
*Central Lymph Node Metastasis in Papillary Thyroid Carcinoma.*

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*Downregulation of SKP2 in papillary thyroid cancer acts synergistically with TRAIL on inducing apoptosis via ROS.*

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Context and Objective: S-phase kinase protein 2 (SKP2), is an F-box protein with proteasomal properties and has been found to be overexpressed in a variety of cancers. However, its role in papillary thyroid cancer (PTC) has not been fully elucidated.

Experimental Design: SKP2 expression was assessed by immunohistochemistry in a tissue microarray format on a cohort of more than 1000 PTC samples. In vitro and in vivo studies were performed using proteasome inhibitor bortezomib and proapoptotic death ligand TRAIL either alone or combination on PTC cell lines. MTT, Flow cytometry and immunoblotting were used to determine apoptosis.

Results: SKP2 was over-expressed in 45.5% of PTC cases and was significantly associated with extra-thyroidal extension (p=0.0451), distant metastasis (p=0.0435) and tall cell variant (p=0.0271). SKP2 over-expression was also directly associated with XIAP overexpression (p<0.0001) and Bcl-xl overexpression (p=0.0005), and inversely associated with Death receptor-5 (DR5) (p<0.0001). The co-treatment of bortezomib and TRAIL synergistically induced apoptosis via mitochondrial apoptotic pathway in PTC cell lines. Furthermore, bortezomib and TRAIL synergistically induced reactive oxygen species (ROS) generation and caused DR5 upregulation through activation of ERK-CHOP signaling cascade. Notably, bortezomib/TRAIL induced ROS generation played a crucial role in the induction of apoptosis in PTC cells. Finally, bortezomib treatment augmented TRAIL mediated anti-cancer effect on PTC xenograft tumor growth in nude mice.

Conclusion: These data suggest that SKP2 is a potential therapeutic target in PTC and combination of bortezomib and TRAIL might be a viable therapeutic option for the treatment of patients with aggressive PTC.
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Context: Routine radioactive iodine (RAI) ablation for low-risk differentiated thyroid cancer (DTC) is not supported by current practice guidelines.
Objective: To assess recent stage-specific trends in utilization of RAI ablation.
Design, Setting and Patients: Retrospective study of patients with DTC (1999-2015) identified from the California Cancer Registry. Statistical analysis included standardized differences, p-values, and multivariable analyses using RAI as the predictor variable.
Main Outcome Measures: Trends and drivers of RAI ablation for low-risk DTC.
Results: Of 46,906 patients with DTC who underwent near-total or total thyroidectomy (mean age 48.2±15.5 [SD] years, 77% female), 25,457 (54%) received RAI. The proportion of patients with regional/distant disease who received RAI remained stable at 68%. Utilization of RAI for patients with localized disease (no extrathyroidal extension, lymph node or distant metastases) decreased from 55% (1999) to 30% (2015), with the most significant change occurring in tumors <1 cm (39% to 11%). The rate also decreased for localized tumors between 1-2 cm (62% to 34%) and 2-4 cm (67% to 49%), and remained stable at 59% for tumors >4 cm. In multivariable analysis, patients with localized disease were less likely to receive RAI if they were >65 years old (OR 0.77, 95% CI: 0.71-0.83), had tumors <1 cm (OR 0.33, 95% CI: 0.31-0.35), or were treated in an academic hospital (OR 0.71, 95% CI: 0.67-0.75).
Conclusions: The rate of RAI ablation has decreased over time, mainly attributable to decreased use for localized DTCs < 2 cm. Many patients with low-risk DTC still receive RAI unnecessarily.
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Natural History of Contralateral Nodules after Lobectomy in Patients with Papillary Thyroid Carcinoma.

