1. **World J Surg. 2018 Oct 19. doi: 10.1007/s00268-018-4823-3. [Epub ahead of print]**
Risk Factors for Readmission After Parathyroidectomy for Renal Hyperparathyroidism.
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BACKGROUND: Patients with renal hyperparathyroidism (RHPT) are susceptible to major electrolyte fluctuations following parathyroidectomy, which may predispose them to early readmission. The purpose of this study is to evaluate risk factors for readmission in patients undergoing parathyroidectomy for RHPT.
METHODS: Patients with renal failure who underwent parathyroidectomy were abstracted from the California Office of Statewide Health Planning and Development (1999-2012). Multivariable logistic regression was used to identify risk factors for readmission within 30 days of discharge.
RESULTS: The cohort included 4411 patients, of whom 17% were readmitted. Procedures included subtotal parathyroidectomy (74% of cases) and total parathyroidectomy with autotransplantation (26%). Median time to readmission was 9 days (interquartile range 4-16 days). Electrolyte disturbances including hypocalcemia were present in 36% of readmissions and were the most common cause for readmission. Independent risk factors for readmission included Black race [odds ratio (OR) 1.26, 95% confidence interval (CI) 1.00-1.57], Hispanic race (OR 1.38, 95% CI 1.12-1.71), disposition with home health (OR 1.94, 95% CI 1.35-2.77), disposition to a skilled nursing facility (OR 2.30, 95% CI 1.58-3.35), and total parathyroidectomy with autotransplantation (OR 1.27, 95% CI 1.06-1.52). Advancing age (OR 0.98, 95% CI 0.98-0.99) and surgery at a high-volume hospital (OR 0.53, 95% CI 0.36-0.77) were protective against readmission.
CONCLUSIONS: Patients undergoing parathyroidectomy for RHPT have a high readmission rate, most frequently for metabolic complications. Increased postoperative vigilance, which may include outpatient laboratory monitoring, may be indicated in patients with risk factors for readmission.
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PMID: 30341470

2. **Ann Surg. 2018 Oct 17. doi: 10.1097/SLA.0000000000003074. [Epub ahead of print]**
Is Less More? A Microsimulation Model Comparing Cost-effectiveness of the Revised American Thyroid Association's 2015 to 2009 Guidelines for the Management of Patients With Thyroid Nodules and Differentiated Thyroid Cancer.
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OBJECTIVE: To assess relative clinical and economic performance of the revised American Thyroid Association (ATA) thyroid cancer guidelines compared to current standard of care.
BACKGROUND: Diagnosis of thyroid cancer in the United States has tripled whereas mortality has only marginally increased. Most patients present with small papillary carcinomas and have historically received at least a total thyroidectomy as a treatment. In 2015, the ATA released the revised guidelines recommending an option for active surveillance (AS) of small papillary thyroid carcinoma and thyroid lobectomy for larger unifocal tumors.
METHODS: We created a Markov microsimulation model to evaluate the performance of the ATA's 2015 guidelines compared to the ATA's 2009 guidelines. We modeled a cohort of simulated patients with demographic and thyroid nodule characteristics representative of those presenting clinically in the United States. Outcome measures include life expectancy, quality-adjusted life years, costs, and frequency of surgical adverse events.
RESULTS: In our base case analysis, the ATA 2015 strategy dominates the ATA 2009 strategy. The ATA 2015 strategy delivers greater discounted average quality-adjusted life years (13.09 vs 12.43) at a lower discounted average cost ($14,752 vs $20,126). Deaths due to thyroid cancer under the 2015 strategy are higher than the 2009 strategy but this is offset by a reduction in surgical deaths, leading to greater average life expectancy under the ATA 2015 strategy. The optimal strategy is sensitive to patients who experience a greater decrement in quality of life while undergoing AS.
CONCLUSIONS: The ATA 2015 Guidelines represent a cost-effective strategy regarding AS and extent of surgery.
DOI: 10.1097/SLA.0000000000003074
PMID: 30339630

3. **J Clin Endocrinol Metab. 2018 Oct 16. doi: 10.1210/jc.2018-01933. [Epub ahead of print]**

Thyroid Ultrasound and the Increase in Diagnosis of Low-risk Thyroid Cancer.

