EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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SR: systematic review, **MA**: meta-analysis, **RCT**: randomized controlled trial, **CG**: consensus statement/guidelines

Pubmed-ID: PubMed-Identifier (unique number for each Pubmed entry)

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Journals covered

Journal	IF2020	Journal	IF2020
Acta Cytol	2.319	J Bone Miner Res	6.741
Am J Kidney Dis	8.860	J Clin Endocrinol Metab	5.958
Am J Nephrol	3.754	J Clin Oncol	44.544
Am J Surg	2.565	J Endocrinol	4.286
Am Surgeon	0.688	J Endocrinol Invest	4.256
Ann Surg	12.969	J Nephrol	3.902
Ann Surg Oncol	5.344	J Nucl Med	10.057
ANZ J Surg	1.872	J Surg Oncol	3.454
Br J Surg	6.939	Lancet	79.321
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Curr Opin Oncol	3.645	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	66.675
Endocr Relat Cancer	5.678	Nephrol Dial Transplant	5.992
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Eur J Endocrinol	6.664	Otolaryngol Head Neck Surg	3.497
Eur J Surg Oncol	4.424	Surg Clin North Am	2.741
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Horm Metab Res	2.936	Surg Oncol	3.279
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	6.223	Surg Oncol Clin N Am	3.495
JAMA Surg (*prev:* Arch Surg)	14.766	Surgery	3.982
Int J Cancer	7.396	Thyroid	6.568
J Am Coll Surg	6.113	Updates In Surgery	2.797
J Am Soc Nephrol	10.121	World J Surg	3.352
J Bone Miner Metab	2.626		

Journal names are links to the journal's homepage!, IF2020: Impact factor 2020

Thyroid

Meta-Analyses

Procalcitonin as an Alternative Tumor Marker of Medullary Thyroid Carcinoma.
J Clin Endocrinol Metab, 106(12):3634-43.
L. Giovanella, M. L. Garo, L. Ceriani, G. Paone, A. Campenni and F. D'Aurizio. 2021.
CONTEXT: Calcitonin (CT) measurement is pivotal in the management of medullary thyroid carcinoma (MTC), but several pitfalls can affect its reliability. Procalcitonin (ProCT) has been reported as a promising alternative MTC tumor marker. OBJECTIVE: This study aimed to determine the ProCT diagnostic accuracy in prediction and treatment monitoring of MTC. METHODS: Electronic databases were searched for observational studies published until May 2021 without language or time restrictions. Studies comparing ProCT and calcitonin accuracy were included. After removing duplicates and exclusion of not-eligible articles, relevant articles were screened independently by 2 reviewers. Eleven studies (4.5% of the identified studies) met the selection criteria. Two reviewers independently extracted data and assessed data quality and validity through QUADAS-2. RESULTS: A meta-analysis was performed on 11 sufficiently clinically and statistically homogeneous studies (n = 5817 patients, 335 MTC patients). Hierarchical summary receiver operating characteristics and bivariate methods were applied. Serum ProCT was found to be a highly accurate test for MTC diagnosis and monitoring. The pooled sensitivity, specificity, positive and negative likelihood ratios, area under the curve, and positive and negative predictive values for ProCT were 0.90 (95% CI: 0.71-0.97), 1.00 (95% CI: 0.85-1.00), 288 (95% CI: 5.6-14 929.3), 0.10 (95% CI: 0.03-0.33), 0.97 (95% CI: 0.95-0.98), 99%, and 2%, respectively. CONCLUSIONS: The high accuracy, compounded with favorable analytical characteristics, give ProCT great potential to replace calcitonin as a new standard of care in the management of MTC.
PubMed-ID: 34382653
http://dx.doi.org/10.1210/clinem/dgab564

Intraoperative Neural Monitoring for Early Vocal Cord Function Assessment After Thyroid Surgery: A Systematic Review and Meta-Analysis.
World J Surg, 45(11):3320-7.
D. H. Kim, S. W. Kim and S. H. Hwang. 2021.
Objective This study evaluated the diagnostic accuracies of various forms of intraoperative neural monitoring (IONM) in terms of predicting vocal cord palsy after thyroidectomy. Methods Two authors independently reviewed the six databases (PubMed, the Cochrane database, Embase, the Web of Science, SCOPUS, and Google Scholar) from their dates of inception to March 2021. Intraoperative electromyographic neuromonitoring (IONM) was compared with laryngoscopic detection (the reference method). True-positive, true-negative, false-positive, and false-negative data were extracted from each study. Methodological quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies ver. 2 tool. Results Twenty-seven prospective or retrospective studies were included. The diagnostic odds ratio for IONM was 152.9623 ([95% confidence interval [75.4249; 310.2085]. The area under the summary receiver operating characteristic curve was 0.966. The sensitivity, specificity, negative predictive value, and positive predictive value were 0.8219 ([0.6862; 0.9069]), 0.9783 ([0.9659; 0.9863]), 0.9943 ([0.9880; 0.9973]), and 0.5523 ([0.4458; 0.6542]), respectively. The correlation between sensitivity and false-positive rate was 0.200, indicating the absence of heterogeneity. Subgroup analysis showed that the diagnostic accuracies of the continuous IONM was higher than those of intermittent IONM, and recent publications (> 2011) was higher than early publication (< 2010). Conclusions As the technology and knowledge of IONM have been accumulated and progressed over the past decades, the predictive value of IONM in postoperative vocal cord palsy has also improved. Moreover, the advances of continuous IONM technology could make a breakthrough in vocal cord evaluation after thyroid surgery.
PubMed-ID: 34191086
http://dx.doi.org/10.1007/s00268-021-06225-x

Meta-analysis on continuous nerve monitoring in thyroidectomies.
Head Neck, 43(12):3966-78.
D. Ku, M. Hui, P. Cheung, O. Chow, M. Smith, F. Riffat, N. Sritharan, D. Kamani and G. Randolph. 2021.
In the last decade, the introduction of continuous intraoperative recurrent laryngeal nerve (RLN) monitoring (C-IONM) has enabled the operator to verify the functional integrity of the vagus nerve-recurrent laryngeal nerve (VN-RLN) axis in real-

time. We aim to present the current evidence on C-IONM utility for thyroid surgery by conducting the first meta-analysis on this technique. A systematic review of literature was conducted by two independent reviewers via Ovid in the Medline, EMBASE, and Cochrane reviews databases. The search was limited to human subject research in peer-reviewed articles of all languages published between Jan 1946 and April 2020. Medical subject headings (MeSH) terms utilized were thyroid surgery, thyroidectomies, recurrent laryngeal nerve, vagal nerve, monitor, and stimulation. Thirty-eight papers were identified from Ovid, another six papers were identified by hand-search. A random effect meta-analysis was performed with assessment of heterogeneity using the I(2) value. A total of 23 papers that investigated the use of continuous vagal nerve monitoring during thyroid surgery were identified. The proportion of nerves at risk (NAR) with temporary RLN paralysis postoperation was 2.26% (95% CI: 1.6-2.9, I(2) = 37). The proportion of NAR with permanent RLN palsy postoperation was 0.05% (95% CI: 0.08-0.2, I(2) = 0). In this meta-analysis, there is one case of temporary vagal nerve paralysis secondary to VN electrode dislodgement, and a case of hemodynamic instability manifested in bradycardia and hypotension in the initial phase of surgery shortly after calibration. C-IONM is a safe and effective means by which RLN paralyses in thyroid surgery can be reduced.
PubMed-ID: 34342380
http://dx.doi.org/10.1002/hed.26828

Effect of TSH Suppression Therapy on Bone Mineral Density in Differentiated Thyroid Cancer: A Systematic Review and Meta-analysis.
J Clin Endocrinol Metab, 106(12):3655-67.
E. J. Ku, W. S. Yoo, E. K. Lee, H. Y. Ahn, S. H. Woo, J. H. Hong, H. K. Chung and J. W. Park. 2021.
CONTEXT: Because subclinical hyperthyroidism increases the risk of osteoporosis and fractures, concerns are growing about the long-term skeletal safety of TSH suppression therapy after total thyroidectomy in patients with differentiated thyroid cancer (DTC). OBJECTIVE: We aimed to determine the effect of TSH suppression therapy on bone mineral density (BMD) in DTC patients. METHODS: We searched PubMed, Embase, the Cochrane library, and other sources. Eligible observational studies included DTC patients who underwent TSH suppression therapy and BMD measurement. Two independent reviewers extracted data on the studies' characteristics and outcomes and determined their risk of bias. Data were extracted from each study for postmenopausal/premenopausal women's and men's lumbar spine (LS), femoral neck (FN), and total hip (TH) BMD and summed using a random-effects meta-analysis model. The weighted mean differences with 95% CIs are expressed for the differences in outcome measurements between groups. RESULTS: Seventeen studies (739 patients and 1085 controls) were included for quantitative analysis. In postmenopausal women, TSH suppression therapy showed a significant decrease in LS BMD (-0.03; -0.05, -0.02), and a similar trend was seen in TH. In premenopausal women, TSH suppression therapy significantly increased LS BMD (0.04; 0.02, 0.06) and FN BMD (0.02; 0.01, 0.04). In men, there was no significant association between TSH suppression therapy and BMD at any site compared with the controls. CONCLUSION: Evidence from observational studies suggests that postmenopausal women treated with TSH suppression therapy are at risk for lower BMD. Attention should be paid to long-term skeletal safety in DTC survivors.
PubMed-ID: 34302730
http://dx.doi.org/10.1210/clinem/dgab539

Cardiovascular Outcomes in Thyroid Cancer Patients Treated With Thyroidectomy: A Meta-analysis.
J Clin Endocrinol Metab, 106(12):3644-54.
E. K. Lee, H. Y. Ahn, E. J. Ku, W. S. Yoo, Y. K. Lee, K. H. Nam, Y. J. Chai, S. Moon and Y. S. Jung. 2021.
CONTEXT: Thyroid dysfunction is associated with an increased risk of cardiovascular disease (CVD) in the general population; however, it remains controversial whether differentiated thyroid cancer (DTC) treatment, including thyroidectomy and thyroid-stimulating hormone suppression, further increases the risk of CVD. OBJECTIVE: This study aimed to evaluate the risk of CVD in patients with DTC. METHODS: We performed a review of observational studies on associations between DTC and cardiovascular outcomes, indexed in MEDLINE, Embase, and Web of Science. We excluded studies that evaluated CVD as comorbidity before DTC diagnosis and those that used active surveillance without thyroidectomy as an intervention. Risk estimates were pooled using random- and fixed-effects models when 3 or more studies reported on the outcome of interest. Echocardiographic and hemodynamic parameters were examined. RESULTS: Eighteen studies were included in the quantitative analysis (193 320 cases with DTC and 225 575 healthy controls). DTC was associated with an increased risk of atrial fibrillation (pooled risk ratio [RR] = 1.55 [95% CI: 1.30-1.84]), coronary artery disease (RR = 1.10 [1.00-1.21]), cerebrovascular accidents (RR = 1.15 [1.09-1.20]), and all-cause mortality (RR = 1.95 [1.03-3.69]). DTC was associated with higher diastolic blood pressure (standardized mean difference [SMD], 0.22 [0.01-0.42]), heart rate (0.37 [0.17-0.57]), left ventricular mass index (0.66 [0.45-0.88]), and interventricular septal thickness (0.91 [0.33-1.49]) and lower early to late ventricular filling velocities (-0.42 [-0.79 to -0.05]), but not with ejection fraction.

CONCLUSION: Patients with DTC are at an increased risk of atrial fibrillation, CVD, increased heart rate, and left ventricular mass development.
PubMed-ID: 34347085
http://dx.doi.org/10.1210/clinem/dgab576

Clinicopathological Significance of Papillary Thyroid Carcinoma Located in the Isthmus: A Meta-Analysis.
World J Surg, 45(9):2759-68.
Y. S. Lyu, J. S. Pyo, W. J. Cho, S. Y. Kim and J. H. Kim. 2021.
BACKGROUND: The thyroid isthmus is located directly anterior to the trachea and is covered by the strap muscles. Several studies have suggested that papillary thyroid carcinoma (PTC) in the isthmus is more aggressive and is associated with a poor prognosis. The purpose of this meta-analysis was to assess the clinicopathological characteristics and recurrence rates of PTC in the isthmus compared to PTC at other sites. METHODS: Relevant articles were obtained by searching the PubMed database. A meta-analysis was performed using 11 eligible studies. RESULTS: The rate of extrathyroidal extension was 0.502 (95% confidence interval [CI]: 0.239-0.764) and 0.454 (95% CI: 0.331-0.582) for isthmus PTC and PTC at other site, respectively; however, the difference in the rates was not statistically significant. Lymphovascular invasion did not significantly differ between isthmus PTC (0.179 [95% CI: 0.102-0.297]) and PTC at other sites (0.114 [95% CI: 0.066-0.188]). The rate of central lymph node (LN) metastasis was significantly higher in isthmus PTC (0.527 [95% CI: 0.435-0.617]) than in PTC at other sites (0.352 [95% CI: 0.280-0.432]). No significant difference was observed between the two groups in terms of lateral cervical LN metastasis rate. Isthmus PTC was more likely to have a prominent recurrence rate (0.046 [95% CI: 0.022-0.094]) than PTC at other sites (0.010 [95% CI: 0.001-0.070]); however, the difference was not statistically significant (because of the small number of included studies). CONCLUSIONS: The results of this meta-analysis indicated that isthmus PTC was associated with an increased risk of central LN metastasis. Isthmus PTC seems to have a slightly higher recurrence rate than PTC at other sites. Therefore, considering the potential of the isthmus location as an unfavorable factor, more attention should be focused on isthmus PTC, and a more aggressive approach such as prophylactic central LN dissection might provide better outcomes in PTC management.
PubMed-ID: 34117511
http://dx.doi.org/10.1007/s00268-021-06178-1

Association of BMI with Clinicopathological Features of Papillary Thyroid Cancer: A Systematic Review and Meta-Analysis.
World J Surg, 45(9):2805-15.
R. J. O'Neill, S. Abd Elwahab, M. J. Kerin and A. J. Lowery. 2021.
BACKGROUND: Papillary thyroid cancer (PTC) is the most common subtype of thyroid cancer. The incidence of PTC is rising in tandem with an obesity epidemic. Associations have been demonstrated between increased body mass index (BMI) and worse oncological outcomes in a number of malignancies. However, research on this topic in PTC to date has been inconsistent, often due to limited data. This study aimed to measure the association between BMI and potentially adverse clinicopathological features of PTC. METHODS: A meta-analysis of studies reporting outcomes after surgical treatment of PTC was performed. PubMed, Embase and the Cochrane Library were searched systematically to identify studies which provided data on BMI and clinicopathologic features of PTC. Relevant data were extracted and synthesis performed using adjusted odds ratios where available and crude values when not. Data were analysed by inverse variance using random and fixed effects models. RESULTS: Data on 35,237 patients from 15 studies met the criteria for inclusion. Obesity was associated with larger tumour size (MD = 0.17 cm [0.05, 0.29]), increased rates of multifocality (OR = 1.41 [1.16, 1.70]), extrathyroidal extension (OR = 1.70 [1.39, 2.07]) and nodal spread (OR = 1.18 [1.07, 1.30]). Associations were more pronounced as BMI increased. There was no association between BMI and bilaterality, vascular invasion or metastatic spread. CONCLUSION: Increased BMI is significantly associated with multiple potentially adverse features of PTC. The effect on long-term oncological outcomes requires further evaluation.
PubMed-ID: 34136926
http://dx.doi.org/10.1007/s00268-021-06193-2

Outcomes of Tracheal Resections in Well-Differentiated Thyroid Cancer-A case series and meta-analysis.
World J Surg, 45(9):2752-8.
A. Warshavsky, R. Rosen, N. Nard-Carmel, N. Muhanna, O. Ungar, A. Abergel, D. M. Fliss and G. Horowitz. 2021.
BACKGROUND: Tracheal invasion in thyroid cancer is a well-known form of advanced disease. There is an ongoing controversy over outcomes of tracheal shaving in this situation. The aim of this study was to compare the results of tracheal shaving to radical resections in patients with low-volume tracheal involvement. METHODS: An institutional case

series and a meta-analysis was conducted. All studies that included patients diagnosed with well-differentiated thyroid cancer (WDTC) and tracheal invasion were analyzed. Patients with low-volume tracheal invasion (according to the Shin classification) were extracted from the various studies and subsequently included in this study. The outcomes of tracheal shaving and radical resection were consolidated and compared. All recurrences and mortality over 10 years of follow-up were calculated using the Kaplan-Meier method. RESULTS: Institutional case series included 22 patients diagnosed with WDTC and tracheal invasion that underwent resection. There was one case of recurrence (4.5%) during the follow-up period and no mortality. The meta-analysis yielded a total of 284 patients from six studies who met the inclusion criteria. The 10-year overall survival was 82.4% for the shave group and 80.8% for the resection group. The combined Kaplan-Meier curves revealed no statistically significant difference between the two techniques (hazard ratio [HR] = 0.86, P = .768). The combined 10-year local control rate of the shave group was 90.2%. CONCLUSIONS: The outcomes of tracheal shaving in low-volume invasion are similar to more aggressive forms of tracheal resections. Shave resection is oncologically safe in carefully selected WDTC patients demonstrating minimal tracheal invasion.
PubMed-ID: 34023920
http://dx.doi.org/10.1007/s00268-021-06172-7

Clinical efficacy of lenvatinib for the treatment of radioiodine-refractory thyroid carcinoma: A systematic review and meta-analysis of clinical trials.
Clin Endocrinol (Oxf), 95(3):478-88.
Z. Yan, M. Yang and C. L. Lai. 2021.
OBJECTIVE: To evaluate the efficacy of lenvatinib in the treatment of radioiodine-refractory thyroid carcinoma. BACKGROUND: Thyroid carcinoma is one of the top ten carcinomas worldwide. Clinically, thyroid cancers are managed with resections and adjuvant therapy with radioiodine. However, radioiodine is not effective for radioiodine-refractory (RR) thyroid carcinoma in some patients. Lenvatinib is a multi-kinase inhibitor for the treatment of RR thyroid carcinoma. Several clinical trials showed its efficacy in prolonging progression-free survival (PFS) and overall survival (OS). DESIGN, PATIENTS AND MEASUREMENTS: A systematic search was done on databases (PubMed, Embase, MEDLINE, Cochrane) on 8 June 2020. Search keywords were lenvatinib, thyroid carcinoma and randomized controlled trials. Clinical trials fulfilling the SELECT protocol were selected to evaluate the efficacy of lenvatinib in terms of prolongation of PFS, OS and objective response rate (ORR). The risk ratio and distribution of grade 3 or above adverse events were documented. RESULTS: Of the 3997 patients of mean age 62.5 years in fifteen selected studies, lenvatinib is associated with prolonged PFS (hazard ratio 0.24, 95% CI, 0.19-0.31, p < .001) and OS (hazard ratio 0.65, 95% CI, 0.52-0.81, p < .001). Compared with placebo, the risk ratio of ORR and incidence of grade 3 or above adverse events are 35.41 (95% CI, 19.42-64.58, p < .001) and 8.25 (95% CI, 6.50-10.46, p < .001), respectively. Subgroup analysis shows that lenvatinib is effective for all patients with RR thyroid carcinoma, regardless of age, histological subtypes, radiological subtypes and mutation status. CONCLUSION: Lenvatinib is effective in the treatment of RR thyroid carcinoma. Close monitoring of serious adverse events is recommended.
PubMed-ID: 33834514
http://dx.doi.org/10.1111/cen.14479

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Less extensive surgery for low-risk papillary thyroid cancers post 2015 American Thyroid Association guidelines in an Australian tertiary centre.
Eur J Surg Oncol, 47(11):2781-7.
M. Adhami, C. R. Bhatt, S. Grodski, J. Serpell and J. C. Lee. 2021.
INTRODUCTION: The 2015 American Thyroid Association guidelines (ATA15) consider hemithyroidectomy (HT) a viable treatment option for low-risk papillary thyroid cancers (PTCs) between 1 and 4 cm. We aimed to examine the impact of ATA15 in a high-volume Australian endocrine surgery unit. METHODS: A retrospective study of all patients undergoing thyroidectomy from January 2010 to December 2019. INCLUSION CRITERIA: PTC histopathology, Bethesda V-VI, size 1-4 cm, and absence of clinical evidence of lymph node or distant metastases pre-operatively. Primary outcome was rate of HT before and after ATA15. RESULTS: Of 5408 thyroidectomy patients, 339 (6.3%) met the inclusion criteria - 186 (54.9%) pre-ATA15 (2010-2015) and 153 (45.1%) post-ATA15 (2016-2019). The patient groups were similar; there were no significant differences between groups in age, sex, tumour size, proportion with Bethesda VI cytology, compressive symptoms, or thyrotoxicosis. Post-ATA15, there was a significant increase in HT rate from 5.4% to 19.6% (P = 0.0001). However, there was no corresponding increase in completion thyroidectomy (CT) rate (50.0% versus 27.6%, P = 0.2). The proportion managed with prophylactic central neck dissection (pCND) fell from 80.5% to 10.8% (P < 0.0001). Pre-ATA15, the only factor significantly associated with HT was Bethesda V. In contrast, post-ATA15, HT was more likely in patients with younger age, smaller tumours, and Bethesda V. CONCLUSION: After the release of 2015 ATA guidelines, we observed a significant increase in HT rate and a significant decrease in pCND rate for low-risk PTCs in our specialised thyroid cancer unit. This reflects a growing clinician uptake of a more conservative approach as recommended by ATA15.
PubMed-ID: 34364721
http://dx.doi.org/10.1016/j.ejso.2021.06.018

Use of Predictive Modeling to Tailor Molecular Testing Utilization for Thyroid Nodules.
Otolaryngol Head Neck Surg, 165(3):406-13.
S. T. Ahmed, S. Fernandes, Q. Gao, T. J. Ow, R. V. Smith, B. A. Schiff and V. Mehta. 2021.
OBJECTIVE: Various risk stratification systems for cytologically indeterminate thyroid nodules are available. However, malignancy risk assessment data, such as ultrasound features, are not always used when the decision is to order molecular testing or not. Our aim was to investigate the utility of molecular testing after incorporating an algorithm with ultrasound-based risk of malignancy (ROM) estimation. STUDY DESIGN: Diagnostic/prognostic study. SETTING: Single-institution urban tertiary care center. METHODS: We performed a single-institution retrospective chart review of all thyroid nodules that had undergone molecular testing. A web-based Malignancy Risk Estimation System for Thyroid Nodules was utilized with ultrasound findings to stratify malignancy risk according to the Korean Thyroid Imaging Reporting and Data System (TI-RADS), French TI-RADS, American Association of Clinical Endocrinology guideline, and American Thyroid Association guideline. A novel algorithm for utilizing molecular testing at our institution was developed with the Korean TI-RADS and with recommendations from the American Thyroid Association and National Comprehensive Cancer Network. RESULTS: The Korean TI-RADS performed best in our population (area under the curve = 0.83). A positive molecular test result had a positive association with a higher ROM according to all 4 models (P < .05). Use of our algorithm prior to molecular testing would have prevented 38% of benign/low-ROM negative nodules (n = 28) from being tested. CONCLUSION: In patients with indeterminate thyroid nodules, an algorithm built on pre- and posttest probability to guide molecular testing might reduce unnecessary testing of benign and low-risk nodules.
PubMed-ID: 33781120
http://dx.doi.org/10.1177/01945998211004155

Long-term cosmetic results of video-assisted thyroidectomy: a comparison with conventional surgery.
Langenbecks Arch Surg, 406(5):1625-33.
P. F. Alesina, W. Wahabie, B. Meier, J. Hinrichs, W. Mohmand, A. Kapakoglou, P. Kniazeva and M. K. Walz. 2021.
PURPOSE: We present the long-term cosmetic results of the video-assisted thyroidectomy (MIVAT) in comparison to the conventional operation. METHODS: Forty-eight patients (four males, 44 females; mean age 47.4 ± 12.5 years) constituted the video-assisted group (VA-Group). These were compared with 48 patients (10 males, 38 females; mean age 47.4 ± 12.5 years) operated by conventional surgery (C-Group). The patients were selected from all thyroid operations performed between January 2016 and June 2017. Patient Scar Assessment Scale (PSAS) and Observer Scar Assessment Scale (OSAS)

were used for the evaluation performed by an independent surgeon. Both scales contained six items scored numerically on a ten-step scale ranging from 1 (normal skin) to 10 (worst result). Moreover, photos of all scars were taken and analyzed by six team surgeons using modified OSAS. RESULTS: The mean follow-up time was 31.7 ± 6.4 months for the MIVAT group and 32.9 ± 4.6 months for the conventional group (p = 0.39). The mean scar length in the VA-Group was 2.6 cm vs. 3.8 cm in the C-Group (p < 0.0001). The total score of PSAS was 9.93 (6-35) for MIVAT and 9.72 (6-29) for conventional thyroidectomy (p = 0.22). The total OSAS score by the independent surgeon showed a better cosmetic outcome for conventional surgery (13.19 vs. 12.33; p = 0.01). The total OSAS score by the six team surgeons did not differ between both groups in five of six ratings; one surgeon favored MIVAT (12.2 vs. 13.6; p = 0.04). CONCLUSIONS: This study does not find cosmetic advantages of minimally invasive video-assisted thyroidectomy compared to conventional thyroidectomy.
PubMed-ID: 33987765
http://dx.doi.org/10.1007/s00423-021-02196-8

Identifying and addressing Health disparities in Thyroid Cancer Care.
J Clin Endocrinol Metab,
E. O. Asamoah, G. Caraballo and M. R. Castro. 2021.
PubMed-ID: 34871424
http://dx.doi.org/10.1210/clinem/dgab875

Transient asystole related to carbon dioxide embolism during transoral endoscopic parathyroidectomy vestibular approach.
Head Neck, 43(11):E51-E5.
N. Aygun, D. Saridemir, K. Bas, F. Tunca, C. Arici and M. Uludag. 2021.
BACKGROUND: Rarely, during the endoscopic thyroidectomy, carbon dioxide (CO(2)) embolism may occur. METHODS: Case 1: A 65-year-old female who was seen with prolonged fatigue and generalized bone pain was diagnosed primary hyperparathyroidism (PHPT) based on her preoperative biochemical profile. Transoral endoscopic parathyroidectomy vestibular approach (TOEPVA) was planned. Case 2: A 52-year-old male patient was seen with weakness and hepatosteatosis and was diagnosed PHPT based on the laboratory workup. TOEPVA was planned. RESULTS: After subplatysmal dissection with vascular tunnel probe, both of the patients developed severe bradycardia and hypotension leading to asystole during the CO(2) insufflation. The possibility of CO(2) embolism was considered and insufflation was terminated. After a successful cardiac massage, sinus rhythm returned. CONCLUSION: TOEPVA may develop CO(2) embolism leading to asystole during the CO(2) insufflation.
PubMed-ID: 34487402
http://dx.doi.org/10.1002/hed.26855

Thresholds of Basal- and Calcium-Stimulated Calcitonin for Diagnosis of Thyroid Malignancy.
Horm Metab Res, 53(12):779-86.
M. Baetu, C. A. Olariu, C. Stancu, A. Caragheorgheopol, D. Ioachim, G. Moldoveanu, C. Corneci and C. Badiu. 2021.
Since medullary thyroid carcinoma is an aggressive cancer, it is important to have an early detection based on stimulated calcitonin (CT), especially when basal-CT is slightly elevated. The objective of this work was to set specific thresholds for basal-CT- and calcium-stimulated calcitonin for prediction of thyroid malignancy in female population. The study included 2 groups: group A-women with elevated basal-CT (>9.82 pg/ml) and group B-women with normal basal-CT (control group). After calcium stimulation test precise protocol, histopathological reports of those that required surgery were correlated with both basal and stimulated calcitonin. The best basal and stimulated calcitonin cut-offs for distinguishing female patients with medullary thyroid carcinoma or C-Cell-hyperplasia from other pathologies or normal cases were: 12.9 pg/ml, respectively 285.25 pg/ml. For basal-CT above 30 pg/ml, malignancy was diagnosed in 9/9 patients (100%): 9 MTC. For stimulated calcitonin above 300 pg/ml, malignancy was diagnosed in 17/21 patients (80.95%): 12 MTC and 5 papillary thyroid carcinomas. The smallest nodule that proved to be medullary thyroid carcinoma had only 0.56/0.34/0.44 cm on ultrasound, with no other sonographic suspicious criteria. In conclusion, we have identified in Romanian female population basal and stimulated calcitonin thresholds to discriminate medullary thyroid carcinoma or C-Cell-hyperplasia from other cases. We recommend thyroid surgery in all women with stimulated calcitonin above 285 pg/ml. Further studies on larger groups are necessary to establish and confirm male and female cut-offs for early diagnosis of medullary thyroid carcinoma, and interestingly, maybe for macro-papillary thyroid carcinomas alike. The calcium administration has minimum side-effects, but continuous cardiac monitoring is required.

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http://dx.doi.org/10.1055/a-1661-4420

Spare Parathyroid Glands During Thyroid Surgery with Perioperative Autofluorescence Imaging: A Diagnostic Study.
World J Surg, 45(9):2785-90.
A. Bellier, Y. Wazne, T. Chollier, N. Sturm and P. Chaffanjon. 2021.
BACKGROUND: The aim of this original study was to determine the number of parathyroid glands that can be saved and reimplanted thanks to autofluorescence during thyroid surgery. Preservation of parathyroid function remains challenging during thyroid surgery. The parathyroid glands must be identified and immediately autotransplanted in the case of devascularization. Near-infrared autofluorescence of parathyroid glands has recently been proposed to help surgeons during the dissection. METHODS: A total of 116 thyroid lobectomies were performed on 70 consecutive adult patients. Each lobectomy specimen was scanned in vitro with an autofluorescence imaging device. Every spot of autofluorescence was examined by the surgeon and subsequently the pathologist. The pathologist also performed a complete study of the rest of the lobe. We compared the results of the macroscopic and microscopic diagnoses. RESULTS: We detected 24 fluorescent spots on the specimens: 13 were considered to be parathyroid tissue by the surgeon and 11, non-parathyroid tissue. The pathologist confirmed the surgical diagnosis but also discovered 15 additional parathyroid glands that were hidden. CONCLUSIONS: Autofluorescence imaging of the thyroidectomy specimen with surgical inspection is safe, quick, noninvasive and can help detect the accidental removal of parathyroid glands. About 60% of these glands can be spared and autotransplanted during the surgery.
PubMed-ID: 33835219
http://dx.doi.org/10.1007/s00268-021-06102-7

Women With Chronic Hypoparathyroidism Have Low Risk of Adverse Pregnancy Outcomes.
J Clin Endocrinol Metab, 106(11):3312-9.
S. Björnsdottir, B. Clarke, O. Mäkitie, A. Sandström, E. Tiblad, T. Spelman and O. Kämpe. 2021.
CONTEXT: There are scarce data on the management of chronic hypoparathyroidism (hypoPT) in pregnant women. OBJECTIVE: The aim of this study was to evaluate pregnancy outcome and total number of births in maternal chronic hypoPT. METHODS: The Swedish National Patient Register, The Swedish Prescribed Drug Register, Swedish Medical Birth Register, and the Total Population Register were used to identify 97 women with chronic hypoPT and 1030 age-matched controls who delivered 139 and 1577 singleton infants, respectively, following diagnosis between 1997 and 2017. RESULTS: Women in the chronic hypoPT group had more frequent diabetes (DM) and chronic kidney disease (CKD) compared with the control group (P = 0.043 and P < 0.001, respectively). After adjusting for DM, CKD, maternal age at delivery, and calendar year of delivery, chronic hypoPT cases were associated with increased risk of induction of labor (OR, 1.82; 95% CI, 1.13-2.94) and birth of infants with lower birth weight (ß-coefficient -188 g; 95% CI, -312.2 to -63.8) compared with controls. No difference was found in infant length, small for gestational age, or head circumference after adjustments. Mean gestational age at delivery after controlling for DM, CKD, and pre-eclampsia was not significantly younger (P = 0.119). There was no difference in congenital malformations or perinatal death and no difference in the total number of infants born between groups (P = 0.518). CONCLUSION: The majority of women with chronic hypoPT had normal pregnancy outcomes, and the overall risks appear low. Maternal chronic hypoPT is, however, associated with higher risk of induction of labor and slightly lower infant birth weight.
PubMed-ID: 34240167
http://dx.doi.org/10.1210/clinem/dgab503

Radioiodine treatment: an historical and future perspective.
Endocr Relat Cancer, 28(10):T121-T4.
P. Borges de Souza and C. J. McCabe. 2021.
PubMed-ID: 33690155
http://dx.doi.org/10.1530/ERC-21-0037

A Comparison of the Seventh and Eighth Editions of the AJCC Staging Systems to Predict Recurrence in Papillary Thyroid Microcarcinoma.
Ann Surg Oncol, 28(11):6564-71.
Z. Chen, J. Ruan, Y. Yao, L. Wen, Z. Mao, S. Chen, H. Zhu, Y. Zhao, Z. Li, T. J. Fahey, L. Teng and W. Wang. 2021.
BACKGROUND: The incidence of papillary thyroid microcarcinoma has been constantly rising in recent decades. The tumor, node, metastasis staging system is designed to predict prognosis in patients with papillary thyroid carcinoma.

Recent studies have shown that the American Joint Committee on Cancer (AJCC) 8th edition is superior to the 7th edition for predicting tumor recurrence in PTC patients. To date, whether the 8th edition is also better able to predict recurrence in papillary thyroid microcarcinoma (PTMC) remains unclear. METHOD: We enrolled 1007 cases from our thyroid cancer database in the First Affiliated Hospital, Zhejiang University School of Medicine, from 1997 to 2011. Univariable and multivariate Cox hazard regression analyses were used to identify the association between variables and recurrence. Disease-free survival was calculated using the Kaplan-Meier method and compared using the log-rank test. RESULTS: A total of 1007 PTMC patients were enrolled, with a median follow-up of 67 months. Of 93 (9.2%) patients downstaged by the changes in versions, 49 (52.7%) were downstaged because the age-at-diagnosis cut-off used for staging increased from 45 to 55 years, while 35 (37.6%) were downstaged due to the weakening of the effects of lymph node metastasis. The recurrence rate of PTMC was 4.17%. Univariate Cox hazards regression analyses showed that TNM stage according to the AJCC 8th edition was significantly associated with recurrence, while the recurrence survival curves showed that TNM stage (stage I vs. stage II-IV) according to the AJCC 8th edition, but not the 7th edition, was significantly associated with disease-free survival ($p < 0.05$). CONCLUSIONS: The AJCC 8th edition has better ability to predict recurrence in PTMC patients than the 7th edition.
PubMed-ID: 33521903
http://dx.doi.org/10.1245/s10434-021-09596-6

Predictors of Bilateral Disease in Pediatric Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e4242-e50.
C. E. Cherella, D. M. Richman, E. Liu, M. C. Frates, B. P. Modi, B. Zendejas, J. R. Smith, J. A. Barletta, M. L. Hollowell and A. J. Wassner. 2021.
CONTEXT: Total thyroidectomy is recommended for children with papillary thyroid carcinoma, partly because of a high prevalence of bilateral disease. Identifying characteristics that predict bilateral disease might identify candidates for more limited surgery. OBJECTIVE: Investigate associations of preoperative or histopathological characteristics with bilateral disease in children with differentiated thyroid cancer. METHODS: Retrospective cohort study (1998-2020) at 2 academic hospitals. Patients <19 years who underwent total thyroidectomy for differentiated thyroid cancer were included. Clinical, sonographic, and histopathological characteristics were evaluated. The presence of bilateral disease on histopathology was assessed by univariable analysis and multivariable logistic regression. RESULTS: One hundred and fifteen subjects were analyzed (90% with papillary carcinoma). Median (range) age at diagnosis was 15.0 (8.1-18.9) years. Bilateral disease was present in 47/115 subjects (41%). Bilateral disease was associated with solid parenchyma, calcifications, irregular margins, and abnormal lymph nodes detected by ultrasound, Bethesda class V/VI cytology, papillary histology, tumor multifocality in the primary lobe, extrathyroidal extension, lymphovascular invasion, and nodal metastases. In multivariable analysis, only multifocality in the primary lobe was independently associated with bilateral disease (OR 7.61, 95% CI 2.44-23.8, $P < .001$). Among clinically node-negative subjects with papillary carcinoma who did not have tumor multifocality in the primary lobe, bilateral disease was present in 5/32 (16%). CONCLUSIONS: In children with differentiated thyroid cancer, tumor multifocality in the primary lobe is associated with bilateral disease and should prompt consideration of completion thyroidectomy after initial lobectomy. Clinically node-negative children with tumors that are unifocal in the primary lobe have a low likelihood of contralateral disease.
PubMed-ID: 33780538
http://dx.doi.org/10.1210/clinem/dgab210

Success rate and learning curve of intraoperative neural monitoring of the external branch of the superior laryngeal nerve in thyroidectomy.
Head Neck, 43(12):3946-54.
H. W. Choi, Y. B. Ji, E. Kim, K. N. Kim and K. Tae. 2021.
BACKGROUND: This study aimed to evaluate the success rate and learning curve of intraoperative neural monitoring (IONM) of the external branch of the superior laryngeal nerve (EBSLN) in thyroidectomy. METHODS: We studied 130 consecutive patients (200 nerves at risk [NARs]) who had undergone conventional thyroidectomy with IONM of the recurrent laryngeal nerve (RLN) and EBSLN from January 2017 to March 2020. The learning curve was defined as the number of NARs required to achieve an effective and reliable neuromonitoring rate. RESULTS: IONM of the EBSLN was successful in 136/200 (68%) NARs. The cutoff point of the learning curve was 45 NARs (28 patients). The neural identification rate of EBSLN was significantly higher in the post-learning 155 NARs group than the pre-learning group (82.6% vs. 17.8%, $p < 0.001$). CONCLUSIONS: Approximately 45 NAR neuromonitoring attempts were required to reach a significant increase in the EBSLN identification rate and overcome the learning curve.

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http://dx.doi.org/10.1002/hed.26895

PSMA Expression in Differentiated Thyroid Cancer: Association With Radioiodine, 18FDG Uptake, and Patient Outcome.
J Clin Endocrinol Metab, 106(12):3536-45.
R. Ciappuccini, V. Saguet-Rysanek, F. Giffard, I. Licaj, M. Dorbeau, B. Clarisse, L. Poulain and S. Bardet. 2021.
CONTEXT: Little is known about prostate-specific membrane antigen (PSMA) expression in patients with cervical involvement of differentiated thyroid cancer (DTC). OBJECTIVE: We investigated PSMA expression in neck persistent/recurrent disease (PRD) using immunohistochemistry and the association with radioiodine (RAI) or 18-fluorodeoxyglucose (18FDG) uptake, and patient outcome. DESIGN, SETTING, AND PATIENTS: Data from 44 consecutive DTC patients who underwent neck reoperation from 2006 to 2018 in a comprehensive cancer center. MAIN OUTCOME MEASURE(S): Immunostaining was performed with vascular endothelial marker CD31 and PSMA. PSMA expression was quantified using the immunoreactive score (IRS). RAI and 18FDG uptake were assessed before surgery using posttherapeutic RAI scintigraphy and 18FDG positron emission tomography with computed tomography. Mean follow-up after reintervention was 6.5 ± 3.7 years. RESULTS: Thirty patients (68%) showed at least 1 PSMA-positive lesion (IRS = 2) with similar proportions in RAI-positive and RAI-negative patients (75% vs 66%). In RAI-negative patients, however, the proportion of PSMA-positive disease (79% vs 25%, P < 0.01) and the mean IRS (4.0 vs 1.0, P = 0.01) were higher in 18FDG-positive than in 18FDG-negative patients. Furthermore, mean IRS was higher in patients = 55 years, large primary tumors (>40 mm) or aggressive subtypes, and was correlated with structural disease at last follow-up. Strong PSMA expression (IRS = 9) was associated with shorter progression-free survival (PFS). CONCLUSIONS: Our findings show that PSMA expression was present in two-thirds of patients with neck PRD, that it was related to poor prognostic factors and that very high expression was associated with poorer PFS. This preliminary study may offer new perspectives for the management of RAI-refractory DTC.
PubMed-ID: 34331544
http://dx.doi.org/10.1210/clinem/dgab563

Revisiting the role of surgery in the treatment of Graves' disease.
Clin Endocrinol (Oxf),
O. Cohen, O. Ronen, A. Khafif, J. P. Rodrigo, R. Simo, P. Pace-Asciak, G. Randolph, L. H. Mikkelsen, L. P. Kowalski, K. D. Olsen, A. Sanabria, R. P. Tufano, S. Babighian, A. R. Shaha, M. Zafereo and A. Ferlito. 2021.
Graves' disease (GD) can be managed by antithyroid drugs (ATD), radioactive iodine (RAI) and surgery. Thyroidectomy offers the highest success rates for both primary and persistent disease, yet it is the least recommended or utilized option reaching <1% for primary disease and <25% for persistent disease. Several surveys have found surgery to be the least recommended by endocrinologists worldwide. With the development of remote access thyroidectomies and intraoperative nerve monitoring of the recurrent laryngeal nerve, combined with current knowledge of possible risks associated with RAI or failure of ATDs, revaluation of the benefit to harm ratio of surgery in the treatment of GD is warranted. The aim of this review is to discuss possible reasons for the low proportion of surgery in the treatment of GD, emphasizing an evidence-based approach to the clinicians' preferences for surgical referrals, surgical indications and confronting traditional reasons and concerns relating to the low referral rate with up-to-date data.
PubMed-ID: 34954838
http://dx.doi.org/10.1111/cen.14653

Impact of rocuronium on intraoperative neuromonitoring vagal amplitudes during thyroidectomy.
Langenbecks Arch Surg, 406(6):2019-25.
O. E. de Vendin, T. Fuchs-Buder, D. Schmartz, D. T. Nguyen, P. Gallet, F. Bihain, C. Nomine-Criqui and L. Brunaud. 2021.
PURPOSE: Neuromuscular blocking agents (NMBA) facilitate endotracheal intubation and reduce related laryngeal morbidity. However, NMBA interfere with intraoperative neuromonitoring amplitudes during thyroidectomy. The goal of this study was to evaluate the impact of rocuronium used for tracheal intubation on early intraoperative neuromonitoring vagal amplitudes observed during first thyroid lobe dissection. METHODS: This is an observational pharmacoepidemiological study with prospective data collection and retrospective analysis. During the study period, all consecutive patients who underwent thyroid surgery with neuromonitoring were included. Patients underwent endotracheal intubation either using a single dose of rocuronium (NMBA group) or without NMBA (NMBA-free group) according to the anesthesiologist's preference. RESULTS: Six hundred six patients were included (213 NMBA and 393 NMBA-free group patients). At V1, 39 patients (18%) in the NMBA group had an amplitude < 100 µV (need for curarization reversal in 30 patients) and 13 patients (3.3%) in the NMBA-free group (p < 0.001). In the remaining 554 patients, the

mean V1 amplitude was significantly decreased in the NMBA group (544 versus 685 μV; p < 0.001). After exclusion of 25 patients with loss of signal types 1 and 2 during dissection, the difference between mean V1 and mean V2 was significantly lower in NMBA group patients (- 22 versus - 86 μV; p = 0.016). CONCLUSION: This study provides new data showing how NMBA used for tracheal intubation significantly decrease V1 amplitude baseline and modify amplitude variations from V1 to V2 values during the first thyroid lobe dissection. LEVEL OF EVIDENCE: Pharmacoepidemiological study.
PubMed-ID: 34120194
http://dx.doi.org/10.1007/s00423-021-02234-5

Late Recovery of Parathyroid Function After Total Thyroidectomy: A Case-Control Study.
Horm Metab Res, 53(10):654-61.
J. J. Díez, E. Anda, J. Sastre, B. P. Corral, C. Álvarez-Escolá, L. Manjón, M. Paja, M. Sambo, P. S. Fernández, C. B. Carrera, J. C. Galofré, E. Navarro, C. Zafón, E. Sanz, A. Oleaga, O. Bandrés, S. Donnay, A. Megía, M. Picallo, C. S. Ragnarsson, G. Baena-Nieto, J. C. Fernández-García, B. Lecumberri, M. S. de la Vega, A. R. Romero-Lluch and P. Iglesias. 2021.
The clinical characteristics of patients with postoperative hypoparathyroidism who recover parathyroid function more than 12 months after surgery have not been studied. We aimed to evaluate whether the intensity of replacement therapy with calcium and calcitriol is related to the late recovery of parathyroid function. We compared the demographic, surgical, pathological, and analytical features of two groups of patients: cases, i. e., late recovery patients (those who recover parathyroid function>1 year after thyroidectomy, n=40), and controls, i. e., patients with permanent hypoparathyroidism (n=260). Replacement therapy with calcium and calcitriol was evaluated at discharge of surgery, 3-6 months, 12 months, and last visit. No significant differences were found in clinical, surgical, pathological, or analytical characteristics between cases and controls. The proportion of cases who required treatment with calcium plus calcitriol at 12 months was significantly lower than that found in controls (p<0.001). Furthermore, daily calcium and calcitriol doses in controls were significantly higher than those in cases at 3-6 months (p=0.014 and p=0.004, respectively) and at 12 months (p<0.001 and p=0.043, respectively). In several models of logistic regression analysis therapy with calcium and calcitriol at 12 months was negatively related to late recovery of parathyroid function. Although delayed recuperation of parathyroid function after total thyroidectomy is uncommon (13%), follow-up beyond 12 months is necessary in patients with postoperative hypoparathyroidism, especially in those whose needs of treatment with Ca and calcitriol are reducing over time.
PubMed-ID: 34517416
http://dx.doi.org/10.1055/a-1608-1373

Medullary Thyroid Cancer: 60 Years of Gradual Understanding.
Ann Surg Oncol, 29(1):7-8.
G. M. Doherty. 2022.
PubMed-ID: 34761334
http://dx.doi.org/10.1245/s10434-021-11077-9

It Helps to Know Where to Look: Visual Identification of Unintentionally Resected Parathyroid Glands is Improved When Inspection is Directed by Near Infrared Autofluorescence Imaging.
World J Surg, 45(9):2791-2.
Q. Y. Duh and C. E. Graves. 2021.
PubMed-ID: 34212210
http://dx.doi.org/10.1007/s00268-021-06200-6

Do Ultrasound Patterns and Clinical Parameters Inform the Probability of Thyroid Cancer Predicted by Molecular Testing in Nodules with Indeterminate Cytology?
Thyroid, 31(11):1673-82.
J. J. Figge, W. E. Gooding, D. L. Steward, L. Yip, R. S. Sippel, S. P. Yang, R. P. Scheri, J. A. Sipos, S. J. Mandel, S. E. Mayson, K. D. Burman, J. M. Folek, B. R. Haugen, J. A. Sosa, R. Parameswaran, W. B. Tan, Y. E. Nikiforov and S. E. Carty. 2021.
Background: Molecular testing (MT) is commonly used to refine cancer probability in thyroid nodules with indeterminate cytology. Whether or not ultrasound (US) patterns and clinical parameters can further inform the risk of thyroid cancer in nodules predicted to be positive or negative by MT remains unknown. The aim of this study was to test if clinical parameters, including patient age, sex, nodule size (by US), Bethesda category (III, IV, V), US pattern (American Thyroid Association [ATA] vs. American College of Radiology Thyroid Image Reporting and Data System [TI-RADS] systems), radiation exposure, or family history of thyroid cancer can modify the probability of thyroid cancer or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) predicted by MT. Methods: We studied 257 thyroid

nodules in 232 patients from 10 study centers with indeterminate fine needle aspiration cytology and informative MT results using the ThyroSeq v3 genomic classifier (TSv3). Univariate and multivariate logistic regression was used for data analysis. Results: The presence of cancer/NIFTP was associated with positive TSv3 results (odds ratio 61.39, $p < 0.0001$). On univariate regression, patient sex, age, and Bethesda category were associated with cancer/NIFTP probability ($p < 0.05$ for each). Although ATA ($p = 0.1211$) and TI-RADS ($p = 0.1359$) US categories demonstrated positive trends, neither was significantly associated with cancer/NIFTP probability. A multivariate regression model incorporating the four most informative non-MT covariates (sex, age, Bethesda category, and ATA US pattern; Model No. 1) yielded a C index of 0.653; $R(2) = 0.108$. When TSv3 was added to Model number 1, the C index increased to 0.888; $R(2) = 0.572$. However, age ($p = 0.341$), Bethesda category ($p = 0.272$), and ATA US pattern ($p = 0.264$) were nonsignificant, and other than TSv3 ($p < 0.0001$), male sex was the only non-MT parameter that potentially contributed to cancer/NIFTP risk ($p = 0.095$). The simplest and most efficient clinical model (No. 3) incorporated TSv3 and sex (C index = 0.889; $R(2) = 0.588$). Conclusions: In this multicenter study of thyroid nodules with indeterminate cytology and MT, neither the ATA nor TI-RADS US scoring systems further informed the risk of cancer/NIFTP beyond that predicted by TSv3. Although age and Bethesda category were associated with cancer/NIFTP probability on univariate analysis, in sequential nomograms they provided limited incremental value above the high predictive ability of TSv3. Patient sex may contribute to cancer/NIFTP risk in thyroid nodules with indeterminate cytology.
PubMed-ID: 34340592
http://dx.doi.org/10.1089/thy.2021.0119

