The Impact of Surgical Strategy on the Consequences of Secondary Hyperparathyroidism.
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Clinical Status and Treatment of Liver Metastasis of Differentiated Thyroid Cancer Using Tyrosine Kinase Inhibitors.
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BACKGROUND: Treatment of patients with liver metastasis of differentiated thyroid carcinoma (DTC) has not been sufficiently defined, because liver metastasis of DTC has been described mostly as case reports. Additionally, such patients are considered end-of-treatment responders. A relatively new approach using tyrosine kinase inhibitors (TKIs) may provide opportunities to manage systemic metastasis. This study aims to define the clinical features of DTC patients with liver metastasis and evaluate the benefits of TKIs.
METHODS: We retrospectively analyzed clinical features of 29 patients (mean age 67.8 years) diagnosed with liver metastasis of DTC at our institution between January 1981 and May 2017.
RESULTS: All patients had distant metastasis at other organ sites upon diagnosis of liver metastasis; 41% of them developed new metastasis afterward. Management after diagnosis of liver metastasis comprised palliative care (48%), radioactive iodine therapy (28%), and TKI therapy (24%). The median survival after diagnosis of liver metastasis was only 4.8 months. Survival rates were significantly better in patients with performance statuses between 0 and 2 on the Eastern Cooperative Oncology Group scale at diagnosis of liver metastasis (n = 22, 76%) treated with TKI compared to those who were not (P = 0.017; log-rank test; hazard ratio 0.19). One-year survival rates were 71.4 and 26.7% for patients treated with or without TKI, respectively.
CONCLUSIONS: Patients with liver metastasis had poor clinical prognosis. When other distant metastases existed at diagnosis of liver metastasis, TKI therapy was considered an effective therapeutic option for patients with liver metastasis of DTC.
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The Updated AJCC/TNM Staging System for Papillary Thyroid Cancer (8th Edition): From the Perspective of Genomic Analysis.
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BACKGROUND: Recently, the American Joint Committee on Cancer published the 8th edition of its Cancer Staging Manual with major changes regarding the staging of thyroid cancer, including the raising of the age cutoff from 45 to 55 years. Using the clinical and genetic data of 505 papillary thyroid cancer (PTC) cases, we aimed to compare overall survival (OS) and recurrence-free survival (RFS) with different age cutoff values, and also investigate the efficacy of the new staging system on a genomic level.
METHODS: We downloaded gene expression data, somatic mutation profile, copy number alteration data and clinical data of 505 PTC patients from The Cancer Genome Atlas data portal. We used multiple statistical analysis and multiplatform genomic analysis to evaluate the efficacy of the 8th edition.
RESULTS: When using 55 years as the cutoff value for analyzing RFS, the Kaplan-Meier plot showed a significant p value but not when using 45 years (p = 0.006 vs. p = 0.493), but both cutoff values were significant when analyzing OS (p = 1.1 × 10-9 with age 55 vs. p = 4.4 × 10-5 with age 45). When looking at stage-dependent survival, both the 7th and 8th edition had significant p values (p = 0.048 vs. p = 3.1 × 10-9 in RFS and p = 5.9 × 10-10 vs. p = 2.2 × 10-10 in OS). Multiplatform genomic analysis showed patients ≥55 years had 103 differently expressed genes when compared with other age groups. Signaling pathway analysis revealed that patients ≥55 years had altered pathways associated with aggressiveness of thyroid cancer.
CONCLUSION: In conclusion, this is the first study to show clinical and genetic evidence supporting the altered age cutoff point of 55 years in the AJCC 8th edition for PTC patients.
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Eliminating the Age Cutoff in Staging of Differentiated Thyroid Cancer: The Safest Road?
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Background: Unlike virtually all other cancer types, thyroid cancer is unique in that patient age is a key component in its staging. Pathologists and clinicians worldwide have accepted an age cutoff of 45 years for staging; in 2018, this advances to age 55 years in the eighth edition of the American Joint Commission on Cancer staging system.

Evidence Acquisition: Clinical and basic research studies, reviews, and previous editions of consensus statements regarding thyroid cancer staging were reviewed, with particular focus on the influence of age in thyroid cancer prognosis.

Purpose: This perspective briefly reviews the basis for this practice and challenges it as no more appropriate than for other malignancies.

Evidence Synthesis: The majority of findings report an association of age with thyroid cancer survival but do not support a specific age cutoff; rather, they suggest that outcome is affected by age as a continuous variable. Conceivably, other factors interact with age on a continuous basis over time, affecting prognosis. When identified, these factors could alter our current concept of the importance of an age cutoff in staging.

Conclusions: Among all cancers, age has an important role in only thyroid cancer staging. The consideration of age as a continuous variable and the search for age-associated prognostic variables could elucidate a more accurate staging system.