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Background: Bilateral thyroid nodularity is considered an indication for total thyroidectomy in papillary thyroid carcinoma (PTC) patients. However, the natural history and outcome of contralateral nodules has never been studied.
Objective: To investigate the natural history of non-suspicious contralateral nodules after lobectomy for PTC.
Methods: We included patients who had ≥1 solid nodules (≥3mm) in the contralateral lobe prior to surgery with benign cytology, or small non suspicious nodules per ultrasound.
Results: One hundred and twelve patients were included. Median age was 57 years, and median size of PTC (initial lobectomy) was 8mm (range 0.5-28). On the contralateral side, the median size of nodules was 7mm (range 3-30). Thirty-three nodules (29%) had fine needle aspiration before surgery, and all were benign. After median follow-up of 6 years, median growth was zero (range -20-19mm). Twenty-six nodules (23%) increased in size ≥3mm (median 6mm, range 4-19mm). Twenty patients (18%) developed new nodules. Twelve patients (11%) underwent completion thyroidectomy for: growth (3), suspicious FNA (7, Bethesda III-V), malignancy (1), or unknown reason (1). Overall, based on the completion thyroidectomy specimen, 6 patients (5%) were diagnosed with contralateral PTC (5 micro-PTC, one 20mm), and are all without evidence of disease at the end of follow-up. There were no surgical difficulties or local complications during completion surgery.
Conclusions: Lobectomy for low risk patients with small PTC and contralateral non-suspicious thyroid nodule/s is a reliable and safe initial treatment option. In the few patients who required completion thyroidectomy, treatment with surgery and radioiodine was effective.
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Risk Factors for Central Neck Lymph Node Metastases in Micro- Versus Macro- Clinically Node Negative Papillary Thyroid Carcinoma.
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BACKGROUND: Tumor size has been advocated as possible risk factors for occult central lymph node metastases (CNM) in papillary thyroid carcinoma (PTC) patients. This prospective study evaluated factors that could identify patients at higher risk of occult CNM, especially comparing micro-PTC and macro-PTC.

METHODS: One hundred and eighty-six patients were recruited. All the patients had cN0 clinically unifocal PTC and underwent total thyroidectomy and bilateral prophylactic central neck dissection. Risk factors for occult CNM in micro- and macro-PTC patients were evaluated.

RESULTS: Eighty-two patients showed CNM. The rate of CNM did not differ among different sizes cut off (≤20 mm, ≤10 mm, ≤5 mm P = NS). Significantly more pN1a than pN0 patients had pT3 tumors (35/82 vs. 26/104) (P < 0.05), extracapsular invasion (35/82 vs. 22/104) (P < 0.01) and microscopic multifocal disease (50/82 vs. 47/104) (P < 0.05). Independent risk factors for CNM were extracapsular invasion and multifocality at multivariate analysis. Risk factors for CNM in 77 micro-PTC were extracapsular invasion (16/31 pN1 vs. 10/46 pN0, P < 0.05) and multifocality (21/31 pN1 vs. 16/46 pN0, P < 0.01). Among 109 macro-PTC, risk factors for CNM were angioinvasion (15/51 pN1 vs. 7/58 pN0, P < 0.05) and classic PTC at the final histology (PTC vs. tall cell variant vs. follicular variant PTC) (P < 0.05).

CONCLUSIONS: Risk factors for CNM can differ between micro- and macro-PTC, but no preoperatively known clinical parameter is predictor of CNM in cN0 clinically unifocal PTC.

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Video-Assisted Thyroidectomy for Papillary Thyroid Carcinoma: Oncologic Outcome in Patients with Follow-Up ≥ 10 Years.
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BACKGROUND: Video-assisted thyroidectomy (VAT) arisen as a valid treatment for selected patients with papillary thyroid carcinoma (PTC), but no data concerning long-term oncologic outcome are available. The primary aim of the study was to evaluate the oncologic outcome of patients who underwent VAT for PTC with a follow-up ≥ 10 years.

METHODS: The medical charts of all the patients who successfully underwent VAT for PTC were reviewed. The patients with a minimum follow-up period of 120-months...
were included. Patients with unifocal PTC ≤ 1 cm, in the absence of lymph node metastases, without gross extracapsular invasion and age < 45 years were considered "low-risk" patients and followed with ultrasound and serum thyroglobulin (sTg) on levothyroxine (LT4); the remaining patients underwent nuclear medicine evaluation.

RESULTS: Two hundred and fifty-seven patients, operated on between May 2000 and October 2006, were included. Postoperative complications included four transient recurrent palsies, 76 transient and 1 permanent hypocalcemia. One hundred and four low-risk patients were followed with ultrasound and sTg on LT4. At a mean follow-up of 136.6 months, mean sTg on LT4 was 0.1 ± 0.1 ng/ml. None of them showed recurrence. The remaining 153 patients underwent nuclear medicine evaluation. Among these 153, 62 did not undergo radioiodine ablation (RAI). At a mean follow-up of 150.8 months, mean sTg on LT4 was 0.1 ± 0.1 ng/ml. None of them showed recurrence. The remaining 91 patients underwent RAI. Mean pre-RAI sTg off-LT4 was 8.3 ± 5.8 ng/ml, mean radioiodine uptake was 2.8 ± 4.4%. Among these 91, three pN1a patients developed a lateral neck node recurrence. No other recurrence was registered. At the latest follow-up mean sTg on LT4 in this subgroup of patients was 0.1 ± 0.2 ng/ml.