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Context: Thyroid cancer incidence increased with the greatest change in adults aged ≥ 65.
Objective: To determine the relationship between area-level use of imaging and thyroid cancer incidence over time.
Design, Setting and Participants: Longitudinal imaging patterns in Medicare patients aged ≥ 65 years residing in Surveillance, Epidemiology, and End Results (SEER) regions were assessed in relationship to differentiated thyroid cancer diagnosis in patients aged ≥ 65 years included in SEER-Medicare. Linear mixed effects modeling was used to determine factors associated with thyroid cancer incidence over time. Multivariable logistic regression was used to determine patient characteristics associated with receipt of thyroid ultrasound as initial imaging.
Main outcome measure: differentiated thyroid cancer incidence.
Results: Between 2002 and 2013, thyroid ultrasound use as initial imaging increased ($p<0.001$). Controlling for time and demographics, use of thyroid ultrasound was associated with thyroid cancer incidence ($p<0.001$). The findings persisted when the cohort was restricted to papillary thyroid cancer ($p<0.001$), localized papillary thyroid cancer ($p=0.004$), and localized papillary thyroid cancer with tumor size ≤ 1 cm ($p=0.01$). Based on our model, from 2003 to 2013 at least 6,594 patients age ≥ 65 years were diagnosed with thyroid cancer in the United States due to increased use of thyroid ultrasound. Females and patients with comorbidities were more likely to have thyroid ultrasound as initial imaging.
Conclusion: Greater thyroid ultrasound use led to increased diagnosis of low-risk thyroid cancer; emphasizing the need to reduce harms through reduction in inappropriate ultrasound use and adoption of nodule risk stratification tools.
DOI: 10.1210/jc.2018-01933
PMID: 30329071

4. **J Clin Endocrinol Metab. 2018 Sep 28. doi: 10.1210/jc.2018-01690. [Epub ahead of print]**

Lung Metastasis in Pediatric Thyroid Cancer: Radiological Pattern, Molecular Genetics, Response to Therapy and Outcome.

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Context: Lung metastases are common in pediatric thyroid cancer. We present an analysis of a series of lung metastasis in pediatric TC.
Patients and methods: Data on 20 patients (16 females, 4 males, median age 14.5 years, range 10-18) were analyzed. The tumors include differentiated thyroid cancer in 19 patients and a single case of poorly differentiated thyroid cancer.
Results: Lung metastasis presented with 3 distinct radiological patterns: lung uptake on diagnostic radioiodine whole body scan (DxWBS) only in 3 patients

(15%), on DxWBS and CT scan as micro metastases (≤ 1 cm) in 16 patients (80%) and on DxWBS and CT scan as macrometastases (>1 cm) in 1 patient (5%). I-131 therapies were administered to all patients (median number 3, range 1-8) with a median cumulative administered activity of 317.5 mCi (range 109-682). None of the patients achieved a complete response but there was a substantial biochemical response. Over a median follow up of 8.2 years (range 0.75-16.3), 1 patient (5%) died, 1 patient (5%) had a biochemically incomplete response, 2 patients (10%) had an indeterminate response, 1 patient (5%) had progressive structural disease and 14 patients (70%) had stable structural disease. Mutational testing of 10/20 tumors revealed only two PIK3CA mutations in a single tumor.
Conclusions: Lung metastases are common in pediatric TC and present most frequently with bilateral radioiodine-avid micrometastases. Known single point mutations in adult TC are rare in pediatric TC. Biochemical response to I-131 is substantial but resolution of structural abnormalities is rare.
DOI: 10.1210/jc.2018-01690
PMID: 30272236

