
Predictors of renal function and calcifications in primary hyperparathyroidism: A nested case-control study.
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Context: Some patients with primary hyperparathyroidism (PHPT) develop renal calcifications. Investigation of urinary and non-urinary risk factors are essential.

Objective: We aimed to study the prevalence and potential biochemical predictors of renal calcifications.

Design: Nested case-control study.

Settings: University Hospital.

Patients or Other Participants: We identified 792 patients with PHPT from 2005-2015. We used biochemical data to validate the diagnosis of PHPT.

Main Outcome Measures: The prevalence of renal calcifications defined as nephrolithiasis or nephrocalcinosis assessed by a routine CT-scan at the time of diagnosis.

Results: A total of 792 PHPT patients were identified among whom 617 patients (78%) had a CT-scan performed. We found a prevalence of renal calcifications of 23%, equally frequent between sexes. A total of 76 patients (12%) had nephrolithiasis and 75 patients (12%) had nephrocalcinosis where seven (1%) patients had both nephrolithiasis and nephrocalcinosis. Compared to patients without renal calcifications, patients with renal calcifications had significantly higher levels of ionized calcium, parathyroid hormone and 24h calcium excretion (pallxuniwbCb0.01). Patients with nephrocalcinosis had higher plasma levels of phosphate and a higher calcium-phosphate product compared to patients with nephrolithiasis, (pallxuniwbCb0.05). Impaired renal function (eGFR<60 ml/min) was observed in 12% of patients. However, no differences in renal function were observed between those with and without renal calcifications.

Conclusion: Renal calcifications are frequent in patients with PHPT and are associated with the severity of the disease. Impaired renal function is also common in PHPT, but renal function was not associated with renal calcifications.

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Letter to the Editor: "p.Val804Met, the most frequent pathogenic mutation in RET, confers a very low lifetime risk of medullary thyroid cancer".

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CORRIGENDUM FOR “DICER1 mutations are frequent in adolescent-onset papillary thyroid carcinoma”.
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Risk Factors for Cardiovascular Disease among Thyroid Cancer Survivors: Findings from the Utah Cancer Survivors Study.
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Context: Thyroid cancer survivors are at high risk to develop multiple cardiac and vascular conditions as consequence of cancer diagnosis and treatment; however, it is still unclear how baseline and prognostic factors, as well as cancer treatments, play a role in increasing cardiac and vascular disease risk among thyroid cancer survivors.

Objective: To investigate the association between potential risk factors, treatment effects, and cardiovascular disease (CVD) outcomes in thyroid cancer survivors.

Design, Setting, Patients: Primary thyroid cancer survivors, diagnosed between 1997-2012, (n=3,822) were identified using the statewide Utah Population Database. Medical records were utilized to ascertain information on risk factors
and CVD outcomes. Cox proportional hazards models were used to assess the risk of CVD with baseline demographics and clinical factors.

Results: Among thyroid cancer survivors, age and year at cancer diagnosis, cancer stage, sex, baseline BMI, baseline comorbidities, and thyroid-stimulating hormone (TSH) suppression therapy were significantly associated with CVD risk 1-5 years after cancer diagnosis. Patients who were male, overweight or obese, older at cancer diagnosis and diagnosed with cancer since 2005 had an increased risk of CVD compared to patients who were female, normal BMI, younger at cancer diagnosis and diagnosed with cancer between 1997-1999. Administration of TSH suppression therapy, distant metastases at cancer diagnosis, and higher Charlson Comorbidity Index (CCI) score were associated with an increased CVD risk among thyroid cancer survivors.

Conclusions: Our findings suggest that examining the impact of thyroid cancer diagnosis, cancer treatment, and demographic characteristics on the risk of CVD is critical.

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Comparison of 68Ga PET/CT to other imaging studies in Medullary Thyroid Cancer: superiority in detecting bone metastases.

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Objective: Evaluate the efficacy of 68Ga PET/CT in detecting MTC lesions and evaluate tumor expression of somatostatin receptors (SSTR) associating with 68Ga PET/CT findings.

Methods: Prospective study evaluating 30 MTC patients; Group 1 (N=16): Biochemical disease and Group 2 (N=14): Metastatic disease. Patients underwent 68Ga PET/CT, bone scan, neck CT and US, CT chest, CT/MRI abdomen, MRI spine. 68Ga PET/CT findings were analyzed by disease site as positive or negative and as concordant or discordant with conventional studies. Sensitivity and specificity were calculated using pathological, cytological analysis or unequivocal
identification by standard imaging studies. Immunohistochemical analysis of SSTRs were compared with 68Ga PET/CT findings.