CONCLUSIONS: The long-term (≥ 10 years) oncologic outcome further demonstrates that VAT is a valid option for selected PTC patients.

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Effect of Age on Response to Therapy and Mortality in Patients with Thyroid Cancer at High-Risk of Recurrence.
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Context: Age at diagnosis has been identified as a major determinant of thyroid cancer-specific survival with older patients being at higher risk for mortality, but the association of age with risk of recurrence has not been studied to date.
Objective: To examine the effect of patient's age on response to therapy and disease-specific mortality in a cohort of thyroid cancer patients at high-risk of recurrence as defined by the American Thyroid Association (ATA) risk stratification system.
Design: Retrospective cohort study of 320 patients, median age 49.3 years, with follicular-cell derived thyroid carcinoma classified at ATA High-Risk and followed for a median of 7 years.
Main Outcomes Measured: Association of age with response to therapy, overall mortality, disease-specific mortality and timing of metastases.
Results: Age was a major determinant of response to therapy. There was a significantly larger percentage of excellent responders among young patients (age <55) than among old patients (age ≥ 55), 40.3% vs. 27.5%, p=0.002, respectively, while the proportion of structural incomplete responders was higher in the old group compared to the young group, 53% vs. 33%, p=0.002, respectively. ATA high-risk young patients with a structural incomplete response to therapy had a
significantly better disease-specific survival than old patients (74% vs. 12%, p<0.001, respectively).

Conclusions: Age was a key predictor of response to therapy and disease-specific survival in ATA High-risk thyroid cancer patients. Its incorporation as a variable in the ATA risk stratification system would improve its power to predict response to therapy as well as mortality.

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131I radiation exposure and thyroid cancer.
Burki TK.
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Thyroid cancer: CAR T cell therapy - potential in advanced thyroid cancer?
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Hypoxia Increases Thyroid Cancer Stem Cell-Enriched Side Population.
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INTRODUCTION: Hypoxic stress is a feature of rapidly growing thyroid tumours. Cancer progression is thought to be driven by a small population of tumour cells possessing stem cell properties. Hypoxia-inducible factors (HIFs) are important mediators of hypoxia. Both HIF-1alpha and HIF-2alpha have been reported to be expressed in thyroid cancers. There is growing evidence that the HIF pathway plays a significant role in the maintenance of thyroid cancer stem cells (CSC).

METHODOLOGY: We have isolated thyroid CSC from a papillary thyroid cancer-derived cell line (BCPAP) and an anaplastic thyroid cancer-derived cell line (SW1736) as side population (SP) cells (a putative stem cell population) and treated them with cobalt chloride (II) to induce hypoxia. RESULTS AND DISCUSSION: We observed
an increase in the SP of cells within the thyroid cancer cell lines following induction of hypoxia.
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Surgery for Primary Hyperparathyroidism with Normal Non-suppressed Parathyroid Hormone can be Both Challenging and Successful.
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BACKGROUND: Criteria for diagnosing primary hyperparathyroidism (PHPT) include hypercalcemia in the presence of parathyroid hormone (PTH) levels that are either elevated (classic PHPT) or normal but non-suppressed. However, there is no standard definition of what constitutes normal non-suppressed levels, and data are lacking regarding the potential for surgical cure in these patients.
METHODS: A retrospective review of patients undergoing parathyroidectomy for sporadic PHPT between 2012 and 2014 was performed. Patients with normal PTH were compared to classic PHPT patients to assess demographics, imaging, operative findings, and outcomes.
RESULTS: In total, 332 patients met study criteria, and 60 (18%) had normal PTH levels. Negative sestamibi scans were seen more often with normal PTH levels (18.3 vs. 4.8%, p < 0.001). Patients with normal PTH were more likely to have ≥2 glands removed (26.7 vs. 14.3%, p = 0.02), and the specimens were more likely to be classified as only mildly hypercellular or normocellular (20 vs. 2.9%, p < 0.001). Average follow-up was 24 months (range 6-55). Cure rate was 88% in the normal PTH group, compared to 96% in classic PHPT (p = 0.02). Among patients with normal PTH, those with PTH ≤ 55 pg/mL had an 83% cure rate, whereas those with PTH 56-65 had a 96% cure rate (p = 0.12).
CONCLUSIONS: Parathyroidectomy can have a high cure rate in the context of normal PTH levels despite an increased likelihood of negative imaging and multigland resection. Operative success is equivalent to classic PHPT when PTH levels are > 55 pg/mL.
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Long-Term Outcome After Surgery for Medullary Thyroid Carcinoma: A Single-Center Experience.
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BACKGROUND: Medullary thyroid carcinoma (MTC) is a rare C cells-derived tumor, with a hardly predictable long-term prognosis. This study was aimed to evaluate the predictive factors of cure and survival after surgery for MTC in a monocentric series.