5. **World J Surg. 2018 Sep 28. doi: 10.1007/s00268-018-4813-5. [Epub ahead of print]**
Usefulness of Stereotactic Radiotherapy Using the CyberKnife for Patients with Inoperable Locoregional Recurrences of Differentiated Thyroid Cancer.
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BACKGROUND: Surgical resection is the preferred treatment for locoregional recurrence of differentiated thyroid cancer (DTC). However, some recurrences are unresectable because of their aggressive invasion or severe adhesions. On the other hand, stereotactic radiotherapy (SRT) enables high-dose irradiation to target lesions, and its usefulness for various cancers has been reported. The objective of the present study was to investigate the feasibility and efficacy of SRT as salvage treatment for locoregional recurrence of DTC.
METHODS: Between August 2011 and December 2017, 52 locoregional recurrent lesions in 31 patients with recurrent DTC were treated by SRT using the CyberKnife system. Information on the adverse events associated with SRT was retrospectively collected from the patients' medical records. Of the 52 lesions, 33 could be evaluated for therapeutic effectiveness by follow-up CT, and response was assessed using the RECIST criteria.
RESULTS: Twenty-five patients had papillary carcinoma, 5 had follicular carcinoma, and 1 had poorly differentiated cancer. SRT was delivered in one to 20 fractions, and the median dose was 30 Gy (range 15-60 Gy). Adverse events were not frequent, but 1 patient developed bilateral vocal cord palsy that required emergent tracheostomy. The median follow-up period of 33 lesions was 14 months (range 1-54 months). Complete response, partial response, stable disease, and progressive disease were seen in 10, 11, 9, and 3 patients, respectively. The 3-year local control rate was 84.6%.

CONCLUSION: SRT using the CyberKnife system was found to be a feasible and effective treatment to suppress the growth of locoregional recurrence of DTC.
DOI: 10.1007/s00268-018-4813-5
PMID: 30267291

6. **J Clin Endocrinol Metab. 2018 Sep 26. doi: 10.1210/jc.2018-00774. [Epub ahead of print]**

Clinical and Molecular Characteristics May Alter Treatment Strategies of Thyroid Malignancies in DICER1-syndrome.

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Context: The DICER1 syndrome is a rare, autosomal dominant inherited disorder that predisposes to a variety of cancerous and noncancerous tumors of mostly pediatric- and adolescent-onset, including differentiated thyroid carcinoma (DTC). DICER1-related DTC has been hypothesized to arise secondary to the increased prevalence of pre-malignant lesions, i.e. thyroid hyperplastic nodules.
Objective: To determine somatic alterations in DICER1-associated differentiated thyroid cancer and to study patient outcomes.
Design: Retrospective series.
Setting: Tertiary referral centers.
Patients: Ten patients with germline pathogenic DICER1 variants and early-onset DTC.
Investigation: Somatic DICER1 mutation analysis and extensive somatic DNA variant and gene fusion analyses on all tumors.
Results: Median age at DTC diagnosis was 13.5 years and no patients developed recurrent or metastatic disease (median follow-up 8 years). All thyroid specimens showed diffuse nodular hyperplasia with at least one focus suspect for DTC, but without infiltrative growth, extra-thyroidal extension, vascular invasion, or lymph node metastasis. Distinct somatic DICER1 RNase IIIb domain variants were identified in most presumed-malignant (and benign) nodules tested from each patient's tumor, suggestive of multiple distinct poly-clonal tumors. Furthermore,

9 of 10 DICER1-related DTC lacked well known oncogenic driver DNA variants and gene rearrangements.
Conclusions: On the basis of our clinical, histological and molecular data, we consider that the majority of DICER1-related DTCs form a low-risk subgroup. As these tumors may arise from one of many benign polyclonal nodules, hemi- or more likely total thyroidectomy may be often required, but radioiodine treatment may be unnecessary, given the patients age and their low propensity for metastases.
DOI: 10.1210/jc.2018-00774
PMID: 30260442