Improving safety in paediatric thyroidectomy by PTH measurements.
Clin Endocrinol (Oxf), 95(5):760-5.
A. V. Freire, M. G. Ropelato, P. Papendieck, A. Vieites, E. Elías, M. G. Ballerini, M. E. Rodriguez, I. Bergadá and A. Chiesa. 2021.
OBJETIVE: We followed our previously reported algorithm based on intra and postoperative parathyroid hormone (PTH) levels to predict postthyroidectomy hypoparathyroid hypocalcemia. The objective of the study was to assess if this strategy is useful and safe to reduce hypocalcemia, hospitalisation length and postsurgery calcium sampling. DESIGN, PATIENTS, MEASSUREMENTS: We classified our series of 66 patients according to their risk of hypoparathyroidism based on PTH determinations. We treated high-risk patients with calcium and vitamin D1-25 supplementation and obtained routine daily calcium samples to control low-risk patients until 48 h postsurgery. We compared the outcomes and overall results of this new approach with those of a historical control group of patients with equivalent PTH measurements who were treated only if they presented hypocalcemia. RESULTS: In the high-risk subgroup (n = 30), five patients had hypocalcemia within the first 24 h. Compared with the high-risk control subgroup, the incidence of hypocalcemia fell from 100% to 17% ($p < .001$), and the median hospitalisation length from 6 to 3 days ($p < .001$). In the low-risk subgroup (n = 36), 28 patients remained normocalcemic with significantly less calcium sampling ($p < .001$). Eight patients had hypocalcemia; seven of them required neck dissection, which was the only risk factor related to postsurgical hypoparathyroidism (RR: 2.1 [confidence interval 95%: 1.4-3.1]; $p < .001$). The overall incidence of hypocalcemia decreased by 58% in our patients compared to the control group. CONCLUSIONS: Assessing PTH levels to classify the risk of hypoparathyroidism and to initiate preventive therapy was an effective approach that improved the safety of our paediatric patients by reducing the incidence of hypocalcemia and the length of hospitalisation after thyroidectomy in paediatric patients.
PubMed-ID: 34219257
http://dx.doi.org/10.1111/cen.14552

Current iodine status in Japan: A cross-sectional nationwide survey of schoolchildren, 2014-2019.
J Clin Endocrinol Metab,
Y. Fuse, Y. Ito, Y. Shishiba and M. Irie. 2021.
CONTEXT: Japan has been regarded as a long-standing iodine sufficient country without iodine fortification; however, data on nationwide iodine status is lacking. OBJECTIVE: This study aimed to characterize the iodine status in Japan. METHODS: From 2014 through 2019 a nationwide school-based survey was conducted across all districts in Japan. Urinary iodine concentration (UIC), creatinine (Cr) concentration and anthropometry were assessed in healthy school-aged children (SAC) aged 6 to 12 years. Their iodine status is regarded as generally representative of the nation's iodine status. RESULTS: A total of 32,025 children participated. The overall median UIC was 269 μg/L which was within the WHO's adequacy range. There was a regional difference in UIC values within 14 regions, and the lowest and highest median UIC were found in Tanegashima Island (209 μg/L) and Nakashibetsu, Hokkaido (1,071 μg/L), respectively. The median UIC = 300 μg/L was observed in 12 out of 46 regions. By using estimated 24-h urinary iodine excretion (UIE), the prevalence of SAC exceeding

the upper tolerable limit of iodine for Japanese children was from 5.2 to 13.7%. The UIC values did not change with age, BSA and BMI percentile, while the Cr concentration simultaneously increased suggesting the effect of urinary creatinine on UI/Cr and estimated 24-h UIE values. CONCLUSIONS: The iodine intake of Japanese people is adequate, but in some areas it is excessive. The incidence and prevalence of thyroid disorders associated with iodine intake should be obtained especially in the areas where high amounts of iodine are consumed.
PubMed-ID: 34935958
http://dx.doi.org/10.1210/clinem/dgab919

Whole Tumor Capsule Is Prognostic of Very Good Outcome in the Classical Variant of Papillary Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e4072-e83.
C. Giani, L. Torregrossa, T. Ramone, C. Romei, A. Matrone, E. Molinaro, L. Agate, G. Materazzi, P. Piaggi, C. Ugolini, F. Basolo, R. Ciampi and R. Elisei. 2021.
CONTEXT: Tumor capsule integrity is becoming a relevant issue to predict the biological behavior of human tumors, including thyroid cancer. OBJECTIVE: This work aims to verify whether a whole tumor capsule in the classical variant of papillary thyroid carcinoma (CVPTC) could have as a predictive role of a good outcome as for follicular variant (FVPTC). METHODS: FVPTC (n = 600) and CVPTC (n = 554) cases were analyzed. We distinguished between encapsulated-FVPTC (E-FVPTC) and encapsulated-CVPTC (E-CVPTC) and, thereafter, invasive (Ei-FVPTC and Ei-CVPTC) and noninvasive (En-FVPTC and En-CVPTC) tumors, according to the invasion or integrity of the tumor capsule, respectively. Cases without a tumor capsule were indicated as invasive-FVPTC (I-FVPTC) and invasive-CVPTC (I-CVPTC). The subgroup of each variant was evaluated for BRAF mutations. RESULTS: E-FVPTC was more frequent than E-CVPTC (P < .001). No differences were found between En-FVPTC and En-CVPTC or between Ei-FVPTC and Ei-CVPTC. After 18 years of follow-up, a greater number of not-cured cases were observed in Ei-CVPTC with respect to Ei-FVPTC, but not in En-CVPTC to En-FVPTC. Multivariate clustering analysis showed that En-FVPTC, En-CVPTC, and Ei-FVPTC have similar features but different from I-FVPTC and I-CVPTC and, to a lesser extent, from Ei-CVPTC. A total of 177 of 614 (28.8%) cases were BRAFV600E mutated, and 10 of 614 (1.6%) carried BRAF-rare alterations. A significantly higher rate of En-CVPTC (22/49, 44.9%) than En-FVPTC (15/195, 7.7%) (P < .0001) were BRAFV600E mutated. CONCLUSION: En-CVPTC is less prevalent than En-FVPTC. However, it has good clinical/ pathological behavior comparable to En-FVPTC. This finding confirms the good prognostic role of a whole tumor capsule in CVPTC as well. New nomenclature for En-CVPTC, similar to that introduced for En-FVPTC (ie, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; NIFTP) could be envisaged.
PubMed-ID: 34231847
http://dx.doi.org/10.1210/clinem/dgab396

Risk stratification of indeterminate thyroid nodules using ultrasound and machine learning algorithms.
Clin Endocrinol (Oxf), 96(4):646-52.
M. L. Gild, M. Chan, J. Gajera, B. Lurie, Z. Gandomkar and R. J. Clifton-Bligh. 2022.
BACKGROUND: Indeterminate thyroid nodules (Bethesda III) are challenging to characterize without diagnostic surgery. Auxiliary strategies including molecular analysis, machine learning models, and ultrasound grading with Thyroid Imaging, Reporting and Data System (TI-RADS) can help to triage accordingly, but further refinement is needed to prevent unnecessary surgeries and increase positive predictive values. DESIGN: Retrospective review of 88 patients with Bethesda III nodules who had diagnostic surgery with final pathological diagnosis. MEASUREMENTS: Each nodule was retrospectively scored through TI-RADS. Two deep learning models were tested, one previously developed and trained on another data set, mainly containing determinate cases and then validated on our data set while the other one trained and tested on our data set (indeterminate cases). RESULTS: The mean TI-RADS score was 3 for benign and 4 for malignant nodules (p = .0022). Radiological high risk (TI-RADS 4,5) and low risk (TI-RADS 2,3) categories were established. The PPV for the high radiological risk category in those with >10 mm nodules was 85% (CI: 70%-93%). The NPV for low radiological risk in patients >60 years (mean age was 100% (CI: 83%-100%). The area under the curve (AUC) value of our novel classifier was 0.75 (CI: 0.62-0.84) and differed significantly from the chance-level (p < .00001). CONCLUSIONS: Novel radiomic and radiologic strategies can be employed to assist with preoperative diagnosis of indeterminate thyroid nodules.
PubMed-ID: 34642976
http://dx.doi.org/10.1111/cen.14612

The volume and outcome relationship for thyroidectomy in England.
Langenbecks Arch Surg, 406(6):1999-2010.
W. K. Gray, S. Aspinall, N. Tolley, J. Day and M. Lansdown. 2021.
PURPOSE: The delivery of surgical care in England has seen a momentum towards centralisation within larger volume

hospitals and surgical teams. The aim of this study was to investigate outcomes in England in relationship to hospital and surgeon annual volumes for total thyroidectomy. METHODS: Data were extracted from the Hospital Episodes Statistics (HES) database for England. A 6-year period (April 2012-March 2018 inclusive) for all adult admissions for thyroidectomy was used in the analysis. The primary outcome measure used was a length of hospital stay greater than 2 days or an emergency readmission within 30 days following surgery. This was used as a proxy for surgical complications. A multilevel modelling strategy was used to adjust for hierarchy and potentially confounding. RESULTS: Data for 22,823 total thyroidectomies across 144 hospital trusts were used for analysis. For total thyroidectomy, larger volume surgeons had reduced levels of post-surgical complications; length of stay > 2 and > 4 days; emergency readmission at 30 days; and hypoparathyroidism, vocal cord palsy, stridor, and tracheostomy at 1-year post-surgery. Larger hospital volume was associated with lower levels of emergency readmission at 30 days and hypoparathyroidism at 1 year. CONCLUSIONS: There is significant correlation between surgeon volume and clinical outcome for total thyroidectomy. The relationship was approximately linear, and a low-volume threshold could not be defined.
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http://dx.doi.org/10.1007/s00423-021-02223-8

Does macroscopic extrathyroidal extension to the strap muscles alone affect survival in papillary thyroid carcinoma?
Surgery,
V. Harries, M. McGill, A. Yuan, L. Y. Wang, R. M. Tuttle, A. R. Shaha, J. P. Shah, R. J. Wong, S. G. Patel and I. Ganly. 2021.
BACKGROUND: Macroscopic extrathyroidal extension to structures adjacent to the thyroid gland is one of the most important predictors of survival in papillary thyroid carcinoma. However, the prognostic significance of macroscopic extrathyroidal extension to strap muscles alone is unknown. The aim of this study is to determine the impact on survival in patients with macroscopic extrathyroidal extension to strap muscles alone compared to those with no macroscopic extrathyroidal extension and macroscopic extrathyroidal extension involving other adjacent structures. METHODS: After institutional review board approval, adult papillary thyroid carcinoma patients were identified from an institutional database of 6,259 patients undergoing initial surgery for well-differentiated thyroid carcinoma from 1986 to 2015. Patients were classified as having no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, or macroscopic extrathyroidal extension to other adjacent structures. Disease-specific survival was calculated using the Kaplan-Meier method and groups were compared using the log-rank test. A P value < .05 was considered statistically significant and significant factors were used in a Cox proportional hazard model to predict disease-specific survival. RESULTS: There were 5,880 patients included in the analysis; 5,485 patients (93.3%) in the no macroscopic extrathyroidal extension group, 179 (3.0%) in the macroscopic extrathyroidal extension to strap muscles alone group and 216 (3.7%) in the macroscopic extrathyroidal extension involving other adjacent structures group. With a median follow-up of 64 months, the estimated 10-year disease-specific survival for patients with no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, and macroscopic extrathyroidal extension involving other adjacent structures were 98.9%, 95.7%, and 83.7%, respectively (P < .0001). In the =55-year-old cohort, the estimated 10-year disease-specific survival for patients with no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, and macroscopic extrathyroidal extension involving other adjacent structures were 97.6%, 89.3%, and 68.1%, respectively (P <.0001). After controlling for pathological nodal stage and distant metastasis stage, extent of extrathyroidal extension remained an independent predictor of disease-specific survival; patients with macroscopic extrathyroidal extension to strap muscles alone had a 3.3-fold increased likelihood of a disease-specific death compared to no macroscopic extrathyroidal extension patients (hazard ratio 3.294; 95% confidence interval 1.076-10.086, P < .0368). CONCLUSION: In our study, patients aged =55 years with papillary thyroid carcinoma and macroscopic extrathyroidal extension to strap muscles alone appear to have an increased likelihood of a disease-specific death compared to patients with no macroscopic extrathyroidal extension.
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http://dx.doi.org/10.1016/j.surg.2021.08.041

A High-throughput Approach to Identify Effective Systemic Agents for the Treatment of Anaplastic Thyroid Carcinoma.
J Clin Endocrinol Metab, 106(10):2962-78.
Y. C. Henderson, A. S. R. Mohamed, A. Maniakas, Y. Chen, R. T. Powell, S. Peng, M. Cardenas, M. D. Williams, D. Bell, M. E. Zafereo, R. J. Wang, S. E. Scherer, D. A. Wheeler, M. E. Cabanillas, M. C. Hofmann, F. M. Johnson, C. C. Stephan, V. Sandulache and S. Y. Lai. 2021.
BACKGROUND: Despite the use of aggressive multimodality treatment, most anaplastic thyroid carcinoma (ATC) patients die within a year of diagnosis. Although the combination of BRAF and MEK inhibitors has recently been approved for use in BRAF-mutated ATC, they remain effective in a minority of patients who are likely to develop drug resistance. There

remains a critical clinical need for effective systemic agents for ATC with a reasonable toxicity profile to allow for rapid translational development. MATERIAL AND METHODS: Twelve human thyroid cancer cell lines with comprehensive genomic characterization were used in a high-throughput screening (HTS) of 257 compounds to select agents with maximal growth inhibition. Cell proliferation, colony formation, orthotopic thyroid models, and patient-derived xenograft (PDX) models were used to validate the selected agents. RESULTS: Seventeen compounds were effective, and docetaxel, LBH-589, and pralatrexate were selected for additional in vitro and in vivo analysis as they have been previously approved by the US Food and Drug Administration for other cancers. Significant tumor growth inhibition (TGI) was detected in all tested models treated with LBH-589; pralatrexate demonstrated significant TGI in the orthotopic papillary thyroid carcinoma model and 2 PDX models; and docetaxel demonstrated significant TGI only in the context of mutant TP53. CONCLUSIONS: HTS identified classes of systemic agents that demonstrate preferential effectiveness against aggressive thyroid cancers, particularly those with mutant TP53. Preclinical validation in both orthotopic and PDX models, which are accurate in vivo models mimicking tumor microenvironment, may support initiation of early-phase clinical trials in non-BRAF mutated or refractory to BRAF/MEK inhibition ATC.
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http://dx.doi.org/10.1210/clinem/dgab424

Optimal cutoff values of primary tumour size to better predict long-term outcomes in patients with papillary thyroid carcinoma undergoing total thyroidectomy: A preliminary study using restricted cubic spline analysis.
Clin Endocrinol (Oxf),
S. W. Jang, J. H. Park, H. J. Kwon and J. H. Yoon. 2021.
OBJECTIVE: Primary tumour size (PTS) is known to be a significant prognostic factor in patients with papillary thyroid carcinoma (PTC) undergoing thyroidectomy. Although cutoff values of 2 and 4 cm are widely used in surgical extent decision and long-term outcomes predictions, the effectiveness of arbitrary cutoff values in stratifying patients for target outcomes is questionable. This study aimed to determine new optimal cutoffs of PTS. DESIGN, PATIENT AND MEASUREMENTS: Patients (n = 529) with PTC who underwent total thyroidectomy were retrospectively reviewed. After risk factor analysis for structural recurrence, the optimal cutoffs of PTS were automatically calculated using restricted cubic spline analysis and X-tile software. Subgroups were classified based on the newly determined cutoff values. Both the recurrence-free survival (RFS) and the proportion of patients in each response-to-therapy category, using the dynamic risk stratification system (DRS), were compared between the subgroups. RESULTS: PTS was confirmed as an independent risk factor for structural recurrence. The optimal cutoff values were calculated as 1.4 and 3.0 cm. The subgroups stratified using these newly determined cutoffs showed significantly different RFS and DRS based on the response to initial therapy, but the subgroups classified using the cutoffs of 2 and 4 cm did not. CONCLUSIONS: The newly determined cutoff values of PTS may be useful in better stratifying patients with PTC undergoing thyroidectomy for target outcomes and can be considered as a new definition in staging and risk stratification systems.
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http://dx.doi.org/10.1111/cen.14657

ASO Author Reflections: Multimodality Treatment in Anaplastic Thyroid Cancer: Improving Survival Outcomes and Balancing Treatment Related Complications.
Ann Surg Oncol, 28(12):7531-2.
P. K. C. Jonker and M. Sywak. 2021.
PubMed-ID: 34131820
http://dx.doi.org/10.1245/s10434-021-10268-8

Multimodality Treatment Improves Locoregional Control, Progression-Free and Overall Survival in Patients with Anaplastic Thyroid Cancer: A Retrospective Cohort Study Comparing Oncological Outcomes and Morbidity between Multimodality Treatment and Limited Treatment.
Ann Surg Oncol, 28(12):7520-30.
P. K. C. Jonker, J. Turchini, S. Kruijff, J. F. Lin, A. J. Gill, T. Eade, A. Aniss, R. Clifton-Bligh, D. Learoyd, B. Robinson, V. Tsang, A. Glover, S. Sidhu and M. Sywak. 2021.
BACKGROUND: Patients with anaplastic thyroid cancer (ATC) have poor overall survival, and the optimal management approach remains unclear. The aim of this study is to evaluate our experience with multimodality (MMT) versus limited treatment (LT) for ATC. PATIENTS AND METHODS: A cohort study of patients with ATC managed in a tertiary referral center was undertaken. The outcomes of MMT were compared with those of LT. The primary outcome measures were locoregional control and progression-free and overall survival. Secondary outcome measures were treatment-related

complications and factors associated with improved survival. RESULTS: In total, 59 patients (35 females) with a median age of 73 years (range 39-99 years) and ATC stage IVA (n = 2), IVB (n = 28), or IVC (n = 29) were included. LT was utilized in 25 patients (42%), and 34 cases had MMT. MMT patients had a longer time of locoregional control (18.5 versus 1.9 months; p < 0.001), progression-free survival (3.5 versus 1.2 months; p < 0.001), and overall survival (6.9 versus 2.0 months; p < 0.001) when compared with LT. For patients with stage IVC ATC, locoregional control (p = 0.03), progression-free survival (p < 0.001), and overall survival (p < 0.001) were superior in the MMT cohort compared with LT. MMT had more treatment-related complications than LT (p < 0.001). An Eastern Cooperative Oncology Group performance status < 2 (HR 0.30; p = 0.001) and MMT (HR 0.35; p = 0.008) were associated with improved overall survival. CONCLUSION: MMT is likely to improve locoregional control, progression-free survival, and overall survival in selected ATC patients including stage IVC tumors but comes with a greater complication risk.
PubMed-ID: 34032961
http://dx.doi.org/10.1245/s10434-021-10146-3

Severe Hypocalcemia After Thyroidectomy: An Analysis of 7366 Patients.
Ann Surg, 274(6):e1014-e21.
H. S. Kazaure, A. Zambeli-Ljepovic, T. Oyekunle, S. A. Roman, J. A. Sosa, M. T. Stang and R. P. Scheri. 2021.
OBJECTIVE: The aim of the study was to determine severe hypocalcemia rate following thyroidectomy and factors associated with its occurrence. BACKGROUND: Hypocalcemia is the most common complication after thyroidectomy. Severe post-thyroidectomy hypocalcemia can be life-threatening; data on this specific complication are scarce. METHODS: Patients who underwent thyroidectomy in the American College of Surgeons-National Surgical Quality Improvement Program thyroidectomy-targeted database (2016-2017) were abstracted. A severe hypocalcemic event was defined as hypocalcemia requiring intravenous calcium, emergent clinic/hospital visit, or a readmission for hypocalcemia. Multivariable regression was used to identify factors independently associated with occurrence of severe hypocalcemia. RESULTS: Severe hypocalcemia occurred in 5.8% (n = 428) of 7366 thyroidectomy patients, with 83.2% necessitating intravenous calcium treatment. Rate of severe hypocalcemia varied by diagnosis and procedure (0.5% for subtotal thyroidectomy to 12.5% for thyroidectomy involving neck dissections). Overall, 38.3% of severe hypocalcemic events occurred after discharge; in this subset, 59.1% experienced severe hypocalcemia despite being discharged with calcium and vitamin D. Severe hypocalcemia patients had higher rates of recurrent laryngeal nerve injury (13.4% vs 6.6%), unplanned reoperations (4.4% vs 1.3%), and longer hospital stay (30.4% vs 6.2% =3 days (all P < 0.01). After multivariate adjustment, severe hypocalcemia was associated with multiple factors including Graves disease [odds ratio (OR) = 2.06], lateral neck dissections (OR: 3.10), and unexpected reoperations (OR = 3.55); all P values less than 0.01. CONCLUSIONS: Severe hypocalcemia and suboptimal hypocalcemia management after thyroidectomy are common. Patients who experienced severe hypocalcemia had higher rates of nerve injury and unexpected reoperations, indicating surgical complexity and provider inexperience. More biochemical surveillance particularly a parathyroid hormone-based protocol, fine-tuned supplementation, and selective referral could reduce occurrence of this morbid complication.
PubMed-ID: 31804395
http://dx.doi.org/10.1097/SLA.0000000000003725

Outcomes of Advanced Medullary Thyroid Carcinoma in the Era of Targeted Therapy.
Ann Surg Oncol, 29(1):64-71.
N. L. Kesby, A. J. Papachristos, M. Gild, A. Aniss, M. S. Sywak, R. Clifton-Bligh, S. B. Sidhu and A. R. Glover. 2022.
BACKGROUND: Medullary thyroid carcinoma (MTC) can be targeted with tyrosine kinase inhibitors (TKIs). We aimed to report the outcomes of surgically managed MTC and to evaluate the impact of TKI use on patient survival. METHODS: Consecutive patients treated surgically for MTC from 1986 to 2020 were identified from a prospectively collected database and were compared on the basis of stage at operation and TKI use. The primary outcome was overall survival (OS). RESULTS: Among 154 patients with a median age of 52 years, 40% presented with stage I/II disease and 60% presented with advanced (stage III or IV) disease. During a median follow-up of 7.5 years, 21% received TKIs for systemic disease. Those presenting with advanced disease were more likely to receive a TKI (31% vs. 7%), present with tumor invasion of the recurrent laryngeal nerve (RLN; 12% vs. 0%) and undergo reoperation (42% vs. 23%) compared with stage I-II patients. For the 11 patients found to have invasion of the RLN, five had preoperative functional vocal cords. Five-year OS was 84% for advanced disease, and stage IV patients who received TKIs had a median survival of 21 years, versus 15 years for those who did not (p = 0.3). CONCLUSIONS: Surgery achieves long-term survival for patients with advanced disease, however these patients are at greater risk of requiring RLN resection due to invasion. A significant OS benefit was not seen for TKI use. For patients with local invasion, neoadjuvant TKI therapy may have a role in reducing local morbidity if confirmed to be of benefit in clinical trials.

PubMed-ID: 34716515
http://dx.doi.org/10.1245/s10434-021-10980-5

Serum thyroglobulin is associated with orbitopathy in Graves' disease.
J Endocrinol Invest, 44(9):1905-11.
S. Khamisi, M. Lundqvist, P. Emadi, K. Almby, Ö. Ljunggren and F. A. Karlsson. 2021.
PURPOSE: Serum thyroglobulin levels are often elevated in Graves' disease (GD) and in most cases decrease during treatment. Its relation to Graves' orbitopathy (GO) has not been clarified. Previously, a risk of GO has been linked to smoking, TSH receptor stimulation, high TSH-receptor antibodies (TRAb), low thyroid peroxidase and thyroglobulin antibodies (TPOAb, TgAb). METHODS: We examined Tg levels in 30 consecutive patients with GD were given drug therapy (methimazole + thyroxine) for up to 24 months. GO was identified by clinical signs and symptoms. 17 patients had GO, 11 of whom had it at diagnosis while 6 developed GO during treatment. During the study, 5 subjects were referred to radioiodine treatment, 3 to surgery. The remaining 22 subjects (GO n = 12, non-GO n = 10) completed the drug regimen. RESULTS: At diagnosis, Tg levels in GO patients (n = 11) were higher (84, 30-555 µg/L, median, range) than in non-GO patients (n = 19) (38, 3.5-287 µg/L), p = 0.042. Adding the 6 subjects who developed eye symptoms during treatment to the GO group (n = 17), yielded p = 0.001 vs. non-GO (n = 13). TRAb tended to be higher, while TPOAb and TgAb tended to be lower in the GO group. For the 22 patients who completed the drug regimen, Tg levels were higher in GO (n = 12) vs. non-GO (n = 10), p = 0.004, whereas TRAb levels did not differ. CONCLUSION: The data may suggest that evaluation of thyroglobulin levels in GD could contribute to identify patients at increased risk of developing GO. Possibly, thyroidal release of Tg in GD reflects a disturbance that also impacts retroorbital tissues.
PubMed-ID: 33515213
http://dx.doi.org/10.1007/s40618-021-01505-8

Predictive Value of Delphian Lymph Node Metastasis in the Thyroid Cancer.
Laryngoscope, 131(9):1990-6.
D. H. Kim, S. W. Kim and S. H. Hwang. 2021.
OBJECTIVE/HYPOTHESIS: To evaluate the diagnostic accuracy of Delphian lymph node (DLN) metastasis for the prediction of central lymph node (CLN) metastasis and lateral lymph node (LLN) metastasis. METHODS: Two authors independently reviewed the six databases (Cochrane database, Embase, Google Scholar, PubMed, SCOPUS, and Web of Science). Four parameters were extracted from each study: true positive, true negative, false positive, and false negative. The quality of the methodology was evaluated using the Quality Assessment of Diagnostic Accuracy Studies ver. 2 tool. RESULTS: The diagnostic odds ratio of DLN in CLN metastasis was 8.859 (95% confidence interval [CI], 4.419; 16.578). The area under the summary receiver operating characteristic curve was 0.748. The diagnostic odds ratio of DLN in LLN metastasis was 7.61 (95% CI, 4.48; 12.94). The area under the summary receiver operating characteristic curve was 0.837. DLN metastasis was moderately predictive of CLN metastasis (sensitivity = 32%, specificity = 95%), LLN metastasis (sensitivity = 52%, specificity = 89%), and contralateral CLN metastasis (sensitivity = 46%, specificity = 85%). DLN metastasis had statistically significant correlation with specific clinicopathological characteristics, including younger age (< 45 years old), bilaterality, capsule invasion, extrathyroidal extension, lymphovascular invasion, male sex, multifocality, and tumor size (> 1 cm). CONCLUSIONS: The higher specificities of DLN pathology may help predict central and lateral compartment involvement in patients with thyroid cancer. LEVEL OF EVIDENCE: NA Laryngoscope, 131:1990-1996, 2021.
PubMed-ID: 33493364
http://dx.doi.org/10.1002/lary.29426

Near-Infrared Autofluorescence Imaging May Reduce Temporary Hypoparathyroidism in Patients Undergoing Total Thyroidectomy and Central Neck Dissection.
Thyroid, 31(9):1400-8.
D. H. Kim, S. W. Kim, P. Kang, J. Choi, H. S. Lee, S. Y. Park, Y. Kim, Y. C. Ahn and K. D. Lee. 2021.
Background: Near-infrared autofluorescence (NIRAF) imaging is known to reduce the incidence of post-thyroidectomy hypocalcemia. However, there are no studies on how much NIRAF imaging affects the serum parathyroid hormone (PTH) level after surgery. We investigated the changes of the serum PTH level and ionized calcium (iCa.) in patients undergoing total thyroidectomy with central neck dissection (CND). Materials and Methods: This retrospective study with historical control enrolled 542 patients who underwent total thyroidectomy with CND. Patients were divided into two groups: the NIRAF group (261 patients) and the control group (281 patients). PTH and iCa. levels were measured at the hospital stay, 1, 3, and 6 months after surgery. In addition, the number of identified parathyroid glands (PGs), autotransplanted PGs, and the inadvertent resection rate of PGs was evaluated. Results: The incidence of postoperative hypoparathyroidism

(PTH <15 pg/mL) was significantly lower in the NIRAF group during the hospitalization (88 patients: 33.7% vs. 131 patients: 46.6%; p = 0.002) and at 1 month postoperatively (23 patients: 8.8% vs. 53 patients: 18.9%; p = 0.001). There was no difference in the permanent hypoparathyroidism rate (6 months after surgery) between the NIRAF group and the control group (4.2% vs. 4.6%; p = 0.816). There was no difference in the incidence of hypocalcemia (iCa. <1.09 mmol/L) (during hospitalization: 6.5% vs. 10.0%; 1 month: 2.3% vs. 2.5%; 3 months: 0.8% vs. 0.7%; 6 months after surgery: 1.1% vs. 1.1%) between the two groups. The number of inadvertently resected PGs was significantly lower in the NIRAF group (18:6.9% vs. 36:12.8%; p = 0.021). Conclusions: These results suggest that NIRAF imaging may reduce temporary hypoparathyroidism and the risk of inadvertent resection of PGs in patients undergoing total thyroidectomy with CND.
PubMed-ID: 33906431
http://dx.doi.org/10.1089/thy.2021.0056

Looking beyond the cosmetic appeal of transoral thyroidectomy.
Br J Surg, 108(8):875-6.
J. Kim and J. A. Sosa. 2021.
PubMed-ID: 34142113
http://dx.doi.org/10.1093/bjs/znab180

Medullary thyroid cancer with ectopic Cushing's syndrome: A multicentre case series.
Clin Endocrinol (Oxf),
V. F. Koehler, C. T. Fuss, C. M. Berr, K. Frank-Raue, F. Raue, E. Hoster, M. Hepprich, E. Christ, T. Pusl, M. Reincke, C. Spitzweg and M. Kroiss. 2021.
OBJECTIVE: Ectopic Cushing's syndrome (ECS) induced by medullary thyroid cancer (MTC) is rare, and data on clinical characteristics, treatment and outcome are limited. DESIGN: Retrospective cohort study in three German and one Swiss referral centres. PATIENTS: Eleven patients with MTC and occurrence of ECS and 22 matched MTC patients without ECS were included. MEASUREMENTS: The primary endpoint of this study was the overall survival (OS) in MTC patients with ECS versus 1:2 matched MTC patients without ECS. RESULTS: The median age at diagnosis of ECS was 59 years (range: 35-81) and the median time between initial diagnosis of MTC and diagnosis of ECS was 29 months (range: 0-193). Median serum morning cortisol was 49 µg/dl (range: 17-141, normal range: 6.2-18). Eight (73%) patients received treatment for ECS. Treatment of ECS consisted of bilateral adrenalectomy (BADX) in four (36%) patients and adrenostatic treatment in eight (73%) patients. One patient received treatment with multityrosine kinase inhibitor (MKI) to control hypercortisolism. All patients experienced complete resolution of symptoms of Cushing's syndrome and biochemical control of hypercortisolism. Patients with ECS showed a shorter median OS of 87 months (95% confidence interval [95% CI]: 64-111) than matched controls (190 months, 95% CI: 95-285). Of the nine deaths, four were related to progressive disease (PD). Four patients showed PD as well as complications and comorbidities of hypercortisolism before death. CONCLUSION: This study shows that ECS occurs in advanced stage MTC and is associated with a poor prognosis. Adrenostatic treatment and BADX were effective systemic treatment options in patients with MTC and ECS to control their hypercortisolism. MKI treatment achieved complete remission of hypercortisolism and sustained tumour control in one treated case.
PubMed-ID: 34743368
http://dx.doi.org/10.1111/cen.14617

Pre-diagnosis thyroid hormone dysfunction is associated with cancer mortality.
Endocr Relat Cancer, 28(11):705-13.
E. Krashin, B. Silverman, D. M. Steinberg, D. Yekutieli, S. Giveon, O. Fabian, A. Hercbergs, P. J. Davis, M. Ellis and O. Ashur-Fabian. 2021.
Research on the association between thyroid hormone levels and cancer mortality remains limited and inconclusive. We determined the relation of thyroid stimulating hormone (TSH), free T4 (FT4), and free T3 (FT3) levels with mortality in overall cancer and specific tumor types. Thyroid hormone levels 1-5 years prior to cancer diagnosis, as well as multiple clinical and demographic parameters, were retrospectively collected for 10,325 Israeli cancer patients, diagnosed between 2000 and 2016. Patients treated with thyroid altering medications were excluded. Cancer diagnosis was determined via the Israel National Cancer Registry. Multivariate-adjusted Cox proportional hazards model was used to assess the hazard ratios (HRs) based on thyroid hormone function for cancer mortality. A total of 5265 patients died during the follow-up period (median of 4.4 years). TSH, FT4, and FT3 levels in the hypothyroid range were associated with increase in overall mortality (adjusted HR 1.20, 1.74, 1.87, respectively). We further analyzed the association between TSH and mortality in 14 cancer subgroups. Specifically, TSH in both the hyperthyroid and hypothyroid range was associated with melanoma mortality (adjusted HR 2.20, 4.47, respectively). In conclusion, pre-diagnosis of thyroid dysfunction is associated with

increased cancer mortality, a relation likely driven by specific cancer types. These findings suggest that thyroid hormones may potentially serve as prognostic markers in cancer.
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http://dx.doi.org/10.1530/ERC-21-0187

The Forks in the Road of Thyroid Eye Disease.
J Clin Endocrinol Metab, 106(12):e5262-e3.
C. C. Krieger. 2021.
PubMed-ID: 34232313
http://dx.doi.org/10.1210/clinem/dgab500

Thyroid Isthmusectomy with Prophylactic Central Compartment Neck Dissection is a Feasible Approach for Papillary Thyroid Cancer on the Isthmus.
Ann Surg Oncol, 28(11):6603-12.
O. Kwon, S. Lee, J. S. Bae and C. K. Jung. 2021.
BACKGROUND: The treatment for papillary thyroid cancer (PTC) has become more conservative, but still no specific guidelines exist for managing isthmic PTC. This study analyzed the outcomes from isthmusectomy in single isthmic PTC and compared it with those for patients who previously had undergone a total thyroidectomy. METHODS: An isthmusectomy with prophylactic central compartment neck dissection (pCCND) was planned for a single isthmic PTC between 2014 and 2018 (isthmusectomy group). For cases with gross extrathyroidal extension (ETE) or multiple nodal metastasis, the procedure was converted to a total thyroidectomy. The study analyzed the characteristics and outcomes of the isthmusectomy group. Additionally, the results were compared with those of the isthmusectomy-feasible group who met the eligibility criteria for isthmusectomy among total thyroidectomies performed between 2009 and 2013. RESULTS: Of the 90 patients in the isthmusectomy group, 81 received isthmusectomy and 9 had conversion to a total thyroidectomy. Microcarcinoma occurred in 72 cases and gross ETE in 3 cases. One patient showed occult satellite cancer, and seven patients showed more than five metastatic nodes. Transient hypocalcemia developed in five and patients and permanent hypocalcemia in one patient with total thyroidectomy. Of 46 patients who began hormone replacement postoperatively, 13 completely stopped taking medication during the follow-up period. Metachronous PTC was diagnosed for one patient 12 months after isthmusectomy. The isthmusectomy group and the isthmusectomy-feasible group showed similar clinicopathologic properties including multifocality, ETE, and nodal metastasis. However, the isthmusectomy group showed significantly less transient or permanent hypocalcemia and thyroid hormone dependency. CONCLUSIONS: Isthmusectomy with pCCND may be a feasible alternative for properly selected isthmic PTC, resulting in a better quality of life than total thyroidectomy.
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http://dx.doi.org/10.1245/s10434-021-09833-y

Thyroid nodules in childhood-onset Hashimoto's thyroiditis: Frequency, risk factors, follow-up course and genetic alterations of thyroid cancer.
Clin Endocrinol (Oxf), 95(4):638-48.
Y. J. Lee, Y. J. Cho, Y. J. Heo, E. J. Chung, Y. H. Choi, J. I. Kim, Y. J. Park, C. H. Shin and Y. A. Lee. 2021.
OBJECTIVE: We evaluated the frequency, risk factors and the follow-up outcomes of thyroid nodules, and genetic alterations in thyroid cancer, in youth with childhood-onset Hashimoto thyroiditis (HT) residing in an iodine-sufficient country. DESIGN: A retrospective cohort study. PATIENTS AND MEASUREMENTS: A total of 213 patients (194 females, mean age 10.6 years at the time of HT diagnosis) were ultrasonographically evaluated. Thyroid nodules were categorized using the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) and the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TI-RADS). RESULTS: Thyroid nodules were detected in 40 (18.8%) patients over a median follow-up period of 3.4 years, usually after the onset of puberty. A family history of thyroid disease (hazard ratio 2.1, p = .031) was predictive of thyroid nodule detection. Papillary thyroid carcinoma (PTC) was diagnosed in 9 (4.2% of all and 22.5% of nodule-positive patients). The malignant nodules had a higher K-TIRADS or ACR-TI-RADS risk level compared with benign nodules ($p < .01$ for both). Genetic alterations were revealed in 7 (BRAF(V600E) in 6 and RET-ERC1 fusion in 1) of the eight available tumour tissue samples. None showed evidence of disease over a median follow-up period of 3.4 years. CONCLUSIONS: The nodule detection rate was 18.8%, with a 22.5% risk of malignancy among the detected nodules in childhood-onset HT patients, showing increased risk in those with a family history. Additional large-scale studies are required to evaluate the usefulness of K-TIRADS or ACR-TI-RADS risk level for the differentiation of paediatric thyroid nodules.

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http://dx.doi.org/10.1111/cen.14490

Identification of New Rare Variants Associated With Familial Autoimmune Thyroid Diseases by Deep Sequencing of Linked Loci.
J Clin Endocrinol Metab, 106(11):e4680-e7.
C. W. Li, R. Sachidanandam, A. Jayaprakash, Z. Yi, W. Zhang, M. Stefan-Lifshitz, E. Concepcion and Y. Tomer. 2021.
CONTEXT: Genetic risk factors play a major role in the pathoetiology of autoimmune thyroid diseases (AITD). So far, only common risk variants have been identified in AITD susceptibility genes. Recently, rare genetic variants have emerged as important contributors to complex diseases, and we hypothesized that rare variants play a key role in the genetic susceptibility to AITD. OBJECTIVE: We aimed to identify new rare variants that are associated with familial AITD. METHODS: We performed deep sequencing of 3 previously mapped AITD-linked loci (10q, 12q, and 14q) in a dataset of 34 families in which AITD clustered (familial AITD). RESULTS: We identified 13 rare variants, located in the inositol polyphosphate multikinase (IPMK) gene, that were associated with AITD (ie, both Graves' disease [GD] and Hashimoto's thyroiditis [HT]); 2 rare variants, within the dihydrolipoamide S-succinyltransferase (DLST) and zinc-finger FYVE domain-containing protein (ZFYVE1) genes, that were associated with GD only; and 3 rare variants, within the phosphoglycerate mutase 1 pseudogene 5 (PGAM1P5), LOC105369879, and methionine aminopeptidase 2 (METAP2) genes, that were associated with HT only. CONCLUSION: Our study demonstrates that, in addition to common variants, rare variants also contribute to the genetic susceptibility to AITD. We identified new rare variants in 6 AITD susceptibility genes that predispose to familial AITD. Of these, 3 genes, IPMK, ZFYVE1, and METAP2, are mechanistically involved in immune pathways and have been previously shown to be associated with autoimmunity. These genes predispose to thyroid autoimmunity and may serve as potential therapeutic targets in the future.
PubMed-ID: 34143178
http://dx.doi.org/10.1210/clinem/dgab440

Psychological Distress and Sleep Disturbance Throughout Thyroid Nodule Screening, Diagnosis, and Treatment.
J Clin Endocrinol Metab, 106(10):e4221-e30.
R. Li, G. Li, Y. Wang, T. Bao, Y. Lei, L. Tian, Z. Li, J. Zhu, J. Lei and H. Tang. 2021.
CONTEXT: Many controversies exist regarding screening and treatment of thyroid cancer (TC), especially papillary thyroid microcarcinoma (PTMC). OBJECTIVE: The aim of this study was to evaluate patients' psychological distress and sleep disturbance throughout thyroid nodule (TN) screening, diagnosis, and treatment. METHODS: A total of 2834 participants (1153 participants with TNs) were enrolled during the screening phase, and 1105 individuals with TNs (87 individuals with TC) were enrolled during the diagnosis phase. Of the 87 TC patients, 66 underwent immediate operation (OP), and 21 patients with PTMC opted for active surveillance (AS). Four validated scales were applied to quantify the outcome indicators at prescreening, postscreening, postdiagnosis, and posttreatment. RESULTS: Higher psychological distress and sleep disturbance were found postscreening than prescreening in subjects with TNs, but no differences in those without nodules. Compared with postscreening, higher scores of psychological distress and sleep disturbance were identified in patients with suspicious TC treated with fine needle aspiration (FNA) or with AS. Lower psychological distress and sleep disturbance were noted for patients with benign nodules than for TC patients. OP for TC, especially PTMC, did not alleviate psychological distress or sleep disturbance compared with the same parameters in patients who underwent AS. CONCLUSION: Based on the findings of impaired psychological health and sleep quality, screening for TNs in adults who show no symptoms should be performed with caution. Psychological distress and sleep disturbance should also be taken into consideration when FNA is performed for suspected TC or OP for papillary thyroid cancer, especially PTMC.
PubMed-ID: 33830242
http://dx.doi.org/10.1210/clinem/dgab224

Clinical relevance of serum immunoglobulin G4 in glucocorticoid therapy of Graves' ophthalmopathy.
Clin Endocrinol (Oxf), 95(4):657-67.
Y. Li, B. Luo, J. Zhang, X. Zhou, S. Shao, W. Xu, Y. Yang and G. Yuan. 2021.
OBJECTIVE: Previous study suggested IgG4 levels were associated with the development of Graves' ophthalmopathy (GO). The aims of the present study were to investigate the role of IgG4 levels in glucocorticoid (GC) treatment in GO patients. DESIGN: 69 GO patients were enrolled. Serum thyroid hormones, thyroid antibodies, IgG, IgG4, ophthalmological examinations and orbital MRI were performed. Furthermore, the clinical outcomes (a composite response endpoint including the clinical activity score (CAS), proptosis, vision, intraocular pressure, diplopia and lid width) after high-dose intravenous GC treatment in 32 active moderate-to-severe GO patients were compared. PATIENTS: 69 consecutive

patients with GO were asked to participate in the study. 32 of 69 GO patients were treated with high-dose intravenous GCs. MEASUREMENTS: Measurement of serum IgG and IgG4, serum thyroid hormones and thyroid autoantibodies. An overall ophthalmic assessment was performed pretherapy (week 0) and post-therapy (week 12). RESULTS: 33.3% of GO patients (23/69) had elevated IgG4 levels. IgG4 levels were positively correlated with the severity and activity of GO. After GC therapy, IgG4, IgG4/IgG, vision and CAS were significantly improved in GO patients. Patients with high IgG4 levels had a significantly reduced extraocular muscle area (EOMs) and better clinical outcomes than patients with normal IgG4 levels. CONCLUSIONS: Our results suggest a possible subgroup of elevated IgG4 GO patients, with more severe ophthalmopathy and better response to GCs treatment compare with normal IgG4 GO patients.
PubMed-ID: 33938028
http://dx.doi.org/10.1111/cen.14493

Indeterminate Thyroid Nodules: The Hazy Genomic Landscape Coming into Focus.
J Clin Endocrinol Metab, 106(11):e4781-e3.
A. L. Limbach and J. A. Sipos. 2021.
PubMed-ID: 34139768
http://dx.doi.org/10.1210/clinem/dgab441

A prediction model incorporating the BRAF(V600E) protein status for determining the risk of cervical lateral lymph node metastasis in papillary thyroid cancer patients with central lymph node metastasis.
Eur J Surg Oncol, 47(11):2774-80.
S. Liu, C. Liu, L. Zhao, K. Wang, S. Li, Y. Tian, B. Jiao, Z. Gui, T. Yu and L. Zhang. 2021.
BACKGROUND AND OBJECTIVES: Cervical lateral lymph node metastasis (LLNM) is a predictor of poor prognosis for papillary thyroid carcinoma (PTC) patients. However, the risk factors for LLNM remain unclear. The purpose of the study was to examine the risk factors for LLNM and construct a prediction model. METHODS: With Ethics Committee approval, a total of 1198 PTC patients were retrospectively included in our study. Univariate and multivariate analyses were performed to explore the relationship between clinicopathological characteristics and LLNM. A nomogram for predicting LLNM in PTC patients with central lymph node metastasis (CLNM) was constructed and validated. RESULTS: The negative BRAF(V600E) protein expression was significantly correlated with positive LLNM status in PTC patients. In PTC patients with CLNM, the number of metastatic central lymph nodes (LNN) = 3 and the ratio of metastatic central lymph nodes (LNR) = 0.565 were found to be significantly associated with positive LLNM status. The nomogram for predicting LLNM risk in PTC patients with CLNM incorporated four risk factors: tumor size, the BRAF(V600E) protein expression, LNN and LNR. The prediction model showed excellent discrimination, with a C-index of 0.714. CONCLUSIONS: The negative BRAF(V600E) protein expression was more likely to lead to LLNM. LNN =3 and LNR =0.565 were associated with LLNM risk in PTC patients with CLNM. Our nomogram might assist clinicians in developing individual suitable follow-up strategies for PTC patients with CLNM.
PubMed-ID: 34483032
http://dx.doi.org/10.1016/j.ejso.2021.08.033

Metastatic Risk Profile of Microscopic Lymphatic and Venous Invasion in Medullary Thyroid Cancer.
Horm Metab Res, 53(9):588-93.
A. Machens, K. Lorenz, F. Weber and H. Dralle. 2021.
The metastatic risk profile of microscopic lymphatic and venous invasion in medullary thyroid cancer is ill-defined. This evidence gap calls for evaluation of the suitability of microscopic lymphatic and venous invasion at thyroidectomy for prediction of lymph node and distant metastases in medullary thyroid cancer. In this study of 484 patients with medullary thyroid cancer who had=5 lymph nodes removed at initial thyroidectomy, microscopic lymphatic and venous invasion were significantly associated with greater primary tumor size (27.6 vs. 14.5 mm, and 30.8 vs. 16.2 mm) and more frequent lymph node metastasis (97.0 vs. 25.9%, and 85.2 vs. 39.5%) and distant metastasis (25.0 vs. 5.1%, and 32.8 vs. 7.3%). Prediction of lymph node metastases by microscopic lymphatic invasion was better than prediction of distant metastases by microscopic venous invasion regarding sensitivity (97.0 vs. 32.8%) and positive predictive value (58.4 vs. 39.2%); comparable regarding negative predictive value (98.5 vs. 90.5%) and accuracy (80.4 vs. 85.1%); and worse regarding specificity (74.1 vs. 92.7%). On multivariable logistic regression, microscopic lymphatic invasion predicted lymph node metastasis better (odds ratio [OR] 65.6) than primary tumor size (OR 4.6 for tumors>40 mm and OR 2.7 for tumors 21-40 mm, relative to tumors=20 mm), whereas primary tumor size was better in predicting distant metastasis (OR 8.3 for tumors>40 mm and OR 3.9 for tumors 21-40 mm, relative to tumors=20 mm) than microscopic venous invasion (OR 3.2). These data show that lymphatic invasion predicts lymph node metastases better in medullary thyroid cancer than venous

invasion heralds distant metastases.
PubMed-ID: 34496409
http://dx.doi.org/10.1055/a-1559-3424