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Comprehensive Genetic Analysis of Follicular Thyroid Carcinoma Predicts Prognosis Independent of Histology.
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Context: Follicular thyroid cancer (FTC) is classified into minimally invasive (miFTC), encapsulated angioinvasive (eaFTC), and widely invasive (wiFTC)
subtypes, according to the 2017 World Health Organization (WHO) guidelines. The genetic signatures of these subtypes may be crucial for diagnosis, prognosis, and treatment, but have not been described.

Objective: Identify and describe the genetic underpinnings of subtypes of follicular thyroid cancer.

Methods: Thirty-nine tumors, comprising 12 miFTCs, 17 eaFTCs, and 10 wiFTCs were whole-exome sequenced and analyzed. Somatic mutations, constitutional sequence variants, somatic copy number alterations, and mutational signatures were described. Clinicopathologic parameters and mutational profiles were assessed for associations with patient outcomes.

Results: Total mutation burden was consistent across FTC subtypes, with a median of 10 (range 1-44) non-synonymous somatic mutations per tumor. Overall, 20.5% of specimens had a mutation in the RAS subfamily (HRAS, KRAS, or NRAS), with no significant difference between subtypes. Mutations in TSHR, DICER1, EIF1AX, KDM5C, NF1, PTEN, and TP53 were also noted to be recurrent across the cohort. Clonality analysis demonstrated more sub-clones in wiFTC. Survival analysis demonstrated worse disease-specific survival in the eaFTC and wiFTC cohorts, with no recurrences or deaths for patients with miFTC. Mutation burden was associated with worse prognosis, independent of histopathological classification.

Conclusions: Though the number and variety of somatic variants are similar in the different histopathological subtypes of FTC in our study, mutational burden was an independent predictor of mortality and recurrence.

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Patient Frailty Should Be Used to Individualize Treatment Decisions in Primary Hyperparathyroidism.
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BACKGROUND: Primary hyperparathyroidism (PHPT) is a common endocrine disorder that predominantly affects patients >60 and is increasing in prevalence. Identifying risk factors for poor outcomes after parathyroidectomy in older adults will help tailor operative decision making. The impact of frailty on surgical outcomes in parathyroidectomy has not been established.

METHODS: We performed a retrospective review of patients ≥40 years who underwent parathyroidectomy in the 2005-2010 ACS NSQIP. Frailty was assessed using the modified frailty index (mFI). Multivariable regression was used to determine the association of frailty with 30-day complications, length of stay (LOS), and reoperation.

RESULTS: We identified 13,123 patients ≥40 who underwent parathyroidectomy for PHPT. The majority of patients were not frail, with 80% with a low NSQIP mFI score (0-1 frailty traits), 19% with an intermediate mFI score (2-3), and 0.9%...
with a high mFI score (≥4). Overall 30-day complications were rare, occurring in 141 (1.1%) patients. Increasing frailty was associated with an increased risk of complications with adjusted odds ratios (ORs) of 1.76 (95% CI 1.20-2.59; p = 0.004) for intermediate and 8.43 (95% CI 4.33-16.41; p < 0.001) for high mFI score. Patient age was independently associated with an increased risk of complications only when ≥75, as was African-American race. Anesthesia with local, monitored anesthesia care, or regional block was the only factor associated with decreased odds of complications. A high NSQIP mFI was also associated with a significant 4.77-day adjusted increase in LOS (95% CI 4.28-5.25; p < 0.001) and increased odds of reoperation (OR 4.20, 95% CI 1.64-10.74; p = 0.003).

CONCLUSION: Patient frailty is associated with increased complications, reoperation and prolonged LOS in patients undergoing parathyroidectomy for PHPT. The risks of surgical management should be weighed against potential benefits in frail patients with PHPT to individualize treatment decisions in this vulnerable population.

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Cribiform-Morular Variant of Papillary Thyroid Carcinoma: Clinical and Pathological Features of 30 Cases.

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BACKGROUND: Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is rare; it may occur in cases of familial adenomatous polyposis (FAP) or be sporadic. To clarify the clinicopathological features of CMV-PTC, the medical records of these patients were investigated retrospectively.

MATERIALS AND METHODS: Between 1979 and 2016, a total of 17,062 cases with PTC underwent initial surgery at Ito Hospital. Of these, 30 (0.2%) cases histologically diagnosed with CMV-PTC were reviewed.