7. **J Clin Endocrinol Metab. 2018 Sep 25. doi: 10.1210/jc.2018-01478. [Epub ahead of print]**
Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers.
Dunn LA(1)(2), Sherman EJ(1)(2), Baxi SS(1)(2), Tchekmedyian V(1), Grewal RK(3), Larson SM(3), Pentlow KS(4), Haque S(3), Tuttle RM(1), Sabra MM(1), Fish S(1), Boucai L(1), Walters J(1), Ghossein RA(5), Seshan VE(6), Ni A(6), Li D(7), Knauf JA(8), Pfister DG(1)(2), Fagin JA(1)(8)(2), Ho AL(1)(2).
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Context: BRAFV600E mutant thyroid cancers are frequently refractory to radioiodine (RAI).
Objectives: To investigate the utility and molecular underpinnings of enhancing lesional iodide uptake with the BRAF inhibitor vemurafenib in RAI-refractory (RAIR) patients.
Design: This was a pilot trial that enrolled from June 2014 to January 2016.
Setting: Academic cancer center.
Patients: Patients with RAIR, BRAF mutant thyroid cancer.
Intervention: Patients underwent thyrotropin-stimulated iodine-124 (I-124) PET scans before and after approximately four weeks of vemurafenib. Those with enhanced RAI concentration exceeding a pre-defined lesional dosimetry threshold ("I-124 responders") were treated with iodine-131 (I-131). Response was evaluated with imaging and serum thyroglobulin. Three patients underwent research biopsies to evaluate the impact of vemurafenib on MAPK signaling and thyroid differentiation.
Main Outcome Measure: The proportion of patients in whom vemurafenib increased RAI incorporation to warrant I-131.
Results: Twelve BRAF mutant patients were enrolled; ten were evaluable. Four patients were I-124 responders on vemurafenib and treated with I-131, resulting in tumor regressions at 6 months. Analysis of research tumor biopsies demonstrated that vemurafenib inhibition of the mitogen-activated protein kinase

(MAPK) pathway was associated with increased thyroid gene expression and RAI uptake. The mean pre-treatment serum thyroglobulin value was higher among I-124 responders than non-responders (30.6 vs. 1.0 ng/ml; p-value= 0.0048).
Conclusions: Vemurafenib restores RAI uptake/efficacy in a subset of BRAF mutant, RAIR patients, likely by upregulating thyroid-specific gene expression via MAPK pathway inhibition. Higher baseline thyroglobulin values among responders suggest the hypothesis that tumor differentiation status may be a predictor of vemurafenib benefit.
DOI: 10.1210/jc.2018-01478
PMID: 30256977

8. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):4216-4223. doi: 10.1210/jc.2018-00803.**
Radioactive Iodine-Related Clonal Hematopoiesis in Thyroid Cancer Is Common and Associated With Decreased Survival.
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Context: Radioactive iodine (RAI) has been epidemiologically associated with the development of hematologic malignancies. Clonal hematopoiesis (CH) is a precursor clonal state that confers increased risk of leukemia and occurs at an elevated rate in patients with thyroid cancer relative to other solid tumors.
Objective: We explore if the high prevalence of CH may be a result of RAI exposure and whether CH may be a surrogate in the association between RAI and leukemia.
Design: CH, CH-potential driver (CH-PD), and overall survival were evaluated in 279 patients with advanced thyroid carcinoma.
Results: The prevalence of CH in patients with thyroid cancer was 37%, and that of CH-PD was 5.2%. Age was the strongest predictor of CH and CH-PD. For every year increase in age, there was a 5% and 13% increase in the odds of CH and CH-PD, respectively. RAI dose was significantly associated with CH and CH-PD, even after adjustment for age, external beam radiation therapy, and chemotherapy. For every 10 mCi increase in the dose of RAI administered, there was a 2% and 4% increase in the odds of CH and CH-PD, respectively. Patients with CH-PD previously exposed to RAI had a significantly poorer survival, even when stratified by age (heart rate = 3.75, 95% CI = 1.23 to 11.5, P = 0.02).
Conclusions: RAI was associated with a high prevalence of CH, and CH is a precursor state of hematologic malignancies. The implications of this study may

favor identification of CH in patients where the risks might outweigh the benefits of receiving RAI therapy for thyroid cancer.
DOI: 10.1210/jc.2018-00803
PMCID: PMC6194804 [Available on 2019-11-01]
PMID: 30137527