Novel Anaplastic Thyroid Cancer PDXs and Cell Lines: Expanding Preclinical Models of Genetic Diversity.
J Clin Endocrinol Metab, 106(11):e4652-e65.
A. Maniakas, Y. C. Henderson, H. Hei, S. Peng, Y. Chen, Y. Jiang, S. Ji, M. Cardenas, Y. Chiu, D. Bell, M. D. Williams, M. C. Hofmann, S. E. Scherer, D. A. Wheeler, N. L. Busaidy, R. Dadu, J. R. Wang, M. E. Cabanillas, M. Zafereo, F. M. Johnson and S. Y. Lai. 2021.
CONTEXT: Anaplastic thyroid cancer (ATC) is a rare, aggressive, and deadly disease. Robust preclinical thyroid cancer models are needed to adequately develop and study novel therapeutic agents. Patient-derived xenograft (PDX) models may resemble patient tumors by recapitulating key genetic alterations and gene expression patterns, making them excellent preclinical models for drug response evaluation. OBJECTIVE: We developed distinct ATC PDX models concurrently with cell lines and characterized them in vitro and in vivo. METHODS: Fresh thyroid tumor from patients with a preoperative diagnosis of ATC was surgically collected and divided for concurrent cell line and PDX model development. Cell lines were created by generating single cells through enzymatic digestion. PDX models were developed following direct subcutaneous implantation of fresh tumor on the flank of immune compromised/athymic mice. RESULTS: Six ATC PDX models and 4 cell lines were developed with distinct genetic profiles. Mutational characterization showed one BRAF/TP53/CDKN2A, one BRAF/CDKN2A, one BRAF/TP53, one TP53 only, one TERT-promoter/HRAS, and one TERT-promoter/KRAS/TP53/NF2/NFE2L2 mutated phenotype. Hematoxylin-eosin staining comparing the PDX models to the original patient surgical specimens show remarkable resemblance, while immunohistochemistry stains for important biomarkers were in full concordance (cytokeratin, TTF-1, PAX8, BRAF). Short tandem repeats DNA fingerprinting analysis of all PDX models and cell lines showed strong concordance with the original tumor. PDX successful establishment rate was 32%. CONCLUSION: We have developed and characterized 6 novel ATC PDX models with 4 matching cell lines. Each PDX model harbors a distinct genetic profile, making them excellent tools for preclinical therapeutic trials.
PubMed-ID: 34147031
http://dx.doi.org/10.1210/clinem/dgab453

Assessing Intraoperative Laser Speckle Contrast Imaging of Parathyroid Glands in Relation to Total Thyroidectomy Patient Outcomes.
Thyroid, 31(10):1558-65.
E. A. Mannoh, G. Thomas, N. Baregamian, S. L. Rohde, C. C. Solórzano and A. Mahadevan-Jansen. 2021.
Background: Accurate assessment of parathyroid gland vascularity is important during thyroidectomy to preserve the function of parathyroid glands and to prevent postoperative hypocalcemia. Laser speckle contrast imaging (LSCI) has been shown to be accurate in detecting differences in parathyroid vascularity. In this surgeon-blinded prognostic study, we evaluate the relationship between intraoperative LSCI measurements and postoperative outcomes of total thyroidectomy patients. Methods: Seventy-two thyroidectomy patients were included in this study. After thyroid resection, an LSCI device was used to image all parathyroid glands identified, and a speckle contrast value was calculated for each. An average value was calculated for each patient, and the data were grouped according to whether the patient had normal (16-77 pg/mL) or low levels of parathyroid hormone (PTH) measured on postoperative day 1 (POD1). The aim of this study was to establish a speckle contrast threshold for classifying a parathyroid gland as adequately perfused and to determine how many such glands are required for normal postoperative parathyroid function. Results: A speckle contrast limit of 0.186 separated the normoparathyroid and hypoparathyroid groups with 87.5% sensitivity and 84.4% specificity: 7 of 8 patients with low PTH on POD1 had an average parathyroid speckle contrast above this limit, while 54 of 64 patients with normal postoperative PTH had an average parathyroid speckle contrast below this limit. Taking this value as the threshold for adequate parathyroid perfusion, it was determined that only one vascularized gland was needed for normal postoperative parathyroid function: 64 of 69 patients (92.8%) with at least one vascularized gland (determined by LSCI) had normal postoperative PTH, while all 3 patients (100%) with no vascularized glands had low postoperative PTH. Overall, the rates of temporary and permanent hypoparathyroidism in this study were 8.3% and 1.4%, respectively. Conclusions: LSCI is a promising technique for assessing parathyroid gland vascularity. It has the potential to help reduce the incidence of hypocalcemia after thyroidectomy by providing surgeons with additional information during surgery to aid in the preservation of parathyroid function.
PubMed-ID: 34078120
http://dx.doi.org/10.1089/thy.2021.0093

Partial Versus Total Thyroidectomy: What Influences Most Surgeons' Decision? Analysis of a Nationwide Cohort of 375,810 Patients Over 10 Years.
Ann Surg, 274(5):829-35.
C. Marciniak, X. Lenne, G. Clément, A. Bruandet, J. C. Lifante, F. Sebag, E. Mirallié, M. Mathonnet, L. Brunaud, G. Donatini, C. Tresallet, F. Ménégaux, D. Theis, F. Pattou and R. Caiazzo. 2021.
National and international guidelines about thyroid surgery seem to be moving more and more towards less radical surgical procedures but everyday practice does not seem to always align with them. We describe for the first time the role of non-surgical parameters in the surgeon's choice for thyroid surgery. OBJECTIVE: The ain of this study was to describe thyroid surgery and to identify the factors leading to either a total or a partial thyroidectomy regardless of the severity of the thyroid disease. SUMMARY BACKGROUND DATA: National and international guidelines about thyroid surgery seem to be moving more and more toward less radical surgical procedures but everyday practice does not seem to always align with them. METHODS: We based this nationwide retrospective cohort study on a national database that compiles discharge abstracts for every admission for thyroidectomy to French acute healthcare facilities (PMSI database 2010 to 2019). RESULTS: In this study, 375,810 patients (male: 23%; age = 53 ± 15 years) had a thyroidectomy (partial: 28%) for cancer (17%), hyperthyroidism (16%), nonfunctioning goiter (64%), or other (3%). We noticed a global trend toward more partial thyroidectomy ($P < 0.001$) with a significant increase in the proportion of lobectomy in the post-ATA recommendations' period ($P < 0.001$) as well as in the "French Levothyrox crisis" period, in which we saw an unexpected rise of adverse events notifications associated with the marketing of a new formula of Levothyrox ($P < 0.001$) amid widespread media coverage. In a multivariate analysis, we also identified that complete resection was more frequently performed in centers with a caseload >40/year [$P < 0.001$, odds ratio (OR) = 1.48], for obese patients (body mass index >30 kg/m2; $P < 0.001$, OR = 1.42), and according to the indication of surgery (OR benign = 1, OR cancer = 2.25, OR hyperthyroidism = 4.13). CONCLUSION: We describe for the first time the role of non-surgical parameters in the surgeon's choice for thyroid surgery.
PubMed-ID: 34353991
http://dx.doi.org/10.1097/SLA.0000000000005134

A Closer Look at "Taller-Than-Wide" Thyroid Nodules: Examining Dimension Ratio to Predict Malignancy.
Otolaryngol Head Neck Surg:1945998211051310.
A. S. Mattingly, J. E. Noel and L. A. Orloff. 2021.
OBJECTIVE: To evaluate nodule height-to-width ratio as a continuous variable predicting likelihood of thyroid malignancy. STUDY DESIGN: Retrospective cohort study. SETTING: All study information was collected from a single academic tertiary care hospital. METHODS: Subjects included adult patients with thyroid nodules who underwent thyroid surgery between 2010 and 2020. The following variables were collected: patient demographics, nodule dimensions via ultrasound, fine-needle aspiration biopsy results, and surgical pathology results. Statistical analysis included logistic regression modeling malignancy with variables of interest. We used a receiver operating characteristic curve to assess the discriminatory value of variables. RESULTS: Height-to-width ratio, as a continuous variable, was associated with malignancy (with each 0.1 increase in ratio; odds ratio [OR], 1.25; 95% CI, 1.14-1.37). The same relationship was true for height-to-length ratio (OR, 1.36; 95% CI, 1.24-1.56). The area under the receiver operating characteristic curve for height-to-width ratio was 63.7%. In line with current emphasis on the transverse ultrasound view, we determined 4 different height-to-width ratio intervals: <0.8, 0.8 to <1.0, 1.0 to <1.5, and =1.5. Likelihood ratios of malignancy for each interval were 0.6, 1.0, 2.3, and 4.9, respectively. CONCLUSION: Our results support the association between greater height-to-width ratio and malignancy but suggest that a multilevel rather than binary variable improves prediction. The likelihood ratios at different intervals give a more nuanced view of how height-to-width ratio predicts malignancy. With continuing review of guidelines for thyroid nodule biopsy, it is important to consider these data for any point total attributed to shape.
PubMed-ID: 34637345
http://dx.doi.org/10.1177/01945998211051310

Multifocality and Progression of Papillary Thyroid Microcarcinoma During Active Surveillance.
World J Surg, 45(9):2769-76.
R. Nagaoka, A. Ebina, K. Toda, T. Jikuzono, M. Saitou, M. Sen, H. Kazusaka, M. Matsui, K. Yamada, H. Mitani and I. Sugitani. 2021.
BACKGROUND: Prospective trials of active surveillance (AS) have shown low rates of progression in low-risk papillary thyroid microcarcinoma (PTMC; T1aN0M0). However, the significance of multifocality as a prognostic factor remains controversial. METHODS: Data from 571 patients (mean age, 53.1 years; 495 females) who underwent AS were reviewed. PTMC was unifocal in 457 patients (80.0%) and multifocal in 114 patients (20.0%), with 2-5 lesions each (261 tumors in

total). Tumor progression was defined as tumor size enlargement = 3 mm and/or development of clinically evident lymph node metastasis (LNM). RESULTS: After a mean duration of AS of 7.6 years, 53 patients (9.3%) showed tumor enlargement and 8 patients (1.4%) developed LNM. The 10-year progression rate was 13.1%. Age, sex, and calcification pattern did not differ significantly between uni- and multifocal diseases. However, anti-thyroglobulin antibody and/or anti-thyroid peroxidase antibody was more frequently positive with multifocal PTMCs (46.7%) than with unifocal disease (34.4%, p = 0.024). Patients with uni- and multifocal disease showed no significant differences in 10-year rate of tumor enlargement (11.4% vs. 14.8%), LNM development (1.1% vs. 2.4%), or progression (12.4% vs 15.9%). Multivariate analysis of predictors for progression showed multifocality was not a significant risk factor (odds ratio, 1.45; 95% confidence interval, 0.79-2.54; p = 0.22). Eventually, 9 patients (7.9%) with multifocal PTMCs underwent surgery and 7 needed total thyroidectomy, although 7 still showed T1N0M0 low-risk cancer. CONCLUSIONS: Even patients with multiple PTMCs (T1amN0M0) are good candidates for AS. Many patients can avoid total thyroidectomy and subsequent surgical complications.
PubMed-ID: 34100116
http://dx.doi.org/10.1007/s00268-021-06185-2

Bilateral Central Neck Dissection via Transoral Approach in Papillary Thyroid Carcinoma.
Ann Surg Oncol, 29(3):1973-4.
D. Q. Ngo, D. T. Le, Q. X. Ngo and Q. V. Le. 2022.
BACKGROUND: The transoral endoscopic vestibular approach (TOETVA) for thyroidectomy is gaining popularity (Russell et al. in Thyroid 28(7):825-829, 2018; Le et al. in Surg Laparosc Endosc Percutan Tech 30(3):209-213, 2020; Liao et al. in Laryngoscope 130(6):1603-1608, 2020). TOETVA has been utilized successfully in performing thyroidectomy, parathyroidectomy, and neck dissection, via both endoscopic and robotic techniques (Razavi et al. in Head Neck 40(10):2246-2253, 2018; Otolaryngol Head Neck Surg 159(4):625-629, 2018; Ngo et al. in J ENT, 2020. https://doi.org/10.1177/0145561320943358 ; Ann Surg Oncol 28(5):2766, 2021). In this video, we show bilateral central neck dissection via transoral approach in papillary thyroid carcinoma. PATIENT AND METHODS: A 37-year-old female with no significant medical history was diagnosed pT3bN0M0 intraoperatively with the tumor having slightly invaded the strap muscle. Thus, we decided to perform total thyroidectomy with bilateral central neck dissection via transoral approach. METHODS: Prelaryngeal dissection: in the prelaryngeal compartment, soft tissue containing these lymph nodes was intimately associated with the pyramidal lobe. Right paratracheal dissection: fibrofatty tissue was dissected off the prevertebral fascia and the trachea with preservation of right parathyroid glands. Pretracheal lymph nodes were removed with paratracheal dissection. Left paratracheal dissection: the lymphatic tissue was then dissected off the prevertebral and esophageal musculature and the trachea after identifying the left parathyroid glands. Finally, bilateral central neck dissection was finished with preservation of the nerve and parathyroid glands. RESULTS: The operation was completed successfully without conversion to open surgery. The operative time for central neck dissection was 20 min. There were nine harvested lymph nodes in the central compartments, while there were two metastatic lymph nodes of papillary thyroid carcinoma with 3 × 3 mm maximal dimension. There were no major postoperative complications. CONCLUSION: Central neck dissection via TOETVA is a safe and feasible method in selected patients.
PubMed-ID: 34694524
http://dx.doi.org/10.1245/s10434-021-10996-x

Recurrence of Papillary Thyroid Cancer: A Systematic Appraisal of Risk Factors.
J Clin Endocrinol Metab,
H. R. Nieto, C. E. M. Thornton, K. Brookes, A. N. de Menezes, A. Fletcher, M. Alshahrani, M. Kocbiyik, N. Sharma, K. Boelaert, J. B. Cazier, H. Mehanna, V. E. Smith, M. L. Read and C. J. McCabe. 2021.
BACKGROUND: Thyroid cancer recurrence is associated with increased mortality and adverse outcomes. Recurrence risk is currently predicted using clinical tools, often restaging patients after treatment. Detailed understanding of recurrence risk at disease-onset could lead to personalised and improved patient care. OBJECTIVE: To perform a comprehensive bioinformatic and experimental analysis of 3 levels of genetic change (mRNA, microRNA, and somatic mutation) apparent in recurrent tumours and construct a new combinatorial prognostic risk model. METHODS: We analysed The Cancer Genome Atlas data (TCGA) to identify differentially expressed genes (mRNA/microRNA) in 46 recurrent versus 455 non-recurrent thyroid tumours. Two exonic mutational pipelines were used to identify somatic mutations. Functional gene analysis was performed in cell-based assays in multiple thyroid cell lines. The prognostic value of genes was evaluated with TCGA datasets. RESULTS: We identified a total of 128 new potential biomarkers associated with recurrence, including 40 mRNAs, 39 miRNAs and 59 genetic variants. Among differentially expressed genes, modulation of FN1, ITGa3 and MET had a significant impact on thyroid cancer cell migration. Similarly, ablation of miR-486 and miR-1179 significantly increased migration of TPC-1 and SW1736 cells. We further utilised genes with a validated functional role and identified a 5 gene risk

score classifier as an independent predictor of thyroid cancer recurrence. CONCLUSIONS: Our newly proposed risk model based on combinatorial mRNA and microRNA expression has potential clinical utility as a prognostic indicator of recurrence. These findings should facilitate earlier prediction of recurrence with implications for improving patient outcome by tailoring treatment to disease risk and increasing post-treatment surveillance.
PubMed-ID: 34791326
http://dx.doi.org/10.1210/clinem/dgab836

Can TP53-mutant follicular adenoma be a precursor of anaplastic thyroid carcinoma?
Endocr Relat Cancer, 28(9):621-30.
A. V. Nikitski, M. N. Nikiforova, L. Yip, E. Karslioglu-French, S. E. Carty and Y. E. Nikiforov. 2021.
Mutations of the TP53 tumor suppressor gene are highly prevalent in thyroid anaplastic carcinomas (AC) but are also reported in some well-differentiated cancers and even in benign adenomas. The natural history of TP53-mutant adenomas and whether they may represent a precursor for well-differentiated cancer or AC is largely unknown. Similarly, the frequency of TP53 mutations in thyroid nodules found on routine molecular analysis of fine-needle aspiration (FNA) samples is not established. A database on 44,510 FNA samples from thyroid nodules with predominantly indeterminate cytology tested using ThyroSeq v3 was reviewed to identify TP53-mutant cases and analyze their genetic profile and available clinicopathological findings. Among 260 (0.6%) selected thyroid nodules, 36 had an isolated TP53 mutation and 224 carried a combination of TP53 with other genetic alterations. No significant difference was observed between these groups with respect to patient age, gender, nodule size, and spectrum of TP53 mutations. Histopathologically, 86% of the resected nodules with isolated TP53 mutations were benign (mostly adenomas), whereas 82% of nodules carrying TP53 mutations co-occurring with other alterations were cancers (P = 0.001), including de-differentiated AC. TP53-mutant benign tumors and well-differentiated cancers often had scattered single neoplastic cells with bizarre nuclei resembling those comprising AC. Our study demonstrates that a small but distinct proportion of thyroid nodules carry a TP53 mutation, either as a single genetic event or in combination with other alterations. While the latter is mostly cancers prone to dedifferentiation, there is at least a theoretical possibility that TP53-mutated adenomas may represent a precursor for such cancers, including AC.
PubMed-ID: 34264855
http://dx.doi.org/10.1530/ERC-21-0095

A Population-Based Analysis of Outpatient Thyroidectomy: Safe and Under-Utilized.
Laryngoscope, 131(11):2625-33.
C. W. Noel, R. Griffiths, J. Siu, D. Forner, D. Urbach, J. Freeman, D. P. Goldstein, J. C. Irish, K. M. Higgins, K. Devon, J. D. Pasternak and A. Eskander. 2021.
OBJECTIVES/HYPOTHESIS: Performance of thyroidectomy on an outpatient basis has gained popularity although many jurisdictions have not shifted their practice despite a strong safety profile. We sought to assess the uptake and safety of outpatient thyroidectomy in Ontario. STUDY DESIGN: Retrospective cohort study. METHODS: This was a population-based retrospecive cohort of adult patients undergoing hemithyroidectomy or total thyroidectomy between 1993 and 2017 in Ontario, Canada. Outpatient surgery was defined as discharge home on the same day of surgery. Outcomes of interest include 30-day all cause death, hematoma, emergency department use, and readmission. To adjust for confounding, propensity scores were calculated. Logistic regression models with inverse probability of treatment weighting (IPTW) were then used to estimate the exposure-outcome relationship. RESULTS: The final cohort consisted of 81,199 patients: 8,442 underwent same day surgery and 72,757 were admitted. The proportion of patients undergoing outpatient thyroidectomy increased overtime (2.3% in 1993-1994 to 17.8% in 2016-2017). Factors associated with higher odds of outpatient thyroidectomy included: younger age, less material deprivation, less comorbidities, and higher surgeon volume. The absolute number of deaths (=5) and hematomas (64, 0.8%) in the outpatient cohort was low. After IPTW adjustment, patients with outpatient management had lower odds of neck hematoma (OR 0.73[95CI% 0.58-0.93)], but higher odds of emergency department use (OR 1.67[95%CI 1.56-1.79]). CONCLUSIONS: Outpatient thyroidectomy is not associated with an increased mortality risk. Less than one in five patients undergo outpatient thyroidectomy in Ontario, despite a well-established safety profile. LEVEL OF EVIDENCE: 3 Laryngoscope, 131:2625-2633, 2021.
PubMed-ID: 34378810
http://dx.doi.org/10.1002/lary.29816

Reduction of overtreatment without reduction of overdiagnosis in patients with differentiated thyroid cancer: mission impossible.
Langenbecks Arch Surg, 406(6):2011-7.
T. Oblak, A. Perhavec, M. Hocevar and B. Peric. 2021.
PURPOSE: Lateral neck nodal metastases are common in patients with differentiated thyroid cancer (DTC) and usually have an indolent nature. They may be detected via neck palpation or preoperative ultrasound (US) of the neck. We hypothesized that preoperative neck metastases detected with US did not affect regional recurrence or long-term survival. METHODS: A retrospective analysis of patients' records treated for DTC at our institution between January 2006 and December 2016 was performed. Information about preoperative US of the neck, treatment, demographics, staging, and histopathology was obtained. The endpoints for the study were nodal recurrence and survival. Differences in survival were analyzed between three groups of patients divided by presence or lack of preoperative US and/or palpable cervical lymph nodes (PLN). Furthermore, the prognostic value of multiple variables was tested by univariate and multivariate analysis. RESULTS: There were 1108 patients with DTC, 221 males and 887 females. The median age was 48.3 years (range 3 to 86), the median time of observation was 68 months (range 0 to 142). Eight hundred sixty-two patients without PLN or preoperative US represented group 1, 112 patients with PLN were in group 2, and 134 patients without PLN and with preoperative US were in group 3. Only five patients had a regional recurrence, one died due to distant metastases. There was no statistically significant difference in survival between the groups (p = 0.841) and neck US was not significantly associated with overall survival neither in univariate nor in multivariate analysis. CONCLUSION: In patients with DTC, the benefits of preoperative US of cervical lymph nodes are probably limited and "less is more" approach is advised.
PubMed-ID: 34097134
http://dx.doi.org/10.1007/s00423-021-02216-7

Transoral endoscopic thyroidectomy by a vestibular approach: cadaver simulation experience and ethicolegal issues.
Br J Surg, 108(12):e396-e7.
A. Oliva, S. Grassi, N. Minelli, M. Zedda, V. Arena, N. Romaniello, G. Dionigi, Ö. Makay, C. De Crea, S. Celik, A. G. Spagnolo, R. Bellantone and M. Raffaelli. 2021.
PubMed-ID: 34570184
http://dx.doi.org/10.1093/bjs/znab325

Predicting risk factors of postoperative hypocalcemia after total thyroidectomy: is safe discharge without supplementation possible? A large cohort study.
Langenbecks Arch Surg, 406(7):2425-31.
N. C. Paladino, C. Guérin, J. Graziani, I. Morange, A. Loundou, D. Taïeb and F. Sebag. 2021.
PURPOSE: With increasing economic pressures to shorten the length of hospital stay, there has been much recent interest in studying risk factors for the development of postoperative hypocalcemia after total thyroidectomy. The aim of this study was to investigate whether serum calcium and/or PTH levels can predict post-thyroidectomy hypoparathyroidism. METHODS: From January to December 2014, 477 consecutive patients undergoing total thyroidectomy were included. Corrected calcemia and PTH were systematically performed on postoperative day 1/(POD1). Symptomatic patients were treated on POD1 or POD2 with calcium and vitamin D. RESULTS: Sixty-eight patients (14.25%) were treated for postoperative hypocalcemia. No patients with calcemia = 2.16 mmol/l and PTH = 1.9 pmol/l were supplemented and therefore were safely discharged on POD1 (specificity = 100%). All patients with calcemia = 1.89 mmol/l were treated regardless the PTH values (n = 10) (specificity = 100%). For calcium value between 1.9 and 2.16 mmol/l with a PTH > 4.7 pmol/l, nobody was treated. With a calcemia between 1.9 and 2.16 mmol/l and a PTH > 1.9 pmol/l, 44 patients did not develop any symptom. ROC curve analysis showed that combination of Cac = 2.16 mmol/l and iPTH = 4.7 pmol/l provided a sensitivity of 97.06% and a specificity of 76.53% (p < 0.0001). We therefore propose an algorithm that would allow to 70% of patients could have been discharged on POD1 without risk of hypocalcemia or overtreatment. CONCLUSION: Combination of corrected calcemia and PTH on POD1 can efficiently predict hypocalcemia and be integrated into clinical practice for personalizing lengths of hospitalization and appropriate treatment. TRIAL REGISTRATION: ClinicalTrials.gov PRS. Unique Identifying number or registration ID: NCT04372225.
PubMed-ID: 34374848
http://dx.doi.org/10.1007/s00423-021-02237-2

Thyroid Hormone Therapy and Incident Stroke.
J Clin Endocrinol Metab, 106(10):e3890-e900.
M. Papaleontiou, D. A. Levine, D. Reyes-Gastelum, S. T. Hawley, M. Banerjee and M. R. Haymart. 2021.
CONTEXT: Stroke is a leading cause of death and disability and there is a need to identify modifiable risk factors. OBJECTIVE: We aimed to determine the relationship between thyroid hormone treatment intensity and incidence of atrial fibrillation and stroke. METHODS: We conducted a retrospective cohort study using data from the Veterans Health Administration between 2004 and 2017, with a median follow-up of 59 months. The study population comprised 733 208 thyroid hormone users aged =18 years with at least 2 thyroid stimulating hormone (TSH) measurements between thyroid hormone initiation and incident event (atrial fibrillation or stroke) or study conclusion (406 030 thyroid hormone users with at least 2 free thyroxine [T4] measurements). RESULTS: Overall, 71 333/643 687 (11.08%) participants developed incident atrial fibrillation and 41 931/663 809 (6.32%) stroke. In multivariable analyses controlling for pertinent factors such as age, sex, and prior history of atrial fibrillation, higher incidence of stroke was associated with low TSH or high free T4 levels (ie, exogenous hyperthyroidism; eg, TSH <0.1 mIU/L; OR 1.33; 95% CI, 1.24-1.43; free T4>1.9 ng/dL, OR 1.17, 95% CI 1.06-1.30) and high TSH or low free T4 levels (ie, exogenous hypothyroidism; eg, TSH >5.5 mIU/L; OR 1.29; 95% CI, 1.26-1.33; free T4 <0.7 ng/dL; OR 1.29; 95% CI, 1.22-1.35) compared with euthyroidism (TSH >0.5-5.5 mIU/L and free T4 0.7-1.9 ng/dL). Risk of developing atrial fibrillation and stroke was cumulative over time for both patients with exogenous hyperthyroidism and hypothyroidism. CONCLUSION: Both exogenous hyper- and hypothyroidism were associated with increased risk of stroke, highlighting the importance of patient medication safety.
PubMed-ID: 34137866
http://dx.doi.org/10.1210/clinem/dgab444

Whole-genome Sequencing of Follicular Thyroid Carcinomas Reveal Recurrent Mutations in MicroRNA Processing Subunit DGCR8.
J Clin Endocrinol Metab, 106(11):3265-82.
J. O. Paulsson, N. Rafati, S. DiLorenzo, Y. Chen, F. Haglund, J. Zedenius and C. C. Juhlin. 2021.
BACKGROUND: The genomic and transcriptomic landscape of widely invasive follicular thyroid carcinomas (wiFTCs) and Hürthle cell carcinoma (HCC) are poorly characterized, and subsets of these tumors lack information on genetic driver events. OBJECTIVE: The aim of this study was to bridge this gap. METHODS: We performed whole-genome and RNA sequencing and subsequent bioinformatic analyses of 11 wiFTCs and 2 HCCs with a particularly poor prognosis, and matched normal tissue. RESULTS: All wiFTCs exhibited one or several mutations in established thyroid cancer genes, including TERT (n = 4), NRAS (n = 3), HRAS, KRAS, AKT, PTEN, PIK3CA, MUTYH, TSHR, and MEN1 (n = 1 each). MutSig2CV analysis revealed recurrent somatic mutations in FAM72D (n = 3, in 2 wiFTCs and in a single HCC), TP53 (n = 3, in 2 wiFTCs and a single HCC), and EIF1AX (n = 3), with DGCR8 (n = 2) as borderline significant. The DGCR8 mutations were recurrent p.E518K missense alterations, known to cause familial multinodular goiter via disruption of microRNA (miRNA) processing. Expression analyses showed reduced DGCR8 messenger RNA expression in FTCs in general, and the 2 DGCR8 mutants displayed a distinct miRNA profile compared to DGCR8 wild-types. Copy number analyses revealed recurrent gains on chromosomes 4, 6, and 10, and fusion gene analyses revealed 27 high-quality events. Both HCCs displayed hyperploidy, which was fairly unusual in the FTC cohort. Based on the transcriptome data, tumors amassed in 2 principal clusters. CONCLUSION: We describe the genomic and transcriptomic landscape in wiFTCs and HCCs and identify novel recurrent mutations and copy number alterations with possible driver properties and lay the foundation for future studies.
PubMed-ID: 34171097
http://dx.doi.org/10.1210/clinem/dgab471

[Is there an indication for thyroidectomy in cases of minimally invasive follicular thyroid carcinoma?].
Chirurg,
S. Peth, R. Hummel, M. Schreckenberger, A. Schad, R. Raabe and T. Weber. 2021.
PubMed-ID: 34936001
http://dx.doi.org/10.1007/s00104-021-01553-z

Tall cell percentage alone in PTC without aggressive features should not guide patients' clinical management.
J Clin Endocrinol Metab, 106(10):e4109-e17.
A. M. Poma, D. Viola, E. Macerola, A. Proietti, E. Molinaro, D. De Vietro, R. Elisei, G. Materazzi, P. Miccoli, F. Basolo and C. Ugolini. 2021.
CONTEXT: Recent diagnostic criteria updates of the tall cell variant of papillary thyroid carcinoma (TCPTC) by the World Health Organization (WHO) have determined the inclusion of tumors with 30% to 49% of tall cells. However, the impact of

tall cell percentage on papillary thyroid carcinoma (PTC) patients' prognosis is still debated. OBJECTIVE: We aimed to evaluate whether tall cell percentage affects patient outcome in the absence of aggressive features. METHODS: Rates of aggressive features, recurrence-free survival (RFS), and distant RFS (5-year median follow-up) were compared among tumors with less than 30%, 30% to 49% and at least 50% tall cells. We also evaluated the impact of the new tall cell cutoff on patient management. RESULTS: Overall, 3092 tumors (15.7% of all PTCs) were collected: A total of 792 PTCs had less than 30%, 503 had 30% to 49%, and 1797 had 50% or more tall cell areas. With the new WHO definition, the number of TCPTCs increased by 28%. There were no differences in recurrence rates according to tall cell percentage. The coexistence of BRAF and TERT promoter mutations predicted a worse RFS. Considering the new definition of TCPTC, the level of risk according to the American Thyroid Association increased from low to intermediate in 4.2% of cases. However, the recurrence rate within this subgroup was comparable to low risk. CONCLUSION: TCPTC and PTC with tall cell areas can be considered as a unique group with similar recurrence risk. However, whenever aggressive features are absent, tumors have a low risk of recurrence independently of tall cell percentage.
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http://dx.doi.org/10.1210/clinem/dgab388

Prognostic Performance of Alternative Lymph Node Classification Systems for Patients with Medullary Thyroid Cancer: A Single Center Cohort Study.
Ann Surg Oncol, 29(4):2561-9.
D. Prassas, A. Kounnamas, K. Cupisti, M. Schott, W. T. Knoefel and A. Krieg. 2022.
BACKGROUND: Lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS) have been proposed as alternative lymph node (LN) classification schemes. Various cut-off values have been defined for each system, with the question of the most appropriate for patients with medullary thyroid cancer (MTC) still remaining open. We aimed to retrospectively compare the predictive impact of different LN classification systems and to define the most appropriate set of cut-off values regarding accurate evaluation of overall survival (OS) in patients with MTC. METHODS: 182 patients with MTC who were operated on between 1985 and 2018 were extracted from our medical database. Cox proportional hazards regression models and C-statistics were performed to assess the discriminative power of 28 LNR and 28 LODDS classifications and compare them with the N category according to the 8th edition of the AJCC/UICC TNM classification in terms of discriminative power. Regression models were adjusted for age, sex, T category, focality, and genetic predisposition. RESULTS: High LNR and LODDS are associated with advanced T categories, distant metastasis, sporadic disease, and male gender. In addition, among 56 alternative LN classifications, only one LNR and one LODDS classification were independently associated with OS, regardless of the presence of metastatic disease. The C-statistic demonstrated comparable results for all classification systems showing no clear superiority over the N category. CONCLUSION: Two distinct alternative LN classification systems demonstrated a better prognostic performance in MTC patients than the N category. However, larger scale studies are needed to further verify our findings.
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http://dx.doi.org/10.1245/s10434-021-11134-3

Tobacco smoking and risk of thyroid cancer according to BRAF(V600E) mutational subtypes.
Clin Endocrinol (Oxf), 95(6):891-900.
S. T. Rahman, N. Pandeya, R. E. Neale, D. S. A. McLeod, P. D. Baade, P. H. Youl, R. Allison, S. Leonard and S. J. Jordan. 2021.
OBJECTIVE: Smoking has been associated with a reduced risk of thyroid cancer, but whether the association varies between higher- and lower-risk cancers remains unclear. We aimed to assess the association between smoking and risk of thyroid cancer overall as well as by tumour BRAF mutational status as a marker of potentially higher-risk cancer. DESIGN AND PATIENTS: We recruited 1013 people diagnosed with thyroid cancer and 1057 population controls frequency-matched on age and sex. METHODS: Multivariable logistic regression was used to assess the association overall and in analyses stratified by tumour characteristics. We used sensitivity analysis to assess the potential for selection bias. RESULTS: We found little evidence of an association with current smoking (odds ratio [OR] = 0.93; 95% confidence interval [CI]: 0.69-1.26; current vs. never smoking), but a higher number of pack-years of smoking was associated with a lower risk of thyroid cancer (OR = 0.75; 95% CI: 0.57-0.99; =20 pack-years vs. never). However, after correcting for potential selection bias, we observed a statistically significant inverse association between current smoking and risk of thyroid cancer (bias-corrected OR = 0.65; 95% CI: 0.51-0.83). Those with BRAF-positive cancers were less likely to be current smokers than those with BRAF-negative cancers (prevalence ratio: 0.79; 95% CI: 0.62-0.99). CONCLUSION: We found smoking was inversely related to thyroid cancer risk and, in particular, current smoking was associated with a reduced risk of potentially more aggressive BRAF-positive than the likely more indolent BRAF-negative papillary thyroid cancers.

PubMed-ID: 34170568
http://dx.doi.org/10.1111/cen.14545

Review of Surgical Therapy of Adrenal Tumors in Guidelines From the German Association of Endocrine Surgeons.
JAMA Surg, 156(11):1061-2.
K. M. Ramonell, J. Fazendin and B. Lindeman. 2021.
PubMed-ID: 34347014
http://dx.doi.org/10.1001/jamasurg.2021.3595

Similar Stage-dependent Survival and Outcome in Sporadic and Hereditary Medullary Thyroid Carcinoma.
J Clin Endocrinol Metab, 106(9):e3582-e91.
F. Raue, T. Bruckner and K. Frank-Raue. 2021.
CONTEXT: Long-term data are scarce on large cohorts with sporadic (sMTC) and hereditary medullary thyroid carcinoma (hMTC). OBJECTIVES: To compare long-term disease-specific survival (DSS) and outcomes between sMTC and hMTC groups. DESIGN: Retrospective analysis. SETTING: German tertiary referral center. PATIENTS: A total of 673 patients with MTC that underwent surgery from January 1974 to July 2019. INTERVENTION: None (observational study). MAIN OUTCOME MEASURE: Differences between sMTC and hMTC in long-term, stage-dependent survival and outcomes. RESULTS: Surgery was performed at median ages of 49 years for sMTC (n = 477, 44% male) and 29 years for hMTC (n = 196, 43% male; P < 0.0001). The mean follow-up times were 9.2 ± 8.0 (sMTC) and 14.6 ± 10.3 years (hMTC). Age and tumor stage at diagnosis were significantly different between the 2 groups (P < 0.0001). The sMTC and hMTC groups had different overall DSS (log rank, P = 0.0183), but similar stage-dependent DSS (log rank, P = 0.1242-0.8981). In a multivariate analysis, sMTC and hMTC did not differ in DSS (hazard ratio [HR] = 1.56; 95% CI, 0.94-2.57), but in both groups, a worse DSS was significantly associated with age at diagnosis (HR = 1.04; 95% CI, 1.02-1.05), male sex (HR = 0.49; 95% CI, 0.32-0.76), and stages III and IV at diagnosis (HR = 20.00; 95% CI, 2.74-145.91 and HR = 97.47; 95% CI, 13.07-726.67, respectively). The groups had significantly different (P < 0.0001) outcomes (i.e., cured, minimal residual disease, structural detectable disease, and death), but similar stage-dependent outcomes (P = 0.9449-0.0511), except for stage III (P = 0.0489). CONCLUSION: Patients with sMTC and hMTC had different ages of onset, but similar stage-dependent DSS and outcomes after the MTC diagnosis. This finding suggested that tumor behavior was similar in sMTC and hMTC.
PubMed-ID: 33974051
http://dx.doi.org/10.1210/clinem/dgab326

The complex regulation of NIS expression and activity in thyroid and extrathyroidal tissues.
Endocr Relat Cancer, 28(10):T141-T65.
G. Riesco-Eizaguirre, P. Santisteban and A. De la Vieja. 2021.
The sodium/iodide symporter (NIS) is an intrinsic plasma membrane protein that mediates active iodide transport into the thyroid gland and into several extrathyroidal tissues. NIS-mediated iodide uptake plays a pivotal role in the biosynthesis of thyroid hormones, of which iodide is an essential constituent. For 80 years, radioiodide has been used for the diagnosis and treatment of thyroid cancer, a successful theranostic agent that is extending its use to extrathyroidal malignancies. The purpose of this review is to focus on the most recent findings regarding the mechanisms that regulate NIS both in thyroid and extra-thyroidal tissues. Among other issues, we discuss the different transcriptional regulatory elements that govern NIS transcription in different tissues, the epigenetic modifications that regulate its expression, and the role that miRNAs play in fine-tuning NIS after being transcribed. A review on how hormones, cytokines, and iodide itself regulate NIS is provided. We also review the present stage of understanding NIS dysregulation in cancer, occupied mainly by convergent signaling pathways and by new insights in the route that NIS follows through different subcellular compartments to the plasma membrane. Furthermore, we cover NIS distribution and function in the increasing number of extrathyroidal tissues that express the symporter, as well as the role that NIS plays in tumor progression independently of its transport activity.
PubMed-ID: 34387194
http://dx.doi.org/10.1530/ERC-21-0217

Raised mortality in old adults with a history of hyperthyroidism following iodine fortification.
Clin Endocrinol (Oxf), 96(2):255-62.
J. Riis, S. L. Andersen, G. V. Gade, M. B. Danielsen, M. G. Jorgensen, A. Carlé, C. Torp-Pedersen and S. Andersen. 2022.
OBJECTIVE: A transient rise in the occurrence of hyperthyroidism ensued the introduction of iodine fortification (IF) of salt in Denmark. Older adults are at risk of complications to hyperthyroidism that could prove fatal to vulnerable individuals.

We evaluated the association between thyroid function and mortality in older adults before and after nationwide implementation of IF. DESIGN: Retrospective cohort study. PATIENTS: All 68-year-olds from the general population in the city of Randers were invited to participate in a clinical study in 1988 and followed until death, emigration or end of study (31 December 2017) using Danish registries. MEASUREMENTS: Baseline measures comprised of a questionnaire, physical examination and blood and urine samples. Kaplan-Meier survival curves and Cox regression were used to determine the association between thyroid function and death before and after IF. Time-stratification of results before and after IF was employed due to violation of proportional hazards assumptions in Cox regression. RESULTS: Median urinary iodine concentration was 42 µg/L at baseline consistent with moderate iodine deficiency. Hyperthyroidism (thyrotropin < 0.4 mIU/L) occurred in 37 (9.1%) participants. Kaplan-Meier survival curves showed an increase in mortality among participants with hyperthyroidism after IF. There was no significant association between hyperthyroidism and mortality before IF compared to euthyroid participants, but after IF hyperthyroid subjects had an increased mortality (adjusted hazard ratio: 2.22, 95% confidence interval: 1.44-3.44). CONCLUSIONS: IF was associated with raised mortality among older adults with a history of hyperthyroidism and moderate iodine deficiency. Our results highlight the need for cautious iodine supplementation and for monitoring of IF.
PubMed-ID: 34743350
http://dx.doi.org/10.1111/cen.14627

Graves' Disease in the Young : could we change the weather ?
J Clin Endocrinol Metab,
P. Rodien. 2021.
PubMed-ID: 34928376
http://dx.doi.org/10.1210/clinem/dgab909

Analysis of Expression of Different Histone Deacetylases in Autoimmune Thyroid Disease.
J Clin Endocrinol Metab, 106(11):3213-27.
P. Sacristán-Gómez, A. Serrano-Somavilla, R. González-Amaro, R. Martínez-Hernández and M. Marazuela. 2021.
CONTEXT: Histone deacetylases (HDACs) and histone acetyltransferases (HAT) have an important role in the regulation of gene transcription as well as in the development and function of CD4+Foxp3+ T regulatory (Treg) cells. Our group and others have reported that patients with autoimmune thyroid disease (AITD) show abnormalities in the levels and function of different Treg cell subsets. OBJECTIVE: We aimed to analyze the levels of expression of several HDACs and the Tip60 HAT in the thyroid gland and immune cells from patients with AITD. METHODS: The expression of HDAC1-11 and the Tip60 HAT, at RNA and protein levels, were determined in thyroid tissue from 20 patients with AITD and 10 healthy controls and these findings were correlated with clinical data. HDAC9 and Tip60 levels were also analyzed in thyroid cell cultures, stimulated or not with proinflammatory cytokines, as well as in different cell subsets from peripheral blood mononuclear cells. RESULTS: Altered expression of different HDACs was observed in thyroid tissue from AITD patients, including a significant increase in HDAC9, at RNA and protein levels. Likewise, HDAC9 expression was increased in peripheral blood mononuclear cells particularly in Treg cells in patients with AITD. In contrast, Tip60 expression was reduced in thyroid gland samples from patients with Hashimoto thyroiditis. CONCLUSION: Our results indicate that HDAC expression is dysregulated in thyroid gland and immune cells from patients with AITD, suggesting involvement in the pathogenesis of this condition.
PubMed-ID: 34272941
http://dx.doi.org/10.1210/clinem/dgab526

ASO Author Reflections:Improving the Quality of Life of Patients with Indeterminate Thyroid Nodules Receiving Molecular Testing.
Ann Surg Oncol, 28(13):8882-3.
M. A. Schumm and M. J. Livhits. 2021.
PubMed-ID: 34215954
http://dx.doi.org/10.1245/s10434-021-10398-z

Guide to Enhanced Recovery for Cancer Patients Undergoing Thyroidectomy.
Ann Surg Oncol, 28(12):6936-8.
U. S. Shah, J. Holder-Murray and K. L. McCoy. 2021.
PubMed-ID: 34128139
http://dx.doi.org/10.1245/s10434-021-10100-3

Avidity and Outcomes of Radioiodine Therapy for Distant Metastasis of Distinct Types of Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e3911-e22.
J. Simões-Pereira, N. Mourinho, T. C. Ferreira, E. Limbert, B. M. Cavaco and V. Leite. 2021.
CONTEXT: The recommendations for radioactive-iodine treatment (RAIT) in metastatic differentiated thyroid cancer (DTC) are mostly based in the experience with papillary histotype and do not consider the differences within the distinct types of DTC, in terms of RAIT uptake and response. OBJECTIVE: This work aims to investigate the association between histology and RAIT avidity and response, and to evaluate whether histotype was an independent prognostic factor in progression-free survival (PFS) and disease-specific survival (DSS) after RAIT for distant metastatic disease. METHODS: A retrospective analysis was conducted of all DTC patients who underwent RAIT for distant metastatic disease, from 2001 to 2018, at a thyroid cancer referral center. We included 126 patients: 42 (33.3%) classical variant papillary thyroid cancer (cvPTC), 45 (35.7%) follicular variant PTC (fvPTC), 17 (13.5%) follicular thyroid cancer (FTC) and 22 (17.5%) Hürthle cell carcinoma. Main outcome measures included RAIT avidity and response. RESULTS: RAIT avidity was independently associated with histology (P < .001) and stimulated thyroglobulin (Tg) at first RAIT for distant lesions (P = .007). Avidity was lowest in HCC (13.6%), intermediate in cvPTC (21.4%), and highest in fvPTC (75.6%) and FTC (76.5%). Regarding RAIT response, HCC and FTC were not different; both showed significantly more often progression after RAIT than fvPTC and cvPTC. Histology influenced PFS (P = .014), but tumor type was not a significant prognostic factor in DSS. Instead, age at diagnosis, resection status, and stimulated Tg at the first RAIT were significantly associated with DSS. CONCLUSION: DTC histotype influenced RAIT avidity and PFS. It is crucial to better detect the metastatic patients that may benefit the most from RAIT.
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http://dx.doi.org/10.1210/clinem/dgab436

Indications of Superselective Neck Dissection in Patients With Lateral Node Metastasis of Papillary Thyroid Carcinoma.
Otolaryngol Head Neck Surg:1945998211038318.
Y. Song, G. Xu, T. Wang, Y. Zhang and B. Zhang. 2021.
OBJECTIVE: The extent of neck dissection in papillary thyroid carcinoma (PTC) patients with lateral neck metastasis is controversial. This work aims to screen the patients suitable for superselective neck dissections including only levels III-IV. STUDY DESIGN: Prospective observational cohort study. SETTING: The study was conducted in a high-volume tertiary care setting. METHODS: A total of 134 consecutive previously untreated PTC patients with lateral neck metastases and subjected to 154 therapeutic lateral neck dissections (including levels II, III, IV, and VB) between June 2018 and March 2021 were enrolled. Fine-needle aspiration was performed preoperatively at each suspicious neck level. Clinical predictors were analyzed for occult lymph node metastases at levels II and VB. RESULTS: As a result, 44.8% and 5.8% of neck specimens exhibited metastatic lymph nodes at levels II and VB. In addition, univariate and multivariate analyses showed that the primary tumor in the ipsilateral thyroid upper lobe (P = .016, odds ratio = 3.528) and clinically multiple metastatic lymph nodes in level III-IV (P = .005, odds ratio = 6.414) were independent predictive factors for occult level II metastases. All 3 (1.9%) occult metastases at level VB were found in necks with preoperative multiple lymph node metastases. CONCLUSIONS: A superselective lateral neck dissection including levels III to IV may be considered in patients with PTC when the preoperative evaluation identifies a single lymph node metastasis located at levels III to IV and the primary tumor is not in the upper lobe of the ipsilateral thyroid.
PubMed-ID: 34488520
http://dx.doi.org/10.1177/01945998211038318

Prophylactic Lateral Neck Dissection for Medullary Thyroid Carcinoma is not Associated with Improved Survival.
Ann Surg Oncol, 28(11):6572-9.
P. M. Spanheimer, I. Ganly, J. F. Chou, M. Capanu, A. Nigam, R. A. Ghossein, R. M. Tuttle, R. J. Wong, A. R. Shaha, M. F. Brennan and B. R. Untch. 2021.
BACKGROUND: Patients with medullary thyroid carcinoma (MTC) often receive lateral lymph node dissection with total thyroidectomy when calcitonin levels are elevated, even in the absence of structural disease, but the effect of this intervention on disease-specific outcomes is not known. PATIENTS AND METHODS: We retrospectively reviewed patients from 1986 to 2017 who underwent thyroidectomy with curative intent for MTC at our institution. The association of disease-specific survival and clinicopathologic features was examined using univariate and multivariate Cox regression. RESULTS: We identified 316 patients who underwent curative resection for MTC. Overall and disease-specific survival were 76% and 86%, respectively, at 10 years. To investigate the effect of prophylactic ipsilateral lateral lymph node dissection, we analyzed 89 patients without known structural disease in the neck lymph nodes at the time of resection and preoperative calcitonin > 200 pg/ml, of whom 45 had an ipsilateral lateral lymph node dissection (LND) and 44 did not.