RESULT: The patients were all women, with a mean age at the time of surgery of 24 years. Seven (23%) cases were thought to have FAP because they had colonic polyposis or a family history of FAP or APC gene mutation. The remaining 23 (77%) were thought to be sporadic. Multiple tumors were detected in 6 cases, with a solitary tumor in 24. One patient had lung metastasis at diagnosis. Eleven patients underwent total thyroidectomy or subtotal thyroidectomy, and 19 underwent lobectomy. Twenty-six (87%) patients underwent neck lymph node dissection. Three patients had tumor metastasis in central lymph nodes, but these were incidentally detected metastatic classical PTC (cPTC) based on histological examination. In this series, there were no cases of LN metastases of CMV-PTC. During a mean follow-up of 15 years, one patient had new cPTC in the remnant thyroid after initial surgery, and the other patients showed no signs of
CONCLUSION: CMV-PTC occurred in young women, their long-term prognosis was excellent. Total thyroidectomy is recommended for FAP-associated CMV-PTC, but modified neck lymph node dissection is not necessary.
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EF24 (a curcumin analog) and ZSTK474 emphasizes the effect of cabozantinib in medullary 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 bio-availability, and ZSTK474 is an inhibitor of the PI3K signaling pathway. We investigated the effect of these compounds, alone and in combination, in two 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, while the Combination Index revealed a significant 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 for the first time that EF24 alone is effective in inhibiting MTC cell viability. We tested the new combinations XL184+ZSTK474 and XL184+EF24 for the first time too, finding that they act synergistically irrespective of RET mutation status.
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An Analysis of The American Joint Committee on Cancer 8th Edition T Staging System for Papillary Thyroid Carcinoma.
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Background: The American Joint Committee on Cancer (AJCC) removed microscopic extrathyroidal extension (m-ETE) from the 8th edition T staging for papillary thyroid carcinoma (PTC) based on increasing evidence that it is not an independent prognostic factor.

Objectives: We aimed to compare 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 impacts TNM stage.

Method: A retrospective analysis of disease-free survival (DFS) in 577 patients with PTC comparing pT8 versus 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 were 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 versus 0.76) and lower PVE (30% versus 45%). In this subset, m-ETE was associated with multiple other adverse prognostic features and reduced DFS (HR 2.8; 95% CI: 1.5-5.2, 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 impacts 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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Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma.
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BACKGROUND: In the eighth edition of the AJCC staging system for differentiated thyroid carcinoma (DTC), minimal extrathyroidal extension (ETE) is no longer a
determinant of T3 category. Instead, gross ETE invading only strap muscles has been designated as a new T3b category. The long-term prognosis of patients with DTC and gross ETE invading only strap muscles was investigated.

METHODS: This was a retrospective analysis of patients who underwent thyroidectomy between 1996 and 2005. Differences in cancer-specific and recurrence-free survival according to extent of ETE were assessed.

RESULTS: A total of 3174 patients with DTC were included. No significant differences were observed in 10-year cancer-specific survival among patients with no ETE (98.6 per cent), microscopic ETE (98.3 per cent) and gross ETE invading only strap muscles (98.9 per cent) (P = 0.375). The 10-year recurrence-free survival rate for patients with gross ETE invading only strap muscles (89.2 per cent) was shorter than that for patients with no ETE (93.7 per cent; P = 0.016), but similar to that of patients with microscopic ETE (90.3 per cent). In univariable analysis, patients with gross ETE invading only strap muscles had a significantly higher risk of recurrence than those with no ETE (hazard ratio (HR) 1.67, 95 per cent c.i. 1.10 to 2.55; P = 0.017). In multivariable analysis, gross ETE invading only strap muscles was not an independent predictor of recurrence (HR 1.09, 0.71 to 1.69; P = 0.685).

CONCLUSION: Although gross ETE invading only strap muscles may provide prognostic information about long-term recurrence, it does not affect mortality. The actual impact of gross ETE invading only strap muscles will be important in revising the staging system in the future.

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Letter to the Editor: "Decreasing Use of Radioactive Iodine for Low-Risk Thyroid Cancer in California, 1999 to 2015".
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Medullary Thyroid Carcinoma: Survival Analysis and Evaluation of Mutation-Specific Immunohistochemistry in Detection of Sporadic Disease.
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INTRODUCTION: Medullary thyroid cancer (MTC) is a rare tumour of neuroendocrine origin with a more aggressive profile than differentiated thyroid cancer. Familial cases of MTC are associated with RET mutations whilst RAS mutations appear to be a frequent finding in RET negative tumours. The aims of this study were to analyse survival outcomes in MTC and to evaluate the role of RAS immunohistochemistry in the identification of sporadic disease.

MATERIALS AND METHODS: A retrospective cohort study of consecutive patients with MTC was undertaken. The primary outcome measures were overall survival and disease-free survival. Survival analysis was performed on the basis of sporadic and familial disease. Patients had routine RET testing using the capillary (Sanger) sequencing method. Histopathological MTC slides from 100 patients were tested for HRASQ61R, a common somatic RAS mutation in MTC, with mutation-specific immunohistochemistry (IHC).