9. **Nat Rev Endocrinol. 2018 Nov;14(11):670-683. doi: 10.1038/s41574-018-0080-7.**
Thyroid surgery for differentiated thyroid cancer - recent advances and future directions.
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Population-based studies have demonstrated that an increasing number of incidental thyroid nodules are being identified. The corresponding increase in thyroid-based diagnostic procedures, such as fine-needle aspiration biopsy, has in part led to an increase in the diagnoses of thyroid cancers and to more thyroid surgeries being performed. Small papillary thyroid cancers account for most of this increase in diagnoses. These cancers are considered to be low risk because of the excellent patient outcomes, with a 5-year disease-specific survival of >98%. As a result, controversy remains regarding the optimal management of newly diagnosed differentiated thyroid cancer, as the complications related to thyroidectomy (primarily recurrent laryngeal nerve injury and hypoparathyroidism) have considerable effects on patient quality of life. This Review highlights current debates, including undertaking active surveillance versus thyroid surgery for papillary thyroid microcarcinoma, the extent of thyroid surgery and lymphadenectomy for low-risk differentiated thyroid cancer, and the use of molecular testing to guide decision-making about whether surgery is required and the extent of the initial operation. This Review includes a discussion of current consensus guideline recommendations regarding these topics in patients with differentiated thyroid cancer. Additionally, innovative thyroidectomy techniques (including robotic and transoral approaches) are discussed, with an emphasis on patient preferences around decision-making and outcomes following thyroidectomy.
DOI: 10.1038/s41574-018-0080-7
PMID: 30131586

10. **J Clin Endocrinol Metab. 2018 Dec 1;103(12):4384-4394. doi: 10.1210/jc.2017-02439.**
Genome-Wide Association Study Reveals Distinct Genetic Susceptibility of Thyroid Nodules From Thyroid Cancer.
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Context: Thyroid nodules are very common, and 7% to 15% of them are diagnosed as thyroid cancer. However, the inherited genetic risk factors for thyroid nodules and their associations with thyroid cancer remain unknown.
Objective: To identify the genetic variants associated with susceptibility to thyroid nodules in comparison with thyroid cancer.
Design and Setting: We performed a three-stage genome-wide association study for thyroid nodules. The discovery stage involved a genome-wide scan of 811 subjects with thyroid nodules and 691 subjects with a normal thyroid from a population-based cohort. Replication studies were conducted in an additional 1981 cases and 3100 controls from the participants of a health checkup. We also performed expression quantitative trait loci analysis of public data.
Results: The most robust association was observed in TRPM3 (rs4745021) in the joint analysis (OR, 1.26; P = 6.12 × 10-8) and meta-analysis (OR, 1.28; P = 2.11 × 10-8). Signals at MBIP/NKX2-1 were replicated but did not reach genome-wide significance in the joint analysis (rs2415317, P = 4.62 × 10-5; rs944289, P = 8.68 × 10-5). The expression quantitative trait loci analysis showed that TRPM3 expression was associated with the rs4745021 genotype in thyroid tissues.
Conclusions: To the best of our knowledge, we have performed the first genome-wide association study of thyroid nodules and identified a susceptibility locus associated with thyroid nodules, suggesting that thyroid nodules have a genetic predisposition distinct from that of thyroid cancer.
DOI: 10.1210/jc.2017-02439
PMID: 30099483

11. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):3993-4004. doi: 10.1210/jc.2018-01225.**
Primary Hyperparathyroidism.
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Background: Primary hyperparathyroidism (PHPT), the most common cause of hypercalcemia, is most often identified in postmenopausal women. The clinical presentation of PHPT has evolved over the past 40 years to include three distinct clinical phenotypes, each of which has been studied in detail and has led to evolving concepts about target organ involvement, natural history, and management.
Methods: In the present review, I provide an evidence-based summary of this disorder as it has been studied worldwide, citing key concepts and data that have helped to shape our concepts about this disease.
Results: PHPT is now recognized to include three clinical phenotypes: overt target organ involvement, mild asymptomatic hypercalcemia, and high PTH levels with persistently normal albumin-corrected and ionized serum calcium values. The factors that determine which of these clinical presentations is more likely to predominate in a given country include the extent to which biochemical screening is used, vitamin D deficiency is present, and whether parathyroid hormone levels are routinely measured in the evaluation of low bone density or frank osteoporosis. Guidelines for parathyroidectomy apply to all three clinical forms of the disease. If surgical guidelines are not met, parathyroidectomy can also be an appropriate option if no medical contraindications are present. If either the serum calcium or bone mineral density is of concern and surgery is not an option, pharmacological approaches are available and effective.
Conclusions: Advances in our knowledge of PHPT have guided new concepts in diagnosis and management.
DOI: 10.1210/jc.2018-01225
PMCID: PMC6182311 [Available on 2019-11-01]
PMID: 30060226

12. **J Clin Endocrinol Metab. 2018 Oct 1;103(10):3640-3646. doi: 10.1210/jc.2018-00381.**

Pilot Dose Comparison of Apatinib in Chinese Patients With Progressive Radioiodine-Refractory Differentiated Thyroid Cancer.

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Context: Apatinib has shown overwhelming efficacy in progressive radioiodine-refractory differentiated thyroid cancer (RAIR-DTC) starting at a 750-mg dosing protocol; however, a relatively high incidence of treatment-associated adverse events (TAAEs) was observed, which reduced quality of life and interrupted the treatment.
Objectives: To evaluate the efficacy and safety of apatinib with two different dosing schedules [750 or 500 mg once a day (q.d.)] in RAIR-DTC.
Participants and Methods: Twenty patients were sequentially recruited to receive apatinib beginning at 750 (n = 10) or 500 (n = 10) mg q.d. Efficacy and safety were compared in each 28-day cycle at the beginning two cycles and every two cycles thereafter.
Results: After six treatment cycles, the best disease control rates were 100% for

the 750- and 500-mg schedules, respectively, and the best objective response rates were 90.0% and 70.0% (P = 0.58), respectively. The two dosing schedules did not differ regarding greatest reduction in target lesion size (-42.7% vs -40.5% for the 750- vs 500-mg schedule, P = 0.48) and thyroglobulin level (-82.5% vs -94.3% for the 750- vs 500-mg schedule, P = 0.14). All patients experienced TAAEs, and the two dosing schedules showed similar incidence in TAAEs of grade ≥3 (100% vs 70% for 750 vs 500 mg, P = 0.21). However, the frequency of TAAEs was much higher in the 750-mg schedule (26.8 ± 6.5 vs 18.1 ± 6.5 in any grades, P = 0.01; 5.2 ± 3.0 vs 1.6 ± 1.3 in grade ≥3, P < 0.01).
Conclusion: Within six cycles of follow-up, the 500-mg starting dose protocol might be less toxic than the 750-mg protocol, whereas the efficacy was similar between the two dosages.
DOI: 10.1210/jc.2018-00381
PMID: 30053006

13. **J Clin Endocrinol Metab. 2018 Oct 1;103(10):3698-3705. doi: 10.1210/jc.2018-00612.**

Targeted Therapy in Advanced Thyroid Cancer to Resensitize Tumors to Radioactive Iodine.