There were no differences in tumor size or preoperative calcitonin levels. There was no difference at 10 years in cumulative incidence of recurrence in the neck (20.9% LND vs. 30.4% no LND, p = 0.46), cumulative incidence of distant recurrence (18.3% vs. 18.4%, p = 0.97), disease-specific survival (86% vs. 93%, p = 0.53), or overall survival (82% vs. 90%, p = 0.6). CONCLUSION: Lateral neck dissection in the absence of clinical or radiologic abnormal lymph nodes is not associated with improved survival in patients with MTC.
PubMed-ID: 33748897
http://dx.doi.org/10.1245/s10434-021-09683-8

Non-surgical management of thyroid nodules - the role of ablative therapies.
J Clin Endocrinol Metab,
M. N. Stan, M. Papaleontiou, J. J. Schmitz and M. R. Castro. 2021.
CONTEXT: After a thorough evaluation most thyroid nodules are deemed of no clinical consequence and can be observed. However, when they are compressive, toxic, or involved by papillary thyroid carcinoma (PTC) surgery or RAI (if toxic) are the treatments of choice. Both interventions can lead to hypothyroidism and other adverse outcomes (e.g. scar, dysphonia, logistical limitation with RAI). Active surveillance might be used for papillary thyroid microcarcinoma (PTMC) initially, but anxiety leads many cases to surgery later. Several ablative therapies have thus evolved over the last few years aimed at treating these nodules while avoiding described risks. CASES: We present 4 cases of thyroid lesions causing concerns (compressive symptoms, thyrotoxicosis, anxiety with active surveillance of PTMC). The common denominator is patients' attempt to preserve thyroid function, bringing into focus percutaneous ethanol injection (PEI) and thermal ablation techniques (radiofrequency ablation - RFA - being the most common). We discuss the evidence supporting these approaches and compare them with standard therapy, where evidence exists. We discuss additional considerations for the utilization of these therapies, their side-effects and conclude with a simplified description of how these procedures are performed. CONCLUSIONS: Thermal ablation, particularly RFA, is becoming an attractive option for managing a subgroup of solid thyroid nodules while PEI has a role in managing thyroid cysts and a select group of PTMC. Their role in the algorithm of thyroid nodule management is still being refined and technical expertise will be essential to reproduce the reported results into everyday practice.
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http://dx.doi.org/10.1210/clinem/dgab917

BRAF V600E Status Sharply Differentiates Lymph Node Metastasis-associated Mortality Risk in Papillary Thyroid Cancer.
J Clin Endocrinol Metab, 106(11):3228-38.
Y. Tao, F. Wang, X. Shen, G. Zhu, R. Liu, D. Viola, R. Elisei, E. Puxeddu, L. Fugazzola, C. Colombo, B. Jarzab, A. Czarniecka, A. K. Lam, C. Mian, F. Vianello, L. Yip, G. Riesco-Eizaguirre, P. Santisteban, C. J. O'Neill, M. S. Sywak, R. Clifton-Bligh, B. Bendlova, V. Sýkorová, S. Zhao, Y. Wang and M. Xing. 2021.
CONTEXT: How lymph node metastasis (LNM)-associated mortality risk is affected by BRAF V600E in papillary thyroid cancer (PTC) remains undefined. OBJECTIVE: To study whether BRAF V600E affected LNM-associated mortality in PTC. DESIGN, SETTING, AND PARTICIPANTS: We retrospectively analyzed the effect of LNM on PTC-specific mortality with respect to BRAF status in 2638 patients (2015 females and 623 males) from 11 centers in 6 countries, with median age of 46 [interquartile range (IQR) 35-58] years and median follow-up time of 58 (IQR 26-107) months. RESULTS: Overall, LNM showed a modest mortality risk in wild-type BRAF patients but a strong one in BRAF V600E patients. In conventional PTC (CPTC), LNM showed no increased mortality risk in wild-type BRAF patients but a robustly increased one in BRAF V600E patients; mortality rates were 2/659 (0.3%) vs 4/321 (1.2%) in non-LNM vs LNM patients (P = 0.094) with wild-type BRAF, corresponding to a hazard ratio (HR) (95% CI) of 4.37 (0.80-23.89), which remained insignificant at 3.32 (0.52-21.14) after multivariate adjustment. In BRAF V600E CPTC, morality rates were 7/515 (1.4%) vs 28/363 (7.7%) in non-LNM vs LNM patients (P < 0.001), corresponding to an HR of 4.90 (2.12-11.29) or, after multivariate adjustment, 5.76 (2.19-15.11). Adjusted mortality HR of coexisting LNM and BRAF V600E vs absence of both was 27.39 (5.15-145.80), with Kaplan-Meier analyses showing a similar synergism. CONCLUSIONS: LNM-associated mortality risk is sharply differentiated by the BRAF status in PTC; in CPTC, LNM showed no increased mortality risk with wild-type BRAF but a robust one with BRAF mutation. These results have strong clinical relevance.
PubMed-ID: 34273152
http://dx.doi.org/10.1210/clinem/dgab286

Comparative Study of ACR TI-RADS and ATA 2015 for Ultrasound Risk Stratification of Thyroid Nodules.
Otolaryngol Head Neck Surg:1945998211064607.
W. Thedinger, E. Raman and J. K. Dhingra. 2021.
OBJECTIVE: To study the adoption rate of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) scoring system over a 3-year period in a community setting and compare its performance with that of the American Thyroid Association 2015 (ATA 2015) ultrasound risk scoring system. STUDY DESIGN: Case series with prospective data collection and retrospective chart review. SETTING: Large community-based practice with multiple satellite offices and a dedicated thyroid ultrasound clinic. METHODS: All patients referred to the thyroid clinic between January 2018 and December 2020 for ultrasound-guided fine-needle biopsy were assigned an ATA 2015 risk score in a prospective manner immediately prior to biopsy. ACR TI-RADS scores were recorded through retrospective chart review of the radiologist report. Performance of the 2 systems was compared with cytology as the gold standard. RESULTS: A total of 949 nodules underwent biopsy, of which 236 had available data for both scoring systems. There was a 33.8% increase in adoption of the ACR TI-RADS over the 3-year study period. The ATA 2015 guidelines yielded sensitivity and specificity of 81.6% and 54.5%, respectively, as opposed to 73.7% and 27.0% for the ACR TI-RADS. CONCLUSION: In our community, there has been a gradual increase in adoption of the ACR TI-RADS, although the ATA 2015 risk scoring system has performed better.
PubMed-ID: 34905442
http://dx.doi.org/10.1177/01945998211064607

Prognostic Implications of Preablation Stimulated Tg: A Retrospective Analysis of 2500 Thyroid Cancer Patients.
J Clin Endocrinol Metab, 106(11):e4688-e97.
T. Tian, Y. Xu, X. Zhang and B. Liu. 2021.
CONTEXT: The risk of persistent and recurrent disease in patients with differentiated thyroid cancer (DTC) is a continuum that ranges from very low to very high, even within the 3 primary risk categories. It is important to identify independent clinicopathological parameters to accurately predict clinical outcomes. OBJECTIVE: To examine the association between pre-ablation stimulated thyroglobulin (ps-Tg) and persistent and recurrent disease in DTC patients and investigate whether incorporation of ps-Tg could provide a more individualized estimate of clinical outcomes. DESIGN, SETTING, AND PARTICIPANTS: Medical records of 2524 DTC patients who underwent total thyroidectomy and radioiodine ablation between 2006 and 2018 were retrospectively reviewed. MAIN OUTCOME MEASURE: Ps-Tg was measured under thyroid hormone withdrawal before remnant ablation. Association of ps-Tg and clinical outcomes. RESULTS: In multivariate analysis, age, American Thyroid Association (ATA) risk stratification, distant metastasis, ps-Tg, and cumulative administered activities were the independent predictive factors for persistent/recurrent disease. Receiver operating characteristic analysis identified ps-Tg cutoff (=10.1 ng/mL) to predict disease-free status with a negative predictive value of 95%, and validated for all ATA categories. Integration of ps-Tg into ATA risk categories indicated that the presence of ps-Tg = 10.1 ng/mL was associated with a significantly decreased chance of having persistent/recurrent disease in intermediate- and high-risk patients (9.9% to 4.1% in intermediate-risk patients, and 33.1% to 8.5% in high-risk patients). CONCLUSION: The ps-Tg (=10.1 ng/mL) was a key predictor of clinical outcomes in DTC patients. Its incorporation as a variable in the ATA risk stratification system could more accurately predict clinical outcomes.
PubMed-ID: 34143886
http://dx.doi.org/10.1210/clinem/dgab445

The use of thyroid cartilage needle electrodes in intraoperative neuromonitoring during thyroidectomy: Case-control study.
Head Neck, 43(11):3287-93.
Y. Türk, G. Kivratma, M. Özdemir, G. Içöz and Ö. Makay. 2021.
BACKGROUND: The most commonly used recording-side method in intraoperative neural monitoring (IONM) detects the stimulus with the endotracheal tube surface (ETS) electrodes placed in the endotracheal tube during thyroidectomy. The thyroid cartilage needle (TCN) electrode method is an alternative recording-side system in IONM. This study compared two recording-side techniques in IONM. METHODS: Data were retrospectively analyzed from 885 patients who underwent thyroidectomy between January 2012 and December 2020, with 110 ETS and 775 TCN electrodes. Patients' demographics, diagnosis, surgery type, and amplitudes of all stimulation steps were compared. Costs per patient were calculated. RESULTS: No significant differences were found in the demographic data between the two groups. All amplitudes were higher in the IONM system where TCN electrodes were used than that with ETS electrodes (all stimulation steps $p < 0.001$, except left-V2 $p = 0.007$). Further, TCN electrodes were 20 times cheaper than the ETS electrodes. CONCLUSION: TCN electrodes are an inexpensive and efficient alternative to ETS electrodes in IONM.

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http://dx.doi.org/10.1002/hed.26810

Comparison of Monopolar and Bipolar Stimulator Probes for Intraoperative Nerve Mapping During Thyroidectomy: A Prospective Study.
Laryngoscope, 131(10):E2718-E26.
Y. Turk, O. Makay, D. Kamani, O. Okose, I. J. Behr, M. Ozdemir, G. Icoz, M. Akyildiz, G. Dionigi, A. H. Abdelhamid Ahmed and G. W. Randolph. 2021.
OBJECTIVES/HYPOTHESIS: During intraoperative neuromonitoring in thyroid surgery, two different kinds of stimulator probes, monopolar and bipolar, are commonly used to stimulate the laryngeal nerves. We explore the unique characteristics of both of these probes as they relate to intraoperative laryngeal nerve mapping. METHODS: Twenty-one patients undergoing neuromonitored thyroidectomy by a single surgeon were enrolled. Electromyography (EMG) amplitude and latency measurements were prospectively recorded concurrently from 1 mA stimulation of vagus nerve (VN) and inferior/superior recurrent laryngeal nerve before (with and without fascia) and after thyroid resection using bipolar and monopolar stimulator probes. RESULTS: Significantly higher amplitudes were obtained with monopolar stimulator probes as compared to bipolar probes, in several stimulation scenarios such as at right VN pre-resection (carotid sheath intact), right VN pre-resection (carotid sheath dissected), right VN post-resection and left VN (carotid sheath dissected). No significant differences were found between amplitudes and latency values in all other stimulation scenarios. CONCLUSIONS: According to this study, both probes are reliable and safe for neural mapping. The kind of probe used during neural monitoring is based on surgical situations and surgeon preference. LEVEL OF EVIDENCE: 3 (According to Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence) Laryngoscope, 131:E2718-E2726, 2021.
PubMed-ID: 34350983
http://dx.doi.org/10.1002/lary.29804

The diagnostic value of thyroglobulin in fine-needle aspiration of metastatic lymph nodes in patients with papillary thyroid cancer and its influential factors.
Surg Oncol, 39:101666.
Y. Wang, Y. Duan, M. Zhou, J. Liu, Q. Lai, B. Ye, D. Liu, L. Li, Y. Fang, K. Yue, C. Jing, Y. Wu and X. Wang. 2021.
Thyroglobulin (Tg) measurement in fine-needle aspiration (FNA-Tg) has proved to be an excellent tool to identify metastatic cervical lymph nodes (CLN) before or after surgery for papillary thyroid cancer (PTC). The diagnostic value of FNA-Tg for metastatic CLN in PTC patients is higher than that of ultrasound (US) and fine-needle aspiration cytology (FNAC), especially for small or cystic LN. The combination of FNAC and FNA-Tg can provide nearly 100% diagnostic sensitivity and specificity for CLN metastasis. However, the cutoff values of FNA-Tg for metastatic CLN have not been standardized, and the reported cutoff values of FNA-Tg range from 0.2 ng/ml to 77 ng/ml because of the differences in study samples, Tg measurement methods, Tg assays kits, etc. Serum anti-thyroglobulin antibody level, serum thyroglobulin level, the presence or absence of thyroid glands, and the characteristics of CLN may be factors affecting the accuracy of FNA-Tg. This review summarizes the recent research on the application of FNA-Tg in the diagnosis of metastatic LN in PTC and provides a reliable basis for the clinical diagnosis of cervical lymph node metastasis.
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http://dx.doi.org/10.1016/j.suronc.2021.101666

Differences in the ultrasonographic appearance of thyroid nodules after radiofrequency ablation.
Clin Endocrinol (Oxf), 95(3):489-97.
M. H. Wu, K. Y. Chen, A. Chen and C. N. Chen. 2021.
CONTEXT: Radiofrequency ablation (RFA) is a well-tolerated approach to treating benign thyroid nodules (TNs), but no index can predict its success. Other than size decrease, little is known about TN appearance on ultrasonography (US) after RFA. OBJECTIVE: This study aimed to (a) assess the effectiveness of single-session RFA treatment, (b) determine whether pre-ablation US characteristics correlate with its effectiveness, and (c) demonstrate TN characteristics on baseline and follow-up US. DESIGN: Retrospective cohort study among the patients who underwent single-session RFA for the treatment of benign TNs at a referral medical center between January 2018 and April 2019. PATIENTS: A total of 116 patients (137 nodules) were included in the study. MEASUREMENTS: Characteristics were quantified using commercial software. TNs were classified into 2015 American Thyroid Association (ATA) sonographic patterns and American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TI-RADS) categories. RESULTS: The average volume reduction ratio (VRR) was 74.51% in 1 year (95% confidence interval, 70.63%-78.39%). The only pre-ablation US feature significantly different between nodules with VRR <50% and VRR >50% was the cyst composition (0.05 vs. 0.02, p-value = .02). The VRR

and margin change in the first 3 months after ablation were found to be leading indicators significantly correlated to the VRR in 6 months with correlation coefficients (r) = .72 and -.28 (p-value < .0001 and = .0008) and VRR in 1 year with r = .65 and -.17 (p-value < .0001 and = .046), respectively. After RFA, more TNs became ATA high suspicion (2.9% vs. 19.7%, p < .0001) and more appeared to be the non-ATA patterns (12.4% vs. 23.4%, p < .0001). Also, a greater number of post-RFA TNs were classified as ACR-TI-RADS categories 4 and 5 (40.1% vs. 70.1%, p < .0001). CONCLUSIONS: Radiofrequency ablation therapy is effective for treating TNs. Pre-ablation cyst components, 3-month post-ablation volume reduction and margin change of TNs were related to the 6-month and 1-year response. Clinicians should consider that TNs would appear peculiar on US after RFA, mistakenly suggesting malignant potential.
PubMed-ID: 33938024
http://dx.doi.org/10.1111/cen.14480

Benefits and harms of hemithyroidectomy, total or near-total thyroidectomy in 1-4 cm differentiated thyroid cancer.
Clin Endocrinol (Oxf), 95(4):668-76.
Y. Xu, K. Huang, P. Huang, N. Ke, J. Zeng, L. Wang, C. Liu, X. Shi, F. Guo, L. Su, M. Lin, X. Li and F. Xiao. 2021.
OBJECTIVE: For 1-4 cm differentiated thyroid cancer (DTC), current ATA guideline recommended hemithyroidectomy (HT) as an acceptable alternative initial procedure to total or near-total thyroidectomy (TT). The aim of this study was to evaluate benefits and harms of HT, TT in 1-4 cm DTC. DESIGN: Retrospective cohort study. PATIENTS: DTC patients aged 18 years or older who underwent initial thyroidectomy in a tertiary medical centre were included from January 2008 to July 2018. MEASUREMENTS: The structural persistent/recurrent disease, reoperation rates and surgical complications were compared using Cox proportional regression and logistic regression. Propensity score matching was performed to adjust for related clinicopathological variables. RESULTS: Among 1824 DTC patients, 795 patients sized 1-4 cm were included. A total of 286 patients underwent HT and 509 patients underwent TT. In the matched analysis, no significant difference in disease-free survival (DFS) between HT and TT was observed during the median follow-up period of 56.5 months (hazard ratio [HR] 0.86; 95% CI, 0.37-2.00; p = .733). The difference in DFS between two groups was consistent regardless of age, sex, tumour size, follow-up duration. Meanwhile, HT was associated with a decreased risk of surgical complications (odds ratio [OR] 0.47, 95% CI 0.31-0.71, p < .001), as well as lower proportion of levothyroxine replacement (p = .007). Two cases in HT group received reoperation. Further multivariate analysis showed surgical procedure was not associated with structural persistence/recurrence (HR 0.68; 95%CI, 0.29-1.58, p = .367). CONCLUSIONS: For patients with 1-4 cm DTC without clinical evidence of lymph node metastasis or extrathyroidal extension, HT was associated with lower risk of surgical complications than TT while provided similar benefits as TT.
PubMed-ID: 33948971
http://dx.doi.org/10.1111/cen.14495

Prognostic value of lymph node ratio in children and adolescents with papillary thyroid cancer.
Clin Endocrinol (Oxf), 95(4):649-56.
Y. Xu, Y. Wang, X. Zhang, R. Huang, R. Tian and B. Liu. 2021.
OBJECTIVE: Neck lymph node (LN) metastasis is a common feature of paediatric papillary thyroid cancer, and LN ratio (LNR) is defined as the ratio of the number of positive LNs excised to the total number of removed. Unlike in adults, few data are available regarding the clinical implication of LNR in the paediatric population. Our purpose was to investigate the association of LNR with clinical outcomes in paediatric papillary thyroid cancer. DESIGN & METHODS: The study retrospectively reviewed 136 consecutive children and adolescents with papillary thyroid cancer and LN involvement but no initial distant metastasis. Initial treatment, included in all patients a total thyroidectomy with central and/or lateral neck dissection followed by radioactive iodine ablation. Within the neck dissections, total number of LNs removed, total positive LNs and LN ratios were determined. The effect of clinicopathologic characteristics and intraoperative findings on persistent and recurrent diseases were analysed by univariate and multivariate analyses. RESULTS: Median number of positive LNs was 9, and median LNR was 0.4. During a median follow-up of 49 months (range, 12.0-139 months), persistent disease occurred in 43 (31.6%) patients. The multivariable analysis showed that age and LNR were the independent factors predictive of persistent disease. Patients with a LNR >0.34 exhibited a threefold higher risk of persistent disease after initial therapy than the counterparts (P = .02). CONCLUSION: Our findings suggest that LNR was an independent determinant predictive of persistent disease after initial therapy in children and adolescents with papillary thyroid cancer.
PubMed-ID: 33914928
http://dx.doi.org/10.1111/cen.14491

Letter to the Editor from Xu and Yang: "Laser Ablation Versus Radiofrequency Ablation for Thyroid Nodules: 12-Month Results of a Randomized Trial (LARA II Study)".
J Clin Endocrinol Metab, 106(10):e4290-e1.
S. Yang and X. Xu. 2021.
PubMed-ID: 34197586
http://dx.doi.org/10.1210/clinem/dgab491

Accuracy of the Lymph Node Yield in Surgery for Papillary Thyroid Cancer in Children.
World J Surg, 45(10):3092-8.
A. Yap, A. Shui, J. Gosnell, C. Y. Huang, J. A. Sosa and S. Roman. 2021.
INTRODUCTION: Our aim was to determine the accuracy of lymph node yield (LNY) for pediatric patients undergoing thyroidectomy with concurrent lymph nodes harvest for clinically node-negative (cN0) papillary thyroid cancer (PTC). METHODS: Patients aged = 18 years with cN0 PTC undergoing thyroidectomy were reviewed in the NCDB, 1998-2016. Demographic and clinical characteristics of patients with = 1 LNY were compared to those without. A truncated beta-binomial distribution estimated the number of lymph nodes needed to detect pathologic nodal positivity, and LNY was calibrated for 90% sensitivity in nodal staging and stratified across clinical tumor size staging (T). RESULTS: 1,948 children with cN0 PTC underwent surgical resection; median age was 17 years; 83.2% were female; 47.6% were T1, 25.3% T2, 9.3% T3. 1,272 (65.3%) of these patients had lymph nodes resected, or = 1 LNY. The median LNY was 5 nodes (interquartile range 2-12); 45.9% of patients had = 1 metastatic lymph nodes. In the overall = 1 LNY cohort, 12 nodes (CI 9-19) were needed to predict nodal positivity with > 90% sensitivity. Based on clinical T-stage, detecting a metastatic lymph node with > 90% sensitivity required a LNY of 14 for T1; 8 for T2; 6 for T3. CONCLUSION: This is the first study estimating the necessary LNY for determining nodal positivity in children with cN0 PTC. The high LNY required in small T1 tumors is likely infeasible and should not be pursued. Accuracy increases with lower LNYs for higher T-stages. Our findings can help guide prognosis and treatment for pediatric patients with PTC.
PubMed-ID: 34180009
http://dx.doi.org/10.1007/s00268-021-06207-z

Prevention of transoral thyroidectomy complications: An analysis of surgical outcomes in 423 consecutive series.
Surgery, 170(4):1155-9.
J. Y. You, H. Kim, D. W. Park, H. W. Yang, G. Dionigi and R. P. Tufano. 2021.
BACKGROUND: Although there are several publications on the new transoral robotic thyroidectomy technique, few have thoroughly reviewed its associated complications. This study analyzed the causes and prevention of transoral robotic thyroidectomy-specific complications and presented preventive measures. METHODS: The medical records of patients who underwent transoral robotic thyroidectomy performed by a single surgeon between March 1, 2009 and April 30, 2019 were retrospectively analyzed. Patient demographic, clinical, and operative data were analyzed using descriptive statistics. We describe the transoral robotic thyroidectomy-related complications experienced at our institution and how to overcome them. RESULTS: This study included a total of 423 patients who underwent transoral robotic thyroidectomy. The general surgical complications included immediate postoperative bleeding (2 cases) and delayed hematoma (3 cases). Chyle leakage and localized wound infection were found in 1 case each. Transient vocal cord palsy occurred in 4 cases, and 1 case developed transient hypoparathyroidism. The transoral robotic thyroidectomy-specific complications included zygoma bruise (2 cases), flap bruise (3 cases), chin flap perforation (2 cases), and oral commissure tearing (2 cases). The complications occurring when creating the flap included flap burns (4 cases), skin dimpling in the midline of the lower chin (2 cases), and hematomas in the intraoral trocar insertion sites (3 cases). CONCLUSION: Surgeons familiar with thyroid surgery and experienced in robotic surgery can perform transoral robotic thyroidectomy without causing more complications than those seen with traditional surgery.
PubMed-ID: 34090673
http://dx.doi.org/10.1016/j.surg.2021.05.003

Drawbacks of neural monitoring troubleshooting algorithms in transoral endoscopic thyroidectomy.
Langenbecks Arch Surg, 406(7):2433-40.
D. Zhang, C. W. Wu, T. Wang, Y. Zhao, H. Y. Kim, A. Pino, G. Dionigi and H. Sun. 2021.
INTRODUCTION: The application of intraoperative neural monitoring (IONM) trouble-shooting algorithms procedures in transoral endoscopic thyroidectomy vestibular approach (TOETVA) was investigated. METHODS: Loss of signal (LOS) is defined as a loss of the primary electromyographic (EMG) normal biphasic waveform with reduced amplitude response to less than 100μV with a stimulation level intensity of 1-2mA. A systematic review of the IONM system at LOS was covered

methodically: (i) correct endotracheal tube verification, (ii) stimulation of the recurrent laryngeal nerve (RLN) at entry point, (iii) ipsilateral or contralateral vagal nerve (VN) stimulation, and (iv) laryngeal twitch (LT). RESULTS: The function of 223 nerves at risk (NAR) was recorded with IONM. Twenty-seven (12%) NAR experienced a suspected LOS. LT could not be appreciated. In 15/27 (55%) cases, the application of the IONM trouble-shooting algorithm revealed upward displacement of the EMG tube (all orotracheal intubations). In 9 (4%) NAR, VN stimulation was not accomplished. In detail, there were n.5 left and n. 4 right VNs. Two VNs were ipsilateral, and 7 VNs contralateral. For EMG tube displacement, because the oral/nasal area is included in the aseptic field, it is less possible to re-check by the laryngoscope or fiberscope. CONCLUSIONS: A limit for applying the IONM trouble-shooting algorithm to TOETVA is determined by (a) inability to appreciate the LT, (b) difficulty in stimulating the ipsilateral and contralateral VN, and (c) remodeling EMG endotracheal tube position. A modified IONM trouble-shooting algorithm for TOETVA is proposed.
PubMed-ID: 34264393
http://dx.doi.org/10.1007/s00423-021-02217-6

The prognostic value of lymph node metastasis and the eighth edition of AJCC for patients with anaplastic thyroid cancer.
Clin Endocrinol (Oxf), 95(3):498-507.
H. Zhang, Y. C. Zhao, Q. Wu, L. Wang and S. Sun. 2021.
OBJECTIVE: The eighth edition of the American Joint Committee on Cancer (AJCC-v8) for anaplastic thyroid cancer (ATC) made a revision in staging for patients with lymph node metastasis (LNM) based on the seventh edition of AJCC (AJCC-v7). Our study aimed to evaluate the predictive ability of AJCC-v8 for survival in patients with ATC by exploring the association between lymph node stage and prognosis of ATC patients. METHODS: Retrospective study of ATC in Surveillance, Epidemiology and End Results (SEER) database. The association between LNM and survival of ATC was estimated by the Kaplan-Meier method and Cox regression model. The predictive performances of the AJCC-v8 and AJCC-v7 were estimated through C-index, Akaike information criterion (AIC) and Bayesian information criterion (BIC). RESULTS: A total of 313 patients with ATC were included in our analysis. Notably, LNM was identified as an independent risk factor for ATC mortality (adjusted HR, 1.47, 95% CI, 1.10-1.96; p = .009), while the risk of mortality in N1a group was comparable to that in N1b group according to univariate (HR, 1.30, 95% CI, 0.92-1.82; p = .133) and multivariate (adjusted HR 0.87, 95% CI, 0.60-1.27; p = .467) cox analyses. Applying the AJCC-v8, the survival of migration population staged T1-3aN1M0 was significantly worse than that of T1-3aN0M0 patients (IVA stage), while was not different from that of T3b-T4bN0/N1M0 patients (IVB stage). With a higher C-index (0.60 vs. 0.59), lower AIC (2728 vs. 2732) and BIC (2732 vs. 2735), AJCC-v8 was demonstrably a more favourable prediction model than AJCC-v7. CONCLUSIONS: This study demonstrated that LNM was independently associated with poor prognosis of ATC, and AJCC-v8 with the modified staging of patients with LNM showed better survival predictive performance in ATC patients than AJCC-v7.
PubMed-ID: 33864292
http://dx.doi.org/10.1111/cen.14482

Transoral Endoscopic Thyroidectomy Vestibular Approach Versus Endoscopic Thyroidectomy Via Areola Approach for Patients With Unilateral Papillary Thyroid Carcinoma: A Retrospective Study.
Surg Laparosc Endosc Percutan Tech, 31(5):550-3.
W. D. Zhang, L. Dai, Y. C. Wang, Y. Y. Xie, J. Y. Guo, J. J. Li and X. J. Wu. 2021.
BACKGROUND: Endoscopic thyroidectomy via areola approach (ETA) has been widely used in thyroidectomy for many years as it can effectively avoid a scar in the neck. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is newly applied and has gained popularity quickly. This study is to compare the safety and effectiveness of TOETVA and ETA. MATERIALS AND METHODS: A total of 95 patients who underwent TOETVA or ETA with unilateral papillary thyroid carcinoma were enrolled in this study from March 2019 to February 2020. The basic information (such as gender, age), intraoperative hemorrhage, postoperative drainage volume, hospital durations, intraoperative and postoperative complications, operative time, central lymph node dissection time, total number of central lymph nodes, and number of metastatic central lymph nodes were compared. RESULTS: The operative time of the TOETVA group was significantly longer than the ETA group (148.11±19.78 vs. 135.90±12.77 min, P<0.05). However, the result was opposite when central lymph node dissection time was compared (10.31±2.93 vs. 12.48±3.55, P<0.05). TOETVA had an advantage on total number of central lymph nodes over ETA (7.82±3.35 vs. 5.26±2.45, P<0.05). No differences were found between the 2 groups on other data. CONCLUSION: TOETVA and ETA have the similarity on surgical safety and effectiveness. TOETVA has its advantage on central lymph node dissection and might be a reasonable alternative for ETA and open surgery in the future.

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http://dx.doi.org/10.1097/SLE.0000000000000932

Non-medullary Thyroid Cancer Susceptibility Genes: Evidence and Disease Spectrum.
Ann Surg Oncol, 28(11):6590-600.
J. Zhou, P. Singh, K. Yin, J. Wang, Y. Bao, M. Wu, K. Pathak, S. K. McKinley, D. Braun, C. C. Lubitz and K. S. Hughes. 2021.
BACKGROUND: The prevalence of non-medullary thyroid cancer (NMTC) is increasing worldwide. Although most NMTCs grow slowly, conventional therapies are less effective in advanced tumors. Approximately 5-15% of NMTCs have a significant germline genetic component. Awareness of the NMTC susceptibility genes may lead to earlier diagnosis and better cancer prevention. OBJECTIVE: The aim of this study was to provide the current panorama of susceptibility genes associated with NMTC and the spectrum of diseases associated with these genes. METHODS: Twenty-five candidate genes were identified by searching for relevant studies in PubMed. Each candidate gene was carefully checked using six authoritative genetic resources: ClinGen, National Comprehensive Cancer Network guidelines, Online Mendelian Inheritance in Man, Genetics Home Reference, GeneCards, and Gene-NCBI, and a validated natural language processing (NLP)-based literature review protocol was used to further assess gene-disease associations where there was ambiguity. RESULTS: Among 25 candidate genes, 10 (APC, DICER1, FOXE1, HABP2, NKX2-1, PRKAR1A, PTEN, SDHB, SDHD, and SRGAP1) were verified among the six genetic resources. Two additional genes, CHEK2 and SEC23B, were verified using the NLP protocol. Seventy-nine diseases were found to be associated with these 12 NMTC susceptibility genes. The following diseases were associated with more than one NMTC susceptibility gene: colorectal cancer, breast cancer, gastric cancer, kidney cancer, gastrointestinal stromal tumor, paraganglioma, pheochromocytoma, and benign skin conditions. CONCLUSION: Twelve genes predisposing to NMTC and their associated disease spectra were identified and verified. Clinicians should be aware that patients with certain pathogenic variants may require more aggressive surveillance beyond their thyroid cancer risk.
PubMed-ID: 33660127
http://dx.doi.org/10.1245/s10434-021-09745-x

Role of primary tumor resection in patients with metastatic medullary thyroid cancer who have unresectable distant metastases.
Head Neck, 43(11):3386-92.
S. M. Zhuang, L. E. Xie, F. Pang, Q. Y. Zhong, X. M. Sun, W. P. Wen and T. R. Liu. 2021.
BACKGROUND: Whether patients with medullary thyroid carcinoma (MTC) who have unresectable synchronous distant metastases should undergo primary surgical resection (PTR) remains controversial. This study aimed to identify predictive factors associated with the survival of such patients. METHODS: We conducted a retrospective study of patients with MTC who were registered in the Surveillance, Epidemiology, and End Results registry. The overall and cancer-specific mortality rates were assessed using risk-adjusted Cox proportional hazards regression modeling and stratified propensity score matching. RESULTS: One hundred and eight matched patients were assessed. Patients in the PTR group had lower overall mortality than did those in the non-PTR group. The 1-, 3-, and 5-year overall and cancer-specific survival rates in the PTR group were significantly higher. CONCLUSIONS: PTR appears to be the most appropriate intervention for patients with good performance status. Such patients are likely to benefit from surgery and to experience long-term stable disease.
PubMed-ID: 34423875
http://dx.doi.org/10.1002/hed.26840

Parathyroids

Meta-Analyses

Parathyroidectomy or cinacalcet: Do we still not know the best option for graft function in kidney-transplanted patients? A meta-analysis.
Surgery, 170(3):727-35.
S. Frey, T. Goronflot, C. Kerleau, P. A. Gourraud, C. Caillard, M. Hourmant, É. Mirallié and L. Figueres. 2021.
BACKGROUND: Tertiary hyperparathyroidism occurs in 25% to 50% of kidney-transplanted patients. Indication of parathyroidectomy is now discussed, since the calcimimetic agent, cinacalcet, is an alternate option. The effects of either of these treatments on graft function remain controversial, studied only in small cohorts showing either decrease or absence of modification. We performed a meta-analysis to evaluate the evolution of graft function after surgical or medical treatment. METHODS: Studies assessing graft function in tertiary hyperparathyroidism after parathyroidectomy or cinacalcet introduction were enrolled into quantitative analysis using Pubmed, Embase, and Cochrane databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guidelines. Among 68 screened studies, 18 had no missing data and were included for statistical analyses. We performed random effect meta-analysis to determine changes in serum creatinine and estimated glomerular filtration rate. RESULTS: Seven studies assessing the evolution of graft function 6 and/or 12 months after parathyroidectomy and 13 after administration of cinacalcet were included. Meta-analysis found no significant variations after parathyroidectomy in serum creatinine (6 studies, 314 patients) and estimated glomerular filtration rate (2 studies, 105 patients). No significant variation was found after administration of cinacalcet in serum creatinine (10 studies, 404 patients) and estimated glomerular filtration rate (6 studies, 149 patients). A significant heterogeneity between the studies (P < .01, Cochran's Q) was found. CONCLUSION: Meta-analysis shows that parathyroidectomy and cinacalcet do not significantly impair graft function in patients with tertiary hyperparathyroidism. However, the significant heterogeneity between selected studies, partially explained by the lack of consensual definition of tertiary hyperparathyroidism, limits the conclusions of all previously published series.
PubMed-ID: 33810851
http://dx.doi.org/10.1016/j.surg.2021.02.048

Randomized controlled trials

- None -

Consensus Statements/Guidelines

Primary hyperparathyroidism in adults-(Part I) assessment and medical management: Position statement of the endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society.
Clin Endocrinol (Oxf),
F. Milat, S. K. Ramchand, M. Herath, J. Gundara, S. Harper, S. Farrell, C. M. Girgis, R. Clifton-Bligh, H. G. Schneider, S. M. C. De Sousa, A. J. Gill, J. Serpell, K. Taubman, J. Christie, R. W. Carroll, J. A. Miller and M. Grossmann. 2021.
OBJECTIVE: To formulate clinical consensus recommendations on the presentation, assessment, and management of primary hyperparathyroidism (PHPT) in adults. METHODS: Representatives from relevant Australian and New Zealand Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing nine key questions. RESULTS: PHPT is a biochemical diagnosis. Serum calcium should be measured in patients with suggestive symptoms, reduced bone mineral density or minimal trauma fractures, and in those with renal stones. Other indications are detailed in the manuscript. In patients with hypercalcaemia, intact parathyroid hormone, 25-hydroxy vitamin D, phosphate, and renal function should be measured. In established PHPT, assessment of bone mineral density, vertebral fractures, urinary tract calculi/nephrocalcinosis and quantification of urinary calcium excretion is warranted. Parathyroidectomy is the only definitive treatment and is warranted for all symptomatic patients and should be considered for asymptomatic patients without contraindications to surgery and with >10 years life expectancy. In

patients who do not undergo surgery, we recommend annual evaluation for disease progression. Where the diagnosis is not clear or the risk-benefit ratio is not obvious, multidisciplinary discussion and formulation of a consensus management plan is appropriate. Genetic testing for familial hyperparathyroidism is recommended in selected patients. CONCLUSIONS: These clinical consensus recommendations were developed to provide clinicians with contemporary guidance on the assessment and management of PHPT in adults. It is anticipated that improved health outcomes for individuals and the population will be achieved at a decreased cost to the community.
PubMed-ID: 34931708
http://dx.doi.org/10.1111/cen.14659

Primary hyperparathyroidism in adults-(Part II) surgical management and postoperative follow-up: Position statement of the Endocrine Society of Australia, The Australian & New Zealand Endocrine Surgeons, and The Australian & New Zealand Bone and Mineral Society.
Clin Endocrinol (Oxf),
J. A. Miller, J. Gundara, S. Harper, M. Herath, S. K. Ramchand, S. Farrell, J. Serpell, K. Taubman, J. Christie, C. M. Girgis, H. G. Schneider, R. Clifton-Bligh, A. J. Gill, S. M. C. De Sousa, R. W. Carroll, F. Milat and M. Grossmann. 2021.
OBJECTIVE: To develop evidence-based recommendations to guide the surgical management and postoperative follow-up of adults with primary hyperparathyroidism. METHODS: Representatives from relevant Australian and New Zealand Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing eight key questions. RESULTS: Diagnostic imaging does not determine suitability for surgery but can guide the planning of surgery in suitable candidates. First-line imaging includes ultrasound and either parathyroid 4DCT or scintigraphy, depending on local availability and expertise. Minimally invasive parathyroidectomy is appropriate in most patients with concordant imaging. Bilateral neck exploration should be considered in those with discordant/negative imaging findings, multi-gland disease and genetic/familial risk factors. Parathyroid surgery, especially re-operative surgery, has better outcomes in the hands of higher volume surgeons. Neuromonitoring is generally not required for initial surgery but should be considered for re-operative surgery. Following parathyroidectomy, calcium and parathyroid hormone levels should be re-checked in the first 24 h and repeated early if there are risk factors for hypocalcaemia. Eucalcaemia at 6 months is consistent with surgical cure; parathyroid hormone levels do not need to be re-checked in the absence of other clinical indications. Longer-term surveillance of skeletal health is recommended. CONCLUSIONS: This position statement provides up-to-date guidance on evidence-based best practice surgical and postoperative management of adults with primary hyperparathyroidism.
PubMed-ID: 34927274
http://dx.doi.org/10.1111/cen.14650

Other Articles

Less extensive surgery for low-risk papillary thyroid cancers post 2015 American Thyroid Association guidelines in an Australian tertiary centre.
Eur J Surg Oncol, 47(11):2781-7.
M. Adhami, C. R. Bhatt, S. Grodski, J. Serpell and J. C. Lee. 2021.
INTRODUCTION: The 2015 American Thyroid Association guidelines (ATA15) consider hemithyroidectomy (HT) a viable treatment option for low-risk papillary thyroid cancers (PTCs) between 1 and 4 cm. We aimed to examine the impact of ATA15 in a high-volume Australian endocrine surgery unit. METHODS: A retrospective study of all patients undergoing thyroidectomy from January 2010 to December 2019. INCLUSION CRITERIA: PTC histopathology, Bethesda V-VI, size 1-4 cm, and absence of clinical evidence of lymph node or distant metastases pre-operatively. Primary outcome was rate of HT before and after ATA15. RESULTS: Of 5408 thyroidectomy patients, 339 (6.3%) met the inclusion criteria - 186 (54.9%) pre-ATA15 (2010-2015) and 153 (45.1%) post-ATA15 (2016-2019). The patient groups were similar; there were no significant differences between groups in age, sex, tumour size, proportion with Bethesda VI cytology, compressive symptoms, or thyrotoxicosis. Post-ATA15, there was a significant increase in HT rate from 5.4% to 19.6% (P = 0.0001). However, there was no corresponding increase in completion thyroidectomy (CT) rate (50.0% versus 27.6%, P = 0.2). The proportion managed with prophylactic central neck dissection (pCND) fell from 80.5% to 10.8% (P < 0.0001). Pre-ATA15, the only factor significantly associated with HT was Bethesda V. In contrast, post-ATA15, HT was more likely in patients with younger age, smaller tumours, and Bethesda V. CONCLUSION: After the release of 2015 ATA guidelines, we observed a significant increase in HT rate and a significant decrease in pCND rate for low-risk PTCs in our specialised thyroid cancer

unit. This reflects a growing clinician uptake of a more conservative approach as recommended by ATA15.
PubMed-ID: 34364721
http://dx.doi.org/10.1016/j.ejso.2021.06.018

Use of Predictive Modeling to Tailor Molecular Testing Utilization for Thyroid Nodules.
Otolaryngol Head Neck Surg, 165(3):406-13.
S. T. Ahmed, S. Fernandes, Q. Gao, T. J. Ow, R. V. Smith, B. A. Schiff and V. Mehta. 2021.
OBJECTIVE: Various risk stratification systems for cytologically indeterminate thyroid nodules are available. However, malignancy risk assessment data, such as ultrasound features, are not always used when the decision is to order molecular testing or not. Our aim was to investigate the utility of molecular testing after incorporating an algorithm with ultrasound-based risk of malignancy (ROM) estimation. STUDY DESIGN: Diagnostic/prognostic study. SETTING: Single-institution urban tertiary care center. METHODS: We performed a single-institution retrospective chart review of all thyroid nodules that had undergone molecular testing. A web-based Malignancy Risk Estimation System for Thyroid Nodules was utilized with ultrasound findings to stratify malignancy risk according to the Korean Thyroid Imaging Reporting and Data System (TI-RADS), French TI-RADS, American Association of Clinical Endocrinology guideline, and American Thyroid Association guideline. A novel algorithm for utilizing molecular testing at our institution was developed with the Korean TI-RADS and with recommendations from the American Thyroid Association and National Comprehensive Cancer Network. RESULTS: The Korean TI-RADS performed best in our population (area under the curve = 0.83). A positive molecular test result had a positive association with a higher ROM according to all 4 models ($P < .05$). Use of our algorithm prior to molecular testing would have prevented 38% of benign/low-ROM negative nodules (n = 28) from being tested. CONCLUSION: In patients with indeterminate thyroid nodules, an algorithm built on pre- and posttest probability to guide molecular testing might reduce unnecessary testing of benign and low-risk nodules.
PubMed-ID: 33781120
http://dx.doi.org/10.1177/01945998211004155

Long-term cosmetic results of video-assisted thyroidectomy: a comparison with conventional surgery.
Langenbecks Arch Surg, 406(5):1625-33.
P. F. Alesina, W. Wahabie, B. Meier, J. Hinrichs, W. Mohmand, A. Kapakoglou, P. Kniazeva and M. K. Walz. 2021.
PURPOSE: We present the long-term cosmetic results of the video-assisted thyroidectomy (MIVAT) in comparison to the conventional operation. METHODS: Forty-eight patients (four males, 44 females; mean age 47.4 ± 12.5 years) constituted the video-assisted group (VA-Group). These were compared with 48 patients (10 males, 38 females; mean age 47.4 ± 12.5 years) operated by conventional surgery (C-Group). The patients were selected from all thyroid operations performed between January 2016 and June 2017. Patient Scar Assessment Scale (PSAS) and Observer Scar Assessment Scale (OSAS) were used for the evaluation performed by an independent surgeon. Both scales contained six items scored numerically on a ten-step scale ranging from 1 (normal skin) to 10 (worst result). Moreover, photos of all scars were taken and analyzed by six team surgeons using modified OSAS. RESULTS: The mean follow-up time was 31.7 ± 6.4 months for the MIVAT group and 32.9 ± 4.6 months for the conventional group ($p = 0.39$). The mean scar length in the VA-Group was 2.6 cm vs. 3.8 cm in the C-Group ($p < 0.0001$). The total score of PSAS was 9.93 (6-35) for MIVAT and 9.72 (6-29) for conventional thyroidectomy ($p = 0.22$). The total OSAS score by the independent surgeon showed a better cosmetic outcome for conventional surgery (13.19 vs. 12.33; $p = 0.01$). The total OSAS score by the six team surgeons did not differ between both groups in five of six ratings; one surgeon favored MIVAT (12.2 vs. 13.6; $p = 0.04$). CONCLUSIONS: This study does not find cosmetic advantages of minimally invasive video-assisted thyroidectomy compared to conventional thyroidectomy.
PubMed-ID: 33987765
http://dx.doi.org/10.1007/s00423-021-02196-8

Identifying and addressing Health disparities in Thyroid Cancer Care.
J Clin Endocrinol Metab,
E. O. Asamoah, G. Caraballo and M. R. Castro. 2021.
PubMed-ID: 34871424
http://dx.doi.org/10.1210/clinem/dgab875

Transient asystole related to carbon dioxide embolism during transoral endoscopic parathyroidectomy vestibular approach.
Head Neck, 43(11):E51-E5.
N. Aygun, D. Saridemir, K. Bas, F. Tunca, C. Arici and M. Uludag. 2021.
BACKGROUND: Rarely, during the endoscopic thyroidectomy, carbon dioxide (CO(2)) embolism may occur. METHODS: Case 1: A 65-year-old female who was seen with prolonged fatigue and generalized bone pain was diagnosed primary hyperparathyroidism (PHPT) based on her preoperative biochemical profile. Transoral endoscopic parathyroidectomy vestibular approach (TOEPVA) was planned. Case 2: A 52-year-old male patient was seen with weakness and hepatosteatosis and was diagnosed PHPT based on the laboratory workup. TOEPVA was planned. RESULTS: After subplatysmal dissection with vascular tunnel probe, both of the patients developed severe bradycardia and hypotension leading to asystole during the CO(2) insufflation. The possibility of CO(2) embolism was considered and insufflation was terminated. After a successful cardiac massage, sinus rhythm returned. CONCLUSION: TOEPVA may develop CO(2) embolism leading to asystole during the CO(2) insufflation.
PubMed-ID: 34487402
http://dx.doi.org/10.1002/hed.26855

Thresholds of Basal- and Calcium-Stimulated Calcitonin for Diagnosis of Thyroid Malignancy.
Horm Metab Res, 53(12):779-86.
M. Baetu, C. A. Olariu, C. Stancu, A. Caragheorgheopol, D. Ioachim, G. Moldoveanu, C. Corneci and C. Badiu. 2021.
Since medullary thyroid carcinoma is an aggressive cancer, it is important to have an early detection based on stimulated calcitonin (CT), especially when basal-CT is slightly elevated. The objective of this work was to set specific thresholds for basal-CT- and calcium-stimulated calcitonin for prediction of thyroid malignancy in female population. The study included 2 groups: group A-women with elevated basal-CT (>9.82 pg/ml) and group B-women with normal basal-CT (control group). After calcium stimulation test precise protocol, histopathological reports of those that required surgery were correlated with both basal and stimulated calcitonin. The best basal and stimulated calcitonin cut-offs for distinguishing female patients with medullary thyroid carcinoma or C-Cell-hyperplasia from other pathologies or normal cases were: 12.9 pg/ml, respectively 285.25 pg/ml. For basal-CT above 30 pg/ml, malignancy was diagnosed in 9/9 patients (100%): 9 MTC. For stimulated calcitonin above 300 pg/ml, malignancy was diagnosed in 17/21 patients (80.95%): 12 MTC and 5 papillary thyroid carcinomas. The smallest nodule that proved to be medullary thyroid carcinoma had only 0.56/0.34/0.44 cm on ultrasound, with no other sonographic suspicious criteria. In conclusion, we have identified in Romanian female population basal and stimulated calcitonin thresholds to discriminate medullary thyroid carcinoma or C-Cell-hyperplasia from other cases. We recommend thyroid surgery in all women with stimulated calcitonin above 285 pg/ml. Further studies on larger groups are necessary to establish and confirm male and female cut-offs for early diagnosis of medullary thyroid carcinoma, and interestingly, maybe for macro-papillary thyroid carcinomas alike. The calcium administration has minimum side-effects, but continuous cardiac monitoring is required.
PubMed-ID: 34687025
http://dx.doi.org/10.1055/a-1661-4420

Spare Parathyroid Glands During Thyroid Surgery with Perioperative Autofluorescence Imaging: A Diagnostic Study.
World J Surg, 45(9):2785-90.
A. Bellier, Y. Wazne, T. Chollier, N. Sturm and P. Chaffanjon. 2021.
BACKGROUND: The aim of this original study was to determine the number of parathyroid glands that can be saved and reimplanted thanks to autofluorescence during thyroid surgery. Preservation of parathyroid function remains challenging during thyroid surgery. The parathyroid glands must be identified and immediately autotransplanted in the case of devascularization. Near-infrared autofluorescence of parathyroid glands has recently been proposed to help surgeons during the dissection. METHODS: A total of 116 thyroid lobectomies were performed on 70 consecutive adult patients. Each lobectomy specimen was scanned in vitro with an autofluorescence imaging device. Every spot of autofluorescence was examined by the surgeon and subsequently the pathologist. The pathologist also performed a complete study of the rest of the lobe. We compared the results of the macroscopic and microscopic diagnoses. RESULTS: We detected 24 fluorescent spots on the specimens: 13 were considered to be parathyroid tissue by the surgeon and 11, non-parathyroid tissue. The pathologist confirmed the surgical diagnosis but also discovered 15 additional parathyroid glands that were hidden. CONCLUSIONS: Autofluorescence imaging of the thyroidectomy specimen with surgical inspection is safe, quick, noninvasive and can help detect the accidental removal of parathyroid glands. About 60% of these glands can be spared and autotransplanted during the surgery.