METHODS: A retrospective analysis of the long-term outcomes was assessed in 255 MTC patients operated between 1980 and 2015 at Padua University hospital.

RESULTS: Sporadic MTC occurred in 65.1% and hereditary MTC in 34.9% of patients. At a median follow-up of 93 months (range 7-430), the cure rate was 56.8%. The overall 10-year survival was 84.4%, and MTC-related death rate was 15.3%. Patients who died because of MTC had a median age of 61 years (range 21-84) and were at stages III-IV in all cases; deaths occurred in 18% of sporadic MTC, 6% of MEN2a and 66.7% of MEN2b patients. None of the patients at stages I-II died because of the disease, but 17.7% had persistent/recurrent disease. Based on univariate analysis, age, gender, genetic variant, extent and year of surgery, tumor size, lymph-nodal metastases and tumor stage significantly affected cure and survival rates. At multivariate analysis, only patient- and tumor-related features (age, lymph-nodal status and stage) remained significant independent prognostic factors.

CONCLUSIONS: Radical surgery is the only chance of definitive cure in MTC, but it is possible only at early stage; in advanced stages, even extensive surgery could not grant cure and prolonged survival. Stage, nodal metastases and age remain the main predictive factors for cure and survival.

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BACKGROUND: Efficient DNA damage repair by MutL-homolog DNA mismatch repair (MMR) enzymes, MLH1, MLH3, PMS1 and PMS2, are required to maintain thyrocyte genomic integrity. We hypothesized that persistent oxidative stress and consequent transcriptional dysregulation observed in thyroid follicles will lead to MMR deficiency and potentiate papillary thyroid tumorigenesis.

METHODS: MMR gene expression was analyzed by targeted microarray in 18 papillary thyroid cancer (PTC), 9 paracarcinoma normal thyroid (PCNT) and 10 normal thyroid (NT) samples. The findings were validated by qRT-PCR, and in follicular thyroid cancers (FTC) and follicular thyroid adenomas (FTA) for comparison. FOXO transcription factor expression was also analyzed. Protein expression was assessed by immunohistochemistry. Genomic integrity was evaluated by whole-exome sequencing-derived read-depth analysis and Mann-Whitney U test. Clinical correlations were assessed using Fisher's exact and t tests.

RESULTS: Microarray and qRT-PCR revealed reduced expression of all four MMR genes in PTC compared with PCNT and of PMS2 compared with NT. FTC and FTA showed upregulation in MLH1, MLH3 and PMS2. PMS2 protein expression correlated with the mRNA expression pattern. FOXO1 showed lower expression in PMS2-deficient PTCs (log2-fold change -1.72 vs. -0.55, U = 11, p < 0.05 two-tailed). Rate of LOH, a measure of genomic instability, was higher in PMS2-deficient PTCs (median 3 and 1, respectively; U = 26, p < 0.05 two-tailed). No correlation was noted between MMR deficiency and clinical characteristics.

CONCLUSIONS: MMR deficiency, potentially promoted by FOXO1 suppression, may explain the etiology for PTC development in some patients. FTC and FTA retain MMR activity and are likely caused by a different tumorigenic pathway.

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Context: High-resolution peripheral quantitative computed tomography (HRpQCT) is a noninvasive imaging technology that can provide insight into skeletal
microstructure and strength. In asymptomatic primary hyperparathyroidism (PHPT), HRpQCT imaging has demonstrated both decreased cortical and trabecular indices, consistent with evidence for increased fracture risk. There are limited data regarding changes in HRpQCT parameters postparathyroidectomy.

Objective: To evaluate changes in skeletal microstructure by HRpQCT in subjects with PHPT after parathyroidectomy.

Design: We studied 29 subjects with PHPT (21 women, 8 men) with HRpQCT at baseline and 6, 12, 18, and 24 months postparathyroidectomy.

Main Outcome Measures: Volumetric bone mineral density, microarchitectural indices, and finite element analysis at the distal radius and tibia.