Results: In both groups 68Ga PET/CT was inferior than currently used imaging studies except for bone scan. In group 2, 68Ga PET/CT sensitivities were 56%, 57% and 9% for detecting neck lymph nodes, lung and liver metastases and 100% for bone metastases, superior than bone scan (44%). Expression of SSTRs, observed in 44% of tumors, was not associated with 68Ga DOTATATE uptake.

Conclusions: 68Ga PET/CT does not provide optimal whole-body imaging as a single procedure in patients with MTC. However, is highly sensitive detecting bone lesions and could substitute bone scan and MRI.

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Methodology, criteria and characterization of patient-matched thyroid cell lines and patient-derived tumor xenografts.


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Objective: In order to investigate the molecular underpinnings of thyroid cancer, preclinical cell line models are crucial; however, ~40% of these have been proven to be either duplicates of existing thyroid lines or even non-thyroid derived lines or are not derived from human at all. Therefore, we set out to establish procedures and guidelines that should proactively avoid these problems, which facilitated the creation of criteria to make valid pre-clinical models for thyroid cancer research.

Design: Based upon our recommendations, we systematically characterized all new cell lines that we generated by a standardized approach that included (i) determination of human origin, (ii) exclusion of lymphoma, (iii) DNA fingerprinting and histological comparisons to establish linkage to presumed tissue of origin, (iv) examining thyroid differentiation by screening 2-3 thyroid markers, (v) examination of biological behavior (growth rate, tumorigenicity) and (vi) presence of common thyroid cancer genetic changes (TP53, BRAF, PTEN, PIK3CA, RAS, TERT promoter, RET/PTC, PAX8/PPARγ, NF1 and EIF1AX).

MC-Th-491, MC-Th-493, MC-Th-504, MC-Th-524, MC-Th-529, MC-Th-560, MC-Th-562) out of 67 attempts. All were successfully validated by our protocols.

Conclusions: This standardized approach for cell line and PDTX characterization should prevent (or detect) future cross-contamination and ensure that only valid preclinical models are used for thyroid cancer research.

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Preferred strategy for postsurgical thyroid ablation in low-risk thyroid cancer.

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Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial.

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BACKGROUND: In ESTIMABL1, a randomised phase 3 trial of radioactive iodine (131I) administration after complete surgical resection in patients with low-risk thyroid cancer, 92% of patients had complete thyroid ablation at 6-10 months, defined as a recombinant human thyroid-stimulating hormone (rhTSH)-stimulated serum thyroglobulin concentration of 1 ng/mL or less and normal findings on neck ultrasonography. Equivalence was shown between low-activity (1·1 GBq) and high-activity (3·7 GBq) radioactive iodine and also between the use of rhTSH injections and thyroid hormone withdrawal. Here, we report outcomes after 5 years of follow-up.

METHODS: This multicentre, randomised, open-label, equivalence trial was done at 24 centres in France. Between March 28, 2007, and Feb 25, 2010, we randomly assigned (1:1:1:1) adults with low-risk differentiated thyroid carcinoma who had undergone total thyroidectomy to one of four strategies, each combining one of two methods of thyrotropin stimulation (rhTSH or thyroid hormone withdrawal) and one of two radioactive iodine activities (1·1 GBq or 3·7 GBq). Randomisation was by computer-generated sequence, with variable block size. Follow-up consisted of a yearly serum thyroglobulin measurement on levothyroxine treatment. Measurement of rhTSH-stimulated thyroglobulin and neck ultrasonography were done at the discretion of the treating physician. No evidence of disease was defined as serum thyroglobulin of 1 ng/mL or less on levothyroxine treatment and normal results on neck ultrasonography, when performed. This study was registered with ClinicalTrials.gov, number NCT00435851.

FINDINGS: 726 patients (97% of the 752 patients originally randomised) were followed up. At a median follow-up since randomisation of 5·4 years (range 0·5-9·2), 715 (98%) had no evidence of disease. The other 11 had either structural disease (n=4), raised serum thyroglobulin concentration (n=5), or indeterminate findings on neck ultrasonography (n=2). At ablation, six of these patients had received 1·1 GBq radioactive iodine (five after rhTSH and one after withdrawal) and five had received 3·7 GBq (two after rhTSH and three after withdrawal). TSH-stimulated (either after rhTSH injections or thyroid hormone withdrawal according to the treatment group) thyroglobulin concentration measured at the time of ablation was prognostic for structural disease status at ablation, ablation status at 6-10 months, and the final outcome.