PubMed-ID: 33835219
http://dx.doi.org/10.1007/s00268-021-06102-7

Women With Chronic Hypoparathyroidism Have Low Risk of Adverse Pregnancy Outcomes.
J Clin Endocrinol Metab, 106(11):3312-9.
S. Björnsdottir, B. Clarke, O. Mäkitie, A. Sandström, E. Tiblad, T. Spelman and O. Kämpe. 2021.
CONTEXT: There are scarce data on the management of chronic hypoparathyroidism (hypoPT) in pregnant women. OBJECTIVE: The aim of this study was to evaluate pregnancy outcome and total number of births in maternal chronic hypoPT. METHODS: The Swedish National Patient Register, The Swedish Prescribed Drug Register, Swedish Medical Birth Register, and the Total Population Register were used to identify 97 women with chronic hypoPT and 1030 age-matched controls who delivered 139 and 1577 singleton infants, respectively, following diagnosis between 1997 and 2017. RESULTS: Women in the chronic hypoPT group had more frequent diabetes (DM) and chronic kidney disease (CKD) compared with the control group (P = 0.043 and P < 0.001, respectively). After adjusting for DM, CKD, maternal age at delivery, and calendar year of delivery, chronic hypoPT cases were associated with increased risk of induction of labor (OR, 1.82; 95% CI, 1.13-2.94) and birth of infants with lower birth weight (ß-coefficient -188 g; 95% CI, -312.2 to -63.8) compared with controls. No difference was found in infant length, small for gestational age, or head circumference after adjustments. Mean gestational age at delivery after controlling for DM, CKD, and pre-eclampsia was not significantly younger (P = 0.119). There was no difference in congenital malformations or perinatal death and no difference in the total number of infants born between groups (P = 0.518). CONCLUSION: The majority of women with chronic hypoPT had normal pregnancy outcomes, and the overall risks appear low. Maternal chronic hypoPT is, however, associated with higher risk of induction of labor and slightly lower infant birth weight.
PubMed-ID: 34240167
http://dx.doi.org/10.1210/clinem/dgab503

Radioiodine treatment: an historical and future perspective.
Endocr Relat Cancer, 28(10):T121-T4.
P. Borges de Souza and C. J. McCabe. 2021.
PubMed-ID: 33690155
http://dx.doi.org/10.1530/ERC-21-0037

A Comparison of the Seventh and Eighth Editions of the AJCC Staging Systems to Predict Recurrence in Papillary Thyroid Microcarcinoma.
Ann Surg Oncol, 28(11):6564-71.
Z. Chen, J. Ruan, Y. Yao, L. Wen, Z. Mao, S. Chen, H. Zhu, Y. Zhao, Z. Li, T. J. Fahey, L. Teng and W. Wang. 2021.
BACKGROUND: The incidence of papillary thyroid microcarcinoma has been constantly rising in recent decades. The tumor, node, metastasis staging system is designed to predict prognosis in patients with papillary thyroid carcinoma. Recent studies have shown that the American Joint Committee on Cancer (AJCC) 8th edition is superior to the 7th edition for predicting tumor recurrence in PTC patients. To date, whether the 8th edition is also better able to predict recurrence in papillary thyroid microcarcinoma (PTMC) remains unclear. METHOD: We enrolled 1007 cases from our thyroid cancer database in the First Affiliated Hospital, Zhejiang University School of Medicine, from 1997 to 2011. Univariable and multivariate Cox hazard regression analyses were used to identify the association between variables and recurrence. Disease-free survival was calculated using the Kaplan-Meier method and compared using the log-rank test. RESULTS: A total of 1007 PTMC patients were enrolled, with a median follow-up of 67 months. Of 93 (9.2%) patients downstaged by the changes in versions, 49 (52.7%) were downstaged because the age-at-diagnosis cut-off used for staging increased from 45 to 55 years, while 35 (37.6%) were downstaged due to the weakening of the effects of lymph node metastasis. The recurrence rate of PTMC was 4.17%. Univariate Cox hazards regression analyses showed that TNM stage according to the AJCC 8th edition was significantly associated with recurrence, while the recurrence survival curves showed that TNM stage (stage I vs. stage II-IV) according to the AJCC 8th edition, but not the 7th edition, was significantly associated with disease-free survival ($p < 0.05$). CONCLUSIONS: The AJCC 8th edition has better ability to predict recurrence in PTMC patients than the 7th edition.
PubMed-ID: 33521903
http://dx.doi.org/10.1245/s10434-021-09596-6

Predictors of Bilateral Disease in Pediatric Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e4242-e50.
C. E. Cherella, D. M. Richman, E. Liu, M. C. Frates, B. P. Modi, B. Zendejas, J. R. Smith, J. A. Barletta, M. L. Hollowell and A. J. Wassner. 2021.
CONTEXT: Total thyroidectomy is recommended for children with papillary thyroid carcinoma, partly because of a high prevalence of bilateral disease. Identifying characteristics that predict bilateral disease might identify candidates for more limited surgery. OBJECTIVE: Investigate associations of preoperative or histopathological characteristics with bilateral disease in children with differentiated thyroid cancer. METHODS: Retrospective cohort study (1998-2020) at 2 academic hospitals. Patients <19 years who underwent total thyroidectomy for differentiated thyroid cancer were included. Clinical, sonographic, and histopathological characteristics were evaluated. The presence of bilateral disease on histopathology was assessed by univariable analysis and multivariable logistic regression. RESULTS: One hundred and fifteen subjects were analyzed (90% with papillary carcinoma). Median (range) age at diagnosis was 15.0 (8.1-18.9) years. Bilateral disease was present in 47/115 subjects (41%). Bilateral disease was associated with solid parenchyma, calcifications, irregular margins, and abnormal lymph nodes detected by ultrasound, Bethesda class V/VI cytology, papillary histology, tumor multifocality in the primary lobe, extrathyroidal extension, lymphovascular invasion, and nodal metastases. In multivariable analysis, only multifocality in the primary lobe was independently associated with bilateral disease (OR 7.61, 95% CI 2.44-23.8, P < .001). Among clinically node-negative subjects with papillary carcinoma who did not have tumor multifocality in the primary lobe, bilateral disease was present in 5/32 (16%). CONCLUSIONS: In children with differentiated thyroid cancer, tumor multifocality in the primary lobe is associated with bilateral disease and should prompt consideration of completion thyroidectomy after initial lobectomy. Clinically node-negative children with tumors that are unifocal in the primary lobe have a low likelihood of contralateral disease.
PubMed-ID: 33780538
http://dx.doi.org/10.1210/clinem/dgab210

Success rate and learning curve of intraoperative neural monitoring of the external branch of the superior laryngeal nerve in thyroidectomy.
Head Neck, 43(12):3946-54.
H. W. Choi, Y. B. Ji, E. Kim, K. N. Kim and K. Tae. 2021.
BACKGROUND: This study aimed to evaluate the success rate and learning curve of intraoperative neural monitoring (IONM) of the external branch of the superior laryngeal nerve (EBSLN) in thyroidectomy. METHODS: We studied 130 consecutive patients (200 nerves at risk [NARs]) who had undergone conventional thyroidectomy with IONM of the recurrent laryngeal nerve (RLN) and EBSLN from January 2017 to March 2020. The learning curve was defined as the number of NARs required to achieve an effective and reliable neuromonitoring rate. RESULTS: IONM of the EBSLN was successful in 136/200 (68%) NARs. The cutoff point of the learning curve was 45 NARs (28 patients). The neural identification rate of EBSLN was significantly higher in the post-learning 155 NARs group than the pre-learning group (82.6% vs. 17.8%, p < 0.001). CONCLUSIONS: Approximately 45 NAR neuromonitoring attempts were required to reach a significant increase in the EBSLN identification rate and overcome the learning curve.
PubMed-ID: 34632669
http://dx.doi.org/10.1002/hed.26895

PSMA Expression in Differentiated Thyroid Cancer: Association With Radioiodine, 18FDG Uptake, and Patient Outcome.
J Clin Endocrinol Metab, 106(12):3536-45.
R. Ciappuccini, V. Saguet-Rysanek, F. Giffard, I. Licaj, M. Dorbeau, B. Clarisse, L. Poulain and S. Bardet. 2021.
CONTEXT: Little is known about prostate-specific membrane antigen (PSMA) expression in patients with cervical involvement of differentiated thyroid cancer (DTC). OBJECTIVE: We investigated PSMA expression in neck persistent/recurrent disease (PRD) using immunohistochemistry and the association with radioiodine (RAI) or 18-fluorodeoxyglucose (18FDG) uptake, and patient outcome. DESIGN, SETTING, AND PATIENTS: Data from 44 consecutive DTC patients who underwent neck reoperation from 2006 to 2018 in a comprehensive cancer center. MAIN OUTCOME MEASURE(S): Immunostaining was performed with vascular endothelial marker CD31 and PSMA. PSMA expression was quantified using the immunoreactive score (IRS). RAI and 18FDG uptake were assessed before surgery using posttherapeutic RAI scintigraphy and 18FDG positron emission tomography with computed tomography. Mean follow-up after reintervention was 6.5 ± 3.7 years. RESULTS: Thirty patients (68%) showed at least 1 PSMA-positive lesion (IRS = 2) with similar proportions in RAI-positive and RAI-negative patients (75% vs 66%). In RAI-negative patients, however, the proportion of PSMA-positive disease (79% vs 25%, P < 0.01) and the mean IRS (4.0 vs 1.0, P = 0.01) were higher in 18FDG-positive than in 18FDG-negative patients. Furthermore, mean IRS was higher in patients = 55 years, large primary tumors

(>40 mm) or aggressive subtypes, and was correlated with structural disease at last follow-up. Strong PSMA expression (IRS = 9) was associated with shorter progression-free survival (PFS). CONCLUSIONS: Our findings show that PSMA expression was present in two-thirds of patients with neck PRD, that it was related to poor prognostic factors and that very high expression was associated with poorer PFS. This preliminary study may offer new perspectives for the management of RAI-refractory DTC.
PubMed-ID: 34331544
http://dx.doi.org/10.1210/clinem/dgab563

Revisiting the role of surgery in the treatment of Graves' disease.
Clin Endocrinol (Oxf),
O. Cohen, O. Ronen, A. Khafif, J. P. Rodrigo, R. Simo, P. Pace-Asciak, G. Randolph, L. H. Mikkelsen, L. P. Kowalski, K. D. Olsen, A. Sanabria, R. P. Tufano, S. Babighian, A. R. Shaha, M. Zafereo and A. Ferlito. 2021.
Graves' disease (GD) can be managed by antithyroid drugs (ATD), radioactive iodine (RAI) and surgery. Thyroidectomy offers the highest success rates for both primary and persistent disease, yet it is the least recommended or utilized option reaching <1% for primary disease and <25% for persistent disease. Several surveys have found surgery to be the least recommended by endocrinologists worldwide. With the development of remote access thyroidectomies and intraoperative nerve monitoring of the recurrent laryngeal nerve, combined with current knowledge of possible risks associated with RAI or failure of ATDs, revaluation of the benefit to harm ratio of surgery in the treatment of GD is warranted. The aim of this review is to discuss possible reasons for the low proportion of surgery in the treatment of GD, emphasizing an evidence-based approach to the clinicians' preferences for surgical referrals, surgical indications and confronting traditional reasons and concerns relating to the low referral rate with up-to-date data.
PubMed-ID: 34954838
http://dx.doi.org/10.1111/cen.14653

Impact of rocuronium on intraoperative neuromonitoring vagal amplitudes during thyroidectomy.
Langenbecks Arch Surg, 406(6):2019-25.
O. E. de Vendin, T. Fuchs-Buder, D. Schmartz, D. T. Nguyen, P. Gallet, F. Bihain, C. Nomine-Criqui and L. Brunaud. 2021.
PURPOSE: Neuromuscular blocking agents (NMBA) facilitate endotracheal intubation and reduce related laryngeal morbidity. However, NMBA interfere with intraoperative neuromonitoring amplitudes during thyroidectomy. The goal of this study was to evaluate the impact of rocuronium used for tracheal intubation on early intraoperative neuromonitoring vagal amplitudes observed during first thyroid lobe dissection. METHODS: This is an observational pharmacoepidemiological study with prospective data collection and retrospective analysis. During the study period, all consecutive patients who underwent thyroid surgery with neuromonitoring were included. Patients underwent endotracheal intubation either using a single dose of rocuronium (NMBA group) or without NMBA (NMBA-free group) according to the anesthesiologist's preference. RESULTS: Six hundred six patients were included (213 NMBA and 393 NMBA-free group patients). At V1, 39 patients (18%) in the NMBA group had an amplitude < 100 µV (need for curarization reversal in 30 patients) and 13 patients (3.3%) in the NMBA-free group ($p < 0.001$). In the remaining 554 patients, the mean V1 amplitude was significantly decreased in the NMBA group (544 versus 685 µV; $p < 0.001$). After exclusion of 25 patients with loss of signal types 1 and 2 during dissection, the difference between mean V1 and mean V2 was significantly lower in NMBA group patients (- 22 versus - 86 µV; $p = 0.016$). CONCLUSION: This study provides new data showing how NMBA used for tracheal intubation significantly decrease V1 amplitude baseline and modify amplitude variations from V1 to V2 values during the first thyroid lobe dissection. LEVEL OF EVIDENCE: Pharmacoepidemiological study.
PubMed-ID: 34120194
http://dx.doi.org/10.1007/s00423-021-02234-5

Late Recovery of Parathyroid Function After Total Thyroidectomy: A Case-Control Study.
Horm Metab Res, 53(10):654-61.
J. J. Díez, E. Anda, J. Sastre, B. P. Corral, C. Álvarez-Escolá, L. Manjón, M. Paja, M. Sambo, P. S. Fernández, C. B. Carrera, J. C. Galofré, E. Navarro, C. Zafón, E. Sanz, A. Oleaga, O. Bandrés, S. Donnay, A. Megía, M. Picallo, C. S. Ragnarsson, G. Baena-Nieto, J. C. Fernández-García, B. Lecumberri, M. S. de la Vega, A. R. Romero-Lluch and P. Iglesias. 2021.
The clinical characteristics of patients with postoperative hypoparathyroidism who recover parathyroid function more than 12 months after surgery have not been studied. We aimed to evaluate whether the intensity of replacement therapy with calcium and calcitriol is related to the late recovery of parathyroid function. We compared the demographic, surgical, pathological, and analytical features of two groups of patients: cases, i. e., late recovery patients (those who recover parathyroid function>1 year after thyroidectomy, n=40), and controls, i. e., patients with permanent hypoparathyroidism

(n=260). Replacement therapy with calcium and calcitriol was evaluated at discharge of surgery, 3-6 months, 12 months, and last visit. No significant differences were found in clinical, surgical, pathological, or analytical characteristics between cases and controls. The proportion of cases who required treatment with calcium plus calcitriol at 12 months was significantly lower than that found in controls (p<0.001). Furthermore, daily calcium and calcitriol doses in controls were significantly higher than those in cases at 3-6 months (p=0.014 and p=0.004, respectively) and at 12 months (p<0.001 and p=0.043, respectively). In several models of logistic regression analysis therapy with calcium and calcitriol at 12 months was negatively related to late recovery of parathyroid function. Although delayed recuperation of parathyroid function after total thyroidectomy is uncommon (13%), follow-up beyond 12 months is necessary in patients with postoperative hypoparathyroidism, especially in those whose needs of treatment with Ca and calcitriol are reducing over time.
PubMed-ID: 34517416
http://dx.doi.org/10.1055/a-1608-1373

Medullary Thyroid Cancer: 60 Years of Gradual Understanding.
Ann Surg Oncol, 29(1):7-8.
G. M. Doherty. 2022.
PubMed-ID: 34761334
http://dx.doi.org/10.1245/s10434-021-11077-9

It Helps to Know Where to Look: Visual Identification of Unintentionally Resected Parathyroid Glands is Improved When Inspection is Directed by Near Infrared Autofluorescence Imaging.
World J Surg, 45(9):2791-2.
Q. Y. Duh and C. E. Graves. 2021.
PubMed-ID: 34212210
http://dx.doi.org/10.1007/s00268-021-06200-6

Do Ultrasound Patterns and Clinical Parameters Inform the Probability of Thyroid Cancer Predicted by Molecular Testing in Nodules with Indeterminate Cytology?
Thyroid, 31(11):1673-82.
J. J. Figge, W. E. Gooding, D. L. Steward, L. Yip, R. S. Sippel, S. P. Yang, R. P. Scheri, J. A. Sipos, S. J. Mandel, S. E. Mayson, K. D. Burman, J. M. Folek, B. R. Haugen, J. A. Sosa, R. Parameswaran, W. B. Tan, Y. E. Nikiforov and S. E. Carty. 2021.
Background: Molecular testing (MT) is commonly used to refine cancer probability in thyroid nodules with indeterminate cytology. Whether or not ultrasound (US) patterns and clinical parameters can further inform the risk of thyroid cancer in nodules predicted to be positive or negative by MT remains unknown. The aim of this study was to test if clinical parameters, including patient age, sex, nodule size (by US), Bethesda category (III, IV, V), US pattern (American Thyroid Association [ATA] vs. American College of Radiology Thyroid Image Reporting and Data System [TI-RADS] systems), radiation exposure, or family history of thyroid cancer can modify the probability of thyroid cancer or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) predicted by MT. Methods: We studied 257 thyroid nodules in 232 patients from 10 study centers with indeterminate fine needle aspiration cytology and informative MT results using the ThyroSeq v3 genomic classifier (TSv3). Univariate and multivariate logistic regression was used for data analysis. Results: The presence of cancer/NIFTP was associated with positive TSv3 results (odds ratio 61.39, p < 0.0001). On univariate regression, patient sex, age, and Bethesda category were associated with cancer/NIFTP probability (p < 0.05 for each). Although ATA (p = 0.1211) and TI-RADS (p = 0.1359) US categories demonstrated positive trends, neither was significantly associated with cancer/NIFTP probability. A multivariate regression model incorporating the four most informative non-MT covariates (sex, age, Bethesda category, and ATA US pattern; Model No. 1) yielded a C index of 0.653; R(2) = 0.108. When TSv3 was added to Model number 1, the C index increased to 0.888; R(2) = 0.572. However, age (p = 0.341), Bethesda category (p = 0.272), and ATA US pattern (p = 0.264) were nonsignificant, and other than TSv3 (p < 0.0001), male sex was the only non-MT parameter that potentially contributed to cancer/NIFTP risk (p = 0.095). The simplest and most efficient clinical model (No. 3) incorporated TSv3 and sex (C index = 0.889; R(2) = 0.588). Conclusions: In this multicenter study of thyroid nodules with indeterminate cytology and MT, neither the ATA nor TI-RADS US scoring systems further informed the risk of cancer/NIFTP beyond that predicted by TSv3. Although age and Bethesda category were associated with cancer/NIFTP probability on univariate analysis, in sequential nomograms they provided limited incremental value above the high predictive ability of TSv3. Patient sex may contribute to cancer/NIFTP risk in thyroid nodules with indeterminate cytology.
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Improving safety in paediatric thyroidectomy by PTH measurements.
Clin Endocrinol (Oxf), 95(5):760-5.
A. V. Freire, M. G. Ropelato, P. Papendieck, A. Vieites, E. Elías, M. G. Ballerini, M. E. Rodriguez, I. Bergadá and A. Chiesa. 2021.
OBJETIVE: We followed our previously reported algorithm based on intra and postoperative parathyroid hormone (PTH) levels to predict postthyroidectomy hypoparathyroid hypocalcemia. The objective of the study was to assess if this strategy is useful and safe to reduce hypocalcemia, hospitalisation length and postsurgery calcium sampling. DESIGN, PATIENTS, MEASSUREMENTS: We classified our series of 66 patients according to their risk of hypoparathyroidism based on PTH determinations. We treated high-risk patients with calcium and vitamin D1-25 supplementation and obtained routine daily calcium samples to control low-risk patients until 48 h postsurgery. We compared the outcomes and overall results of this new approach with those of a historical control group of patients with equivalent PTH measurements who were treated only if they presented hypocalcemia. RESULTS: In the high-risk subgroup (n = 30), five patients had hypocalcemia within the first 24 h. Compared with the high-risk control subgroup, the incidence of hypocalcemia fell from 100% to 17% (p < .001), and the median hospitalisation length from 6 to 3 days (p < .001). In the low-risk subgroup (n = 36), 28 patients remained normocalcemic with significantly less calcium sampling (p < .001). Eight patients had hypocalcemia; seven of them required neck dissection, which was the only risk factor related to postsurgical hypoparathyroidism (RR: 2.1 [confidence interval 95%: 1.4-3.1]; p < .001). The overall incidence of hypocalcemia decreased by 58% in our patients compared to the control group. CONCLUSIONS: Assessing PTH levels to classify the risk of hypoparathyroidism and to initiate preventive therapy was an effective approach that improved the safety of our paediatric patients by reducing the incidence of hypocalcemia and the length of hospitalisation after thyroidectomy in paediatric patients.
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http://dx.doi.org/10.1111/cen.14552

Current iodine status in Japan: A cross-sectional nationwide survey of schoolchildren, 2014-2019.
J Clin Endocrinol Metab,
Y. Fuse, Y. Ito, Y. Shishiba and M. Irie. 2021.
CONTEXT: Japan has been regarded as a long-standing iodine sufficient country without iodine fortification; however, data on nationwide iodine status is lacking. OBJECTIVE: This study aimed to characterize the iodine status in Japan. METHODS: From 2014 through 2019 a nationwide school-based survey was conducted across all districts in Japan. Urinary iodine concentration (UIC), creatinine (Cr) concentration and anthropometry were assessed in healthy school-aged children (SAC) aged 6 to 12 years. Their iodine status is regarded as generally representative of the nation's iodine status. RESULTS: A total of 32,025 children participated. The overall median UIC was 269 μg/L which was within the WHO's adequacy range. There was a regional difference in UIC values within 14 regions, and the lowest and highest median UIC were found in Tanegashima Island (209 μg/L) and Nakashibetsu, Hokkaido (1,071 μg/L), respectively. The median UIC = 300 μg/L was observed in 12 out of 46 regions. By using estimated 24-h urinary iodine excretion (UIE), the prevalence of SAC exceeding the upper tolerable limit of iodine for Japanese children was from 5.2 to 13.7%. The UIC values did not change with age, BSA and BMI percentile, while the Cr concentration simultaneously increased suggesting the effect of urinary creatinine on UI/Cr and estimated 24-h UIE values. CONCLUSIONS: The iodine intake of Japanese people is adequate, but in some areas it is excessive. The incidence and prevalence of thyroid disorders associated with iodine intake should be obtained especially in the areas where high amounts of iodine are consumed.
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http://dx.doi.org/10.1210/clinem/dgab919

Whole Tumor Capsule Is Prognostic of Very Good Outcome in the Classical Variant of Papillary Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e4072-e83.
C. Giani, L. Torregrossa, T. Ramone, C. Romei, A. Matrone, E. Molinaro, L. Agate, G. Materazzi, P. Piaggi, C. Ugolini, F. Basolo, R. Ciampi and R. Elisei. 2021.
CONTEXT: Tumor capsule integrity is becoming a relevant issue to predict the biological behavior of human tumors, including thyroid cancer. OBJECTIVE: This work aims to verify whether a whole tumor capsule in the classical variant of papillary thyroid carcinoma (CVPTC) could have as a predictive role of a good outcome as for follicular variant (FVPTC). METHODS: FVPTC (n = 600) and CVPTC (n = 554) cases were analyzed. We distinguished between encapsulated-FVPTC (E-FVPTC) and encapsulated-CVPTC (E-CVPTC) and, thereafter, invasive (Ei-FVPTC and Ei-CVPTC) and noninvasive (En-FVPTC and En-CVPTC) tumors, according to the invasion or integrity of the tumor capsule, respectively. Cases without a tumor

capsule were indicated as invasive-FVPTC (I-FVPTC) and invasive-CVPTC (I-CVPTC). The subgroup of each variant was evaluated for BRAF mutations. RESULTS: E-FVPTC was more frequent than E-CVPTC (P < .001). No differences were found between En-FVPTC and En-CVPTC or between Ei-FVPTC and Ei-CVPTC. After 18 years of follow-up, a greater number of not-cured cases were observed in Ei-CVPTC with respect to Ei-FVPTC, but not in En-CVPTC to En-FVPTC. Multivariate clustering analysis showed that En-FVPTC, En-CVPTC, and Ei-FVPTC have similar features but different from I-FVPTC and I-CVPTC and, to a lesser extent, from Ei-CVPTC. A total of 177 of 614 (28.8%) cases were BRAFV600E mutated, and 10 of 614 (1.6%) carried BRAF-rare alterations. A significantly higher rate of En-CVPTC (22/49, 44.9%) than En-FVPTC (15/195, 7.7%) (P < .0001) were BRAFV600E mutated. CONCLUSION: En-CVPTC is less prevalent than En-FVPTC. However, it has good clinical/ pathological behavior comparable to En-FVPTC. This finding confirms the good prognostic role of a whole tumor capsule in CVPTC as well. New nomenclature for En-CVPTC, similar to that introduced for En-FVPTC (ie, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; NIFTP) could be envisaged.
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http://dx.doi.org/10.1210/clinem/dgab396

Risk stratification of indeterminate thyroid nodules using ultrasound and machine learning algorithms.
Clin Endocrinol (Oxf), 96(4):646-52.
M. L. Gild, M. Chan, J. Gajera, B. Lurie, Z. Gandomkar and R. J. Clifton-Bligh. 2022.
BACKGROUND: Indeterminate thyroid nodules (Bethesda III) are challenging to characterize without diagnostic surgery. Auxiliary strategies including molecular analysis, machine learning models, and ultrasound grading with Thyroid Imaging, Reporting and Data System (TI-RADS) can help to triage accordingly, but further refinement is needed to prevent unnecessary surgeries and increase positive predictive values. DESIGN: Retrospective review of 88 patients with Bethesda III nodules who had diagnostic surgery with final pathological diagnosis. MEASUREMENTS: Each nodule was retrospectively scored through TI-RADS. Two deep learning models were tested, one previously developed and trained on another data set, mainly containing determinate cases and then validated on our data set while the other one trained and tested on our data set (indeterminate cases). RESULTS: The mean TI-RADS score was 3 for benign and 4 for malignant nodules (p = .0022). Radiological high risk (TI-RADS 4,5) and low risk (TI-RADS 2,3) categories were established. The PPV for the high radiological risk category in those with >10 mm nodules was 85% (CI: 70%-93%). The NPV for low radiological risk in patients >60 years (mean age was 100% (CI: 83%-100%). The area under the curve (AUC) value of our novel classifier was 0.75 (CI: 0.62-0.84) and differed significantly from the chance-level (p < .00001). CONCLUSIONS: Novel radiomic and radiologic strategies can be employed to assist with preoperative diagnosis of indeterminate thyroid nodules.
PubMed-ID: 34642976
http://dx.doi.org/10.1111/cen.14612

The volume and outcome relationship for thyroidectomy in England.
Langenbecks Arch Surg, 406(6):1999-2010.
W. K. Gray, S. Aspinall, N. Tolley, J. Day and M. Lansdown. 2021.
PURPOSE: The delivery of surgical care in England has seen a momentum towards centralisation within larger volume hospitals and surgical teams. The aim of this study was to investigate outcomes in England in relationship to hospital and surgeon annual volumes for total thyroidectomy. METHODS: Data were extracted from the Hospital Episodes Statistics (HES) database for England. A 6-year period (April 2012-March 2018 inclusive) for all adult admissions for thyroidectomy was used in the analysis. The primary outcome measure used was a length of hospital stay greater than 2 days or an emergency readmission within 30 days following surgery. This was used as a proxy for surgical complications. A multilevel modelling strategy was used to adjust for hierarchy and potentially confounding. RESULTS: Data for 22,823 total thyroidectomies across 144 hospital trusts were used for analysis. For total thyroidectomy, larger volume surgeons had reduced levels of post-surgical complications; length of stay > 2 and > 4 days; emergency readmission at 30 days; and hypoparathyroidism, vocal cord palsy, stridor, and tracheostomy at 1-year post-surgery. Larger hospital volume was associated with lower levels of emergency readmission at 30 days and hypoparathyroidism at 1 year. CONCLUSIONS: There is significant correlation between surgeon volume and clinical outcome for total thyroidectomy. The relationship was approximately linear, and a low-volume threshold could not be defined.
PubMed-ID: 34106320
http://dx.doi.org/10.1007/s00423-021-02223-8

Does macroscopic extrathyroidal extension to the strap muscles alone affect survival in papillary thyroid carcinoma?
Surgery,
V. Harries, M. McGill, A. Yuan, L. Y. Wang, R. M. Tuttle, A. R. Shaha, J. P. Shah, R. J. Wong, S. G. Patel and I. Ganly. 2021.
BACKGROUND: Macroscopic extrathyroidal extension to structures adjacent to the thyroid gland is one of the most important predictors of survival in papillary thyroid carcinoma. However, the prognostic significance of macroscopic extrathyroidal extension to strap muscles alone is unknown. The aim of this study is to determine the impact on survival in patients with macroscopic extrathyroidal extension to strap muscles alone compared to those with no macroscopic extrathyroidal extension and macroscopic extrathyroidal extension involving other adjacent structures. METHODS: After institutional review board approval, adult papillary thyroid carcinoma patients were identified from an institutional database of 6,259 patients undergoing initial surgery for well-differentiated thyroid carcinoma from 1986 to 2015. Patients were classified as having no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, or macroscopic extrathyroidal extension to other adjacent structures. Disease-specific survival was calculated using the Kaplan-Meier method and groups were compared using the log-rank test. A P value < .05 was considered statistically significant and significant factors were used in a Cox proportional hazard model to predict disease-specific survival. RESULTS: There were 5,880 patients included in the analysis; 5,485 patients (93.3%) in the no macroscopic extrathyroidal extension group, 179 (3.0%) in the macroscopic extrathyroidal extension to strap muscles alone group and 216 (3.7%) in the macroscopic extrathyroidal extension involving other adjacent structures group. With a median follow-up of 64 months, the estimated 10-year disease-specific survival for patients with no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, and macroscopic extrathyroidal extension involving other adjacent structures were 98.9%, 95.7%, and 83.7%, respectively (P < .0001). In the =55-year-old cohort, the estimated 10-year disease-specific survival for patients with no macroscopic extrathyroidal extension, macroscopic extrathyroidal extension to strap muscles alone, and macroscopic extrathyroidal extension involving other adjacent structures were 97.6%, 89.3%, and 68.1%, respectively (P <.0001). After controlling for pathological nodal stage and distant metastasis stage, extent of extrathyroidal extension remained an independent predictor of disease-specific survival; patients with macroscopic extrathyroidal extension to strap muscles alone had a 3.3-fold increased likelihood of a disease-specific death compared to no macroscopic extrathyroidal extension patients (hazard ratio 3.294; 95% confidence interval 1.076-10.086, P < .0368). CONCLUSION: In our study, patients aged =55 years with papillary thyroid carcinoma and macroscopic extrathyroidal extension to strap muscles alone appear to have an increased likelihood of a disease-specific death compared to patients with no macroscopic extrathyroidal extension.
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http://dx.doi.org/10.1016/j.surg.2021.08.041

A High-throughput Approach to Identify Effective Systemic Agents for the Treatment of Anaplastic Thyroid Carcinoma.
J Clin Endocrinol Metab, 106(10):2962-78.
Y. C. Henderson, A. S. R. Mohamed, A. Maniakas, Y. Chen, R. T. Powell, S. Peng, M. Cardenas, M. D. Williams, D. Bell, M. E. Zafereo, R. J. Wang, S. E. Scherer, D. A. Wheeler, M. E. Cabanillas, M. C. Hofmann, F. M. Johnson, C. C. Stephan, V. Sandulache and S. Y. Lai. 2021.
BACKGROUND: Despite the use of aggressive multimodality treatment, most anaplastic thyroid carcinoma (ATC) patients die within a year of diagnosis. Although the combination of BRAF and MEK inhibitors has recently been approved for use in BRAF-mutated ATC, they remain effective in a minority of patients who are likely to develop drug resistance. There remains a critical clinical need for effective systemic agents for ATC with a reasonable toxicity profile to allow for rapid translational development. MATERIAL AND METHODS: Twelve human thyroid cancer cell lines with comprehensive genomic characterization were used in a high-throughput screening (HTS) of 257 compounds to select agents with maximal growth inhibition. Cell proliferation, colony formation, orthotopic thyroid models, and patient-derived xenograft (PDX) models were used to validate the selected agents. RESULTS: Seventeen compounds were effective, and docetaxel, LBH-589, and pralatrexate were selected for additional in vitro and in vivo analysis as they have been previously approved by the US Food and Drug Administration for other cancers. Significant tumor growth inhibition (TGI) was detected in all tested models treated with LBH-589; pralatrexate demonstrated significant TGI in the orthotopic papillary thyroid carcinoma model and 2 PDX models; and docetaxel demonstrated significant TGI only in the context of mutant TP53. CONCLUSIONS: HTS identified classes of systemic agents that demonstrate preferential effectiveness against aggressive thyroid cancers, particularly those with mutant TP53. Preclinical validation in both orthotopic and PDX models, which are accurate in vivo models mimicking tumor microenvironment, may support initiation of early-phase clinical trials in non-BRAF mutated or refractory to BRAF/MEK inhibition ATC.
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http://dx.doi.org/10.1210/clinem/dgab424

Optimal cutoff values of primary tumour size to better predict long-term outcomes in patients with papillary thyroid carcinoma undergoing total thyroidectomy: A preliminary study using restricted cubic spline analysis.
Clin Endocrinol (Oxf),
S. W. Jang, J. H. Park, H. J. Kwon and J. H. Yoon. 2021.
OBJECTIVE: Primary tumour size (PTS) is known to be a significant prognostic factor in patients with papillary thyroid carcinoma (PTC) undergoing thyroidectomy. Although cutoff values of 2 and 4 cm are widely used in surgical extent decision and long-term outcomes predictions, the effectiveness of arbitrary cutoff values in stratifying patients for target outcomes is questionable. This study aimed to determine new optimal cutoffs of PTS. DESIGN, PATIENT AND MEASUREMENTS: Patients (n = 529) with PTC who underwent total thyroidectomy were retrospectively reviewed. After risk factor analysis for structural recurrence, the optimal cutoffs of PTS were automatically calculated using restricted cubic spline analysis and X-tile software. Subgroups were classified based on the newly determined cutoff values. Both the recurrence-free survival (RFS) and the proportion of patients in each response-to-therapy category, using the dynamic risk stratification system (DRS), were compared between the subgroups. RESULTS: PTS was confirmed as an independent risk factor for structural recurrence. The optimal cutoff values were calculated as 1.4 and 3.0 cm. The subgroups stratified using these newly determined cutoffs showed significantly different RFS and DRS based on the response to initial therapy, but the subgroups classified using the cutoffs of 2 and 4 cm did not. CONCLUSIONS: The newly determined cutoff values of PTS may be useful in better stratifying patients with PTC undergoing thyroidectomy for target outcomes and can be considered as a new definition in staging and risk stratification systems.
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http://dx.doi.org/10.1111/cen.14657

ASO Author Reflections: Multimodality Treatment in Anaplastic Thyroid Cancer: Improving Survival Outcomes and Balancing Treatment Related Complications.
Ann Surg Oncol, 28(12):7531-2.
P. K. C. Jonker and M. Sywak. 2021.
PubMed-ID: 34131820
http://dx.doi.org/10.1245/s10434-021-10268-8

Multimodality Treatment Improves Locoregional Control, Progression-Free and Overall Survival in Patients with Anaplastic Thyroid Cancer: A Retrospective Cohort Study Comparing Oncological Outcomes and Morbidity between Multimodality Treatment and Limited Treatment.
Ann Surg Oncol, 28(12):7520-30.
P. K. C. Jonker, J. Turchini, S. Kruijff, J. F. Lin, A. J. Gill, T. Eade, A. Aniss, R. Clifton-Bligh, D. Learoyd, B. Robinson, V. Tsang, A. Glover, S. Sidhu and M. Sywak. 2021.
BACKGROUND: Patients with anaplastic thyroid cancer (ATC) have poor overall survival, and the optimal management approach remains unclear. The aim of this study is to evaluate our experience with multimodality (MMT) versus limited treatment (LT) for ATC. PATIENTS AND METHODS: A cohort study of patients with ATC managed in a tertiary referral center was undertaken. The outcomes of MMT were compared with those of LT. The primary outcome measures were locoregional control and progression-free and overall survival. Secondary outcome measures were treatment-related complications and factors associated with improved survival. RESULTS: In total, 59 patients (35 females) with a median age of 73 years (range 39-99 years) and ATC stage IVA (n = 2), IVB (n = 28), or IVC (n = 29) were included. LT was utilized in 25 patients (42%), and 34 cases had MMT. MMT patients had a longer time of locoregional control (18.5 versus 1.9 months; $p < 0.001$), progression-free survival (3.5 versus 1.2 months; $p < 0.001$), and overall survival (6.9 versus 2.0 months; $p < 0.001$) when compared with LT. For patients with stage IVC ATC, locoregional control ($p = 0.03$), progression-free survival ($p < 0.001$), and overall survival ($p < 0.001$) were superior in the MMT cohort compared with LT. MMT had more treatment-related complications than LT ($p < 0.001$). An Eastern Cooperative Oncology Group performance status < 2 (HR 0.30; $p = 0.001$) and MMT (HR 0.35; $p = 0.008$) were associated with improved overall survival. CONCLUSION: MMT is likely to improve locoregional control, progression-free survival, and overall survival in selected ATC patients including stage IVC tumors but comes with a greater complication risk.
PubMed-ID: 34032961
http://dx.doi.org/10.1245/s10434-021-10146-3

Severe Hypocalcemia After Thyroidectomy: An Analysis of 7366 Patients.
Ann Surg, 274(6):e1014-e21.
H. S. Kazaure, A. Zambeli-Ljepovic, T. Oyekunle, S. A. Roman, J. A. Sosa, M. T. Stang and R. P. Scheri. 2021.
OBJECTIVE: The aim of the study was to determine severe hypocalcemia rate following thyroidectomy and factors associated with its occurrence. BACKGROUND: Hypocalcemia is the most common complication after thyroidectomy. Severe post-thyroidectomy hypocalcemia can be life-threatening; data on this specific complication are scarce. METHODS: Patients who underwent thyroidectomy in the American College of Surgeons-National Surgical Quality Improvement Program thyroidectomy-targeted database (2016-2017) were abstracted. A severe hypocalcemic event was defined as hypocalcemia requiring intravenous calcium, emergent clinic/hospital visit, or a readmission for hypocalcemia. Multivariable regression was used to identify factors independently associated with occurrence of severe hypocalcemia. RESULTS: Severe hypocalcemia occurred in 5.8% (n = 428) of 7366 thyroidectomy patients, with 83.2% necessitating intravenous calcium treatment. Rate of severe hypocalcemia varied by diagnosis and procedure (0.5% for subtotal thyroidectomy to 12.5% for thyroidectomy involving neck dissections). Overall, 38.3% of severe hypocalcemic events occurred after discharge; in this subset, 59.1% experienced severe hypocalcemia despite being discharged with calcium and vitamin D. Severe hypocalcemia patients had higher rates of recurrent laryngeal nerve injury (13.4% vs 6.6%), unplanned reoperations (4.4% vs 1.3%), and longer hospital stay (30.4% vs 6.2% =3 days (all $P < 0.01$). After multivariate adjustment, severe hypocalcemia was associated with multiple factors including Graves disease [odds ratio (OR) = 2.06], lateral neck dissections (OR: 3.10), and unexpected reoperations (OR = 3.55); all P values less than 0.01. CONCLUSIONS: Severe hypocalcemia and suboptimal hypocalcemia management after thyroidectomy are common. Patients who experienced severe hypocalcemia had higher rates of nerve injury and unexpected reoperations, indicating surgical complexity and provider inexperience. More biochemical surveillance particularly a parathyroid hormone-based protocol, fine-tuned supplementation, and selective referral could reduce occurrence of this morbid complication.
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http://dx.doi.org/10.1097/SLA.0000000000003725

Outcomes of Advanced Medullary Thyroid Carcinoma in the Era of Targeted Therapy.
Ann Surg Oncol, 29(1):64-71.
N. L. Kesby, A. J. Papachristos, M. Gild, A. Aniss, M. S. Sywak, R. Clifton-Bligh, S. B. Sidhu and A. R. Glover. 2022.
BACKGROUND: Medullary thyroid carcinoma (MTC) can be targeted with tyrosine kinase inhibitors (TKIs). We aimed to report the outcomes of surgically managed MTC and to evaluate the impact of TKI use on patient survival. METHODS: Consecutive patients treated surgically for MTC from 1986 to 2020 were identified from a prospectively collected database and were compared on the basis of stage at operation and TKI use. The primary outcome was overall survival (OS). RESULTS: Among 154 patients with a median age of 52 years, 40% presented with stage I/II disease and 60% presented with advanced (stage III or IV) disease. During a median follow-up of 7.5 years, 21% received TKIs for systemic disease. Those presenting with advanced disease were more likely to receive a TKI (31% vs. 7%), present with tumor invasion of the recurrent laryngeal nerve (RLN; 12% vs. 0%) and undergo reoperation (42% vs. 23%) compared with stage I-II patients. For the 11 patients found to have invasion of the RLN, five had preoperative functional vocal cords. Five-year OS was 84% for advanced disease, and stage IV patients who received TKIs had a median survival of 21 years, versus 15 years for those who did not ($p = 0.3$). CONCLUSIONS: Surgery achieves long-term survival for patients with advanced disease, however these patients are at greater risk of requiring RLN resection due to invasion. A significant OS benefit was not seen for TKI use. For patients with local invasion, neoadjuvant TKI therapy may have a role in reducing local morbidity if confirmed to be of benefit in clinical trials.
PubMed-ID: 34716515
http://dx.doi.org/10.1245/s10434-021-10980-5

Serum thyroglobulin is associated with orbitopathy in Graves' disease.
J Endocrinol Invest, 44(9):1905-11.
S. Khamisi, M. Lundqvist, P. Emadi, K. Almby, Ö. Ljunggren and F. A. Karlsson. 2021.
PURPOSE: Serum thyroglobulin levels are often elevated in Graves' disease (GD) and in most cases decrease during treatment. Its relation to Graves' orbitopathy (GO) has not been clarified. Previously, a risk of GO has been linked to smoking, TSH receptor stimulation, high TSH-receptor antibodies (TRAb), low thyroid peroxidase and thyroglobulin antibodies (TPOAb, TgAb). METHODS: We examined Tg levels in 30 consecutive patients with GD were given drug therapy (methimazole + thyroxine) for up to 24 months. GO was identified by clinical signs and symptoms. 17 patients had GO, 11 of whom had it at diagnosis while 6 developed GO during treatment. During the study, 5 subjects were referred to radioiodine treatment, 3 to surgery. The remaining 22 subjects (GO n = 12, non-GO n = 10) completed the drug regimen.

RESULTS: At diagnosis, Tg levels in GO patients (n = 11) were higher (84, 30-555 µg/L, median, range) than in non-GO patients (n = 19) (38, 3.5-287 µg/L), p = 0.042. Adding the 6 subjects who developed eye symptoms during treatment to the GO group (n = 17), yielded p = 0.001 vs. non-GO (n = 13). TRAb tended to be higher, while TPOAb and TgAb tended to be lower in the GO group. For the 22 patients who completed the drug regimen, Tg levels were higher in GO (n = 12) vs. non-GO (n = 10), p = 0.004, whereas TRAb levels did not differ. CONCLUSION: The data may suggest that evaluation of thyroglobulin levels in GD could contribute to identify patients at increased risk of developing GO. Possibly, thyroidal release of Tg in GD reflects a disturbance that also impacts retroorbital tissues.
PubMed-ID: 33515213
http://dx.doi.org/10.1007/s40618-021-01505-8

Predictive Value of Delphian Lymph Node Metastasis in the Thyroid Cancer.
Laryngoscope, 131(9):1990-6.
D. H. Kim, S. W. Kim and S. H. Hwang. 2021.
OBJECTIVE/HYPOTHESIS: To evaluate the diagnostic accuracy of Delphian lymph node (DLN) metastasis for the prediction of central lymph node (CLN) metastasis and lateral lymph node (LLN) metastasis. METHODS: Two authors independently reviewed the six databases (Cochrane database, Embase, Google Scholar, PubMed, SCOPUS, and Web of Science). Four parameters were extracted from each study: true positive, true negative, false positive, and false negative. The quality of the methodology was evaluated using the Quality Assessment of Diagnostic Accuracy Studies ver. 2 tool. RESULTS: The diagnostic odds ratio of DLN in CLN metastasis was 8.859 (95% confidence interval [CI], 4.419; 16.578). The area under the summary receiver operating characteristic curve was 0.748. The diagnostic odds ratio of DLN in LLN metastasis was 7.61 (95% CI, 4.48; 12.94). The area under the summary receiver operating characteristic curve was 0.837. DLN metastasis was moderately predictive of CLN metastasis (sensitivity = 32%, specificity = 95%), LLN metastasis (sensitivity = 52%, specificity = 89%), and contralateral CLN metastasis (sensitivity = 46%, specificity = 85%). DLN metastasis had statistically significant correlation with specific clinicopathological characteristics, including younger age (< 45 years old), bilaterality, capsule invasion, extrathyroidal extension, lymphovascular invasion, male sex, multifocality, and tumor size (> 1 cm). CONCLUSIONS: The higher specificities of DLN pathology may help predict central and lateral compartment involvement in patients with thyroid cancer. LEVEL OF EVIDENCE: NA Laryngoscope, 131:1990-1996, 2021.
PubMed-ID: 33493364
http://dx.doi.org/10.1002/lary.29426

Near-Infrared Autofluorescence Imaging May Reduce Temporary Hypoparathyroidism in Patients Undergoing Total Thyroidectomy and Central Neck Dissection.
Thyroid, 31(9):1400-8.
D. H. Kim, S. W. Kim, P. Kang, J. Choi, H. S. Lee, S. Y. Park, Y. Kim, Y. C. Ahn and K. D. Lee. 2021.
Background: Near-infrared autofluorescence (NIRAF) imaging is known to reduce the incidence of post-thyroidectomy hypocalcemia. However, there are no studies on how much NIRAF imaging affects the serum parathyroid hormone (PTH) level after surgery. We investigated the changes of the serum PTH level and ionized calcium (iCa.) in patients undergoing total thyroidectomy with central neck dissection (CND). Materials and Methods: This retrospective study with historical control enrolled 542 patients who underwent total thyroidectomy with CND. Patients were divided into two groups: the NIRAF group (261 patients) and the control group (281 patients). PTH and iCa. levels were measured at the hospital stay, 1, 3, and 6 months after surgery. In addition, the number of identified parathyroid glands (PGs), autotransplanted PGs, and the inadvertent resection rate of PGs was evaluated. Results: The incidence of postoperative hypoparathyroidism (PTH <15 pg/mL) was significantly lower in the NIRAF group during the hospitalization (88 patients: 33.7% vs. 131 patients: 46.6%; p = 0.002) and at 1 month postoperatively (23 patients: 8.8% vs. 53 patients: 18.9%; p = 0.001). There was no difference in the permanent hypoparathyroidism rate (6 months after surgery) between the NIRAF group and the control group (4.2% vs. 4.6%; p = 0.816). There was no difference in the incidence of hypocalcemia (iCa. <1.09 mmol/L) (during hospitalization: 6.5% vs. 10.0%; 1 month: 2.3% vs. 2.5%; 3 months: 0.8% vs. 0.7%; 6 months after surgery: 1.1% vs. 1.1%) between the two groups. The number of inadvertently resected PGs was significantly lower in the NIRAF group (18:6.9% vs. 36:12.8%; p = 0.021). Conclusions: These results suggest that NIRAF imaging may reduce temporary hypoparathyroidism and the risk of inadvertent resection of PGs in patients undergoing total thyroidectomy with CND.
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http://dx.doi.org/10.1089/thy.2021.0056

Looking beyond the cosmetic appeal of transoral thyroidectomy.
Br J Surg, 108(8):875-6.
J. Kim and J. A. Sosa. 2021.
PubMed-ID: 34142113
http://dx.doi.org/10.1093/bjs/znab180

Medullary thyroid cancer with ectopic Cushing's syndrome: A multicentre case series.
Clin Endocrinol (Oxf),
V. F. Koehler, C. T. Fuss, C. M. Berr, K. Frank-Raue, F. Raue, E. Hoster, M. Hepprich, E. Christ, T. Pusl, M. Reincke, C. Spitzweg and M. Kroiss. 2021.
OBJECTIVE: Ectopic Cushing's syndrome (ECS) induced by medullary thyroid cancer (MTC) is rare, and data on clinical characteristics, treatment and outcome are limited. DESIGN: Retrospective cohort study in three German and one Swiss referral centres. PATIENTS: Eleven patients with MTC and occurrence of ECS and 22 matched MTC patients without ECS were included. MEASUREMENTS: The primary endpoint of this study was the overall survival (OS) in MTC patients with ECS versus 1:2 matched MTC patients without ECS. RESULTS: The median age at diagnosis of ECS was 59 years (range: 35-81) and the median time between initial diagnosis of MTC and diagnosis of ECS was 29 months (range: 0-193). Median serum morning cortisol was 49 µg/dl (range: 17-141, normal range: 6.2-18). Eight (73%) patients received treatment for ECS. Treatment of ECS consisted of bilateral adrenalectomy (BADX) in four (36%) patients and adrenostatic treatment in eight (73%) patients. One patient received treatment with multityrosine kinase inhibitor (MKI) to control hypercortisolism. All patients experienced complete resolution of symptoms of Cushing's syndrome and biochemical control of hypercortisolism. Patients with ECS showed a shorter median OS of 87 months (95% confidence interval [95% CI]: 64-111) than matched controls (190 months, 95% CI: 95-285). Of the nine deaths, four were related to progressive disease (PD). Four patients showed PD as well as complications and comorbidities of hypercortisolism before death. CONCLUSION: This study shows that ECS occurs in advanced stage MTC and is associated with a poor prognosis. Adrenostatic treatment and BADX were effective systemic treatment options in patients with MTC and ECS to control their hypercortisolism. MKI treatment achieved complete remission of hypercortisolism and sustained tumour control in one treated case.
PubMed-ID: 34743368
http://dx.doi.org/10.1111/cen.14617

Pre-diagnosis thyroid hormone dysfunction is associated with cancer mortality.
Endocr Relat Cancer, 28(11):705-13.
E. Krashin, B. Silverman, D. M. Steinberg, D. Yekutieli, S. Giveon, O. Fabian, A. Hercbergs, P. J. Davis, M. Ellis and O. Ashur-Fabian. 2021.
Research on the association between thyroid hormone levels and cancer mortality remains limited and inconclusive. We determined the relation of thyroid stimulating hormone (TSH), free T4 (FT4), and free T3 (FT3) levels with mortality in overall cancer and specific tumor types. Thyroid hormone levels 1-5 years prior to cancer diagnosis, as well as multiple clinical and demographic parameters, were retrospectively collected for 10,325 Israeli cancer patients, diagnosed between 2000 and 2016. Patients treated with thyroid altering medications were excluded. Cancer diagnosis was determined via the Israel National Cancer Registry. Multivariate-adjusted Cox proportional hazards model was used to assess the hazard ratios (HRs) based on thyroid hormone function for cancer mortality. A total of 5265 patients died during the follow-up period (median of 4.4 years). TSH, FT4, and FT3 levels in the hypothyroid range were associated with increase in overall mortality (adjusted HR 1.20, 1.74, 1.87, respectively). We further analyzed the association between TSH and mortality in 14 cancer subgroups. Specifically, TSH in both the hyperthyroid and hypothyroid range was associated with melanoma mortality (adjusted HR 2.20, 4.47, respectively). In conclusion, pre-diagnosis of thyroid dysfunction is associated with increased cancer mortality, a relation likely driven by specific cancer types. These findings suggest that thyroid hormones may potentially serve as prognostic markers in cancer.
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http://dx.doi.org/10.1530/ERC-21-0187

The Forks in the Road of Thyroid Eye Disease.
J Clin Endocrinol Metab, 106(12):e5262-e3.
C. C. Krieger. 2021.
PubMed-ID: 34232313
http://dx.doi.org/10.1210/clinem/dgab500

Thyroid Isthmusectomy with Prophylactic Central Compartment Neck Dissection is a Feasible Approach for Papillary Thyroid Cancer on the Isthmus.
Ann Surg Oncol, 28(11):6603-12.
O. Kwon, S. Lee, J. S. Bae and C. K. Jung. 2021.
BACKGROUND: The treatment for papillary thyroid cancer (PTC) has become more conservative, but still no specific guidelines exist for managing isthmic PTC. This study analyzed the outcomes from isthmusectomy in single isthmic PTC and compared it with those for patients who previously had undergone a total thyroidectomy. METHODS: An isthmusectomy with prophylactic central compartment neck dissection (pCCND) was planned for a single isthmic PTC between 2014 and 2018 (isthmusectomy group). For cases with gross extrathyroidal extension (ETE) or multiple nodal metastasis, the procedure was converted to a total thyroidectomy. The study analyzed the characteristics and outcomes of the isthmusectomy group. Additionally, the results were compared with those of the isthmusectomy-feasible group who met the eligibility criteria for isthmusectomy among total thyroidectomies performed between 2009 and 2013. RESULTS: Of the 90 patients in the isthmusectomy group, 81 received isthmusectomy and 9 had conversion to a total thyroidectomy. Microcarcinoma occurred in 72 cases and gross ETE in 3 cases. One patient showed occult satellite cancer, and seven patients showed more than five metastatic nodes. Transient hypocalcemia developed in five and patients and permanent hypocalcemia in one patient with total thyroidectomy. Of 46 patients who began hormone replacement postoperatively, 13 completely stopped taking medication during the follow-up period. Metachronous PTC was diagnosed for one patient 12 months after isthmusectomy. The isthmusectomy group and the isthmusectomy-feasible group showed similar clinicopathologic properties including multifocality, ETE, and nodal metastasis. However, the isthmusectomy group showed significantly less transient or permanent hypocalcemia and thyroid hormone dependency. CONCLUSIONS: Isthmusectomy with pCCND may be a feasible alternative for properly selected isthmic PTC, resulting in a better quality of life than total thyroidectomy.
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http://dx.doi.org/10.1245/s10434-021-09833-y

Thyroid nodules in childhood-onset Hashimoto's thyroiditis: Frequency, risk factors, follow-up course and genetic alterations of thyroid cancer.
Clin Endocrinol (Oxf), 95(4):638-48.
Y. J. Lee, Y. J. Cho, Y. J. Heo, E. J. Chung, Y. H. Choi, J. I. Kim, Y. J. Park, C. H. Shin and Y. A. Lee. 2021.
OBJECTIVE: We evaluated the frequency, risk factors and the follow-up outcomes of thyroid nodules, and genetic alterations in thyroid cancer, in youth with childhood-onset Hashimoto thyroiditis (HT) residing in an iodine-sufficient country. DESIGN: A retrospective cohort study. PATIENTS AND MEASUREMENTS: A total of 213 patients (194 females, mean age 10.6 years at the time of HT diagnosis) were ultrasonographically evaluated. Thyroid nodules were categorized using the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) and the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TI-RADS). RESULTS: Thyroid nodules were detected in 40 (18.8%) patients over a median follow-up period of 3.4 years, usually after the onset of puberty. A family history of thyroid disease (hazard ratio 2.1, p = .031) was predictive of thyroid nodule detection. Papillary thyroid carcinoma (PTC) was diagnosed in 9 (4.2% of all and 22.5% of nodule-positive patients). The malignant nodules had a higher K-TIRADS or ACR-TI-RADS risk level compared with benign nodules (p < .01 for both). Genetic alterations were revealed in 7 (BRAF(V600E) in 6 and RET-ERC1 fusion in 1) of the eight available tumour tissue samples. None showed evidence of disease over a median follow-up period of 3.4 years. CONCLUSIONS: The nodule detection rate was 18.8%, with a 22.5% risk of malignancy among the detected nodules in childhood-onset HT patients, showing increased risk in those with a family history. Additional large-scale studies are required to evaluate the usefulness of K-TIRADS or ACR-TI-RADS risk level for the differentiation of paediatric thyroid nodules.
PubMed-ID: 33894068
http://dx.doi.org/10.1111/cen.14490

Identification of New Rare Variants Associated With Familial Autoimmune Thyroid Diseases by Deep Sequencing of Linked Loci.
J Clin Endocrinol Metab, 106(11):e4680-e7.
C. W. Li, R. Sachidanandam, A. Jayaprakash, Z. Yi, W. Zhang, M. Stefan-Lifshitz, E. Concepcion and Y. Tomer. 2021.
CONTEXT: Genetic risk factors play a major role in the pathoetiology of autoimmune thyroid diseases (AITD). So far, only common risk variants have been identified in AITD susceptibility genes. Recently, rare genetic variants have emerged as important contributors to complex diseases, and we hypothesized that rare variants play a key role in the genetic susceptibility to AITD. OBJECTIVE: We aimed to identify new rare variants that are associated with familial AITD.