Results: At both the radius and tibia, there were significant improvements in total, cortical, and trabecular volumetric bone density as early as 6 months postparathyroidectomy (24-month values for total volumetric bone density, radius: +2.8 ± 4%, tibia: +4.4 ± 4%; P < 0.0001 for both), cortical thickness (radius: +1.1 ± 2%, tibia: +2.0 ± 3%; P < 0.01 for both), and trabecular bone volume (radius: +3.8 ± 5%, tibia: +3.2 ± 4%; P < 0.0001 for both). At both sites, by finite element analysis, stiffness and failure load were improved starting at 6 months postparathyroidectomy (24-month values for failure load, radius: +6.2 ± 6%, tibia: +4.8 ± 7%; P < 0.0001 for both).

Conclusions: These results provide information about skeletal microarchitecture in subjects with PHPT followed through 2 years after parathyroidectomy. Estimated bone strength is improved, consistent with data showing decreased fracture risk postparathyroidectomy.

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Less is More: The Impact of Multidisciplinary Thyroid Conference on the Treatment of Well-Differentiated Thyroid Carcinoma.


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BACKGROUND: In 2006, a multidisciplinary thyroid conference (MDTC) was implemented to better plan management of thyroid cancer patients at our
institution. This study assessed the clinical impact of a MDTC on radioactive iodine (RAI) treatment patterns.

METHODS: A prospective database (2003-2014) collected patient and tumor characteristics, RAI doses, and tumor recurrences. Patients treated with total thyroidectomy for differentiated thyroid carcinoma ≥1 cm were stratified based on American Thyroid Association (ATA) risk classification. RAI regimens were compared before initiation of MDTC (2003-2005, n = 88), after establishment of MDTC (2007-2009, n = 95), and after the release of 2009 ATA guidelines (2011-2014, n = 181). RAI doses were defined as low (≤75 mCi), intermediate (76-150 mCi), and high (>150 mCi).

RESULTS: There was a significant decrease in the number of patients who received high-dose RAI after implementation of MDTC compared to before initiation of MDTC in the intermediate and high-risk patient groups (p = 0.04 and p < 0.01) without an associated increase in tumor recurrence (11 vs. 7%, p = 0.74). On multivariable analysis, presentation of a patient at MDTC was a negative predictor for receiving high-dose RAI (p = 0.002). As might be expected, there was also a significant decrease in use of RAI after the 2009 ATA guidelines were issued compared to after implementation of MDTC (p < 0.01).

CONCLUSION: In conjunction with implementation of a thyroid malignancy multidisciplinary conference, we observed significantly decreased postoperative dosing of RAI without increased tumor recurrence. The 2009 ATA guidelines were associated with a further decrease in RAI administration. Treatment for patients with thyroid carcinoma is optimized by a multidisciplinary approach.

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Differential Growth Rates of Benign vs. Malignant Thyroid Nodules.

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Context: Thyroid nodule growth was once considered concerning for malignancy, but data showing that benign nodules grow questioned the use of this paradigm. To date, however, no studies have adequately evaluated whether growth rates differ
in malignant vs. benign nodules.
Objective: To sonographically evaluate growth rates in benign and malignant thyroid nodules ≥1 cm.

Design: Prospective, cohort study of patients with tissue diagnosis of benign or malignant disease, with repeated ultrasound evaluation six or more months apart.

Main Outcomes: Growth rate in largest dimension of malignant compared with benign thyroid nodules. Regression models were used to evaluate predictors of growth.

Results: Malignant nodules (126) met inclusion criteria (≥6-month nonoperative followup) and were compared with 1363 benign nodules. Malignant nodules were not found to be uniquely selected or prospectively observed solely for low-risk phenotype. Median ultrasound intervals were similar (21.8 months for benign nodules; 20.9 months for malignant nodules). Malignant nodules were more likely to grow >2 mm/y compared with benign nodules [relative risk (RR) = 2.5, 95% confidence interval (CI), 1.6 to 3.1; P < 0.001], which remained true after adjustment for clinical factors. The RR of a nodule being malignant increased with faster growth rates. Malignant nodules growing >2 mm/y had greater odds of being more aggressive cancers [intermediate risk: odds ratio (OR) = 2.99; 95% CI, 1.20 to 7.47; P = 0.03; higher risk: OR = 8.69; 95% CI, 1.78 to 42.34; P = 0.02].