INTERPRETATION: Our findings suggest that disease recurrence was not related to the strategy used for ablation. These data validate the use of 1·1 GBq radioactive iodine after rhTSH for postoperative ablation in patients with low-risk thyroid cancer.


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XL184 is a small-molecule kinase inhibitor recently included in first-line systemic therapy for patients with advanced, progressive medullary thyroid cancer (MTC). EF24 is a curcumin analog with a high bioavailability, and ZSTK474 is an inhibitor of the phosphatidylinositol 3-kinase signaling pathway. We investigated the effect of these compounds, alone and in combination, in two rearranged during transfection (RET)-mutated TT and MZ-CRC-1 MTC cell lines and in six mostly RET wild-type human MTC primary cultures. Low IC50 values demonstrated the efficacy of the drugs, whereas the combination index revealed an important synergistic effect of combinations of XL184 + ZSTK474 and XL184 + EF24. Cell-cycle changes and the induction of apoptosis or necrosis were modulated by single compounds or combinations thereof. Both XL184 and EF24, alone or combined, were effective in reducing calcitonin secretion. Western blot and in-cell Western analysis showed that the compounds prompted a decrease in general reactivity to phosphorylated antibodies. Our data confirm XL184 alone as the reference drug for RET-mutated MTC, but we also demonstrated that EF24 alone is effective in inhibiting MTC cell viability. We tested the combinations XL184 + ZSTK474 and XL184 + EF24 too, finding that they act synergistically, irrespective of RET mutation status.

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Background: The American Joint Committee on Cancer (AJCC) removed microscopic extrathyroidal extension (ETE) from the 8th edition T staging for papillary thyroid cancer (PTC) based on increasing evidence that it is not an independent prognostic factor.

Objectives: We compared the prognostic performance of AJCC 7th (pT7) and 8th (pT8) edition T stage systems, particularly in patients ≥55 years old without macroscopic ETE or distant metastases in whom T classification affects AJCC Tumor Node Metastasis (TNM) stage.

Method: A retrospective analysis of disease-free survival (DFS) in 577 patients with PTC comparing pT8 vs pT7 using the Akaike information criterion (AIC),
Harrell's C-index, and Proportion of Variation Explained (PVE).

Results: Of 105 patients with AJCC7 T3 disease, 74 were down-staged. Overall, the prognostic performance of pT7 and pT8 was similar. However, in patients ≥55 years old without macroscopic ETE or distant metastases, pT8 was inferior to pT7 on the basis of higher AIC, lower C-index (0.67 vs 0.76), and lower PVE (30% vs 45%). In this subset, microscopic ETE was associated with multiple other adverse prognostic features and reduced DFS (hazard ratio, 2.8; 95% confidence interval, 1.5 to 5.2; P = 0.002), irrespective of tumor size.

Discussion: In our cohort, pT8 was inferior to pT7 in patients ≥55 years old without macroscopic ETE or distant metastases in whom T classification affects TNM stage. Microscopic ETE was strongly associated with other adverse prognostic factors and reduced DFS in this patient subgroup and may be an effective surrogate for disease biology in PTC, irrespective of whether it is an independent prognostic factor.

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Identification of Differential Transcriptional Patterns in Primary and Secondary Hyperparathyroidism.


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Context: Hyperparathyroidism is associated with hypercalcemia and the excess of parathyroid hormone secretion; however, the alterations in molecular pattern of functional genes during parathyroid tumorigenesis have not been unraveled. We aimed at establishing transcriptional patterns of normal and pathological parathyroid glands (PGs) in sporadic primary (HPT1) and secondary hyperparathyroidism (HPT2).

Objective: To evaluate dynamic alterations in molecular patterns as a function of the type of PG pathology, a comparative transcript analysis was conducted in subgroups of healthy samples, sporadic HPT1 adenoma and hyperplasia, and HPT2.
Design: Normal, adenomatous, HPT1, and HPT2 hyperplastic PG formalin-fixed paraffin-embedded samples were subjected to NanoString analysis. In silico microRNA (miRNA) analyses and messenger RNA-miRNA network in PG pathologies were conducted. Individual messenger RNA and miRNA levels were assessed in snap-frozen PG samples.

Results: The expression levels of c-MET, MYC, TIMP1, and clock genes NFIL3 and PER1 were significantly altered in HPT1 adenoma compared with normal PG tissue when assessed by NanoString and quantitative reverse transcription polymerase chain reaction. RET was affected in HPT1 hyperplasia, whereas CaSR and VDR transcripts were downregulated in HPT2 hyperplastic PG tissue. CDH1, c-MET, MYC, and CaSR were altered in adenoma compared with hyperplasia. Correlation analyses suggest that c-MET, MYC, and NFIL3 exhibit collective expression level changes associated with HPT1 adenoma development. miRNAs, predicted in silico to target these genes, did not exhibit a clear tendency upon experimental validation.