Jaber T(1), Waguespack SG(1), Cabanillas ME(1), Elbanan M(2), Vu T(3), Dadu R(1), Sherman SI(1), Amit M(4), Santos EB(5), Zafereo M(4), Busaidy NL(1).
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Context: Many differentiated thyroid cancers (DTC) dedifferentiate and become radioactive iodine (RAI)-refractory (RAIR) with worse outcomes. Targeted therapy (TTx) may downregulate MAPK signaling and sensitize tumors to RAI.
Objective: We describe patients with RAIR DTC receiving TTx with demonstrated RAI uptake allowing for iodine-131 (I131) administration.
Design: Charts of patients with metastatic, progressive, RAIR DTC in whom TTx increased RAI uptake on a diagnostic whole-body scan (WBS), were reviewed. Results of WBS, I131 administration, thyroglobulin (TG) panels, and cross-sectional studies were recorded.
Setting: Thirteen patients [median age (range), 56 (45 to 75) years; seven men] were included; 11 (85%) had DTC, two (15%) had poorly DTC. Nine (69%) had BRAF mutations, three (23%) had RAS mutations, and one (8%) was wild type. Selective BRAF or an MEK inhibitor TTx was continued for a median (range) of 14.3 (1 to 76.4) months before diagnostic WBS.
Results: Nine (69%) patients were treated with I131 [median (range) activity, 204.4 (150 to 253) mCi], after which TTx was discontinued. Median (range) follow-up was 8.3 (0 to 17.4) months after I131 therapy. All nine patients had

durable disease control (three had partial response, six had stable disease). TG and TG antibody levels increased in patients who demonstrated uptake before TTx, and declined in eight of the nine patients after I131 treatment. Adverse events included pneumonitis and sialadenitis.
Conclusion: TTx in BRAF-/RAS-mutated RAIR DTC resensitizes tumors to iodine. Subsequent I131 administration results in meaningful responses. Patient selection, adverse events, response duration, and survival impact require additional study.
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14. **World J Surg. 2018 Oct;42(10):3215-3222. doi: 10.1007/s00268-018-4629-3.**
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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15. **World J Surg. 2018 Nov;42(11):3616-3623. doi: 10.1007/s00268-018-4644-4.**
Cribriform-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 recurrence.
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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16. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):4275-4282. doi: 10.1210/jc.2017-02529.**
p.Val804Met, the Most Frequent Pathogenic Mutation in RET, Confers a Very Low Lifetime Risk of Medullary Thyroid Cancer.
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Context: To date, penetrance figures for medullary thyroid cancer (MTC) for variants in rearranged during transfection (RET) have been estimated from families ascertained because of the presence of MTC.
Objective: To gain estimates of penetrance, unbiased by ascertainment, we analyzed 61 RET mutations assigned as disease causing by the American Thyroid Association (ATA) in population whole-exome sequencing data.
Design: For the 61 RET mutations, we used analyses of the observed allele frequencies in ∼51,000 individuals from the Exome Aggregation Consortium (ExAC) database that were not contributed via The Cancer Genome Atlas (TCGA; non-TCGA ExAC), assuming lifetime penetrance for MTC of 90%, 50%, and unbounded.
Setting: Population-based.
Results: Ten of 61 ATA disease-causing RET mutations were present in the non-TCGA ExAC population with observed frequency consistent with penetrance for MTC of >90%. For p.Val804Met, the lifetime penetrance for MTC, estimated from the allele frequency observed, was 4% [95% confidence interval (CI), 0.9% to 8%].
Conclusions: Based on penetrance analysis in carrier relatives of p.Val804Met-positive cases of MTC, p.Val804Met is currently understood to have high-lifetime penetrance for MTC (87% by age 70), albeit of later onset of MTC than other RET mutations. Given our unbiased estimate of penetrance for RET p.Val804Met of 4% (95% CI, 0.9% to 8%), the current recommendation by the ATA of prophylactic thyroidectomy as standard for all RET mutation carriers is likely inappropriate.
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