Conclusions: Malignant nodules, especially higher-risk phenotypes, grow faster than benign nodules. As growth >2 mm/y predicts malignant compared with benign disease, this clinical parameter can contribute to the assessment of thyroid cancer risk.

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CDC73-Related Disorders: Clinical Manifestations and Case Detection in Primary Hyperparathyroidism.

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Context: Heterozygous pathogenic germline variants in CDC73 predispose to the development of primary hyperparathyroidism (pHPT) and, less frequently, ossifying fibroma of the jaw and renal and uterine tumors. Clinical information on CDC73-related disorders has so far been limited to small case series.

Objective: To assess the clinical manifestations and penetrance in CDC73-related disorders and to improve case detection in pHPT.

Design: Nationwide retrospective Dutch cohort study.

Setting: Tertiary referral center.

Patients: We studied 89 patients with pHPT referred for germline CDC73 analysis and 43 subsequently tested relatives who proved to be mutation carriers.

Investigation: Germline CDC73 mutation analysis.

Mean Outcome: CDC73 mutation detection yield, referral rate, and CDC73-related disease penetrance.

Results: Pathogenic germline CDC73 variants were identified in 11 of the 89 referred pHPT patients (12.4%), with (suspected) hyperparathyroidism-jaw tumor (HPT-JT) syndrome (n = 3), familial isolated pHPT (n = 5), apparently sporadic parathyroid carcinoma (n = 2), and apparently sporadic parathyroid adenoma (n = 1). The estimated penetrance of CDC73-related disorders was 65% at age 50 years (95% confidence interval, 48% to 82%) in 43 nonindex mutation carriers.

Conclusions: Germline CDC73 analysis is recommended in individuals with (suspected) HPT-JT syndrome, familial isolated pHPT, atypical or malignant parathyroid histology, and young individuals with pHPT. These criteria would increase germline CDC73 mutation detection, enabling optimal clinical management of pHPT as well as genetic counseling and surveillance for family members at risk for developing CDC73-related disorders.

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Papillary Thyroid Carcinoma (PTC) in Children and Adults: Comparison of Initial Presentation and Long-Term Postoperative Outcome in 4432 Patients Consecutively Treated at the Mayo Clinic During Eight Decades (1936-2015).
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The image contains a partially obscured page of a document. The text appears to be related to the management of thyroid cancer, specifically papillary thyroid carcinoma (PTC), and the outcomes of treatment in children compared to adults. The text outlines the background, subject and methods, results, and conclusions of a study on the treatment and outcomes of PTC in children and adults over a period from 1936 to 2015.

BACKGROUND: Contemporary guidelines for managing PTC advise an approach wherein primary tumor and regional metastases (RM) are completely resected at first surgery and radioiodine remnant ablation (RRA) is restricted to high-risk patients, policies our group has long endorsed. To assess our therapeutic efficacy, we studied 190 children and 4242 adults consecutively treated during 1936-2015.

SUBJECTS AND METHODS: Mean follow-up durations for children and adults were 26.9 and 15.2 years, respectively. Bilateral lobar resection was performed in 86% of children and 88% of adults, followed by RRA in 30% of children and 29% of adults; neck nodes were excised in 86% of children and 66% of adults. Tumor recurrence (TR) and cause-specific mortality (CSM) details were taken from a computerized database.

RESULTS: Children, when compared to adults, had larger primary tumors which more often were grossly invasive and incompletely resected. At presentation, children, as compared to adults, had more RM and distant metastases (DM). Thirty-year TR rates were no different in children than adults at any site. Thirty-year CSM rates were lower in children than adults (1.1 vs. 4.9%; p = 0.01). Comparing 1936-1975 (THEN) with 1976-2015 (NOW), 30-year CSM rates were similar in MACIS <6 children (p = 0.67) and adults (p = 0.08). However, MACIS <6 children and adults in 1976-2015 had significantly higher recurrence at local and regional, but not at distant, sites. MACIS 6+ adults, NOW, compared to THEN, had lower 30-year CSM rates (30 vs. 47%; p < 0.001), unassociated with decreased TR at any site.

CONCLUSIONS: Children, despite presenting with more extensive PTC when compared to adults, have postoperative recurrences at similar frequency, typically coexist with DM and die of PTC less often. Since 1976, both children and adults with MACIS <6 PTC have a <1% chance at 30 years of CSM; adults with higher MACIS scores (6 or more) have a 30-year CSM rate of 30%.