METHODS: We performed deep sequencing of 3 previously mapped AITD-linked loci (10q, 12q, and 14q) in a dataset of 34 families in which AITD clustered (familial AITD). RESULTS: We identified 13 rare variants, located in the inositol polyphosphate multikinase (IPMK) gene, that were associated with AITD (ie, both Graves' disease [GD] and Hashimoto's thyroiditis [HT]); 2 rare variants, within the dihydrolipoamide S-succinyltransferase (DLST) and zinc-finger FYVE domain-containing protein (ZFYVE1) genes, that were associated with GD only; and 3 rare variants, within the phosphoglycerate mutase 1 pseudogene 5 (PGAM1P5), LOC105369879, and methionine aminopeptidase 2 (METAP2) genes, that were associated with HT only. CONCLUSION: Our study demonstrates that, in addition to common variants, rare variants also contribute to the genetic susceptibility to AITD. We identified new rare variants in 6 AITD susceptibility genes that predispose to familial AITD. Of these, 3 genes, IPMK, ZFYVE1, and METAP2, are mechanistically involved in immune pathways and have been previously shown to be associated with autoimmunity. These genes predispose to thyroid autoimmunity and may serve as potential therapeutic targets in the future.
PubMed-ID: 34143178
http://dx.doi.org/10.1210/clinem/dgab440

Psychological Distress and Sleep Disturbance Throughout Thyroid Nodule Screening, Diagnosis, and Treatment.
J Clin Endocrinol Metab, 106(10):e4221-e30.
R. Li, G. Li, Y. Wang, T. Bao, Y. Lei, L. Tian, Z. Li, J. Zhu, J. Lei and H. Tang. 2021.
CONTEXT: Many controversies exist regarding screening and treatment of thyroid cancer (TC), especially papillary thyroid microcarcinoma (PTMC). OBJECTIVE: The aim of this study was to evaluate patients' psychological distress and sleep disturbance throughout thyroid nodule (TN) screening, diagnosis, and treatment. METHODS: A total of 2834 participants (1153 participants with TNs) were enrolled during the screening phase, and 1105 individuals with TNs (87 individuals with TC) were enrolled during the diagnosis phase. Of the 87 TC patients, 66 underwent immediate operation (OP), and 21 patients with PTMC opted for active surveillance (AS). Four validated scales were applied to quantify the outcome indicators at prescreening, postscreening, postdiagnosis, and posttreatment. RESULTS: Higher psychological distress and sleep disturbance were found postscreening than prescreening in subjects with TNs, but no differences in those without nodules. Compared with postscreening, higher scores of psychological distress and sleep disturbance were identified in patients with suspicious TC treated with fine needle aspiration (FNA) or with AS. Lower psychological distress and sleep disturbance were noted for patients with benign nodules than for TC patients. OP for TC, especially PTMC, did not alleviate psychological distress or sleep disturbance compared with the same parameters in patients who underwent AS. CONCLUSION: Based on the findings of impaired psychological health and sleep quality, screening for TNs in adults who show no symptoms should be performed with caution. Psychological distress and sleep disturbance should also be taken into consideration when FNA is performed for suspected TC or OP for papillary thyroid cancer, especially PTMC.
PubMed-ID: 33830242
http://dx.doi.org/10.1210/clinem/dgab224

Clinical relevance of serum immunoglobulin G4 in glucocorticoid therapy of Graves' ophthalmopathy.
Clin Endocrinol (Oxf), 95(4):657-67.
Y. Li, B. Luo, J. Zhang, X. Zhou, S. Shao, W. Xu, Y. Yang and G. Yuan. 2021.
OBJECTIVE: Previous study suggested IgG4 levels were associated with the development of Graves' ophthalmopathy (GO). The aims of the present study were to investigate the role of IgG4 levels in glucocorticoid (GC) treatment in GO patients. DESIGN: 69 GO patients were enrolled. Serum thyroid hormones, thyroid antibodies, IgG, IgG4, ophthalmological examinations and orbital MRI were performed. Furthermore, the clinical outcomes (a composite response endpoint including the clinical activity score (CAS), proptosis, vision, intraocular pressure, diplopia and lid width) after high-dose intravenous GC treatment in 32 active moderate-to-severe GO patients were compared. PATIENTS: 69 consecutive patients with GO were asked to participate in the study. 32 of 69 GO patients were treated with high-dose intravenous GCs. MEASUREMENTS: Measurement of serum IgG and IgG4, serum thyroid hormones and thyroid autoantibodies. An overall ophthalmic assessment was performed pretherapy (week 0) and post-therapy (week 12). RESULTS: 33.3% of GO patients (23/69) had elevated IgG4 levels. IgG4 levels were positively correlated with the severity and activity of GO. After GC therapy, IgG4, IgG4/IgG, vision and CAS were significantly improved in GO patients. Patients with high IgG4 levels had a significantly reduced extraocular muscle area (EOMs) and better clinical outcomes than patients with normal IgG4 levels. CONCLUSIONS: Our results suggest a possible subgroup of elevated IgG4 GO patients, with more severe ophthalmopathy and better response to GCs treatment compare with normal IgG4 GO patients.
PubMed-ID: 33938028
http://dx.doi.org/10.1111/cen.14493

Indeterminate Thyroid Nodules: The Hazy Genomic Landscape Coming into Focus.
J Clin Endocrinol Metab, 106(11):e4781-e3.
A. L. Limbach and J. A. Sipos. 2021.
PubMed-ID: 34139768
http://dx.doi.org/10.1210/clinem/dgab441

A prediction model incorporating the BRAF(V600E) protein status for determining the risk of cervical lateral lymph node metastasis in papillary thyroid cancer patients with central lymph node metastasis.
Eur J Surg Oncol, 47(11):2774-80.
S. Liu, C. Liu, L. Zhao, K. Wang, S. Li, Y. Tian, B. Jiao, Z. Gui, T. Yu and L. Zhang. 2021.
BACKGROUND AND OBJECTIVES: Cervical lateral lymph node metastasis (LLNM) is a predictor of poor prognosis for papillary thyroid carcinoma (PTC) patients. However, the risk factors for LLNM remain unclear. The purpose of the study was to examine the risk factors for LLNM and construct a prediction model. METHODS: With Ethics Committee approval, a total of 1198 PTC patients were retrospectively included in our study. Univariate and multivariate analyses were performed to explore the relationship between clinicopathological characteristics and LLNM. A nomogram for predicting LLNM in PTC patients with central lymph node metastasis (CLNM) was constructed and validated. RESULTS: The negative BRAF(V600E) protein expression was significantly correlated with positive LLNM status in PTC patients. In PTC patients with CLNM, the number of metastatic central lymph nodes (LNN) = 3 and the ratio of metastatic central lymph nodes (LNR) = 0.565 were found to be significantly associated with positive LLNM status. The nomogram for predicting LLNM risk in PTC patients with CLNM incorporated four risk factors: tumor size, the BRAF(V600E) protein expression, LNN and LNR. The prediction model showed excellent discrimination, with a C-index of 0.714. CONCLUSIONS: The negative BRAF(V600E) protein expression was more likely to lead to LLNM. LNN =3 and LNR =0.565 were associated with LLNM risk in PTC patients with CLNM. Our nomogram might assist clinicians in developing individual suitable follow-up strategies for PTC patients with CLNM.
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http://dx.doi.org/10.1016/j.ejso.2021.08.033

Metastatic Risk Profile of Microscopic Lymphatic and Venous Invasion in Medullary Thyroid Cancer.
Horm Metab Res, 53(9):588-93.
A. Machens, K. Lorenz, F. Weber and H. Dralle. 2021.
The metastatic risk profile of microscopic lymphatic and venous invasion in medullary thyroid cancer is ill-defined. This evidence gap calls for evaluation of the suitability of microscopic lymphatic and venous invasion at thyroidectomy for prediction of lymph node and distant metastases in medullary thyroid cancer. In this study of 484 patients with medullary thyroid cancer who had=5 lymph nodes removed at initial thyroidectomy, microscopic lymphatic and venous invasion were significantly associated with greater primary tumor size (27.6 vs. 14.5 mm, and 30.8 vs. 16.2 mm) and more frequent lymph node metastasis (97.0 vs. 25.9%, and 85.2 vs. 39.5%) and distant metastasis (25.0 vs. 5.1%, and 32.8 vs. 7.3%). Prediction of lymph node metastases by microscopic lymphatic invasion was better than prediction of distant metastases by microscopic venous invasion regarding sensitivity (97.0 vs. 32.8%) and positive predictive value (58.4 vs. 39.2%); comparable regarding negative predictive value (98.5 vs. 90.5%) and accuracy (80.4 vs. 85.1%); and worse regarding specificity (74.1 vs. 92.7%). On multivariable logistic regression, microscopic lymphatic invasion predicted lymph node metastasis better (odds ratio [OR] 65.6) than primary tumor size (OR 4.6 for tumors>40 mm and OR 2.7 for tumors 21-40 mm, relative to tumors=20 mm), whereas primary tumor size was better in predicting distant metastasis (OR 8.3 for tumors>40 mm and OR 3.9 for tumors 21-40 mm, relative to tumors=20 mm) than microscopic venous invasion (OR 3.2). These data show that lymphatic invasion predicts lymph node metastases better in medullary thyroid cancer than venous invasion heralds distant metastases.
PubMed-ID: 34496409
http://dx.doi.org/10.1055/a-1559-3424

Novel Anaplastic Thyroid Cancer PDXs and Cell Lines: Expanding Preclinical Models of Genetic Diversity.
J Clin Endocrinol Metab, 106(11):e4652-e65.
A. Maniakas, Y. C. Henderson, H. Hei, S. Peng, Y. Chen, Y. Jiang, S. Ji, M. Cardenas, Y. Chiu, D. Bell, M. D. Williams, M. C. Hofmann, S. E. Scherer, D. A. Wheeler, N. L. Busaidy, R. Dadu, J. R. Wang, M. E. Cabanillas, M. Zafereo, F. M. Johnson and S. Y. Lai. 2021.
CONTEXT: Anaplastic thyroid cancer (ATC) is a rare, aggressive, and deadly disease. Robust preclinical thyroid cancer models are needed to adequately develop and study novel therapeutic agents. Patient-derived xenograft (PDX) models

may resemble patient tumors by recapitulating key genetic alterations and gene expression patterns, making them excellent preclinical models for drug response evaluation. OBJECTIVE: We developed distinct ATC PDX models concurrently with cell lines and characterized them in vitro and in vivo. METHODS: Fresh thyroid tumor from patients with a preoperative diagnosis of ATC was surgically collected and divided for concurrent cell line and PDX model development. Cell lines were created by generating single cells through enzymatic digestion. PDX models were developed following direct subcutaneous implantation of fresh tumor on the flank of immune compromised/athymic mice. RESULTS: Six ATC PDX models and 4 cell lines were developed with distinct genetic profiles. Mutational characterization showed one BRAF/TP53/CDKN2A, one BRAF/CDKN2A, one BRAF/TP53, one TP53 only, one TERT-promoter/HRAS, and one TERT-promoter/KRAS/TP53/NF2/NFE2L2 mutated phenotype. Hematoxylin-eosin staining comparing the PDX models to the original patient surgical specimens show remarkable resemblance, while immunohistochemistry stains for important biomarkers were in full concordance (cytokeratin, TTF-1, PAX8, BRAF). Short tandem repeats DNA fingerprinting analysis of all PDX models and cell lines showed strong concordance with the original tumor. PDX successful establishment rate was 32%. CONCLUSION: We have developed and characterized 6 novel ATC PDX models with 4 matching cell lines. Each PDX model harbors a distinct genetic profile, making them excellent tools for preclinical therapeutic trials.
PubMed-ID: 34147031
http://dx.doi.org/10.1210/clinem/dgab453

Assessing Intraoperative Laser Speckle Contrast Imaging of Parathyroid Glands in Relation to Total Thyroidectomy Patient Outcomes.
Thyroid, 31(10):1558-65.
E. A. Mannoh, G. Thomas, N. Baregamian, S. L. Rohde, C. C. Solórzano and A. Mahadevan-Jansen. 2021.
Background: Accurate assessment of parathyroid gland vascularity is important during thyroidectomy to preserve the function of parathyroid glands and to prevent postoperative hypocalcemia. Laser speckle contrast imaging (LSCI) has been shown to be accurate in detecting differences in parathyroid vascularity. In this surgeon-blinded prognostic study, we evaluate the relationship between intraoperative LSCI measurements and postoperative outcomes of total thyroidectomy patients. Methods: Seventy-two thyroidectomy patients were included in this study. After thyroid resection, an LSCI device was used to image all parathyroid glands identified, and a speckle contrast value was calculated for each. An average value was calculated for each patient, and the data were grouped according to whether the patient had normal (16-77 pg/mL) or low levels of parathyroid hormone (PTH) measured on postoperative day 1 (POD1). The aim of this study was to establish a speckle contrast threshold for classifying a parathyroid gland as adequately perfused and to determine how many such glands are required for normal postoperative parathyroid function. Results: A speckle contrast limit of 0.186 separated the normoparathyroid and hypoparathyroid groups with 87.5% sensitivity and 84.4% specificity: 7 of 8 patients with low PTH on POD1 had an average parathyroid speckle contrast above this limit, while 54 of 64 patients with normal postoperative PTH had an average parathyroid speckle contrast below this limit. Taking this value as the threshold for adequate parathyroid perfusion, it was determined that only one vascularized gland was needed for normal postoperative parathyroid function: 64 of 69 patients (92.8%) with at least one vascularized gland (determined by LSCI) had normal postoperative PTH, while all 3 patients (100%) with no vascularized glands had low postoperative PTH. Overall, the rates of temporary and permanent hypoparathyroidism in this study were 8.3% and 1.4%, respectively. Conclusions: LSCI is a promising technique for assessing parathyroid gland vascularity. It has the potential to help reduce the incidence of hypocalcemia after thyroidectomy by providing surgeons with additional information during surgery to aid in the preservation of parathyroid function.
PubMed-ID: 34078120
http://dx.doi.org/10.1089/thy.2021.0093

Partial Versus Total Thyroidectomy: What Influences Most Surgeons' Decision? Analysis of a Nationwide Cohort of 375,810 Patients Over 10 Years.
Ann Surg, 274(5):829-35.
C. Marciniak, X. Lenne, G. Clément, A. Bruandet, J. C. Lifante, F. Sebag, E. Mirallié, M. Mathonnet, L. Brunaud, G. Donatini, C. Tresallet, F. Ménégaux, D. Theis, F. Pattou and R. Caiazzo. 2021.
National and international guidelines about thyroid surgery seem to be moving more and more towards less radical surgical procedures but everyday practice does not seem to always align with them. We describe for the first time the role of non-surgical parameters in the surgeon's choice for thyroid surgery. OBJECTIVE: The ain of this study was to describe thyroid surgery and to identify the factors leading to either a total or a partial thyroidectomy regardless of the severity of the thyroid disease. SUMMARY BACKGROUND DATA: National and international guidelines about thyroid surgery seem to be moving more and more toward less radical surgical procedures but everyday practice does not seem to always align

with them. METHODS: We based this nationwide retrospective cohort study on a national database that compiles discharge abstracts for every admission for thyroidectomy to French acute healthcare facilities (PMSI database 2010 to 2019). RESULTS: In this study, 375,810 patients (male: 23%; age = 53 ± 15 years) had a thyroidectomy (partial: 28%) for cancer (17%), hyperthyroidism (16%), nonfunctioning goiter (64%), or other (3%). We noticed a global trend toward more partial thyroidectomy (P < 0.001) with a significant increase in the proportion of lobectomy in the post-ATA recommendations' period (P < 0.001) as well as in the "French Levothyrox crisis" period, in which we saw an unexpected rise of adverse events notifications associated with the marketing of a new formula of Levothyrox (P < 0.001) amid widespread media coverage. In a multivariate analysis, we also identified that complete resection was more frequently performed in centers with a caseload >40/year [P < 0.001, odds ratio (OR) = 1.48], for obese patients (body mass index >30 kg/m2; P < 0.001, OR = 1.42), and according to the indication of surgery (OR benign = 1, OR cancer = 2.25, OR hyperthyroidism = 4.13). CONCLUSION: We describe for the first time the role of non-surgical parameters in the surgeon's choice for thyroid surgery.
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http://dx.doi.org/10.1097/SLA.0000000000005134

A Closer Look at "Taller-Than-Wide" Thyroid Nodules: Examining Dimension Ratio to Predict Malignancy.
Otolaryngol Head Neck Surg:1945998211051310.
A. S. Mattingly, J. E. Noel and L. A. Orloff. 2021.
OBJECTIVE: To evaluate nodule height-to-width ratio as a continuous variable predicting likelihood of thyroid malignancy. STUDY DESIGN: Retrospective cohort study. SETTING: All study information was collected from a single academic tertiary care hospital. METHODS: Subjects included adult patients with thyroid nodules who underwent thyroid surgery between 2010 and 2020. The following variables were collected: patient demographics, nodule dimensions via ultrasound, fine-needle aspiration biopsy results, and surgical pathology results. Statistical analysis included logistic regression modeling malignancy with variables of interest. We used a receiver operating characteristic curve to assess the discriminatory value of variables. RESULTS: Height-to-width ratio, as a continuous variable, was associated with malignancy (with each 0.1 increase in ratio; odds ratio [OR], 1.25; 95% CI, 1.14-1.37). The same relationship was true for height-to-length ratio (OR, 1.36; 95% CI, 1.24-1.56). The area under the receiver operating characteristic curve for height-to-width ratio was 63.7%. In line with current emphasis on the transverse ultrasound view, we determined 4 different height-to-width ratio intervals: <0.8, 0.8 to <1.0, 1.0 to <1.5, and =1.5. Likelihood ratios of malignancy for each interval were 0.6, 1.0, 2.3, and 4.9, respectively. CONCLUSION: Our results support the association between greater height-to-width ratio and malignancy but suggest that a multilevel rather than binary variable improves prediction. The likelihood ratios at different intervals give a more nuanced view of how height-to-width ratio predicts malignancy. With continuing review of guidelines for thyroid nodule biopsy, it is important to consider these data for any point total attributed to shape.
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http://dx.doi.org/10.1177/01945998211051310

Multifocality and Progression of Papillary Thyroid Microcarcinoma During Active Surveillance.
World J Surg, 45(9):2769-76.
R. Nagaoka, A. Ebina, K. Toda, T. Jikuzono, M. Saitou, M. Sen, H. Kazusaka, M. Matsui, K. Yamada, H. Mitani and I. Sugitani. 2021.
BACKGROUND: Prospective trials of active surveillance (AS) have shown low rates of progression in low-risk papillary thyroid microcarcinoma (PTMC; T1aN0M0). However, the significance of multifocality as a prognostic factor remains controversial. METHODS: Data from 571 patients (mean age, 53.1 years; 495 females) who underwent AS were reviewed. PTMC was unifocal in 457 patients (80.0%) and multifocal in 114 patients (20.0%), with 2-5 lesions each (261 tumors in total). Tumor progression was defined as tumor size enlargement = 3 mm and/or development of clinically evident lymph node metastasis (LNM). RESULTS: After a mean duration of AS of 7.6 years, 53 patients (9.3%) showed tumor enlargement and 8 patients (1.4%) developed LNM. The 10-year progression rate was 13.1%. Age, sex, and calcification pattern did not differ significantly between uni- and multifocal diseases. However, anti-thyroglobulin antibody and/or anti-thyroid peroxidase antibody was more frequently positive with multifocal PTMCs (46.7%) than with unifocal disease (34.4%, p = 0.024). Patients with uni- and multifocal disease showed no significant differences in 10-year rate of tumor enlargement (11.4% vs. 14.8%), LNM development (1.1% vs. 2.4%), or progression (12.4% vs 15.9%). Multivariate analysis of predictors for progression showed multifocality was not a significant risk factor (odds ratio, 1.45; 95% confidence interval, 0.79-2.54; p = 0.22). Eventually, 9 patients (7.9%) with multifocal PTMCs underwent surgery and 7 needed total thyroidectomy, although 7 still showed T1N0M0 low-risk cancer. CONCLUSIONS: Even patients with multiple PTMCs (T1amN0M0) are good candidates for AS. Many patients can avoid total thyroidectomy and subsequent surgical complications.

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http://dx.doi.org/10.1007/s00268-021-06185-2

Bilateral Central Neck Dissection via Transoral Approach in Papillary Thyroid Carcinoma.
Ann Surg Oncol, 29(3):1973-4.
D. Q. Ngo, D. T. Le, Q. X. Ngo and Q. V. Le. 2022.
BACKGROUND: The transoral endoscopic vestibular approach (TOETVA) for thyroidectomy is gaining popularity (Russell et al. in Thyroid 28(7):825-829, 2018; Le et al. in Surg Laparosc Endosc Percutan Tech 30(3):209-213, 2020; Liao et al. in Laryngoscope 130(6):1603-1608, 2020). TOETVA has been utilized successfully in performing thyroidectomy, parathyroidectomy, and neck dissection, via both endoscopic and robotic techniques (Razavi et al. in Head Neck 40(10):2246-2253, 2018; Otolaryngol Head Neck Surg 159(4):625-629, 2018; Ngo et al. in J ENT, 2020. https://doi.org/10.1177/0145561320943358 ; Ann Surg Oncol 28(5):2766, 2021). In this video, we show bilateral central neck dissection via transoral approach in papillary thyroid carcinoma. PATIENT AND METHODS: A 37-year-old female with no significant medical history was diagnosed pT3bN0M0 intraoperatively with the tumor having slightly invaded the strap muscle. Thus, we decided to perform total thyroidectomy with bilateral central neck dissection via transoral approach. METHODS: Prelaryngeal dissection: in the prelaryngeal compartment, soft tissue containing these lymph nodes was intimately associated with the pyramidal lobe. Right paratracheal dissection: fibrofatty tissue was dissected off the prevertebral fascia and the trachea with preservation of right parathyroid glands. Pretracheal lymph nodes were removed with paratracheal dissection. Left paratracheal dissection: the lymphatic tissue was then dissected off the prevertebral and esophageal musculature and the trachea after identifying the left parathyroid glands. Finally, bilateral central neck dissection was finished with preservation of the nerve and parathyroid glands. RESULTS: The operation was completed successfully without conversion to open surgery. The operative time for central neck dissection was 20 min. There were nine harvested lymph nodes in the central compartments, while there were two metastatic lymph nodes of papillary thyroid carcinoma with 3 × 3 mm maximal dimension. There were no major postoperative complications. CONCLUSION: Central neck dissection via TOETVA is a safe and feasible method in selected patients.
PubMed-ID: 34694524
http://dx.doi.org/10.1245/s10434-021-10996-x

Recurrence of Papillary Thyroid Cancer: A Systematic Appraisal of Risk Factors.
J Clin Endocrinol Metab,
H. R. Nieto, C. E. M. Thornton, K. Brookes, A. N. de Menezes, A. Fletcher, M. Alshahrani, M. Kocbiyik, N. Sharma, K. Boelaert, J. B. Cazier, H. Mehanna, V. E. Smith, M. L. Read and C. J. McCabe. 2021.
BACKGROUND: Thyroid cancer recurrence is associated with increased mortality and adverse outcomes. Recurrence risk is currently predicted using clinical tools, often restaging patients after treatment. Detailed understanding of recurrence risk at disease-onset could lead to personalised and improved patient care. OBJECTIVE: To perform a comprehensive bioinformatic and experimental analysis of 3 levels of genetic change (mRNA, microRNA, and somatic mutation) apparent in recurrent tumours and construct a new combinatorial prognostic risk model. METHODS: We analysed The Cancer Genome Atlas data (TCGA) to identify differentially expressed genes (mRNA/microRNA) in 46 recurrent versus 455 non-recurrent thyroid tumours. Two exonic mutational pipelines were used to identify somatic mutations. Functional gene analysis was performed in cell-based assays in multiple thyroid cell lines. The prognostic value of genes was evaluated with TCGA datasets. RESULTS: We identified a total of 128 new potential biomarkers associated with recurrence, including 40 mRNAs, 39 miRNAs and 59 genetic variants. Among differentially expressed genes, modulation of FN1, ITGa3 and MET had a significant impact on thyroid cancer cell migration. Similarly, ablation of miR-486 and miR-1179 significantly increased migration of TPC-1 and SW1736 cells. We further utilised genes with a validated functional role and identified a 5 gene risk score classifier as an independent predictor of thyroid cancer recurrence. CONCLUSIONS: Our newly proposed risk model based on combinatorial mRNA and microRNA expression has potential clinical utility as a prognostic indicator of recurrence. These findings should facilitate earlier prediction of recurrence with implications for improving patient outcome by tailoring treatment to disease risk and increasing post-treatment surveillance.
PubMed-ID: 34791326
http://dx.doi.org/10.1210/clinem/dgab836

Can TP53-mutant follicular adenoma be a precursor of anaplastic thyroid carcinoma?
Endocr Relat Cancer, 28(9):621-30.
A. V. Nikitski, M. N. Nikiforova, L. Yip, E. Karslioglu-French, S. E. Carty and Y. E. Nikiforov. 2021.
Mutations of the TP53 tumor suppressor gene are highly prevalent in thyroid anaplastic carcinomas (AC) but are also

reported in some well-differentiated cancers and even in benign adenomas. The natural history of TP53-mutant adenomas and whether they may represent a precursor for well-differentiated cancer or AC is largely unknown. Similarly, the frequency of TP53 mutations in thyroid nodules found on routine molecular analysis of fine-needle aspiration (FNA) samples is not established. A database on 44,510 FNA samples from thyroid nodules with predominantly indeterminate cytology tested using ThyroSeq v3 was reviewed to identify TP53-mutant cases and analyze their genetic profile and available clinicopathological findings. Among 260 (0.6%) selected thyroid nodules, 36 had an isolated TP53 mutation and 224 carried a combination of TP53 with other genetic alterations. No significant difference was observed between these groups with respect to patient age, gender, nodule size, and spectrum of TP53 mutations. Histopathologically, 86% of the resected nodules with isolated TP53 mutations were benign (mostly adenomas), whereas 82% of nodules carrying TP53 mutations co-occurring with other alterations were cancers (P = 0.001), including de-differentiated AC. TP53-mutant benign tumors and well-differentiated cancers often had scattered single neoplastic cells with bizarre nuclei resembling those comprising AC. Our study demonstrates that a small but distinct proportion of thyroid nodules carry a TP53 mutation, either as a single genetic event or in combination with other alterations. While the latter is mostly cancers prone to dedifferentiation, there is at least a theoretical possibility that TP53-mutated adenomas may represent a precursor for such cancers, including AC.
PubMed-ID: 34264855
http://dx.doi.org/10.1530/ERC-21-0095

A Population-Based Analysis of Outpatient Thyroidectomy: Safe and Under-Utilized.
Laryngoscope, 131(11):2625-33.
C. W. Noel, R. Griffiths, J. Siu, D. Forner, D. Urbach, J. Freeman, D. P. Goldstein, J. C. Irish, K. M. Higgins, K. Devon, J. D. Pasternak and A. Eskander. 2021.
OBJECTIVES/HYPOTHESIS: Performance of thyroidectomy on an outpatient basis has gained popularity although many jurisdictions have not shifted their practice despite a strong safety profile. We sought to assess the uptake and safety of outpatient thyroidectomy in Ontario. STUDY DESIGN: Retrospective cohort study. METHODS: This was a population-based retrospecive cohort of adult patients undergoing hemithyroidectomy or total thyroidectomy between 1993 and 2017 in Ontario, Canada. Outpatient surgery was defined as discharge home on the same day of surgery. Outcomes of interest include 30-day all cause death, hematoma, emergency department use, and readmission. To adjust for confounding, propensity scores were calculated. Logistic regression models with inverse probability of treatment weighting (IPTW) were then used to estimate the exposure-outcome relationship. RESULTS: The final cohort consisted of 81,199 patients: 8,442 underwent same day surgery and 72,757 were admitted. The proportion of patients undergoing outpatient thyroidectomy increased overtime (2.3% in 1993-1994 to 17.8% in 2016-2017). Factors associated with higher odds of outpatient thyroidectomy included: younger age, less material deprivation, less comorbidities, and higher surgeon volume. The absolute number of deaths (=5) and hematomas (64, 0.8%) in the outpatient cohort was low. After IPTW adjustment, patients with outpatient management had lower odds of neck hematoma (OR 0.73[95CI% 0.58-0.93)], but higher odds of emergency department use (OR 1.67[95%CI 1.56-1.79]). CONCLUSIONS: Outpatient thyroidectomy is not associated with an increased mortality risk. Less than one in five patients undergo outpatient thyroidectomy in Ontario, despite a well-established safety profile. LEVEL OF EVIDENCE: 3 Laryngoscope, 131:2625-2633, 2021.
PubMed-ID: 34378810
http://dx.doi.org/10.1002/lary.29816

Reduction of overtreatment without reduction of overdiagnosis in patients with differentiated thyroid cancer: mission impossible.
Langenbecks Arch Surg, 406(6):2011-7.
T. Oblak, A. Perhavec, M. Hocevar and B. Peric. 2021.
PURPOSE: Lateral neck nodal metastases are common in patients with differentiated thyroid cancer (DTC) and usually have an indolent nature. They may be detected via neck palpation or preoperative ultrasound (US) of the neck. We hypothesized that preoperative neck metastases detected with US did not affect regional recurrence or long-term survival. METHODS: A retrospective analysis of patients' records treated for DTC at our institution between January 2006 and December 2016 was performed. Information about preoperative US of the neck, treatment, demographics, staging, and histopathology was obtained. The endpoints for the study were nodal recurrence and survival. Differences in survival were analyzed between three groups of patients divided by presence or lack of preoperative US and/or palpable cervical lymph nodes (PLN). Furthermore, the prognostic value of multiple variables was tested by univariate and multivariate analysis. RESULTS: There were 1108 patients with DTC, 221 males and 887 females. The median age was 48.3 years (range 3 to 86), the median time of observation was 68 months (range 0 to 142). Eight hundred sixty-two patients without PLN or

preoperative US represented group 1, 112 patients with PLN were in group 2, and 134 patients without PLN and with preoperative US were in group 3. Only five patients had a regional recurrence, one died due to distant metastases. There was no statistically significant difference in survival between the groups (p = 0.841) and neck US was not significantly associated with overall survival neither in univariate nor in multivariate analysis. CONCLUSION: In patients with DTC, the benefits of preoperative US of cervical lymph nodes are probably limited and "less is more" approach is advised.
PubMed-ID: 34097134
http://dx.doi.org/10.1007/s00423-021-02216-7

Transoral endoscopic thyroidectomy by a vestibular approach: cadaver simulation experience and ethicolegal issues.
Br J Surg, 108(12):e396-e7.
A. Oliva, S. Grassi, N. Minelli, M. Zedda, V. Arena, N. Romaniello, G. Dionigi, Ö. Makay, C. De Crea, S. Celik, A. G. Spagnolo, R. Bellantone and M. Raffaelli. 2021.
PubMed-ID: 34570184
http://dx.doi.org/10.1093/bjs/znab325

Predicting risk factors of postoperative hypocalcemia after total thyroidectomy: is safe discharge without supplementation possible? A large cohort study.
Langenbecks Arch Surg, 406(7):2425-31.
N. C. Paladino, C. Guérin, J. Graziani, I. Morange, A. Loundou, D. Taïeb and F. Sebag. 2021.
PURPOSE: With increasing economic pressures to shorten the length of hospital stay, there has been much recent interest in studying risk factors for the development of postoperative hypocalcemia after total thyroidectomy. The aim of this study was to investigate whether serum calcium and/or PTH levels can predict post-thyroidectomy hypoparathyroidism. METHODS: From January to December 2014, 477 consecutive patients undergoing total thyroidectomy were included. Corrected calcemia and PTH were systematically performed on postoperative day 1/(POD1). Symptomatic patients were treated on POD1 or POD2 with calcium and vitamin D. RESULTS: Sixty-eight patients (14.25%) were treated for postoperative hypocalcemia. No patients with calcemia = 2.16 mmol/l and PTH = 1.9 pmol/l were supplemented and therefore were safely discharged on POD1 (specificity = 100%). All patients with calcemia = 1.89 mmol/l were treated regardless the PTH values (n = 10) (specificity = 100%). For calcium value between 1.9 and 2.16 mmol/l with a PTH > 4.7 pmol/l, nobody was treated. With a calcemia between 1.9 and 2.16 mmol/l and a PTH > 1.9 pmol/l, 44 patients did not develop any symptom. ROC curve analysis showed that combination of Cac = 2.16 mmol/l and iPTH = 4.7 pmol/l provided a sensitivity of 97.06% and a specificity of 76.53% (p < 0.0001). We therefore propose an algorithm that would allow to 70% of patients could have been discharged on POD1 without risk of hypocalcemia or overtreatment. CONCLUSION: Combination of corrected calcemia and PTH on POD1 can efficiently predict hypocalcemia and be integrated into clinical practice for personalizing lengths of hospitalization and appropriate treatment. TRIAL REGISTRATION: ClinicalTrials.gov PRS. Unique Identifying number or registration ID: NCT04372225.
PubMed-ID: 34374848
http://dx.doi.org/10.1007/s00423-021-02237-2

Thyroid Hormone Therapy and Incident Stroke.
J Clin Endocrinol Metab, 106(10):e3890-e900.
M. Papaleontiou, D. A. Levine, D. Reyes-Gastelum, S. T. Hawley, M. Banerjee and M. R. Haymart. 2021.
CONTEXT: Stroke is a leading cause of death and disability and there is a need to identify modifiable risk factors. OBJECTIVE: We aimed to determine the relationship between thyroid hormone treatment intensity and incidence of atrial fibrillation and stroke. METHODS: We conducted a retrospective cohort study using data from the Veterans Health Administration between 2004 and 2017, with a median follow-up of 59 months. The study population comprised 733 208 thyroid hormone users aged =18 years with at least 2 thyroid stimulating hormone (TSH) measurements between thyroid hormone initiation and incident event (atrial fibrillation or stroke) or study conclusion (406 030 thyroid hormone users with at least 2 free thyroxine [T4] measurements). RESULTS: Overall, 71 333/643 687 (11.08%) participants developed incident atrial fibrillation and 41 931/663 809 (6.32%) stroke. In multivariable analyses controlling for pertinent factors such as age, sex, and prior history of atrial fibrillation, higher incidence of stroke was associated with low TSH or high free T4 levels (ie, exogenous hyperthyroidism; eg, TSH <0.1 mIU/L; OR 1.33; 95% CI, 1.24-1.43; free T4>1.9 ng/dL, OR 1.17, 95% CI 1.06-1.30) and high TSH or low free T4 levels (ie, exogenous hypothyroidism; eg, TSH >5.5 mIU/L; OR 1.29; 95% CI, 1.26-1.33; free T4 <0.7 ng/dL; OR 1.29; 95% CI, 1.22-1.35) compared with euthyroidism (TSH >0.5-5.5 mIU/L and free T4 0.7-1.9 ng/dL). Risk of developing atrial fibrillation and stroke was cumulative over time for both patients with exogenous hyperthyroidism and hypothyroidism. CONCLUSION: Both exogenous hyper- and hypothyroidism were associated with

increased risk of stroke, highlighting the importance of patient medication safety.
PubMed-ID: 34137866
http://dx.doi.org/10.1210/clinem/dgab444

Whole-genome Sequencing of Follicular Thyroid Carcinomas Reveal Recurrent Mutations in MicroRNA Processing Subunit DGCR8.
J Clin Endocrinol Metab, 106(11):3265-82.
J. O. Paulsson, N. Rafati, S. DiLorenzo, Y. Chen, F. Haglund, J. Zedenius and C. C. Juhlin. 2021.
BACKGROUND: The genomic and transcriptomic landscape of widely invasive follicular thyroid carcinomas (wiFTCs) and Hürthle cell carcinoma (HCC) are poorly characterized, and subsets of these tumors lack information on genetic driver events. OBJECTIVE: The aim of this study was to bridge this gap. METHODS: We performed whole-genome and RNA sequencing and subsequent bioinformatic analyses of 11 wiFTCs and 2 HCCs with a particularly poor prognosis, and matched normal tissue. RESULTS: All wiFTCs exhibited one or several mutations in established thyroid cancer genes, including TERT (n = 4), NRAS (n = 3), HRAS, KRAS, AKT, PTEN, PIK3CA, MUTYH, TSHR, and MEN1 (n = 1 each). MutSig2CV analysis revealed recurrent somatic mutations in FAM72D (n = 3, in 2 wiFTCs and in a single HCC), TP53 (n = 3, in 2 wiFTCs and a single HCC), and EIF1AX (n = 3), with DGCR8 (n = 2) as borderline significant. The DGCR8 mutations were recurrent p.E518K missense alterations, known to cause familial multinodular goiter via disruption of microRNA (miRNA) processing. Expression analyses showed reduced DGCR8 messenger RNA expression in FTCs in general, and the 2 DGCR8 mutants displayed a distinct miRNA profile compared to DGCR8 wild-types. Copy number analyses revealed recurrent gains on chromosomes 4, 6, and 10, and fusion gene analyses revealed 27 high-quality events. Both HCCs displayed hyperploidy, which was fairly unusual in the FTC cohort. Based on the transcriptome data, tumors amassed in 2 principal clusters. CONCLUSION: We describe the genomic and transcriptomic landscape in wiFTCs and HCCs and identify novel recurrent mutations and copy number alterations with possible driver properties and lay the foundation for future studies.
PubMed-ID: 34171097
http://dx.doi.org/10.1210/clinem/dgab471

[Is there an indication for thyroidectomy in cases of minimally invasive follicular thyroid carcinoma?].
Chirurg,
S. Peth, R. Hummel, M. Schreckenberger, A. Schad, R. Raabe and T. Weber. 2021.
PubMed-ID: 34936001
http://dx.doi.org/10.1007/s00104-021-01553-z

Tall cell percentage alone in PTC without aggressive features should not guide patients' clinical management.
J Clin Endocrinol Metab, 106(10):e4109-e17.
A. M. Poma, D. Viola, E. Macerola, A. Proietti, E. Molinaro, D. De Vietro, R. Elisei, G. Materazzi, P. Miccoli, F. Basolo and C. Ugolini. 2021.
CONTEXT: Recent diagnostic criteria updates of the tall cell variant of papillary thyroid carcinoma (TCPTC) by the World Health Organization (WHO) have determined the inclusion of tumors with 30% to 49% of tall cells. However, the impact of tall cell percentage on papillary thyroid carcinoma (PTC) patients' prognosis is still debated. OBJECTIVE: We aimed to evaluate whether tall cell percentage affects patient outcome in the absence of aggressive features. METHODS: Rates of aggressive features, recurrence-free survival (RFS), and distant RFS (5-year median follow-up) were compared among tumors with less than 30%, 30% to 49% and at least 50% tall cells. We also evaluated the impact of the new tall cell cutoff on patient management. RESULTS: Overall, 3092 tumors (15.7% of all PTCs) were collected: A total of 792 PTCs had less than 30%, 503 had 30% to 49%, and 1797 had 50% or more tall cell areas. With the new WHO definition, the number of TCPTCs increased by 28%. There were no differences in recurrence rates according to tall cell percentage. The coexistence of BRAF and TERT promoter mutations predicted a worse RFS. Considering the new definition of TCPTC, the level of risk according to the American Thyroid Association increased from low to intermediate in 4.2% of cases. However, the recurrence rate within this subgroup was comparable to low risk. CONCLUSION: TCPTC and PTC with tall cell areas can be considered as a unique group with similar recurrence risk. However, whenever aggressive features are absent, tumors have a low risk of recurrence independently of tall cell percentage.
PubMed-ID: 34061965
http://dx.doi.org/10.1210/clinem/dgab388

Prognostic Performance of Alternative Lymph Node Classification Systems for Patients with Medullary Thyroid Cancer: A Single Center Cohort Study.
Ann Surg Oncol, 29(4):2561-9.
D. Prassas, A. Kounnamas, K. Cupisti, M. Schott, W. T. Knoefel and A. Krieg. 2022.
BACKGROUND: Lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS) have been proposed as alternative lymph node (LN) classification schemes. Various cut-off values have been defined for each system, with the question of the most appropriate for patients with medullary thyroid cancer (MTC) still remaining open. We aimed to retrospectively compare the predictive impact of different LN classification systems and to define the most appropriate set of cut-off values regarding accurate evaluation of overall survival (OS) in patients with MTC. METHODS: 182 patients with MTC who were operated on between 1985 and 2018 were extracted from our medical database. Cox proportional hazards regression models and C-statistics were performed to assess the discriminative power of 28 LNR and 28 LODDS classifications and compare them with the N category according to the 8th edition of the AJCC/UICC TNM classification in terms of discriminative power. Regression models were adjusted for age, sex, T category, focality, and genetic predisposition. RESULTS: High LNR and LODDS are associated with advanced T categories, distant metastasis, sporadic disease, and male gender. In addition, among 56 alternative LN classifications, only one LNR and one LODDS classification were independently associated with OS, regardless of the presence of metastatic disease. The C-statistic demonstrated comparable results for all classification systems showing no clear superiority over the N category. CONCLUSION: Two distinct alternative LN classification systems demonstrated a better prognostic performance in MTC patients than the N category. However, larger scale studies are needed to further verify our findings.
PubMed-ID: 34890024
http://dx.doi.org/10.1245/s10434-021-11134-3

Tobacco smoking and risk of thyroid cancer according to BRAF(V600E) mutational subtypes.
Clin Endocrinol (Oxf), 95(6):891-900.
S. T. Rahman, N. Pandeya, R. E. Neale, D. S. A. McLeod, P. D. Baade, P. H. Youl, R. Allison, S. Leonard and S. J. Jordan. 2021.
OBJECTIVE: Smoking has been associated with a reduced risk of thyroid cancer, but whether the association varies between higher- and lower-risk cancers remains unclear. We aimed to assess the association between smoking and risk of thyroid cancer overall as well as by tumour BRAF mutational status as a marker of potentially higher-risk cancer. DESIGN AND PATIENTS: We recruited 1013 people diagnosed with thyroid cancer and 1057 population controls frequency-matched on age and sex. METHODS: Multivariable logistic regression was used to assess the association overall and in analyses stratified by tumour characteristics. We used sensitivity analysis to assess the potential for selection bias. RESULTS: We found little evidence of an association with current smoking (odds ratio [OR] = 0.93; 95% confidence interval [CI]: 0.69-1.26; current vs. never smoking), but a higher number of pack-years of smoking was associated with a lower risk of thyroid cancer (OR = 0.75; 95% CI: 0.57-0.99; =20 pack-years vs. never). However, after correcting for potential selection bias, we observed a statistically significant inverse association between current smoking and risk of thyroid cancer (bias-corrected OR = 0.65; 95% CI: 0.51-0.83). Those with BRAF-positive cancers were less likely to be current smokers than those with BRAF-negative cancers (prevalence ratio: 0.79; 95% CI: 0.62-0.99). CONCLUSION: We found smoking was inversely related to thyroid cancer risk and, in particular, current smoking was associated with a reduced risk of potentially more aggressive BRAF-positive than the likely more indolent BRAF-negative papillary thyroid cancers.
PubMed-ID: 34170568
http://dx.doi.org/10.1111/cen.14545

