Hypoparathyroidism was defined by treatment with calcium/active vitamin D. Recurrent laryngeal nerve (RLN) palsy was diagnosed on laryngoscopy. Complications were considered at least transient if present at last follow-up. Risk factors for at-least transient hypoparathyroidism and RLN palsy were identified by logistic regression analysis.

RESULTS: A total of 650 patients underwent surgery in 69 centres at a median age of 56 years. Hypoparathyroidism, RLN palsy and bleeding requiring reoperation occurred in 170 (26·2 per cent), 62 (13·7 per cent) and 17 (2·6 per cent) respectively. Factors associated with hypoparathyroidism were central lymph node dissection (CLND) (odds ratio (OR) 2·20, 95 per cent c.i. 1·04 to 4·67), CLND plus unilateral lateral lymph node dissection (LLND) (OR 2·78, 1·20 to 6·43), CLND plus bilateral LLND (OR 2·83, 1·13 to 7·05) and four or more parathyroid glands observed (OR 4·18, 1·46 to 12·00). RLN palsy was associated with CLND plus LLND (OR 4·04, 1·12 to 14·58) and T4 tumours (OR 12·16, 4·46 to 33·18). After compartment-oriented lymph node dissection, N0 status was achieved in 248 of 537 patients (46·2 per cent).

CONCLUSION: Complications after surgery for MTC are procedure-specific and may relate to the unavoidable consequences of radical dissection needed in some patients.

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Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study.

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BACKGROUND: Ultrasound guided thermal ablation plays an important role in the management of thyroid disease. The objective of this study was to evaluate the feasibility, efficacy, and safety of thermal ablation for patients with solitary T1bN0M0 PTC who are ineligible for or unwilling to undergo surgery.

MATERIALS AND METHODS: Data pertaining to 172 patients (38 males and 134 females) who received thermal ablation therapy at 12 hospitals between April 2015 and March 2020 were retrospectively analyzed. The mean duration of follow-up was 24.9 ± 14.1 months (range, 12-60). The technical feasibility, technical success, efficacy, and safety of treatment were analyzed. Post-ablation tumor size at various time-points was compared with pre-ablation measurement.

RESULTS: All patients selected for thermal ablation received enlarged ablation according to contrast-enhanced ultrasound post-ablation. The maximum diameter and volume of ablation zone at 6, 12, 18, 24, 36, and 48 months post-ablation were significantly smaller than those recorded pre-ablation (P < 0.05 for all). At the most recent follow-up, 106 (61.6%) tumors had completely disappeared. The rate of lymph node metastasis (LNM) was 0.6% (1/172) and the incidence of new tumor was 1.2% (2/172). The overall complication rate was 5.2% (9/172) (major complications: 4.6% [8/172]; minor complications: 0.6% [1/172]). All major complications were relieved within four months post-ablation.

CONCLUSION: Thermal ablation may be a feasible, effective, and safe treatment option for patients with solitary T1bN0M0 PTC who are ineligible for or unwilling to undergo surgery. It may provide a novel treatment option for selected patients.

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Use of Preoperative Imaging in Primary Hyperparathyroidism.
CONTEXT: Preoperative imaging is performed routinely to guide surgical management in primary hyperparathyroidism, but the optimal imaging modalities are debated.

OBJECTIVE: Our objectives were to evaluate which imaging modalities are associated with improved cure rate and higher concordance rates with intraoperative findings. A secondary aim was to determine whether additive imaging is associated with higher cure rate.

DESIGN, SETTING, AND PATIENTS: This is a retrospective cohort review of 1,485 adult patients during a 14-year period (2004-2017) at an academic tertiary referral center that presented for initial parathyroidectomy for de novo primary hyperparathyroidism.

MAIN OUTCOME MEASURES: Surgical cure rate, concordance of imaging with operative findings, and imaging performance.

RESULTS: The overall cure rate was 94.1% (95% CI 0.93-0.95). Cure rate was significantly improved if sestamibi/SPECT was concordant with operative findings (95.9% vs. 92.5%, p = 0.010). Adding a third imaging modality did not improve cure rate (1 imaging type 91.8% vs. 2 imaging types 94.4% vs. 3 imaging types 87.2%, p = 0.59). Despite having a low number of cases (n=28), 4-D CT scan outperformed (higher sensitivity, specificity, PPV, NPV) all imaging modalities in multi-glandular disease and double adenomas, and sestamibi/SPECT in single adenomas.