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Survival in Response to Multimodal Therapy in Anaplastic Thyroid Cancer.
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Context: Historical outcomes in anaplastic thyroid cancer (ATC) have been dismal.
Objective: To determine whether an initial intensive multimodal therapy (MMT) is associated with improved ATC survival.
Design: MMT was offered to all patients with newly diagnosed ATC treated at the Mayo Clinic from 2003 through 2015; MMT vs care with palliative intent (PI) was individualized considering clinical status and patient preferences. Outcomes were retrospectively analyzed by American Joint Committee on Cancer stage and treatments compared with patient cohort data from 1949 through 1999.
Patients: Forty-eight patients (60% male; median age, 62 years); 18 treated with PI, 30 with MMT.
Main Outcome Measure: Overall survival (OS) and progression-free survival determined by Kaplan-Meier method.
Results: Median OS and 1-year survival for the later cohort were 9 months [95% confidence interval (CI), 4 to 22 months] and 42% (95% CI, 28% to 56%) vs 3 months and 10% for the earlier cohort. Median OS was 21 months compared with 3.9 months in the pooled MMT vs PI groups for the later cohort [hazard ratio (HR), 0.32; P = 0.0006]. Among only patients in the later cohort who had stage IVB disease, median OS was 22.4 vs 4 months (HR, 0.12; 95% CI, 0.03 to 0.44; P = 0.0001), with 68% vs 0% alive at 1 year (MMT vs PI). Among patients with stage IVC cancer, OS did not differ by therapy.
Conclusion: MMT appears to convey longer survival in ATC among patients with stage IVA/B disease.
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knowledge in these areas will improve the management of the disorder.

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Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign?
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BACKGROUND: Renaming encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was recently suggested to prevent the overtreatment, cost and stigma associated with this low-risk entity. The purpose of this study is to document the incidence and further assess the clinical outcomes of reclassifying EFVPTC to NIFTP.
METHODS: We searched synoptic pathologic reports from a high-volume academic endocrine surgery hospital from 2004 to 2013. The standard of surgical pathology practice was based on complete submission of malignant thyroid nodules along with the nontumorous thyroid parenchyma. Rigid morphological criteria were used for the diagnosis of noninvasive EFVPTC, currently known as NIFTP. A retrospective chart review was conducted looking for evidence of malignant behavior.
RESULTS: One hundred and two patients met the strict inclusion criteria of NIFTP. The incidence of NIFTP in our cohort was 2.1% of papillary thyroid cancer cases during the studied time period. Mean follow-up was 5.7 years (range 0-11). Five patients were identified with nodal metastasis and one patient with distant metastasis. Overall, six patients showed evidence of malignant behavior representing 6% of patients with NIFTP.
CONCLUSION: Our study demonstrates that the incidence of NIFTP is significantly lower than previously thought. Furthermore, evidence of malignant behavior was seen in a significant number of NIFTP patients. Although the authors fully support the de-escalation of aggressive treatment for low-risk thyroid cancers, NIFTP behaves as a low-risk thyroid cancer rather than a benign entity and ongoing surveillance is warranted.
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Relationship Between 18F-fluorodeoxyglucose Accumulation and the BRAF V600E Mutation in Papillary Thyroid Cancer.
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BACKGROUND: To determine whether 18F-fluoro-2-deoxyglucose (18F-FDG)-PET/CT is useful for predicting the BRAF V600E mutation status of a primary papillary thyroid carcinoma (PTC).

METHODS: A retrospective analysis was performed in 108 patients who underwent 18F-FDG positron emission tomography-computed tomography (PET/CT) for staging before thyroidectomy and BRAF analysis in biopsy-confirmed PTC. The maximum standardized uptake value (SUVmax) of the primary tumor was calculated according to FDG accumulation. Univariate and multivariate analyses were performed to assess the association between the SUVmax and clinicopathological variables.

RESULTS: The BRAF V600E mutation was detected in 71 of 108 (65.7%) patients. In all subjects, the tumor size and BRAF V600E mutation were independently related to the SUVmax according to multivariate analyses (P = 0.002 and 0.007, respectively). The SUVmax was significantly higher in tumors with the BRAF V600E mutation than in tumors with wild-type BRAF (10.24 ± 11.89 versus 4.02 ± 3.86; P = 0.007). In the tumor size >1 cm subgroup, the BRAF V600E mutation was the only factor significantly associated with the SUVmax (P = 0.016). A SUVmax cutoff level of 4.9 was determined to be significant for predicting the BRAF V600E mutation status (sensitivity 77.4%, specificity 100.0%, area under the curve 0.929; P < 0.0001) according to ROC curve analysis.