Review of Surgical Therapy of Adrenal Tumors in Guidelines From the German Association of Endocrine Surgeons.
JAMA Surg, 156(11):1061-2.
K. M. Ramonell, J. Fazendin and B. Lindeman. 2021.
PubMed-ID: 34347014
http://dx.doi.org/10.1001/jamasurg.2021.3595

Similar Stage-dependent Survival and Outcome in Sporadic and Hereditary Medullary Thyroid Carcinoma.
J Clin Endocrinol Metab, 106(9):e3582-e91.
F. Raue, T. Bruckner and K. Frank-Raue. 2021.
CONTEXT: Long-term data are scarce on large cohorts with sporadic (sMTC) and hereditary medullary thyroid carcinoma (hMTC). OBJECTIVES: To compare long-term disease-specific survival (DSS) and outcomes between sMTC and hMTC groups. DESIGN: Retrospective analysis. SETTING: German tertiary referral center. PATIENTS: A total of 673 patients with MTC that underwent surgery from January 1974 to July 2019. INTERVENTION: None (observational study). MAIN

OUTCOME MEASURE: Differences between sMTC and hMTC in long-term, stage-dependent survival and outcomes. RESULTS: Surgery was performed at median ages of 49 years for sMTC (n = 477, 44% male) and 29 years for hMTC (n = 196, 43% male; P < 0.0001). The mean follow-up times were 9.2 ± 8.0 (sMTC) and 14.6 ± 10.3 years (hMTC). Age and tumor stage at diagnosis were significantly different between the 2 groups (P < 0.0001). The sMTC and hMTC groups had different overall DSS (log rank, P = 0.0183), but similar stage-dependent DSS (log rank, P = 0.1242-0.8981). In a multivariate analysis, sMTC and hMTC did not differ in DSS (hazard ratio [HR] = 1.56; 95% CI, 0.94-2.57), but in both groups, a worse DSS was significantly associated with age at diagnosis (HR = 1.04; 95% CI, 1.02-1.05), male sex (HR = 0.49; 95% CI, 0.32-0.76), and stages III and IV at diagnosis (HR = 20.00; 95% CI, 2.74-145.91 and HR = 97.47; 95% CI, 13.07-726.67, respectively). The groups had significantly different (P < 0.0001) outcomes (i.e., cured, minimal residual disease, structural detectable disease, and death), but similar stage-dependent outcomes (P = 0.9449-0.0511), except for stage III (P = 0.0489). CONCLUSION: Patients with sMTC and hMTC had different ages of onset, but similar stage-dependent DSS and outcomes after the MTC diagnosis. This finding suggested that tumor behavior was similar in sMTC and hMTC.
PubMed-ID: 33974051
http://dx.doi.org/10.1210/clinem/dgab326

The complex regulation of NIS expression and activity in thyroid and extrathyroidal tissues.
Endocr Relat Cancer, 28(10):T141-T65.
G. Riesco-Eizaguirre, P. Santisteban and A. De la Vieja. 2021.
The sodium/iodide symporter (NIS) is an intrinsic plasma membrane protein that mediates active iodide transport into the thyroid gland and into several extrathyroidal tissues. NIS-mediated iodide uptake plays a pivotal role in the biosynthesis of thyroid hormones, of which iodide is an essential constituent. For 80 years, radioiodide has been used for the diagnosis and treatment of thyroid cancer, a successful theranostic agent that is extending its use to extrathyroidal malignancies. The purpose of this review is to focus on the most recent findings regarding the mechanisms that regulate NIS both in thyroid and extra-thyroidal tissues. Among other issues, we discuss the different transcriptional regulatory elements that govern NIS transcription in different tissues, the epigenetic modifications that regulate its expression, and the role that miRNAs play in fine-tuning NIS after being transcribed. A review on how hormones, cytokines, and iodide itself regulate NIS is provided. We also review the present stage of understanding NIS dysregulation in cancer, occupied mainly by convergent signaling pathways and by new insights in the route that NIS follows through different subcellular compartments to the plasma membrane. Furthermore, we cover NIS distribution and function in the increasing number of extrathyroidal tissues that express the symporter, as well as the role that NIS plays in tumor progression independently of its transport activity.
PubMed-ID: 34387194
http://dx.doi.org/10.1530/ERC-21-0217

Raised mortality in old adults with a history of hyperthyroidism following iodine fortification.
Clin Endocrinol (Oxf), 96(2):255-62.
J. Riis, S. L. Andersen, G. V. Gade, M. B. Danielsen, M. G. Jorgensen, A. Carlé, C. Torp-Pedersen and S. Andersen. 2022.
OBJECTIVE: A transient rise in the occurrence of hyperthyroidism ensued the introduction of iodine fortification (IF) of salt in Denmark. Older adults are at risk of complications to hyperthyroidism that could prove fatal to vulnerable individuals. We evaluated the association between thyroid function and mortality in older adults before and after nationwide implementation of IF. DESIGN: Retrospective cohort study. PATIENTS: All 68-year-olds from the general population in the city of Randers were invited to participate in a clinical study in 1988 and followed until death, emigration or end of study (31 December 2017) using Danish registries. MEASUREMENTS: Baseline measures comprised of a questionnaire, physical examination and blood and urine samples. Kaplan-Meier survival curves and Cox regression were used to determine the association between thyroid function and death before and after IF. Time-stratification of results before and after IF was employed due to violation of proportional hazards assumptions in Cox regression. RESULTS: Median urinary iodine concentration was 42 μg/L at baseline consistent with moderate iodine deficiency. Hyperthyroidism (thyrotropin < 0.4 mIU/L) occurred in 37 (9.1%) participants. Kaplan-Meier survival curves showed an increase in mortality among participants with hyperthyroidism after IF. There was no significant association between hyperthyroidism and mortality before IF compared to euthyroid participants, but after IF hyperthyroid subjects had an increased mortality (adjusted hazard ratio: 2.22, 95% confidence interval: 1.44-3.44). CONCLUSIONS: IF was associated with raised mortality among older adults with a history of hyperthyroidism and moderate iodine deficiency. Our results highlight the need for cautious iodine supplementation and for monitoring of IF.
PubMed-ID: 34743350
http://dx.doi.org/10.1111/cen.14627

Graves' Disease in the Young : could we change the weather ?
J Clin Endocrinol Metab,
P. Rodien. 2021.
PubMed-ID: 34928376
http://dx.doi.org/10.1210/clinem/dgab909

Analysis of Expression of Different Histone Deacetylases in Autoimmune Thyroid Disease.
J Clin Endocrinol Metab, 106(11):3213-27.
P. Sacristán-Gómez, A. Serrano-Somavilla, R. González-Amaro, R. Martínez-Hernández and M. Marazuela. 2021.
CONTEXT: Histone deacetylases (HDACs) and histone acetyltransferases (HAT) have an important role in the regulation of gene transcription as well as in the development and function of CD4+Foxp3+ T regulatory (Treg) cells. Our group and others have reported that patients with autoimmune thyroid disease (AITD) show abnormalities in the levels and function of different Treg cell subsets. OBJECTIVE: We aimed to analyze the levels of expression of several HDACs and the Tip60 HAT in the thyroid gland and immune cells from patients with AITD. METHODS: The expression of HDAC1-11 and the Tip60 HAT, at RNA and protein levels, were determined in thyroid tissue from 20 patients with AITD and 10 healthy controls and these findings were correlated with clinical data. HDAC9 and Tip60 levels were also analyzed in thyroid cell cultures, stimulated or not with proinflammatory cytokines, as well as in different cell subsets from peripheral blood mononuclear cells. RESULTS: Altered expression of different HDACs was observed in thyroid tissue from AITD patients, including a significant increase in HDAC9, at RNA and protein levels. Likewise, HDAC9 expression was increased in peripheral blood mononuclear cells particularly in Treg cells in patients with AITD. In contrast, Tip60 expression was reduced in thyroid gland samples from patients with Hashimoto thyroiditis. CONCLUSION: Our results indicate that HDAC expression is dysregulated in thyroid gland and immune cells from patients with AITD, suggesting involvement in the pathogenesis of this condition.
PubMed-ID: 34272941
http://dx.doi.org/10.1210/clinem/dgab526

ASO Author Reflections:Improving the Quality of Life of Patients with Indeterminate Thyroid Nodules Receiving Molecular Testing.
Ann Surg Oncol, 28(13):8882-3.
M. A. Schumm and M. J. Livhits. 2021.
PubMed-ID: 34215954
http://dx.doi.org/10.1245/s10434-021-10398-z

Guide to Enhanced Recovery for Cancer Patients Undergoing Thyroidectomy.
Ann Surg Oncol, 28(12):6936-8.
U. S. Shah, J. Holder-Murray and K. L. McCoy. 2021.
PubMed-ID: 34128139
http://dx.doi.org/10.1245/s10434-021-10100-3

Avidity and Outcomes of Radioiodine Therapy for Distant Metastasis of Distinct Types of Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 106(10):e3911-e22.
J. Simões-Pereira, N. Mourinho, T. C. Ferreira, E. Limbert, B. M. Cavaco and V. Leite. 2021.
CONTEXT: The recommendations for radioactive-iodine treatment (RAIT) in metastatic differentiated thyroid cancer (DTC) are mostly based in the experience with papillary histotype and do not consider the differences within the distinct types of DTC, in terms of RAIT uptake and response. OBJECTIVE: This work aims to investigate the association between histology and RAIT avidity and response, and to evaluate whether histotype was an independent prognostic factor in progression-free survival (PFS) and disease-specific survival (DSS) after RAIT for distant metastatic disease. METHODS: A retrospective analysis was conducted of all DTC patients who underwent RAIT for distant metastatic disease, from 2001 to 2018, at a thyroid cancer referral center. We included 126 patients: 42 (33.3%) classical variant papillary thyroid cancer (cvPTC), 45 (35.7%) follicular variant PTC (fvPTC), 17 (13.5%) follicular thyroid cancer (FTC) and 22 (17.5%) Hürthle cell carcinoma. Main outcome measures included RAIT avidity and response. RESULTS: RAIT avidity was independently associated with histology ($P < .001$) and stimulated thyroglobulin (Tg) at first RAIT for distant lesions ($P = .007$). Avidity was lowest in HCC (13.6%), intermediate in cvPTC (21.4%), and highest in fvPTC (75.6%) and FTC (76.5%). Regarding RAIT response, HCC and FTC were not different; both showed significantly more often progression after RAIT than fvPTC and cvPTC. Histology

influenced PFS (P = .014), but tumor type was not a significant prognostic factor in DSS. Instead, age at diagnosis, resection status, and stimulated Tg at the first RAIT were significantly associated with DSS. CONCLUSION: DTC histotype influenced RAIT avidity and PFS. It is crucial to better detect the metastatic patients that may benefit the most from RAIT.
PubMed-ID: 34134139
http://dx.doi.org/10.1210/clinem/dgab436

Indications of Superselective Neck Dissection in Patients With Lateral Node Metastasis of Papillary Thyroid Carcinoma.
Otolaryngol Head Neck Surg:1945998211038318.
Y. Song, G. Xu, T. Wang, Y. Zhang and B. Zhang. 2021.
OBJECTIVE: The extent of neck dissection in papillary thyroid carcinoma (PTC) patients with lateral neck metastasis is controversial. This work aims to screen the patients suitable for superselective neck dissections including only levels III-IV. STUDY DESIGN: Prospective observational cohort study. SETTING: The study was conducted in a high-volume tertiary care setting. METHODS: A total of 134 consecutive previously untreated PTC patients with lateral neck metastases and subjected to 154 therapeutic lateral neck dissections (including levels II, III, IV, and VB) between June 2018 and March 2021 were enrolled. Fine-needle aspiration was performed preoperatively at each suspicious neck level. Clinical predictors were analyzed for occult lymph node metastases at levels II and VB. RESULTS: As a result, 44.8% and 5.8% of neck specimens exhibited metastatic lymph nodes at levels II and VB. In addition, univariate and multivariate analyses showed that the primary tumor in the ipsilateral thyroid upper lobe (P = .016, odds ratio = 3.528) and clinically multiple metastatic lymph nodes in level III-IV (P = .005, odds ratio = 6.414) were independent predictive factors for occult level II metastases. All 3 (1.9%) occult metastases at level VB were found in necks with preoperative multiple lymph node metastases. CONCLUSIONS: A superselective lateral neck dissection including levels III to IV may be considered in patients with PTC when the preoperative evaluation identifies a single lymph node metastasis located at levels III to IV and the primary tumor is not in the upper lobe of the ipsilateral thyroid.
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http://dx.doi.org/10.1177/01945998211038318

Prophylactic Lateral Neck Dissection for Medullary Thyroid Carcinoma is not Associated with Improved Survival.
Ann Surg Oncol, 28(11):6572-9.
P. M. Spanheimer, I. Ganly, J. F. Chou, M. Capanu, A. Nigam, R. A. Ghossein, R. M. Tuttle, R. J. Wong, A. R. Shaha, M. F. Brennan and B. R. Untch. 2021.
BACKGROUND: Patients with medullary thyroid carcinoma (MTC) often receive lateral lymph node dissection with total thyroidectomy when calcitonin levels are elevated, even in the absence of structural disease, but the effect of this intervention on disease-specific outcomes is not known. PATIENTS AND METHODS: We retrospectively reviewed patients from 1986 to 2017 who underwent thyroidectomy with curative intent for MTC at our institution. The association of disease-specific survival and clinicopathologic features was examined using univariate and multivariate Cox regression. RESULTS: We identified 316 patients who underwent curative resection for MTC. Overall and disease-specific survival were 76% and 86%, respectively, at 10 years. To investigate the effect of prophylactic ipsilateral lateral lymph node dissection, we analyzed 89 patients without known structural disease in the neck lymph nodes at the time of resection and preoperative calcitonin > 200 pg/ml, of whom 45 had an ipsilateral lateral lymph node dissection (LND) and 44 did not. There were no differences in tumor size or preoperative calcitonin levels. There was no difference at 10 years in cumulative incidence of recurrence in the neck (20.9% LND vs. 30.4% no LND, p = 0.46), cumulative incidence of distant recurrence (18.3% vs. 18.4%, p = 0.97), disease-specific survival (86% vs. 93%, p = 0.53), or overall survival (82% vs. 90%, p = 0.6). CONCLUSION: Lateral neck dissection in the absence of clinical or radiologic abnormal lymph nodes is not associated with improved survival in patients with MTC.
PubMed-ID: 33748897
http://dx.doi.org/10.1245/s10434-021-09683-8

Non-surgical management of thyroid nodules - the role of ablative therapies.
J Clin Endocrinol Metab,
M. N. Stan, M. Papaleontiou, J. J. Schmitz and M. R. Castro. 2021.
CONTEXT: After a thorough evaluation most thyroid nodules are deemed of no clinical consequence and can be observed. However, when they are compressive, toxic, or involved by papillary thyroid carcinoma (PTC) surgery or RAI (if toxic) are the treatments of choice. Both interventions can lead to hypothyroidism and other adverse outcomes (e.g. scar, dysphonia, logistical limitation with RAI). Active surveillance might be used for papillary thyroid microcarcinoma (PTMC) initially, but anxiety leads many cases to surgery later. Several ablative therapies have thus evolved over the last few years

aimed at treating these nodules while avoiding described risks. CASES: We present 4 cases of thyroid lesions causing concerns (compressive symptoms, thyrotoxicosis, anxiety with active surveillance of PTMC). The common denominator is patients' attempt to preserve thyroid function, bringing into focus percutaneous ethanol injection (PEI) and thermal ablation techniques (radiofrequency ablation - RFA - being the most common). We discuss the evidence supporting these approaches and compare them with standard therapy, where evidence exists. We discuss additional considerations for the utilization of these therapies, their side-effects and conclude with a simplified description of how these procedures are performed. CONCLUSIONS: Thermal ablation, particularly RFA, is becoming an attractive option for managing a subgroup of solid thyroid nodules while PEI has a role in managing thyroid cysts and a select group of PTMC. Their role in the algorithm of thyroid nodule management is still being refined and technical expertise will be essential to reproduce the reported results into everyday practice.
PubMed-ID: 34953163
http://dx.doi.org/10.1210/clinem/dgab917

BRAF V600E Status Sharply Differentiates Lymph Node Metastasis-associated Mortality Risk in Papillary Thyroid Cancer.
J Clin Endocrinol Metab, 106(11):3228-38.
Y. Tao, F. Wang, X. Shen, G. Zhu, R. Liu, D. Viola, R. Elisei, E. Puxeddu, L. Fugazzola, C. Colombo, B. Jarzab, A. Czarniecka, A. K. Lam, C. Mian, F. Vianello, L. Yip, G. Riesco-Eizaguirre, P. Santisteban, C. J. O'Neill, M. S. Sywak, R. Clifton-Bligh, B. Bendlova, V. Sýkorová, S. Zhao, Y. Wang and M. Xing. 2021.
CONTEXT: How lymph node metastasis (LNM)-associated mortality risk is affected by BRAF V600E in papillary thyroid cancer (PTC) remains undefined. OBJECTIVE: To study whether BRAF V600E affected LNM-associated mortality in PTC. DESIGN, SETTING, AND PARTICIPANTS: We retrospectively analyzed the effect of LNM on PTC-specific mortality with respect to BRAF status in 2638 patients (2015 females and 623 males) from 11 centers in 6 countries, with median age of 46 [interquartile range (IQR) 35-58] years and median follow-up time of 58 (IQR 26-107) months. RESULTS: Overall, LNM showed a modest mortality risk in wild-type BRAF patients but a strong one in BRAF V600E patients. In conventional PTC (CPTC), LNM showed no increased mortality risk in wild-type BRAF patients but a robustly increased one in BRAF V600E patients; mortality rates were 2/659 (0.3%) vs 4/321 (1.2%) in non-LNM vs LNM patients (P = 0.094) with wild-type BRAF, corresponding to a hazard ratio (HR) (95% CI) of 4.37 (0.80-23.89), which remained insignificant at 3.32 (0.52-21.14) after multivariate adjustment. In BRAF V600E CPTC, morality rates were 7/515 (1.4%) vs 28/363 (7.7%) in non-LNM vs LNM patients (P < 0.001), corresponding to an HR of 4.90 (2.12-11.29) or, after multivariate adjustment, 5.76 (2.19-15.11). Adjusted mortality HR of coexisting LNM and BRAF V600E vs absence of both was 27.39 (5.15-145.80), with Kaplan-Meier analyses showing a similar synergism. CONCLUSIONS: LNM-associated mortality risk is sharply differentiated by the BRAF status in PTC; in CPTC, LNM showed no increased mortality risk with wild-type BRAF but a robust one with BRAF mutation. These results have strong clinical relevance.
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http://dx.doi.org/10.1210/clinem/dgab286

Comparative Study of ACR TI-RADS and ATA 2015 for Ultrasound Risk Stratification of Thyroid Nodules.
Otolaryngol Head Neck Surg:1945998211064607.
W. Thedinger, E. Raman and J. K. Dhingra. 2021.
OBJECTIVE: To study the adoption rate of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) scoring system over a 3-year period in a community setting and compare its performance with that of the American Thyroid Association 2015 (ATA 2015) ultrasound risk scoring system. STUDY DESIGN: Case series with prospective data collection and retrospective chart review. SETTING: Large community-based practice with multiple satellite offices and a dedicated thyroid ultrasound clinic. METHODS: All patients referred to the thyroid clinic between January 2018 and December 2020 for ultrasound-guided fine-needle biopsy were assigned an ATA 2015 risk score in a prospective manner immediately prior to biopsy. ACR TI-RADS scores were recorded through retrospective chart review of the radiologist report. Performance of the 2 systems was compared with cytology as the gold standard. RESULTS: A total of 949 nodules underwent biopsy, of which 236 had available data for both scoring systems. There was a 33.8% increase in adoption of the ACR TI-RADS over the 3-year study period. The ATA 2015 guidelines yielded sensitivity and specificity of 81.6% and 54.5%, respectively, as opposed to 73.7% and 27.0% for the ACR TI-RADS. CONCLUSION: In our community, there has been a gradual increase in adoption of the ACR TI-RADS, although the ATA 2015 risk scoring system has performed better.
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http://dx.doi.org/10.1177/01945998211064607

Prognostic Implications of Preablation Stimulated Tg: A Retrospective Analysis of 2500 Thyroid Cancer Patients.
J Clin Endocrinol Metab, 106(11):e4688-e97.
T. Tian, Y. Xu, X. Zhang and B. Liu. 2021.
CONTEXT: The risk of persistent and recurrent disease in patients with differentiated thyroid cancer (DTC) is a continuum that ranges from very low to very high, even within the 3 primary risk categories. It is important to identify independent clinicopathological parameters to accurately predict clinical outcomes. OBJECTIVE: To examine the association between pre-ablation stimulated thyroglobulin (ps-Tg) and persistent and recurrent disease in DTC patients and investigate whether incorporation of ps-Tg could provide a more individualized estimate of clinical outcomes. DESIGN, SETTING, AND PARTICIPANTS: Medical records of 2524 DTC patients who underwent total thyroidectomy and radioiodine ablation between 2006 and 2018 were retrospectively reviewed. MAIN OUTCOME MEASURE: Ps-Tg was measured under thyroid hormone withdrawal before remnant ablation. Association of ps-Tg and clinical outcomes. RESULTS: In multivariate analysis, age, American Thyroid Association (ATA) risk stratification, distant metastasis, ps-Tg, and cumulative administered activities were the independent predictive factors for persistent/recurrent disease. Receiver operating characteristic analysis identified ps-Tg cutoff (=10.1 ng/mL) to predict disease-free status with a negative predictive value of 95%, and validated for all ATA categories. Integration of ps-Tg into ATA risk categories indicated that the presence of ps-Tg = 10.1 ng/mL was associated with a significantly decreased chance of having persistent/recurrent disease in intermediate- and high-risk patients (9.9% to 4.1% in intermediate-risk patients, and 33.1% to 8.5% in high-risk patients). CONCLUSION: The ps-Tg (=10.1 ng/mL) was a key predictor of clinical outcomes in DTC patients. Its incorporation as a variable in the ATA risk stratification system could more accurately predict clinical outcomes.
PubMed-ID: 34143886
http://dx.doi.org/10.1210/clinem/dgab445

The use of thyroid cartilage needle electrodes in intraoperative neuromonitoring during thyroidectomy: Case-control study.
Head Neck, 43(11):3287-93.
Y. Türk, G. Kivratma, M. Özdemir, G. Içöz and Ö. Makay. 2021.
BACKGROUND: The most commonly used recording-side method in intraoperative neural monitoring (IONM) detects the stimulus with the endotracheal tube surface (ETS) electrodes placed in the endotracheal tube during thyroidectomy. The thyroid cartilage needle (TCN) electrode method is an alternative recording-side system in IONM. This study compared two recording-side techniques in IONM. METHODS: Data were retrospectively analyzed from 885 patients who underwent thyroidectomy between January 2012 and December 2020, with 110 ETS and 775 TCN electrodes. Patients' demographics, diagnosis, surgery type, and amplitudes of all stimulation steps were compared. Costs per patient were calculated. RESULTS: No significant differences were found in the demographic data between the two groups. All amplitudes were higher in the IONM system where TCN electrodes were used than that with ETS electrodes (all stimulation steps $p < 0.001$, except left-V2 $p = 0.007$). Further, TCN electrodes were 20 times cheaper than the ETS electrodes. CONCLUSION: TCN electrodes are an inexpensive and efficient alternative to ETS electrodes in IONM.
PubMed-ID: 34264539
http://dx.doi.org/10.1002/hed.26810

Comparison of Monopolar and Bipolar Stimulator Probes for Intraoperative Nerve Mapping During Thyroidectomy: A Prospective Study.
Laryngoscope, 131(10):E2718-E26.
Y. Turk, O. Makay, D. Kamani, O. Okose, I. J. Behr, M. Ozdemir, G. Icoz, M. Akyildiz, G. Dionigi, A. H. Abdelhamid Ahmed and G. W. Randolph. 2021.
OBJECTIVES/HYPOTHESIS: During intraoperative neuromonitoring in thyroid surgery, two different kinds of stimulator probes, monopolar and bipolar, are commonly used to stimulate the laryngeal nerves. We explore the unique characteristics of both of these probes as they relate to intraoperative laryngeal nerve mapping. METHODS: Twenty-one patients undergoing neuromonitored thyroidectomy by a single surgeon were enrolled. Electromyography (EMG) amplitude and latency measurements were prospectively recorded concurrently from 1 mA stimulation of vagus nerve (VN) and inferior/superior recurrent laryngeal nerve before (with and without fascia) and after thyroid resection using bipolar and monopolar stimulator probes. RESULTS: Significantly higher amplitudes were obtained with monopolar stimulator probes as compared to bipolar probes, in several stimulation scenarios such as at right VN pre-resection (carotid sheath intact), right VN pre-resection (carotid sheath dissected), right VN post-resection and left VN (carotid sheath dissected). No significant differences were found between amplitudes and latency values in all other stimulation scenarios. CONCLUSIONS: According to this study, both probes are reliable and safe for neural mapping. The kind of probe

used during neural monitoring is based on surgical situations and surgeon preference. LEVEL OF EVIDENCE: 3 (According to Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence) Laryngoscope, 131:E2718-E2726, 2021.
PubMed-ID: 34350983
http://dx.doi.org/10.1002/lary.29804

The diagnostic value of thyroglobulin in fine-needle aspiration of metastatic lymph nodes in patients with papillary thyroid cancer and its influential factors.
Surg Oncol, 39:101666.
Y. Wang, Y. Duan, M. Zhou, J. Liu, Q. Lai, B. Ye, D. Liu, L. Li, Y. Fang, K. Yue, C. Jing, Y. Wu and X. Wang. 2021.
Thyroglobulin (Tg) measurement in fine-needle aspiration (FNA-Tg) has proved to be an excellent tool to identify metastatic cervical lymph nodes (CLN) before or after surgery for papillary thyroid cancer (PTC). The diagnostic value of FNA-Tg for metastatic CLN in PTC patients is higher than that of ultrasound (US) and fine-needle aspiration cytology (FNAC), especially for small or cystic LN. The combination of FNAC and FNA-Tg can provide nearly 100% diagnostic sensitivity and specificity for CLN metastasis. However, the cutoff values of FNA-Tg for metastatic CLN have not been standardized, and the reported cutoff values of FNA-Tg range from 0.2 ng/ml to 77 ng/ml because of the differences in study samples, Tg measurement methods, Tg assays kits, etc. Serum anti-thyroglobulin antibody level, serum thyroglobulin level, the presence or absence of thyroid glands, and the characteristics of CLN may be factors affecting the accuracy of FNA-Tg. This review summarizes the recent research on the application of FNA-Tg in the diagnosis of metastatic LN in PTC and provides a reliable basis for the clinical diagnosis of cervical lymph node metastasis.
PubMed-ID: 34634575
http://dx.doi.org/10.1016/j.suronc.2021.101666

Differences in the ultrasonographic appearance of thyroid nodules after radiofrequency ablation.
Clin Endocrinol (Oxf), 95(3):489-97.
M. H. Wu, K. Y. Chen, A. Chen and C. N. Chen. 2021.
CONTEXT: Radiofrequency ablation (RFA) is a well-tolerated approach to treating benign thyroid nodules (TNs), but no index can predict its success. Other than size decrease, little is known about TN appearance on ultrasonography (US) after RFA. OBJECTIVE: This study aimed to (a) assess the effectiveness of single-session RFA treatment, (b) determine whether pre-ablation US characteristics correlate with its effectiveness, and (c) demonstrate TN characteristics on baseline and follow-up US. DESIGN: Retrospective cohort study among the patients who underwent single-session RFA for the treatment of benign TNs at a referral medical center between January 2018 and April 2019. PATIENTS: A total of 116 patients (137 nodules) were included in the study. MEASUREMENTS: Characteristics were quantified using commercial software. TNs were classified into 2015 American Thyroid Association (ATA) sonographic patterns and American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TI-RADS) categories. RESULTS: The average volume reduction ratio (VRR) was 74.51% in 1 year (95% confidence interval, 70.63%-78.39%). The only pre-ablation US feature significantly different between nodules with VRR <50% and VRR >50% was the cyst composition (0.05 vs. 0.02, p-value = .02). The VRR and margin change in the first 3 months after ablation were found to be leading indicators significantly correlated to the VRR in 6 months with correlation coefficients (r) = .72 and -.28 (p-value < .0001 and = .0008) and VRR in 1 year with r = .65 and -.17 (p-value < .0001 and = .046), respectively. After RFA, more TNs became ATA high suspicion (2.9% vs. 19.7%, p < .0001) and more appeared to be the non-ATA patterns (12.4% vs. 23.4%, p < .0001). Also, a greater number of post-RFA TNs were classified as ACR-TI-RADS categories 4 and 5 (40.1% vs. 70.1%, p < .0001). CONCLUSIONS: Radiofrequency ablation therapy is effective for treating TNs. Pre-ablation cyst components, 3-month post-ablation volume reduction and margin change of TNs were related to the 6-month and 1-year response. Clinicians should consider that TNs would appear peculiar on US after RFA, mistakenly suggesting malignant potential.
PubMed-ID: 33938024
http://dx.doi.org/10.1111/cen.14480

Benefits and harms of hemithyroidectomy, total or near-total thyroidectomy in 1-4 cm differentiated thyroid cancer.
Clin Endocrinol (Oxf), 95(4):668-76.
Y. Xu, K. Huang, P. Huang, N. Ke, J. Zeng, L. Wang, C. Liu, X. Shi, F. Guo, L. Su, M. Lin, X. Li and F. Xiao. 2021.
OBJECTIVE: For 1-4 cm differentiated thyroid cancer (DTC), current ATA guideline recommended hemithyroidectomy (HT) as an acceptable alternative initial procedure to total or near-total thyroidectomy (TT). The aim of this study was to evaluate benefits and harms of HT, TT in 1-4 cm DTC. DESIGN: Retrospective cohort study. PATIENTS: DTC patients aged 18 years or older who underwent initial thyroidectomy in a tertiary medical centre were included from January 2008 to July 2018. MEASUREMENTS: The structural persistent/recurrent disease, reoperation rates and surgical complications were

compared using Cox proportional regression and logistic regression. Propensity score matching was performed to adjust for related clinicopathological variables. RESULTS: Among 1824 DTC patients, 795 patients sized 1-4 cm were included. A total of 286 patients underwent HT and 509 patients underwent TT. In the matched analysis, no significant difference in disease-free survival (DFS) between HT and TT was observed during the median follow-up period of 56.5 months (hazard ratio [HR] 0.86; 95% CI, 0.37-2.00; p = .733). The difference in DFS between two groups was consistent regardless of age, sex, tumour size, follow-up duration. Meanwhile, HT was associated with a decreased risk of surgical complications (odds ratio [OR] 0.47, 95% CI 0.31-0.71, p < .001), as well as lower proportion of levothyroxine replacement (p = .007). Two cases in HT group received reoperation. Further multivariate analysis showed surgical procedure was not associated with structural persistence/recurrence (HR 0.68; 95%CI, 0.29-1.58, p = .367). CONCLUSIONS: For patients with 1-4 cm DTC without clinical evidence of lymph node metastasis or extrathyroidal extension, HT was associated with lower risk of surgical complications than TT while provided similar benefits as TT.
PubMed-ID: 33948971
http://dx.doi.org/10.1111/cen.14495

Prognostic value of lymph node ratio in children and adolescents with papillary thyroid cancer.
Clin Endocrinol (Oxf), 95(4):649-56.
Y. Xu, Y. Wang, X. Zhang, R. Huang, R. Tian and B. Liu. 2021.
OBJECTIVE: Neck lymph node (LN) metastasis is a common feature of paediatric papillary thyroid cancer, and LN ratio (LNR) is defined as the ratio of the number of positive LNs excised to the total number of removed. Unlike in adults, few data are available regarding the clinical implication of LNR in the paediatric population. Our purpose was to investigate the association of LNR with clinical outcomes in paediatric papillary thyroid cancer. DESIGN & METHODS: The study retrospectively reviewed 136 consecutive children and adolescents with papillary thyroid cancer and LN involvement but no initial distant metastasis. Initial treatment, included in all patients a total thyroidectomy with central and/or lateral neck dissection followed by radioactive iodine ablation. Within the neck dissections, total number of LNs removed, total positive LNs and LN ratios were determined. The effect of clinicopathologic characteristics and intraoperative findings on persistent and recurrent diseases were analysed by univariate and multivariate analyses. RESULTS: Median number of positive LNs was 9, and median LNR was 0.4. During a median follow-up of 49 months (range, 12.0-139 months), persistent disease occurred in 43 (31.6%) patients. The multivariable analysis showed that age and LNR were the independent factors predictive of persistent disease. Patients with a LNR >0.34 exhibited a threefold higher risk of persistent disease after initial therapy than the counterparts (P = .02). CONCLUSION: Our findings suggest that LNR was an independent determinant predictive of persistent disease after initial therapy in children and adolescents with papillary thyroid cancer.
PubMed-ID: 33914928
http://dx.doi.org/10.1111/cen.14491

Letter to the Editor from Xu and Yang: "Laser Ablation Versus Radiofrequency Ablation for Thyroid Nodules: 12-Month Results of a Randomized Trial (LARA II Study)".
J Clin Endocrinol Metab, 106(10):e4290-e1.
S. Yang and X. Xu. 2021.
PubMed-ID: 34197586
http://dx.doi.org/10.1210/clinem/dgab491

Accuracy of the Lymph Node Yield in Surgery for Papillary Thyroid Cancer in Children.
World J Surg, 45(10):3092-8.
A. Yap, A. Shui, J. Gosnell, C. Y. Huang, J. A. Sosa and S. Roman. 2021.
INTRODUCTION: Our aim was to determine the accuracy of lymph node yield (LNY) for pediatric patients undergoing thyroidectomy with concurrent lymph nodes harvest for clinically node-negative (cN0) papillary thyroid cancer (PTC). METHODS: Patients aged = 18 years with cN0 PTC undergoing thyroidectomy were reviewed in the NCDB, 1998-2016. Demographic and clinical characteristics of patients with = 1 LNY were compared to those without. A truncated beta-binomial distribution estimated the number of lymph nodes needed to detect pathologic nodal positivity, and LNY was calibrated for 90% sensitivity in nodal staging and stratified across clinical tumor size staging (T). RESULTS: 1,948 children with cN0 PTC underwent surgical resection; median age was 17 years; 83.2% were female; 47.6% were T1, 25.3% T2, 9.3% T3. 1,272 (65.3%) of these patients had lymph nodes resected, or = 1 LNY. The median LNY was 5 nodes (interquartile range 2-12); 45.9% of patients had = 1 metastatic lymph nodes. In the overall = 1 LNY cohort, 12 nodes (CI 9-19) were needed to predict nodal positivity with > 90% sensitivity. Based on clinical T-stage, detecting a metastatic lymph node with

> 90% sensitivity required a LNY of 14 for T1; 8 for T2; 6 for T3. CONCLUSION: This is the first study estimating the necessary LNY for determining nodal positivity in children with cN0 PTC. The high LNY required in small T1 tumors is likely infeasible and should not be pursued. Accuracy increases with lower LNYs for higher T-stages. Our findings can help guide prognosis and treatment for pediatric patients with PTC.
PubMed-ID: 34180009
http://dx.doi.org/10.1007/s00268-021-06207-z

Prevention of transoral thyroidectomy complications: An analysis of surgical outcomes in 423 consecutive series.
Surgery, 170(4):1155-9.
J. Y. You, H. Kim, D. W. Park, H. W. Yang, G. Dionigi and R. P. Tufano. 2021.
BACKGROUND: Although there are several publications on the new transoral robotic thyroidectomy technique, few have thoroughly reviewed its associated complications. This study analyzed the causes and prevention of transoral robotic thyroidectomy-specific complications and presented preventive measures. METHODS: The medical records of patients who underwent transoral robotic thyroidectomy performed by a single surgeon between March 1, 2009 and April 30, 2019 were retrospectively analyzed. Patient demographic, clinical, and operative data were analyzed using descriptive statistics. We describe the transoral robotic thyroidectomy-related complications experienced at our institution and how to overcome them. RESULTS: This study included a total of 423 patients who underwent transoral robotic thyroidectomy. The general surgical complications included immediate postoperative bleeding (2 cases) and delayed hematoma (3 cases). Chyle leakage and localized wound infection were found in 1 case each. Transient vocal cord palsy occurred in 4 cases, and 1 case developed transient hypoparathyroidism. The transoral robotic thyroidectomy-specific complications included zygoma bruise (2 cases), flap bruise (3 cases), chin flap perforation (2 cases), and oral commissure tearing (2 cases). The complications occurring when creating the flap included flap burns (4 cases), skin dimpling in the midline of the lower chin (2 cases), and hematomas in the intraoral trocar insertion sites (3 cases). CONCLUSION: Surgeons familiar with thyroid surgery and experienced in robotic surgery can perform transoral robotic thyroidectomy without causing more complications than those seen with traditional surgery.
PubMed-ID: 34090673
http://dx.doi.org/10.1016/j.surg.2021.05.003

Drawbacks of neural monitoring troubleshooting algorithms in transoral endoscopic thyroidectomy.
Langenbecks Arch Surg, 406(7):2433-40.
D. Zhang, C. W. Wu, T. Wang, Y. Zhao, H. Y. Kim, A. Pino, G. Dionigi and H. Sun. 2021.
INTRODUCTION: The application of intraoperative neural monitoring (IONM) trouble-shooting algorithms procedures in transoral endoscopic thyroidectomy vestibular approach (TOETVA) was investigated. METHODS: Loss of signal (LOS) is defined as a loss of the primary electromyographic (EMG) normal biphasic waveform with reduced amplitude response to less than 100μV with a stimulation level intensity of 1-2mA. A systematic review of the IONM system at LOS was covered methodically: (i) correct endotracheal tube verification, (ii) stimulation of the recurrent laryngeal nerve (RLN) at entry point, (iii) ipsilateral or contralateral vagal nerve (VN) stimulation, and (iv) laryngeal twitch (LT). RESULTS: The function of 223 nerves at risk (NAR) was recorded with IONM. Twenty-seven (12%) NAR experienced a suspected LOS. LT could not be appreciated. In 15/27 (55%) cases, the application of the IONM trouble-shooting algorithm revealed upward displacement of the EMG tube (all orotracheal intubations). In 9 (4%) NAR, VN stimulation was not accomplished. In detail, there were n.5 left and n. 4 right VNs. Two VNs were ipsilateral, and 7 VNs contralateral. For EMG tube displacement, because the oral/nasal area is included in the aseptic field, it is less possible to re-check by the laryngoscope or fiberscope. CONCLUSIONS: A limit for applying the IONM trouble-shooting algorithm to TOETVA is determined by (a) inability to appreciate the LT, (b) difficulty in stimulating the ipsilateral and contralateral VN, and (c) remodeling EMG endotracheal tube position. A modified IONM trouble-shooting algorithm for TOETVA is proposed.
PubMed-ID: 34264393
http://dx.doi.org/10.1007/s00423-021-02217-6

The prognostic value of lymph node metastasis and the eighth edition of AJCC for patients with anaplastic thyroid cancer.
Clin Endocrinol (Oxf), 95(3):498-507.
H. Zhang, Y. C. Zhao, Q. Wu, L. Wang and S. Sun. 2021.
OBJECTIVE: The eighth edition of the American Joint Committee on Cancer (AJCC-v8) for anaplastic thyroid cancer (ATC) made a revision in staging for patients with lymph node metastasis (LNM) based on the seventh edition of AJCC (AJCC-v7). Our study aimed to evaluate the predictive ability of AJCC-v8 for survival in patients with ATC by exploring the association

between lymph node stage and prognosis of ATC patients. METHODS: Retrospective study of ATC in Surveillance, Epidemiology and End Results (SEER) database. The association between LNM and survival of ATC was estimated by the Kaplan-Meier method and Cox regression model. The predictive performances of the AJCC-v8 and AJCC-v7 were estimated through C-index, Akaike information criterion (AIC) and Bayesian information criterion (BIC). RESULTS: A total of 313 patients with ATC were included in our analysis. Notably, LNM was identified as an independent risk factor for ATC mortality (adjusted HR, 1.47, 95% CI, 1.10-1.96; p = .009), while the risk of mortality in N1a group was comparable to that in N1b group according to univariate (HR, 1.30, 95% CI, 0.92-1.82; p = .133) and multivariate (adjusted HR 0.87, 95% CI, 0.60-1.27; p = .467) cox analyses. Applying the AJCC-v8, the survival of migration population staged T1-3aN1M0 was significantly worse than that of T1-3aN0M0 patients (IVA stage), while was not different from that of T3b-T4bN0/N1M0 patients (IVB stage). With a higher C-index (0.60 vs. 0.59), lower AIC (2728 vs. 2732) and BIC (2732 vs. 2735), AJCC-v8 was demonstrably a more favourable prediction model than AJCC-v7. CONCLUSIONS: This study demonstrated that LNM was independently associated with poor prognosis of ATC, and AJCC-v8 with the modified staging of patients with LNM showed better survival predictive performance in ATC patients than AJCC-v7.
PubMed-ID: 33864292
http://dx.doi.org/10.1111/cen.14482

Transoral Endoscopic Thyroidectomy Vestibular Approach Versus Endoscopic Thyroidectomy Via Areola Approach for Patients With Unilateral Papillary Thyroid Carcinoma: A Retrospective Study.
Surg Laparosc Endosc Percutan Tech, 31(5):550-3.
W. D. Zhang, L. Dai, Y. C. Wang, Y. Y. Xie, J. Y. Guo, J. J. Li and X. J. Wu. 2021.
BACKGROUND: Endoscopic thyroidectomy via areola approach (ETA) has been widely used in thyroidectomy for many years as it can effectively avoid a scar in the neck. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is newly applied and has gained popularity quickly. This study is to compare the safety and effectiveness of TOETVA and ETA. MATERIALS AND METHODS: A total of 95 patients who underwent TOETVA or ETA with unilateral papillary thyroid carcinoma were enrolled in this study from March 2019 to February 2020. The basic information (such as gender, age), intraoperative hemorrhage, postoperative drainage volume, hospital durations, intraoperative and postoperative complications, operative time, central lymph node dissection time, total number of central lymph nodes, and number of metastatic central lymph nodes were compared. RESULTS: The operative time of the TOETVA group was significantly longer than the ETA group (148.11±19.78 vs. 135.90±12.77 min, P<0.05). However, the result was opposite when central lymph node dissection time was compared (10.31±2.93 vs. 12.48±3.55, P<0.05). TOETVA had an advantage on total number of central lymph nodes over ETA (7.82±3.35 vs. 5.26±2.45, P<0.05). No differences were found between the 2 groups on other data. CONCLUSION: TOETVA and ETA have the similarity on surgical safety and effectiveness. TOETVA has its advantage on central lymph node dissection and might be a reasonable alternative for ETA and open surgery in the future.
PubMed-ID: 33734209
http://dx.doi.org/10.1097/SLE.0000000000000932

Non-medullary Thyroid Cancer Susceptibility Genes: Evidence and Disease Spectrum.
Ann Surg Oncol, 28(11):6590-600.
J. Zhou, P. Singh, K. Yin, J. Wang, Y. Bao, M. Wu, K. Pathak, S. K. McKinley, D. Braun, C. C. Lubitz and K. S. Hughes. 2021.
BACKGROUND: The prevalence of non-medullary thyroid cancer (NMTC) is increasing worldwide. Although most NMTCs grow slowly, conventional therapies are less effective in advanced tumors. Approximately 5-15% of NMTCs have a significant germline genetic component. Awareness of the NMTC susceptibility genes may lead to earlier diagnosis and better cancer prevention. OBJECTIVE: The aim of this study was to provide the current panorama of susceptibility genes associated with NMTC and the spectrum of diseases associated with these genes. METHODS: Twenty-five candidate genes were identified by searching for relevant studies in PubMed. Each candidate gene was carefully checked using six authoritative genetic resources: ClinGen, National Comprehensive Cancer Network guidelines, Online Mendelian Inheritance in Man, Genetics Home Reference, GeneCards, and Gene-NCBI, and a validated natural language processing (NLP)-based literature review protocol was used to further assess gene-disease associations where there was ambiguity. RESULTS: Among 25 candidate genes, 10 (APC, DICER1, FOXE1, HABP2, NKX2-1, PRKAR1A, PTEN, SDHB, SDHD, and SRGAP1) were verified among the six genetic resources. Two additional genes, CHEK2 and SEC23B, were verified using the NLP protocol. Seventy-nine diseases were found to be associated with these 12 NMTC susceptibility genes. The following diseases were associated with more than one NMTC susceptibility gene: colorectal cancer, breast cancer, gastric cancer, kidney cancer, gastrointestinal stromal tumor, paraganglioma, pheochromocytoma, and benign skin conditions. CONCLUSION: Twelve genes predisposing to NMTC and their associated disease spectra were identified and verified.