CONCLUSIONS: Preoperative ultrasound combined with sestamibi/SPECT were associated with the highest cure and concordance rates. If pathology was not found on ultrasound and sestamibi/SPECT, additional imaging did not improve the cure rate or concordance. 4-D CT scan outperformed all imaging modalities in multiglandular disease and double adenomas, and sestamibi/SPECT in single adenomas, but these findings were underpowered.

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Most primary thyroid tumours are of epithelial origin. Primary thyroid mesenchymal tumours are rare but are being increasingly detected. A vast majority of thyroid mesenchymal tumours occur between the fourth and seventh decades of life, presenting as progressively enlarging thyroid nodules that often yield non-diagnostic results or spindle cells on fine needle aspiration biopsy. Surgery is the preferred mode of treatment, with adjuvant chemoradiotherapy used for malignant thyroid mesenchymal tumours. Benign thyroid mesenchymal tumours have excellent prognosis, whereas the outcome of malignant thyroid mesenchymal tumours is variable. Each thyroid mesenchymal tumour is characterised by its unique histopathology and immunohistochemistry. Because of the rarity and aggressive nature of malignant thyroid mesenchymal tumours, a multidisciplinary team-based approach should ideally be used in the management of these tumours. Comprehensive guidelines on the management of thyroid mesenchymal tumours are currently lacking. In this Review, we provide a detailed description of thyroid mesenchymal tumours, their clinical characteristics and tumour behaviour, and provide recommendations for the optimal management of these tumours.

**CSN5 promotes carcinogenesis of thyroid carcinoma cells through ANGPTL2.**


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COP9 signalosome subunit 5 (CSN5) plays a key role in carcinogenesis of multiple cancers, and contributes to stabilization of target proteins through deubiquitylation. However, the underlying role of CSN5 in thyroid carcinoma has not been reported. In this research, our data showed that CSN5 was overexpressed in thyroid carcinoma tissues compared with para-cancerous tissues. Furthermore, a series of gain/loss functional assays were performed to demonstrate the role of CSN5 in facilitating thyroid carcinoma cell proliferation and metastasis. Additionally, we found that there was a positive correlation between CSN5 and angiopoietin-like protein 2 (ANGPTL2) protein levels in thyroid carcinoma tissues and that CSN5 promoted thyroid carcinoma cell proliferation and metastasis through ANGPTL2. We also identified the underlying mechanism that CSN5 elevated ANGPTL2 protein level through directly binding it, and decreasing its ubiquitination and degradation. Overall, our results highlight the significance of CSN5 in promoting thyroid carcinoma carcinogenesis and implicate CSN5 as a promising candidate for thyroid carcinoma treatment.

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**Role of Age at Diagnosis in Defining Potential Familial Non-Medullary Thyroid Cancer in Kindreds with Only Two Affected Members.**

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CONTEXT: The definition of familial non medullary thyroid cancer (FNMT), as presence of the disease in two or more first degree relatives, is controversial due to the high probability to observe a sporadic association when only two members are affected.

OBJECTIVE: To evaluate the role of age at diagnosis in differentiating the true cases of FNMT.

DESIGN, SETTING, PARTICIPANTS, AND MAIN OUTCOME: From a group of 721 papillary thyroid cancer (PTC), 95 familial PTC (FPTC) patients with two first degree relatives, have been identified. They were split in two groups: Group 1 consisting of both the proband and the affected relative with age at diagnosis ≤ 45 years; Group 2 consisting of proband and/or affected family member with age at diagnosis >45 years. The clinical-pathological features and outcome of both FPTC groups were compared with 626 sporadic PTC patients (SPTC).

RESULTS: FPTC patients with age at diagnosis ≤ 45yrs, compared to the matched group of sporadic PTCs, had more frequently multifocal, bilateral and extrathyroidal extension of tumor and showed worse outcome. No differences were found between FPTC and SPTC patients with age >45yrs. At multivariate analysis, distant metastases, ATA risk and FPTC ≤ 45yrs were independent predictors of outcome.

CONCLUSIONS: Based on the observation that PTC is more aggressive when the diagnosis is made in two family members, both with age <45yrs, we suggest that definition of FPTC in kindreds with 2 affected members should take into account also the age at diagnosis, as key element of familial cancer.

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Letter to the Editor: (18)F-fluorocholine PET/CT in MEN1 Patients with Primary Hyperparathyroidism.
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