CONCLUSIONS: The BRAF V600E mutation is independently associated with high 18F-FDG uptake in PTC, especially in those with a tumor size >1 cm.
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Macrometastasis in Papillary Thyroid Cancer Patients is Associated with Higher Recurrence in Lateral Neck Nodes.
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BACKGROUND: The use of routine central compartment neck dissection surgery for papillary thyroid carcinoma (PTC) is controversial. Although macroscopic central neck lymph node metastasis (CNLN) in PTC is a poor prognostic factor correlated with increased loco-regional recurrence, the significance of microscopic metastasis to the central lymph nodes is not established. Herein, we aimed to assess the influence of the size of CNLN on disease recurrence among PTC patients.

METHODS: Data from 233 patients who underwent less than total thyroidectomy with CNLN dissection in 1989-1999 were retrospectively reviewed. The patients were assigned to three groups according to the central node metastasis: no metastasis (Group I), micrometastasis (<2 mm, Group II), and macrometastasis (≥2 mm, Group III). Clinicopathological features, recurrence rate, site of recurrence, and disease-free survival (DFS) were assessed.

RESULTS: Of the 233 patients enrolled (mean follow-up period, 16.1 years), 134 (57.5%) had no central neck metastasis, 37 (15.9%) had micrometastasis, and 62 (26.6%) had macrometastasis. Demographics and tumour variables were similar among the three groups. Recurrence rates were 12.7, 16.2, and 43.5% in Groups I, II, and III, respectively (p < 0.001). Group III had a 3.2-fold increased relative risk of recurrence and a significantly decreased DFS compared to Group I. Group III showed significantly higher rates of lateral neck nodes metastasis than Groups I and II.

CONCLUSIONS: In conclusion, macroscopic metastasis significantly affects disease recurrence in PTC patients, whereas microscopic metastasis has only marginal effects. Macroscopic CNLN metastasis showed a significantly higher recurrence in the lateral neck node compared to micrometastasis.

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BACKGROUND: We occasionally experience cases of severe secondary hyperparathyroidism (SHPT) that require parathyroidectomy (PTX) despite undergoing short-term renal replacement therapy (RRT). Because the characteristics of such cases have never been discussed, we aimed to elucidate...
the pathophysiology of severe SHPT after short-term RRT by retrospectively analyzing clinical data.

METHODS: A total of 1013 patients with severe SHPT underwent PTX between January 2007 and April 2016 at Nagoya Daini Red Cross Hospital. Of these patients, 570 underwent RRT for ≥10 years (long RRT group) and 23 for ≤1 year (short RRT group). We retrospectively investigated and compared patient characteristics, preoperative data, subjective symptoms, and bone lesion incidence between the two groups.

RESULTS: A higher proportion of subjects with congenital or hereditary diseases as primary disease for chronic kidney disease (CKD) (21.7% (5/23) vs. 6.3% (36/570); P = 0.016) and longer predialysis period (21.2 ± 14.0 vs. 10.1 ± 9.2 years; P < 0.001) were observed in the short RRT group than in the long RRT group. Furthermore, lower serum calcium and phosphate levels, heavier parathyroid glands, and severe bone lesions were observed in the short RRT group than in the long RRT group.

CONCLUSION: Severe SHPT after short-term RRT appeared to occur because of long-term CKD before initiating RRT. Therefore, treating mineral and bone disorders during the early CKD stage might prevent severe SHPT development before initiating RRT.

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BACKGROUND: We investigated the expression of angiopoietins in patients with papillary thyroid carcinoma (PTC) and the role of angiopoietins as biomarkers predicting the aggressiveness of PTC.
METHODS: Expression of angiopoietins was evaluated by immunohistochemistry of tumor specimens from patients with PTC. We demonstrated potential correlations between expression of angiopoietins and clinicopathologic features.
RESULTS: High expression of Ang-1 was positively correlated with a tumor size >1 cm, capsular invasion, extrathyroid extension, lymphovascular invasion, lymph
node metastasis, and recurrence (P < 0.05). Moreover, multivariate analysis revealed that high expression of Ang-1 was an independent risk factor for lymph node metastasis (P < 0.001, odds ratio [OR] = 62.113) and lymphovascular invasion (P = 0.027, OR 4.405). However, there was no significant correlation between Ang-2 and clinicopathologic features.

CONCLUSIONS: Our results suggest that Ang-1 can serve as a valuable prognostic biomarker for lymph node metastasis and invasiveness in patients with PTC.
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