Conclusions: The presented gene expression analysis provides a differential molecular characterization of PG adenoma and hyperplasia pathologies, advancing our understanding of their etiology.

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Benign Thyroid Diseases and Risk of Thyroid Cancer: A Nationwide Cohort Study.
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Context: Thyroid nodules, adenomas, and goiter have consistently been associated with thyroid cancer risk. Few studies have assessed whether thyroid dysfunction and thyroid autoimmunity influence this risk.

Objective: To examine thyroid cancer risk after diagnoses of a wide range of benign thyroid conditions.

Design: Hospital and cancer registry linkage cohort study for the years 1978 to 2013.

Setting: Nationwide (Denmark).

Participants: Patients diagnosed with hyperthyroidism (n = 85,169), hypothyroidism (n = 63,143), thyroiditis (n = 12,532), nontoxic nodular goiter (n = 65,782), simple goiter (n = 11,582), other/unspecified goiter (n = 21,953), or adenoma (n = 6,481) among 8,258,807 residents of Denmark during the study period.

Main Outcome Measures: We computed standardized incidence ratios (SIRs) for differentiated thyroid cancer, excluding the first 12 months of follow-up after benign thyroid disease diagnosis.

Results: SIRs were significantly elevated for all benign thyroid diseases apart from hypothyroidism. SIRs were higher for men than women and in the earlier follow-up periods. Elevated SIRs were observed for localized and regional/distant...
thyroid cancer. After excluding the first 10 years of follow-up, hyperthyroidism
[n = 27 thyroid cancer cases; SIR = 2.00; 95% confidence interval (CI): 1.32 to
2.92], nontoxic nodular goiter (n = 83; SIR = 4.91; 95% CI: 3.91 to 6.09), simple
goiter (n = 8; SIR = 4.33; 95% CI: 1.87 to 8.53), other/unspecified goiter (n =
20; SIR = 3.94; 95% CI: 2.40 to 6.08), and adenoma (n = 9; SIR = 6.02; 95% CI:
2.76 to 11.5) remained positively associated with thyroid cancer risk.
Conclusions: We found an unexpected increased risk of differentiated thyroid
cancer, including regional/distant disease, following diagnosis of
hyperthyroidism and thyroiditis that could not be solely attributed to increased
medical surveillance. Hypothyroidism was less clearly associated with thyroid
cancer risk.
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Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features
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Comment on
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Yonsei Experience of 5000 Gasless Transaxillary Robotic Thyroidectomies: Reply.
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Comment on
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BACKGROUND: Lymph node metastasis is important when evaluating the prognosis of patients with differentiated thyroid cancer (DTC). However, the current N-staging system cannot fully reflect the clinical significance of cervical lymph node metastasis in DTC. In this study, we employed Surveillance, Epidemiology, and End Results (SEER)-registered DTC cases with lymph node metastasis to determine whether the positive lymph node number (PLNN) could be used to improve stratification of patients in terms of survival.

METHODS: We used the SEER dataset to identify all DTC patients with at least one positive cervical lymph node who were examined between 1988 and 2008. Multivariable modeling was used to compare cancer-specific survival (CSS) and overall survival (OS) and to calculate different PLNN cutoff points.

RESULTS: In total, 14,359 pN + DTC patients identified in the SEER were included. In multivariate Cox regression analysis, the PLNN was significantly associated with both CSS and OS, whereas neither the lymph node ratio (LNR) nor the (numbers) of lymph nodes examined (LNE) were so associated. The highest C-index value (0.933) and the lowest AIC value (9362.687) obtained indicated that the PLNN better predicted the CSS of DTC than did the LNR or LNE. As the p values for both CSS and OS were minimized, and as the PLNN performed best when cases were grouped, PLNN cutoff points of 10 and 3/10 efficiently stratified DTC patients into two and three levels, respectively. Based on the 3/10 trichotomy, the benefits of radioactive iodine (RAI) treatment were evaluated for each group. Such treatment afforded about a 10% survival benefit in patients with more than 10 lymph node metastases.

CONCLUSIONS: Compared with the LNR and LNE under different statistical models, PLNN was superior in terms of DTC staging. A cutoff point of 3/10 was optimal for stratifying patients according to prognosis and was of clinical significance in terms of RAI treatment selection.