RESULTS: A total of 195 patients had surgical treatment of MTC in the period 1980 to 2016. There were 83 males and 112 females with a mean age of 53.0 years. A total of 39 (20%) patients had familial disease. Sporadic cases had a higher median pre-op calcitonin (969.5 vs. 257.5 pg/ml), greater mean primary tumour size (23.5 vs. 12.5 mm) and more distant metastases (12.8 vs. 10.3%). Multivariate analysis showed age (p = 0.005), Multiple Endocrine Neoplasia Type 2 (MEN2) status (p = 0.021) and distant metastasis (p = 0.002) to be significant independent predictors of survival. Significant independent predictors for disease-free survival were age (p = 0.015), MEN2 (p = 0.002), pre-op calcitonin (p = 0.033) and venous invasion (p = 0.001). The overall 5-year survival was 100% for familial MTC and 78% for sporadic MTC. The 10-year disease-free survival was 94% for familial MTC and 61% for sporadic cases. A total of 100 cases of MTC underwent mutation-specific IHC for HRASQ61R. Of these, 18 had confirmed MEN2. IHC had 100% specificity in excluding MEN2. Twelve (12%) of 100 patients stained positive for HRASQ61R mutation.

CONCLUSION: In the era of genetic testing, RET status significantly influences disease-specific survival in MTC. Mutation-specific IHC for HRASQ61R may have a role in the identification of patients presenting with sporadic disease.

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Context: Papillary thyroid carcinoma (PTC) is a common malignancy in adolescence and is molecularly and clinically distinct from adult PTC. Mutations in the DICER1 gene are associated with thyroid abnormalities, including multinodular goiter and differentiated thyroid carcinoma.

Objective: In this study, we sought to characterize the prevalence of DICER1 variants in pediatric PTC, specifically in tumors without conventional PTC oncogenic alterations.

Patients: Patients (N = 40) who underwent partial or total thyroidectomy and who were <18 years of age at the time of surgery were selected.

Design: The 40 consecutive thyroidectomy specimens (30 malignant, 10 benign) underwent genotyping for 17 PTC-associated variants, as well as full sequencing of the exons and exon-intron boundaries of DICER1.

Results: Conventional alterations were found in 12 of 30 (40%) PTCs (five BRAFV600E, three RET/PTC1, four RET/PTC3). Pathogenic DICER1 variants were identified in 3 of 30 (10%) PTCs and in 2 of 10 (20%) benign nodules, all of which lacked conventional alterations and did not recur during follow-up. DICER1 alterations thus constituted 3 of 18 (16.7%) PTCs without conventional alterations. The three DICER1-mutated carcinomas each had two somatic DICER1 alterations, whereas two follicular-nodular lesions arose in those with germline DICER1 mutations and harbored characteristic second somatic RNase IIIb "hotspot" mutations.

Conclusions: DICER1 is a driver of pediatric thyroid nodules, and DICER1-mutated PTC may represent a distinct class of low-risk malignancies. Given the prevalence of variants in children, we advocate for inclusion of DICER1 sequencing and gene dosage determination in molecular analysis of pediatric thyroid specimens.

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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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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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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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BACKGROUND: The association between iodine levels and the risk of papillary thyroid cancer (PTC) has been suggested, but not definitively established. This study is to compare the iodine status of a group of patients with PTC (with and without BRAF V600E) with that of a healthy population cohort.

METHODS: A cohort of patients scheduled for thyroidectomy was enrolled, along with a community-based health-screening cohort with no known history of thyroid
disease. Median urinary iodine (UI) levels, creatinine-adjusted median UI levels, and food frequency questionnaire (FFQ) scores (mean ± SD) were compared. In a subgroup analysis, these values were compared between BRAF V600E-positive and BRAF V600E-negative patients in the PTC group.

RESULTS: The PTC group consisted of 210 patients, and the control group consisted of 90 healthy individuals. Among the 191 PTC patients whose BRAF V600E mutational status was reported, 169 (88.5%) were revealed positive for the mutation. The median UI levels were significantly higher in the PTC group (786.0 μg/l) than the control group (112.0 μg/l; p < 0.001), as was the case with creatinine-adjusted median UI levels (884.6 μg/g creatinine versus 182.0 μg/g creatinine; p < 0.001) and FFQ scores (66.2 ± 17.5, range 13-114 versus 54.6 ± 21.5, range 16-134; p < 0.001). No significant differences were seen in the subgroup analysis between BRAF V600E-positive and BRAF V600E-negative patients.

CONCLUSIONS: Our results indicate that iodine status differs significantly between patients with PTC and healthy controls, suggesting that iodine may be involved in the occurrence of PTC, although the association between iodine levels and BRAF mutational status did not reach statistical significance.

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