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Impact of "Tailored" Parathyroidectomy for Treatment of Primary Hyperparathyroidism in Patients with Multiple Endocrine Neoplasia Type 1.

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BACKGROUND: Whether total parathyroidectomy (TPTX) or subtotal parathyroidectomy (SPTX) should be performed for primary hyperparathyroidism (PHPT) in patients with multiple endocrine neoplasia type 1 (MEN1) is controversial. At our institution, the parathyroidectomy strategy is based on the number of enlarged intraoperative parathyroid glands. We retrospectively analyzed our parathyroidectomy procedures.

METHODS: Data of PHPT treatment in patients with MEN1 who underwent parathyroidectomy from 1982 to 2012 at our department were retrospectively collected. The data were grouped according to the surgical procedure: TPTX, SPTX, and less than SPTX (LPTX). TPTX or SPTX was selected based on the preoperative examination findings and number of enlarged intraoperative parathyroid glands. The outcomes were the disease-free survival (DFS) rate and postoperative calcium replacement rate based on Kaplan-Meier analysis for each type of surgical procedure.

RESULTS: Forty-five patients were analyzed. The overall 5- and 10-year DFS was 91.7 and 55.8%, respectively. The 5- and 10-year DFS in each subgroup was 100.0 and 85.7% in the TPTX group, 89.4 and 57.3% in the SPTX group, and 91.6 and 57.3% in the LPTX group, respectively. The postoperative calcium replacement rate at 1 and 12 months was 91.7 and 58.3% in the TPTX group, 21.1 and 7.0% in the SPTX group, and 30.0 and 0.0% in the LPTX group, respectively.

CONCLUSIONS: Although LPTX was not satisfactory as a standard procedure, both SPTX and TPTX are effective treatment methods for PHPT in patients with MEN1. The parathyroidectomy strategy should be based on intraoperative evaluation of the parathyroid glands.

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Yonsei Experience of 5000 Gasless Transaxillary Robotic Thyroidectomies.

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Comment in
Outcome of Thyroid Carcinoma Showing Thymus-Like Differentiation in Patients Undergoing Radical Resection.
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BACKGROUND: Carcinoma showing thymus-like differentiation (CASTLE) is a rare malignant tumor of the thyroid. It is difficult to diagnose, and there is no universally recognized therapeutic regimen. This study aims to define the clinicopathological features and discuss the optimal management of CASTLE.
METHODS: We retrospectively analyzed six patients with CASTLE who accepted surgery at the First Hospital of China Medical University between January 2010 and December 2015.
RESULTS: The six patients (three women and three men) had median age of 53 years (range 47-61 years). All patients presented with a slow-growing, painless neck mass; three patients also had hoarseness. All tumors were located in middle-lower or lower lobe, and two tumors extended to the substernal region. All patients underwent radical surgery without postoperative radiotherapy or chemotherapy. Five patients had extrathyroidal extension and two had lymph node metastasis. All six tumors were positive for CD5 and negative for thyroglobulin (Tg) and thyroid transcription factor (TTF)-1. Median follow-up was 32 months (range 23-81 months). Lateral cervical lymph node metastasis occurred in one patient at 26 months after initial treatment.
CONCLUSIONS: CASTLE is a rare, aggressive malignant tumor of the thyroid. Ultrasound, computed tomography, and fine-needle aspiration biopsy may not be sufficient to establish the diagnosis preoperatively; pathological examination and immunohistochemistry, particularly positive CD5 staining, are necessary to establish the diagnosis. Patients with CASTLE can yield a favorable outcome after radical surgery.
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Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): Did We Trade Six for a Half a Dozen?
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Follicular thyroid cancer and Hürthle cell carcinoma: challenges in diagnosis, treatment, and clinical management.
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Follicular thyroid cancer is the second most common differentiated thyroid cancer histological type and has been overshadowed by its more common counterpart-papillary thyroid cancer-despite its unique biological behaviour and less favourable outcomes. In this Review, we comprehensively review the literature on follicular thyroid cancer to provide an evidence-based guide to the management of these tumours, to highlight the lack of evidence behind guideline recommendations, and to identify changes and challenges over the past decades in diagnosis, prognosis, and treatment. We highlight that correct identification of cancer in indeterminate cytological samples is challenging and ultrasonographic features can be misleading. Despite certain unique aspects of follicular thyroid cancer presentation and prognosis, no specific recommendations exist for follicular thyroid cancer and Hürthle cell carcinoma in evidence-based guidelines. Efforts should be made to stimulate additional research in this field.

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