Clinicians should be aware that patients with certain pathogenic variants may require more aggressive surveillance beyond their thyroid cancer risk.
PubMed-ID: 33660127
http://dx.doi.org/10.1245/s10434-021-09745-x

Role of primary tumor resection in patients with metastatic medullary thyroid cancer who have unresectable distant metastases.
Head Neck, 43(11):3386-92.
S. M. Zhuang, L. E. Xie, F. Pang, Q. Y. Zhong, X. M. Sun, W. P. Wen and T. R. Liu. 2021.
BACKGROUND: Whether patients with medullary thyroid carcinoma (MTC) who have unresectable synchronous distant metastases should undergo primary surgical resection (PTR) remains controversial. This study aimed to identify predictive factors associated with the survival of such patients. METHODS: We conducted a retrospective study of patients with MTC who were registered in the Surveillance, Epidemiology, and End Results registry. The overall and cancer-specific mortality rates were assessed using risk-adjusted Cox proportional hazards regression modeling and stratified propensity score matching. RESULTS: One hundred and eight matched patients were assessed. Patients in the PTR group had lower overall mortality than did those in the non-PTR group. The 1-, 3-, and 5-year overall and cancer-specific survival rates in the PTR group were significantly higher. CONCLUSIONS: PTR appears to be the most appropriate intervention for patients with good performance status. Such patients are likely to benefit from surgery and to experience long-term stable disease.
PubMed-ID: 34423875
http://dx.doi.org/10.1002/hed.26840

Adrenals

Meta-Analyses

Effect of surgical treatment on myocardial strain in patients with pheochromocytoma and paraganglioma: a mini-review and meta-analysis.
J Endocrinol Invest, 44(11):2327-32.
M. Tadic, C. Sala, S. Carugo and C. Cuspidi. 2021.
AIM: Information on systolic dysfunction, as assessed by left-ventricular (LV) mechanics, in patients with pheochromocytoma after surgical treatment is scanty. We performed a systematic meta-analysis of speckle tracking echocardiographic studies to provide an updated comprehensive information on this issue. METHODS: The PubMed, OVID-MEDLINE, and Cochrane library databases were analyzed to search for articles published from the inception up to May 31st 2021. Studies were identified using MeSH terms and crossing the following search items: "myocardial strain" "left ventricular mechanics", "speckle tracking echocardiography", "systolic dysfunction", "pheochromocytoma", and "paraganglioma". RESULTS: A total of 92 surgically treated patients with pheochromocytoma/paraganglioma were included in 3 longitudinal studies. Successful surgical treatment was associated with a decrease in relative wall thickness (SMD - 0.25 ± 0.10, CI - 0.45/- 0.05, $p < 0.01$) and an improvement in global longitudinal strain (SMD - 0.45 ± 0.10, CI - 0.66/- 0.24, $p < 0.0001$). The favorable effects of treatment on LV geometry and mechanics were not accompanied by significant changes in ejection fraction (SMD - 0.07 ± 0.10, CI - 0.27/0.12, $p = 0.44$). CONCLUSIONS: This meta-analysis adds a new piece of evidence, suggesting that surgical treatment of patients with pheochromocytoma impacts favorably on LV geometry and LV mechanics, and, more importantly, the assessment of LV changes in this setting can no longer rely on conventional echocardiographic parameters such as ejection fraction.
PubMed-ID: 34235707
http://dx.doi.org/10.1007/s40618-021-01631-3

Randomized controlled trials

- None –

Consensus Statements/Guidelines

- None -

Other Articles

Expression of CYP11B1 and CYP11B2 in adrenal adenoma correlates with clinical characteristics of primary aldosteronism.
Clin Endocrinol (Oxf), 96(1):30-9.
C. H. Ahn, H. Y. Na, S. Y. Park, H. W. Yu, S. J. Kim, J. Y. Choi, K. E. Lee, S. W. Kim, K. C. Jung and J. H. Kim. 2022.
OBJECTIVE: Primary aldosteronism (PA) shows histological heterogeneity and clinical variability, including the coexistence of hypercortisolemia. Immunohistochemical analyses of steroidogenic enzymes in adrenal tissues have provided new insights into the pathogenesis of PA. However, a comprehensive analysis of the association between enzyme expression and clinical characteristics of PA has rarely been conducted. We aimed to investigate the correlation between clinical characteristics and steroidogenic enzyme expression in PA. DESIGN: A retrospective case-control study. PATIENTS: Consecutive patients who underwent unilateral adrenalectomy for PA (n = 180). Patients with adrenal Cushing's syndrome (CS) (n = 29) and nonfunctioning adenoma (n = 6) as comparator groups. MEASUREMENTS: A tissue microarray of adrenal adenomas was constructed and immunostained for CYP11B1, CYP11B2 and CYP17A1. The expression of the three enzymes was compared between PA and other adrenal diseases and between PA with and without mild autonomous cortisol excess (MACE). RESULTS: Adrenal adenomas in PA showed lower CYP11B1, higher CYP11B2 and lower CYP17A1 expression than

those in adrenal CS (p < .001). Nonfunctioning adenomas showed low expression of the three enzymes. PA with MACE showed higher CYP11B1 expression than PA without MACE. CYP11B1 expression was positively correlated with the severity of hypercortisolemia, and CYP11B2 was positively correlated with that of hyperaldosteronism. The expression of CYP11B1 and CYP11B2 had a negative correlation. Patients with absent clinical improvement after adrenalectomy had lower CYP11B2 expression than those with complete success. CONCLUSIONS: Variable expression of steroidogenic enzymes in adrenal adenoma underlies the clinical heterogeneity of PA and is associated with treatment outcomes.
PubMed-ID: 34743356
http://dx.doi.org/10.1111/cen.14628

Risk factors for intraoperative complications in pheochromocytomas.
Endocr Relat Cancer, 28(11):695-703.
M. Araujo-Castro, R. Garcia Centeno, M. C. López-García, C. Lamas, C. Álvarez-Escolá, M. Calatayud Gutiérrez, C. Blanco-Carrera, P. de Miguel Novoa, N. Valdés, P. Gracia Gimeno, M. T. Fernández-Ladreda, C. Mínguez Ojeda, J. C. Percovich Hualpa, M. Mora, Ó. Vidal, A. Serrano Romero, F. A. Hanzu and V. Gómez Dos Santos. 2021.
We aimed to identify presurgical and surgical risk factors for intraoperative complications in patients with pheochromocytomas. A retrospective study of patients with pheochromocytomas who underwent surgery in ten Spanish hospitals between 2011 and 2021 was performed. One hundred and sixty-two surgeries performed in 159 patients were included. The mean age was 51.6 ± 16.4 years old and 52.8% were women. Median tumour size was 40 mm (range 10-110). Laparoscopic adrenalectomy was performed in 148 patients and open adrenalectomy in 14 patients. Presurgical alpha- and beta-blockade was performed in 95.1% and 51.9% of the surgeries, respectively. 33.3% of the patients (n = 54) had one or more intraoperative complications. The most common complication was the hypertensive crisis in 21.0%, followed by prolonged hypotension in 20.0%, and hemodynamic instability in 10.5%. Patients pre-treated with doxazosin required intraoperative hypotensive treatment more commonly than patients pre-treated with other antihypertensive drugs (51.1% vs 26.5%, P = 0.002). Intraoperative complications were more common in patients with higher levels of urine metanephrine (OR = 1.01 for each 100 µg/24 h, P = 0.026) and normetanephrine (OR = 1.00 for each 100 µg/24 h, P = 0.025), larger tumours (OR = 1.4 for each 10 mm, P < 0.001), presurgical blood pressure > 130/80 mmHg (OR = 2.25, P = 0.027), pre-treated with doxazosin (OR = 2.20, P = 0.023) and who had not received perioperative hydrocortisone (OR = 3.95, P = 0.008). In conclusion, intraoperative complications in pheochromocytoma surgery are common and can be potentially life-threatening. Higher metanephrine and normetanephrine levels, larger tumour size, insufficient blood pressure control before surgery, pre-treatment with doxazosin, and the lack of treatment with perioperative hydrocortisone are associated with higher risk of intraoperative complications.
PubMed-ID: 34379605
http://dx.doi.org/10.1530/ERC-21-0230

Approach to the Patient With Adrenal Incidentaloma.
J Clin Endocrinol Metab, 106(11):3331-53.
I. Bancos and A. Prete. 2021.
Adrenal tumors are commonly discovered incidentally on cross-sectional abdominal imaging performed for reasons other than adrenal mass. Incidence of adrenal tumors increased 10-fold in the past 2 decades, with most diagnosed in older adults. In any patient with a newly discovered adrenal mass, determining whether the adrenal mass is malignant and whether it is hormonally active is equally important to guide the best management. Malignancy is diagnosed in 5% to 8% of patients with adrenal tumors, with a higher risk in young patients, if history of extra-adrenal malignancy, in those with large adrenal tumors with indeterminate imaging characteristics, and in bilateral adrenal tumors. Although overt hormone excess is uncommon in adrenal incidentalomas, mild autonomous cortisol secretion can be diagnosed in up to 30% to 50% of patients. Because autonomous cortisol secretion is associated with increased cardiovascular morbidity and metabolic abnormalities, all patients with adrenal incidentalomas require work up with dexamethasone suppression test. Management of adrenal tumors varies based on etiology, associated comorbidities, and patient's preference. This article reviews the current evidence on the diagnosis and evaluation of patients with adrenal mass and focuses on management of the most common etiologies of adrenal incidentalomas.
PubMed-ID: 34260734
http://dx.doi.org/10.1210/clinem/dgab512

The association between adrenal adenoma size, autonomous cortisol secretion and metabolic derangements.
Clin Endocrinol (Oxf), 96(3):311-8.
J. Bleier, J. Pickovsky, S. Apter, B. Fishman, Z. Dotan, A. Tirosh and G. Shlomai. 2022.
OBJECTIVE: Autonomous cortisol secretion (ACS) is common in patients with adrenal incidentalomas (AI). ACS is associated with increased cardiovascular morbidity and mortality. Data regarding the association between radiological characteristics of adrenal adenomas, their hormonal functionality and metabolic outcomes, are scarce and inconclusive. In this study, we aim to delineate the association between radiological characteristics of AI, ACS and metabolic status. METHODS: A cross-sectional study of 77 patients with AI who underwent a comprehensive hormonal evaluation. Radiological assessments were performed by an independent radiologist blinded to the clinical and hormonal phenotype of each case. Linear regression models were used to evaluate the association between post dexamethasone suppression test (DST) cortisol levels, metabolic indices and radiological measurements. RESULTS: Mean maximal adenoma diameter was greater in patients with versus without ACS (20.35 ± 6 vs. 27.09 ± 9.3 mm, respectively, $p < .01$). Maximal adenoma diameter was found to be positively and linearly correlated with post-DST morning cortisol levels across their entire range ($R = .474$, $p < .01$). Linear correlations between maximal adenoma diameter and indices of glycemic control showed a correlation coefficient (R) of .481 and .463 for fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c), respectively, $p < .01$. When analysis included only patients with ACS, an $R = .584$ and $R = .565$ was observed for FPG and HbA1c, respectively ($p < .01$ for both). The association between maximal adenoma diameter and both FPG and post-DST morning cortisol intensified in patients with metabolic syndrome. CONCLUSION: There is a quantitative positive mild correlation between AI size and both cortisol autonomy and metabolic parameters.
PubMed-ID: 34877671
http://dx.doi.org/10.1111/cen.14651

Combination of Mitotane and Locoregional Treatments in Low-volume Metastatic Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 106(11):e4698-e707.
A. Boilève, E. Mathy, C. Roux, M. Faron, J. Hadoux, L. Tselikas, A. Al Ghuzlan, S. Hescot, S. Leboulleux, T. de Baere, L. Lamartina, F. Deschamps and E. Baudin. 2021.
CONTEXT: European and French guidelines for ENSAT stage IV low tumor burden or indolent adrenocortical carcinoma (ACC) recommend a combination of mitotane and locoregional treatments (LRT) as first-line treatment. Nevertheless, the benefit of LRT in combination with mitotane has never been evaluated in this selected group of patients. OBJECTIVE: This work aimed to evaluate the therapeutic strategy of LRT combined with mitotane in patients with low tumor burden stage IVA ACC. METHODS: A retrospective chart review was performed from 2003 to 2018 of patients with stage IV ACC with 2 or fewer tumoral organs who received mitotane in our center. The primary end point was the delay between mitotane initiation and first systemic chemotherapy. Secondary end points were progression-free survival (PFS) and overall survival (OS) from mitotane initiation. Adjusted analyses were performed on the main prognostic factors. RESULTS: Out of 79 included patients, 48 (61%) patients were female and the median age at stage IVA diagnosis was 49.8 years (interquartile range [IQR], 38.8-60.0 years). Metastatic sites were mainly lungs (76%) and liver (48%). Fifty-eight (73%) patients received LRT including adrenal bed radiotherapy (14 patients, 18%), surgery (37 patients, 47%), and/or interventional radiology (35 patients, 44%). Median time between mitotane initiation and first chemotherapy administration was 9 months (IQR, 4-18 months). Median PFS1 (first tumor-progression) was 6.0 months (95% CI, 4.5-8.6). Median OS was 46 months (95% CI, 41-68). PFS1, PFS2, and OS were statistically longer in the mitotane plus LRT group compared to the mitotane-only group (hazard ratio [HR] = 0.39; 95% CI, 0.22-0.68; HR = 0.35; 95% CI, 0.20-0.63; and HR = 0.27; 95% CI, 0.14-0.50, respectively). Ten (13%) patients achieved complete response (CR), all from the mitotane plus LRT group. CONCLUSION: Our results endorse European and French guidelines for stage IV ACC with 2 or fewer tumor organs and favor the combination of mitotane and LRT as first-line treatment. For the first time, a significant number of CRs were observed. Prospective studies are expected to confirm these findings.
PubMed-ID: 34143888
http://dx.doi.org/10.1210/clinem/dgab449

ASO Author Reflections: Predicting Postoperative Resolution of Hypertension in Primary Hyperaldosteronism.
Ann Surg Oncol, 28(12):7496.
P. D. Chatani, D. A. Dominguez and N. Nilubol. 2021.
PubMed-ID: 33721134
http://dx.doi.org/10.1245/s10434-021-09762-w

Endocrine hypertension secondary to adrenal tumors: clinical course and predictive factors of clinical remission.
Langenbecks Arch Surg, 406(6):2027-35.
U. Clemente-Gutiérrez, R. H. Pérez-Soto, J. D. Hernández-Acevedo, N. M. Iñiguez-Ariza, E. Casanueva-Pérez, J. P. Pantoja-Millán, M. Sierra-Salazar, M. F. Herrera and D. Velázquez-Fernández. 2021.
PURPOSE: Endocrinopathies constitute ~ 10% of secondary hypertension (SH) etiologies. Primary aldosteronism, pheochromocytoma (PHEO), and Cushing's syndrome are common causes. Early identification and treatment result in resolution/improvement of SH. The aim of this study was to characterize the clinical course, outcomes, and remission-associated prognostic factors of SH related to adrenal tumors. METHODS: Retrospective cohort study including patients with SH who underwent adrenalectomy from 2000 to 2019. Postoperative outcomes were analyzed. Remission was defined as normalization of blood pressure without drug use. RESULTS: Eighty-three patients with SH were included. Mean ± SD age was 38.8 ± 14.2 years and 75.9% were women. Diagnosis was PHEO in 35 patients (42.2%), aldosteronoma (APA) in 28 (33.7%), cortisol producing adenoma (CPA) in 16 (19.3%), and ACTH-dependent Cushing's in 4 (4.8%). Laparoscopic adrenalectomy was performed in 81 (97.6%) patients. Mean ± SD follow-up was 57.4 ± 49.6 months (range 1-232). Surgical morbidity occurred in 7.2% of patients and there was no mortality. Remission of SH occurred in 61(73.5%): 100% of ACTH-dependent Cushing's, 85.7% of PHEO, 68.8% of CPA, and 57.1% of APA. Biochemical phenotype and the combination of larger tumor size, number of antihypertensive drugs, male gender, older age, obesity, and preoperative SH for more than 5 years were associated with less likely clinical remission in patients with APA ($p = 0.004$), CPA ($p < 0.0001$), and PHEO ($p < 0.0001$). CONCLUSION: SH remission rates are 57-100% after adrenalectomy. Several prognostic factors could be used to predict SH control. Adrenalectomy provides good clinical outcome and must be considered a treatment option in all surgical candidates.
PubMed-ID: 34159439
http://dx.doi.org/10.1007/s00423-021-02245-2

Progression of vertebral fractures in patients with adrenocortical carcinoma undergoing mitotane therapy.
J Clin Endocrinol Metab,
D. Cosentini, S. Grisanti, J. Hadoux, R. Libè, M. Frigerio, M. Laganà, F. Deschamps, M. Zamparini, L. Lamartina, R. Pedersini, C. Valsecchi, R. Maroldi, A. Al Ghuzlan, M. Terzolo, R. Gasparotti, E. Baudin and A. Berruti. 2021.
CONTEXT: patients with adrenocortical carcinoma (ACC) are frequently on mitotane therapy for a long-time period. The drug exerts an adrenolytic activity requiring glucocorticoid supplementation, which can be potentially detrimental for bone. OBJECTIVES: to explore whether mitotane plus/minus chemotherapy is associated with an increased proportion of morphometric vertebral fractures (VFs) in ACC patients. Secondary objectives were: proportion of patients with VF progression, or worsening of the spinal deformity index (SDI) during mitotane therapy; predictive factors of VF progression and prognostic role of VF progression. DESIGN AND SETTING: multicenter, retrospective cohort study of patients with ACC who received mitotane alone or in association to chemotherapy, recruited from January 2010 to January 2020 in two reference centers in Italy and France. RESULTS: a significant increase in the frequency of VFs before and after mitotane therapy was seen both in Italian (28.3% vs 47.8%, p: 0.04) and French (17.8% vs 35.6%, p 0.04) series. VF progression was observed in 39.1%, and 28.9% of patients, respectively. Baseline VFs and increased patient body mass index, but not the dose of cortisol supplementation, showed an independent association with VF progression at multivariate analysis. Among the 72 advanced ACC patients, progression of VFs was associated with a poorer survival. CONCLUSIONS: the administration of mitotane plus/minus chemotherapy in ACC patients impairs bone health independently from cortisol supplementation. Appropriate preventive measures to decrease the fracture risk should be implemented in these patients.
PubMed-ID: 34905056
http://dx.doi.org/10.1210/clinem/dgab899

Robotic Posterior Retroperitoneal Adrenalectomy: Patient Selection and Long-Term Outcomes.
Ann Surg Oncol, 28(12):7497-505.
M. Gokceimam, B. Kahramangil, S. Akbulut, O. Erten and E. Berber. 2021.
BACKGROUND: Recently, efficacy of laparoscopic posterior retroperitoneal adrenalectomy (PRA) for pheochromocytoma and malignancy has been questioned. Although robotic technique using wristed instruments may improve limitations of laparoscopic PRA, the worldwide experience with robotic PRA is limited. This study aimed to describe patient characteristics, surgical technique, and long-term outcomes of robotic PRA from a 12-year single-center experience. METHODS: This analysis was an institutional review board-approved retrospective study. In this study, PRA was performed robotically, with intraoperative ultrasound and indocyanine green imaging guidance. Long-term outcomes and predictors of operative time (OT) were assessed using descriptive and regression analyses. Using OT as a surrogate for difficulty of

procedure, receiver operating characteristic curve analysis was performed to quantify anthropometric thresholds that would predict a more challenging procedure. RESULTS: Altogether, 112 robotic PRA procedures were performed. Three cases (3%) were converted to a lateral approach, and one case (1%) was converted to open surgery. The morbidity rate was 2%. Microscopic capsular disruption occurred for one patient. No patient experienced persistent disease or local recurrence from pheochromocytoma or malignant adrenal tumors during the follow-up period (median, 48 months). Operating time was independently predicted by perirenal fat thickness, with 18.5 mm as the critical threshold. CONCLUSION: In this study, favorable PRA outcomes were achieved with careful patient selection and meticulous surgical technique that used robotic articulation guided by intraoperative imaging.
PubMed-ID: 33987759
http://dx.doi.org/10.1245/s10434-021-10088-w

Adrenalectomy for incidental and symptomatic phaeochromocytoma: retrospective multicentre study based on the Eurocrine(r) database.
Br J Surg, 108(10):1199-206.
L. Hallin Thompson, Ö. Makay, L. Brunaud, M. Raffaelli and A. Bergenfelz. 2021.
BACKGROUND: Phaeochromocytoma is sometimes not diagnosed before surgery and may present as an adrenal incidentaloma. The aim of this study was to investigate differences in clinical presentation and perioperative outcome in patients with subclinical and symptomatic phaeochromocytoma, and in patients operated with and without preoperative a-blockade. METHODS: This was a retrospective observational study of patients with a histopathological diagnosis of phaeochromocytoma registered in Eurocrine(r), the European registry for endocrine tumours, between 1 January 2015 and 31 March 2020. Patient characteristics, clinical presentation, tumour detection, and perioperative variables were analysed. RESULTS: Some 551 patients were included. Of these, 486 patients (88.2 per cent) had a preoperative diagnosis of phaeochromocytoma. Tumours were detected as incidentalomas in 239 patients (43.4 per cent) and 265 (48.1 per cent) had a preoperative diagnosis of hypertension. Preoperative a-blockade was more frequently used in patients with a known phaeochromocytoma (350, 90.9 per cent) than in patients with other indications for adrenalectomy (16, 31 per cent). Complications did not differ between patients who had surgery because of catecholamine excess compared with those who had other indications for surgery (19 (3.9 per cent) versus 2 (3 per cent); P = 0.785), nor did the conversion rate from minimally invasive to open surgery differ between the groups. There were no obvious differences in complications, according to the Clavien-Dindo classification, based on preoperative a-blockade or not. CONCLUSION: Subclinical phaeochromocytoma detected incidentally is common. A significant proportion of patients with phaeochromocytoma did not have a-blockade before surgery, without an apparent effect on complications.
Phaeochromocytoma is an unusual adrenal tumour with hormonal overproduction of catecholamines leading to a severe condition, including extreme hypertension in some situations. It is treated with surgery. Medical treatment before surgery is used to minimize surgical complications related to high blood pressure. A large proportion of phaeochromocytomas are detected incidentally, without symptoms, on radiological examination for other reasons. The aim of this study was to investigate differences in patient characteristics and surgical results in patients operated with or without symptoms of phaeochromocytoma. Patients registered in the large, European database, Eurocrine(r), between 2015 and 2020 were included in the study. The study showed that phaeochromocytoma without symptoms is common. Medical treatment before surgery does not seem to affect complications.
PubMed-ID: 34270711
http://dx.doi.org/10.1093/bjs/znab199

Outcomes of malignant pheochromocytoma based on operative approach: A National Cancer Database analysis.
Surgery, 170(4):1093-8.
J. J. Hue, C. Alvarado, K. Bachman, S. M. Wilhelm, J. B. Ammori, C. W. Towe and L. D. Rothermel. 2021.
BACKGROUND: Malignant pheochromocytoma is often managed with adrenalectomy. Most literature focusing on postoperative outcomes are from single institutions. This study aimed to describe outcomes of adrenalectomy for malignant pheochromocytoma using a national database. We hypothesized that minimally invasive approaches might be associated with improved short-term outcomes but potentially inferior oncologic efficacy. METHODS: Patients who underwent adrenalectomy for malignant pheochromocytoma were identified in the National Cancer Database (2010-2016). Patients were categorized as minimally invasive adrenalectomy or open adrenalectomy. Short- and long-term outcomes were compared. RESULTS: A total of 276 patients underwent adrenalectomy for malignant pheochromocytoma: 50.7% open adrenalectomy and 49.3% minimally invasive adrenalectomy. Demographics were similar, except those who underwent open adrenalectomy had larger tumors compared to minimally invasive adrenalectomy (8.2 cm vs 4.7 cm; P < .001). Tumor size =6 cm was associated with a reduced likelihood of minimally invasive adrenalectomy (relative to open

adrenalectomy) on multivariable regression (odds ratio = 0.23; P < .001). Open adrenalectomy was associated with longer duration of stay relative to minimally invasive adrenalectomy (6 vs 3 days; P < .001). Rates of positive margins, unplanned readmissions, or 30-/90-day mortalities were similar based on operative approach. Five-year survival rates were similar (open adrenalectomy 74.3%, minimally invasive adrenalectomy 79.1%). There was no association between overall survival and operative approach on multivariable Cox analysis when controlling for tumor size, laterality, and clinicodemographic variables. CONCLUSION: Patients with larger malignant pheochromocytomas were more likely to undergo an open adrenalectomy. With the exception of an increased duration of stay, there was no difference in short- or long-term postoperative outcomes. These data suggest that minimally invasive adrenalectomy appears safe among tumors <6 cm.
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http://dx.doi.org/10.1016/j.surg.2021.04.001

Cost-effectiveness analysis of screening for primary aldosteronism in China.
Clin Endocrinol (Oxf), 95(3):414-22.
N. Li, J. Huang, B. Zheng, H. Cai, M. Liu and L. Liu. 2021.
OBJECTIVE: Primary aldosteronism (PA) is an underdiagnosed cause of hypertension. Although the medical costs will increase if all patients with elevated blood pressure are screened, the number of missed diagnosed patients with PA and the medical resources subsequently consumed by adverse cardiovascular and cerebrovascular events can be reduced. This study aimed to conduct economic evaluation PA screening strategies in Chinese patients with hypertension, that is PA screening in patients with high-risk hypertension and all patients with hypertension, to determine the cost-effective method. METHODS: The decision tree and Markov model were constructed using TreeAge Pro 2020. Using the latter, a 30-year course of hypertension after different screening strategies was simulated, with a cycle of one year. The model parameters included epidemiological data, clinical efficacy, cost and effectiveness. The total cost of treatment and quality-adjusted life year (QALY) were simulated to conduct a cost-effectiveness analysis. Univariate and probabilistic sensitivity analyses of the model were also performed. RESULTS: PA screening patients with high-risk hypertension and all patients with hypertension obtained 15.75 and 15.77 QALYs and the costs were $2488.39 and $2482.15, respectively. The strategy of PA screening in all patients with hypertension is cost-saving and produces more health outcomes. The sensitivity analysis showed that the results were reliable. CONCLUSION: From the perspective of China's health system, the strategy of screening all hypertensive patients for PA may be more cost-effective than screening only high-risk patients and providing standard antihypertensive treatment for low-risk hypertensive patients.
PubMed-ID: 33837588
http://dx.doi.org/10.1111/cen.14478

The Importance of Recognizing a Locally Advanced Pheochromocytoma.
J Clin Endocrinol Metab, 106(9):e3771-e2.
E. S. Lim and S. A. Akker. 2021.
PubMed-ID: 34036314
http://dx.doi.org/10.1210/clinem/dgab366

Addition of 3-methoxytyramine or chromogranin A to plasma free metanephrines as the initial test for pheochromocytoma and paraganglioma: Which is the best diagnostic strategy.
Clin Endocrinol (Oxf), 96(2):132-8.
L. Liu, W. Xie, Z. Song, T. Wang, X. Li, Y. Gao, Y. Li, J. Zhang and X. Guo. 2022.
OBJECTIVE: Measurements of plasma free metanephrines (MNs), including MN and normetanephrine, provide high sensitivity and specificity for the diagnosis of pheochromocytoma and paraganglioma (PPGL). 3-Methoxytyramine (3-MT) and chromogranin A (CgA) may allow the detection of dopamine-producing or biochemically silent PPGL. The aim of this study was to evaluate whether measurements of plasma 3-MT or CgA as a supplement of plasma MNs offer a better diagnostic strategy for initial testing of PPGL. PATIENTS AND DESIGN: We enroled 125 patients who underwent surgery from 2015 to 2016 for our study and identified 33 patients with PPGL and 92 patients with non-PPGL masses. MEASUREMENT: The levels of plasma free MNs and 3-MT were measured for all 125 patients using liquid chromatography-tandem mass spectrometry. Plasma CgA concentrations were determined using a radioimmunoassay. To evaluate the diagnostic performance of plasma free MNs, 3-MT and CgA, sensitivity and specificity were determined, and receiver operating characteristic curves were constructed. RESULTS: We found that combining 3-MT and MNs increased the diagnostic sensitivity from 93.9% (95% confidence interval [CI]: 78.4%-98.9%) to 97.0% (95% CI: 82.5%-99.8%). In contrast, addition of plasma CgA test reduced the diagnostic specificity significantly from 91.3% (95% CI: 83.1%-95.9%) to 75.0% (95% CI: 64.7%-83.2%). CONCLUSION: Here, we demonstrated that 3-MT represents a valuable supplementary test

to plasma MNs, which can further enhance the sensitivity of the assay, while plasma CgA added no additional diagnostic value to MNs due to the lowered diagnostic specificity.
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Impaired aldosterone response to ACTH without hypoaldosteronism: An unrecognized secretory pattern in search of clinical implications.
Clin Endocrinol (Oxf), 96(4):513-20.
Y. Marcus, G. Shefer, K. Tordjman, Y. Sofer, Y. Greenman and N. Stern. 2022.
CONTEXT: Aldosterone has been recently characterized as a 'stress hormone'. Stress per se elicits a sizable rise in aldosterone secretion, which could be replicated by the administration of a low dose (0.03-1 μg, IV) of adrenocorticotropic hormone (ACTH). Whether or not the aldosterone response to ACTH could be selectively impaired, that is, in association with intact cortisol response, is presently unknown. OBJECTIVE: To determine whether or not the aldosterone response to low dose of ACTH is impaired in subjects referred to assess the hypothalamic-pituitary-adrenal axis (HPA). DESIGN: Retrospective analysis. SETTING: Outpatient referral endocrine day care centre. PATIENTS: One hundred and ninety-five consecutive subjects who underwent the low dose (1 μg) ACTH test, in whom decreased cortisol reserve was suspected due to former/present glucocorticoid excess, pituitary disease or/and unexplained weakness. MAIN OUTCOME MEASURES: The outcome was the detection of lack of aldosterone response, defined as a rise <111 pmol/l. RESULTS: In all, 46/195 subjects had subnormal aldosterone response as compared with 52/195 subjects showing diminished cortisol response. Nine subjects had combined deficient aldosterone and cortisol response. In the 37 subjects with isolated subnormal aldosterone response common associations were the use of exogenous glucocorticoids, mostly prednisone (n = 16); former Cushing disease (n = 2); nonfunctioning pituitary adenoma (n = 8); hypothyroidism (n = 11); the use of statins (n = 11), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 6), sex steroids in transgenders and orthostatic hypotension (n = 3). Twenty-seven percent (25/93) of the subjects with recent exposure to glucocorticoids had impaired aldosterone response to ACTH. CONCLUSION: Blunted aldosterone response to ACTH in the absence of hypoaldosteronism was seen in ~27% of subjects referred for HPA assessment using the low dose 1 μg ACTH test. Exposure to glucocorticoid excess was often linked to this impairment, independent of the cortisol response to ACTH.
PubMed-ID: 34590343
http://dx.doi.org/10.1111/cen.14603

Recurrence-Free Survival Analysis in Locally Advanced Pheochromocytoma: First Appraisal.
J Clin Endocrinol Metab, 106(9):2726-37.
S. Moog, F. Castinetti, C. DoCao, L. Amar, J. Hadoux, C. Lussey-Lepoutre, F. Borson-Chazot, D. Vezzosi, D. Drui, S. Laboureau, M. L. Raffin Sanson, L. Lamartina, P. Pierre, M. Batisse Ligner, S. Hescot, A. Al Ghuzlan, K. Renaudin, R. Libé, S. Laroche, G. Deniziaut, A. P. Gimenez-Roqueplo, A. Jannin, S. Leboulleux, C. Guerin, M. Faron and E. Baudin. 2021.
CONTEXT: The behavior of locally advanced pheochromocytoma (LAP) remains unknown. OBJECTIVE: We characterized the population with LAP and recurrence-free survival (RFS). METHODS: This retrospective multicentric study was run within the ENDOCAN-COMETE network and French Group of Endocrine Tumors (GTE) from 2003 to 2018, including patients from 11 French referral centers with LAP as defined by capsular invasion, vascular invasion, adipose tissue invasion, and/or positive locoregional lymph nodes at diagnosis without evidence of distant metastasis. The main outcome measure was recurrence, defined as tumor reappearance, including local site and/or distant metastasis. The primary endpoint was RFS analysis; secondary endpoints were characterization, overall survival (OS), and prognostic factors of recurrence. RESULTS: Among 950 patients, 90 (9%) exhibited LAP criteria and 55 met inclusion criteria (median age, 53 years; 61% males; 14% with germline mutation; 84% with catecholamine excess). LAP was defined by 31 (56%) capsular invasions, 27 (49%) fat invasions, 6 (11%) positive lymph nodes, and 22 (40%) vascular invasions. After median follow-up of 54 months (range, 6-180), 12 patients (22%) had recurrences and 3 (5%) died of metastatic disease. Median RFS was 115 months (range, 6-168). Recurrences were local in 2 patients, distant in 2, and both local and distant in 8 patients. Median OS of patients was not reached. Size above 6.5 cm (P = 0.019) and Ki-67 > 2% (P = 0.028) were identified as independent significant prognostic factors in multivariate analysis. CONCLUSION: LAP represents 9% of pheochromocytoma's population and has a metastatic behavior. This study paves the way for future pathological TNM classification.
PubMed-ID: 33782697
http://dx.doi.org/10.1210/clinem/dgab202

Rare Causes of Hypercalcemia: 2021 Update.
J Clin Endocrinol Metab, 106(11):3113-28.
Y. Motlaghzadeh, J. P. Bilezikian and D. E. Sellmeyer. 2021.
CONTEXT: Primary hyperparathyroidism and malignancy are the etiologies in 90% of cases of hypercalcemia. When these entities are not the etiology of hypercalcemia, uncommon conditions need to be considered. In 2005, Jacobs and Bilezikian published a clinical review of rare causes of hypercalcemia, focusing on mechanisms and pathophysiology. This review is an updated synopsis of rare causes of hypercalcemia, extending the observations of the original article. EVIDENCE ACQUISITION: Articles reporting rare associations between hypercalcemia and unusual conditions were identified through a comprehensive extensive PubMed-based search using the search terms "hypercalcemia" and "etiology," as well as examining the references in the identified case reports. We categorized the reports by adults vs pediatric and further categorized the adult reports based on etiology. Some included reports lacked definitive assessment of etiology and are reported as unknown mechanism with discussion of likely etiology. EVIDENCE SYNTHESIS: There is a growing understanding of the breadth of unusual causes of hypercalcemia. When the cause of hypercalcemia is elusive, a focus on mechanism and review of prior reported cases is key to successful determination of the etiology. CONCLUSIONS: The ever-expanding reports of patients with rare and even unknown mechanisms of hypercalcemia illustrate the need for continued investigation into the complexities of human calcium metabolism.
PubMed-ID: 34240162
http://dx.doi.org/10.1210/clinem/dgab504

Steroid Sulfation in Adrenal Tumors.
J Clin Endocrinol Metab, 106(12):3385-97.
J. W. Mueller, N. Vogg, T. A. Lightning, I. Weigand, C. L. Ronchi, P. A. Foster and M. Kroiss. 2021.
CONTEXT: The adrenal cortex produces specific steroid hormones including steroid sulfates such as dehydroepiandrosterone sulfate (DHEAS), the most abundant steroid hormone in the human circulation. Steroid sulfation involves a multistep enzyme machinery that may be impaired by inborn errors of steroid metabolism. Emerging data suggest a role of steroid sulfates in the pathophysiology of adrenal tumors and as potential biomarkers. EVIDENCE ACQUISITION: Selective literature search using "steroid," "sulfat*," "adrenal," "transport," "mass spectrometry" and related terms in different combinations. EVIDENCE SYNTHESIS: A recent study highlighted the tissue abundance of estrogen sulfates to be of prognostic impact in adrenocortical carcinoma tissue samples using matrix-assisted laser desorption ionization mass spectrometry imaging. General mechanisms of sulfate uptake, activation, and transfer to substrate steroids are reasonably well understood. Key aspects of this pathway, however, have not been investigated in detail in the adrenal; these include the regulation of substrate specificity and the secretion of sulfated steroids. Both for the adrenal and targeted peripheral tissues, steroid sulfates may have relevant biological actions beyond their cognate nuclear receptors after desulfation. Impaired steroid sulfation such as low DHEAS in Cushing adenomas is of diagnostic utility, but more comprehensive studies are lacking. In bioanalytics, the requirement of deconjugation for gas-chromatography/mass-spectrometry has precluded the study of steroid sulfates for a long time. This limitation may be overcome by liquid chromatography/tandem mass spectrometry. CONCLUSIONS: A role of steroid sulfation in the pathophysiology of adrenal tumors has been suggested and a diagnostic utility of steroid sulfates as biomarkers is likely. Recent analytical developments may target sulfated steroids specifically.
PubMed-ID: 33739426
http://dx.doi.org/10.1210/clinem/dgab182

Identification of Surgically Curable Primary Aldosteronism by Imaging in a Large, Multiethnic International Study.
J Clin Endocrinol Metab, 106(11):e4340-e9.
G. P. Rossi, F. Crimì, G. Rossitto, L. Amar, M. Azizi, A. Riester, M. Reincke, C. Degenhart, J. Widimsky, M. Naruse, J. Deinum, L. Schultze Kool, T. Kocjan, A. Negro, E. Rossi, G. Kline, A. Tanabe, F. Satoh, L. Christian Rump, O. Vonend, H. S. Willenberg, P. J. Fuller, J. Yang, N. Y. N. Chee, S. B. Magill, Z. Shafigullina, M. Quinkler, A. Oliveras, V. Cent Wu, Z. Kratka, G. Barbiero, T. M. Seccia and M. Battistel. 2021.
CONTEXT: Adrenal gland imaging is recommended by the current guidelines for the workup of primary aldosteronism (PA). However, its diagnostic performance has not been established in large, multiethnic cohorts of patients who undergo adrenal vein sampling (AVS) and adrenalectomy. OBJECTIVE: This work aims to assess the diagnostic accuracy of cross-sectional adrenal imaging. METHODS: This international multicenter study took place in tertiary referral centers. A total of 1625 PA patients seeking surgical cure were enrolled in an international study involving 19 centers in North America, Europe, Asia, and Australia. Of these, 1311 (81%) had imaging data available and 369 (23%), who received a final diagnosis of surgically cured unilateral PA, were examined. Patients underwent AVS and imaging by computed tomography and/or

magnetic resonance imaging. The accuracy of detection of unilateral PA at imaging was estimated by the area under the receiver operator characteristics curve using cure (biochemical and/or full clinical success) as the reference at follow-up after unilateral adrenalectomy. RESULTS: In the cohort of 1311 patients with imaging data available, 34% and 7% of cases showed no detectable or bilateral nodules, respectively. Imaging did not detect the culprit adrenal in 28% of the surgically cured unilateral PA patients. Moreover, the clinical outcome did not differ significantly between the imaging-positive and imaging-negative patients. CONCLUSION: Cross-sectional imaging did not identify a lateralized cause of disease in around 40% of PA patients and failed to identify the culprit adrenal in more than one-fourth of patients with unilateral PA.
PubMed-ID: 34212188
http://dx.doi.org/10.1210/clinem/dgab482

Adrenal wash-out CT: moderate diagnostic value in distinguishing benign from malignant adrenal masses.
Eur J Endocrinol, 186(2):183-93.
W. Schloetelburg, I. Ebert, B. Petritsch, A. M. Weng, U. Dischinger, S. Kircher, A. K. Buck, T. A. Bley, T. Deutschbein and M. Fassnacht. 2021.
OBJECTIVE: Reliable results of wash-out CT in the diagnostic workup of adrenal incidentalomas are scarce. Thus, we evaluated the diagnostic accuracy of delayed wash-out CT and determined thresholds to accurately differentiate adrenal masses. DESIGN: Retrospective, single-center cohort study including 216 patients with 252 adrenal lesions who underwent delayed wash-out CT. Definitive diagnoses based on histopathology (n = 92) or comprehensive follow-up. METHODS: Size, average attenuation values of the adrenal lesions in all CT scan phases, and absolute and relative percentage wash-out (APW/RPW) were determined by an expert radiologist blinded for clinical data. Adrenal lesions with unenhanced attenuation values >10 Hounsfield units (HU) built a subgroup (n = 142). Diagnostic accuracy was calculated. RESULTS: The study group consisted of 171 adenomas, 32 other benign tumors, 11 pheochromocytomas, 9 adrenocortical carcinomas, and 29 other malignant tumors. All (potentially) malignant and 46% of benign lesions showed unenhanced attenuation values >10 HU. In this most relevant subgroup, the established thresholds of 60% for APW and 40% for RPW misclassified 35.9 and 35.2% of the masses, respectively. When we applied optimized cutoffs (APW >83%; RPW >58%) and excluded pheochromocytomas, we missed only one malignant tumor by APW and none by RPW. However, only 11 and 15% of the benign tumors were correctly identified. CONCLUSIONS: Wash-out CT with the established thresholds for APW and RPW is insufficient to reliably diagnose adrenal masses. Using the proposed cutoff of 58% for RPW, malignant tumors will be correctly identified, but the added value is limited, namely 15% of patients with benign tumors can be prevented from additional imaging or even unnecessary surgery.
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http://dx.doi.org/10.1530/EJE-21-0650

Predictors of prolonged hypotension requiring vasopressor support after resection of pheochromocytoma and paraganglioma.
Clin Endocrinol (Oxf), 95(6):841-8.
Q. Shu, L. Lan, Y. Zhang, C. Yu and Y. Huang. 2021.
OBJECTIVE: Prolonged hypotension is a common complication after resection of pheochromocytoma (PCC) or paraganglioma (PGL). The objective of our study was to identify preoperative or intraoperative clinical factors that can predict prolonged hypotension after PCC/PGL resection. PATIENTS AND METHODS: A total of 414 patients who underwent resection of PCC or PGL at our institution between January 2013 and January 2020 were included. Patients were divided into two groups according to whether or not vasopressor support was required postoperatively. Associations between preoperative and intraoperative variables and prolonged hypotension were evaluated. RESULTS: Two hundred and one (48.6%) patients had postoperative hypotension that required vasopressor support with a median duration of 20 h. Multivariable analysis demonstrated that increased 24-h urinary norepinephrine (NE) levels (odds ratio [OR] = 1.091, 95% confidence interval [CI]: 1.052-1.132, p < .001), longer operative time (OR = 1.008, CI: 1.004-1.011, p < .001) and lower preoperative phenoxybenzamine dose (OR = 0.336, CI: 0.150-0.753, p = .008) were predictors of prolonged hypotension. Moreover, operative time, body mass index, 24-h urinary level of NE and preoperative phenoxybenzamine dose were significantly correlated with the duration of postoperative vasopressor support. CONCLUSIONS: Increased urine NE level, longer operative time and lower preoperative phenoxybenzamine dose were predictors of prolonged hypotension requiring vasopressor support. Clinicians can identify these factors to manage their patients better and prevent severe complications.
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http://dx.doi.org/10.1111/cen.14542

ACTH Stimulation Maximizes the Accuracy of Peripheral Steroid Profiling in Primary Aldosteronism Subtyping.
J Clin Endocrinol Metab, 106(10):e3969-e78.
Y. Tezuka, K. Ishii, L. Zhao, Y. Yamazaki, R. Morimoto, H. Sasano, A. M. Udager, F. Satoh and A. F. Turcu. 2021.
CONTEXT: Adrenocorticotropic hormone (ACTH) can contribute to aldosterone excess in primary aldosteronism (PA) via increased melanocortin type 2 receptor expression. Dynamic manipulation of the hypothalamic-pituitary-adrenal (HPA) axis could assist PA subtyping, but a direct comparison of dynamic tests is lacking. OBJECTIVE: To investigate plasma steroid differences between aldosterone-producing adenoma (APA) and bilateral PA (BPA) relative to ACTH variations. METHODS: We conducted comprehensive dynamic testing in 80 patients: 40 with APA and 40 with BPA. Peripheral plasma was collected from each patient at 6 time points: morning; midnight; after 1 mg dexamethasone suppression; and 15, 30, and 60 minutes after ACTH stimulation. We quantified 17 steroids by mass spectrometry in response to ACTH variations in all patients and compared their discriminative power between the 2 PA subtypes. RESULTS: Patients with APA had higher morning and midnight concentrations of 18-hydroxycortisol, 18-oxocortisol, aldosterone, and 18-hydroxycorticosterone than those with BPA ($P < 0.001$ for all). In response to cosyntropin stimulation, the APA group had larger increments of aldosterone, 18-oxocortisol, 11-deoxycorticosterone, corticosterone, and 11-deoxycortisol ($P < 0.05$ for all). Following dexamethasone suppression, the APA group had larger decrements of aldosterone, 18-hydroxycortisol, and 18-oxocortisol ($P < 0.05$ for all), but their concentrations remained higher than in the BPA group ($P < 0.01$ for all). The highest discriminatory performance between the PA subtypes was achieved using steroids measured 15 minutes post-ACTH stimulation (area under receiver operating characteristic curve 0.957). CONCLUSION: Steroid differences between APA and BPA are enhanced by dynamic HPA testing; such noninvasive tests could circumvent the need for adrenal vein sampling in a subset of patients with PA.
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http://dx.doi.org/10.1210/clinem/dgab420

Impact of Adrenalectomy on Morbidity in Patients with Non-Functioning Adrenal Cortical Tumours, Mild Hypercortisolism and Cushing's Syndrome as Assessed by National and Quality Registries.
World J Surg, 45(10):3099-107.
L. H. Thompson, J. Ranstam, M. Almquist, E. Nordenström and A. Bergenfelz. 2021.
BACKGROUND: The impact of adrenalectomy on morbidity in patients with mild hypercortisolism and non-functioning adrenocortical adenoma is unclear. The present study evaluated morbidity before and after adrenalectomy in patients with benign adrenocortical tumour with Cushing´s syndrome (CS), autonomous cortisol secretion (ACS) and non-functioning adrenocortical adenoma as assessed by national and quality registries. METHODS: Patients registered in the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) 2009-2017 with CS, ACS or non-functioning adrenocortical adenoma, were included in this retrospective study and analysed with age- and sex-matched controls, 1:3. Morbidity associated with CS was assessed pre- and postoperatively by analysing data from the Swedish National Patient Register and the Swedish Prescribed Drug Register. RESULTS: Some 271 patients were included, CS (127), ACS (45) and non-functioning adrenocortical adenoma (99), with 813 matched controls. The frequency of hypertension was almost 50% in all tumour groups. Antihypertensive medication preoperatively was more frequent in all tumour groups compared with controls. No preoperative differences in medication were detected between patients with CS and ACS. A decrease in the use of hypertensive drugs was noticed annually for all patient groups after adrenalectomy. CONCLUSIONS: Hypertension is common in patients with benign adrenocortical tumours regardless of cortisol hypersecretion. The use of antihypertensive drugs in patients with CS, ACS and non-functioning adrenocortical adenoma was reduced after adrenalectomy. These findings highlight the need for a randomized controlled trial to investigate the impact of adrenalectomy on morbidity in patients with mild hypercortisolism.
PubMed-ID: 34180008
http://dx.doi.org/10.1007/s00268-021-06214-0

Malignant prediction in paragangliomas: analysis for clinical risk factors.
Langenbecks Arch Surg, 406(7):2441-8.
M. Torres-Costa, B. Flores, N. Torregrosa, M. González, A. Ríos, B. Febrero, D. Flores, P. Rodríguez, P. Carbonell, M. I. Ortuño and J. M. Rodríguez. 2021.
INTRODUCTION: Paragangliomas are infrequent neuroendocrine tumours whose only criterion for malignancy is presence of metastases; thus, all paragangliomas show malignant potential. Actually, different risk factors have been analyzed to predict metastases but they remain unclear. PURPOSE: To analyze clinical, histological, and genetic factors to predict the occurrence of metastasis. PATIENTS AND METHOD: A multicentre retrospective observational analysis was performed between January 1990 and July 2019. Patients diagnosed with paraganglioma were selected. Clinical, histological, and

genetic features were analyzed for the prediction of malignancy. RESULTS: A total of 83 patients diagnosed with paraganglioma were included, of which nine (10.8%) had malignant paraganglioma. Tumour size was greater in malignant tumours than in benign (6 cm vs. 4 cm, respectively; p = 0.027). The most frequent location of malignancy was the thorax-abdomen-pelvis area observed in six cases (p = 0.024). No differences were observed in histological differentiation, age, symptoms, and catecholaminergic production. The most frequent genetic mutation was SDHD followed by SDHB but no differences were observed between benign and malignant tumours. In the univariate analysis for predictive factors for malignancy, location, tumour size, and histological differentiation showed statistical significance (p = 0.025, p = 0.014, and p = 0.046, respectively); however, they were not confirmed as predictive factors for malignancy in the multivariate analysis. CONCLUSION: In this study, no risk factors for malignancy have been established; therefore, we recommend follow-up of all patients diagnosed with paraganglioma.
PubMed-ID: 34101001
http://dx.doi.org/10.1007/s00423-021-02222-9

Adrenocortical Carcinoma: The Value of Lymphadenectomy.
Ann Surg Oncol, 29(3):1965-70.
J. Tseng, T. DiPeri, Y. Chen, D. Shouhed, A. Ben-Shlomo, M. Burch, E. Phillips and M. Jain. 2022.
BACKGROUND: Adrenocortical carcinoma (ACC) staging does not account for the number of positive nodes. The prognostic value of quantitative metastatic nodal burden is unknown. METHODS: The National Cancer Database was retrospectively queried from 2004-2016 to identify patients with Stage I-III ACC undergoing adrenalectomy. Patients who underwent lymphadenectomy (LAD) were further studied. Demographics, TNM staging, tumor characteristics, and surgical approach were analyzed. RESULTS: 386 LADs were identified. The median number of nodes examined was 2 (IQR 2-6), with no difference by surgical approach '[laparoscopic, 3 (1-3); robotic, 1.5 (1-4.5); open, 2 (1-7), p = 0.493]. In LADs with cN0 disease, positive nodes were seen in 17.5% of patients; an average of 6 (1-12) nodes were examined in patients who upstaged to pN1 disease compared with an average of 2 (1-6) nodes in those who remained pN0. Median survival was incrementally worse for patients with more positive nodes (62.8 vs. 21.9 vs. 13.7 vs. 11.3 vs. 10.7 months for 0, 1, 2, 3, and = 4 positive nodes, respectively, p < 0.01). On multivariate analysis, significant prognostic factors for poor survival included older age, = 2 comorbidities, pT3, and pT4. The strongest prognostic factor for poor survival was the number of positive nodes (1 node, hazards ratio [HR] 2.3, 95% confidence interval [CI] 1.5-3.6; 2 nodes, HR 1.3, 95% CI 0.6-3.0; 3 nodes, HR 3.0, 95% CI 1.1-8.0; = 4 nodes, HR 4.0, 95% CI 2.5-6.2). Lymphadenectomy was associated with improved survival (HR 0.82, 95% CI 0.67-0.99). CONCLUSIONS: Higher quantitative metastatic nodal burden is a robust prognostic factor for worse survival in ACC.
PubMed-ID: 34792698
http://dx.doi.org/10.1245/s10434-021-11051-5

Volumetric evaluation of CT images of adrenal glands in primary aldosteronism.
J Endocrinol Invest, 44(11):2359-66.
M. S. Velema, L. Canu, T. Dekkers, A. Hermus, H. Timmers, L. J. Schultze Kool, H. Groenewoud, C. Jacobs and J. Deinum. 2021.
OBJECTIVES: To investigate whether adrenal volumetry provides better agreement with adrenal vein sampling (AVS) than conventional CT for subtyping PA. Furthermore, we evaluated whether the size of this contralateral adrenal was a prognostic factor for clinical outcome after unilateral adrenalectomy. METHODS: We retrospectively analyzed volumes of both adrenal glands of the 180 CT-scans (88/180 with unilateral and 92/180 with bilateral disease) of the patients with PA included in the SPARTACUS trial of which 85 also had undergone an AVS. In addition, we examined CT-scans of 20 healthy individuals to compare adrenal volumes with published normal values. RESULTS: Adrenal volume was higher for the left than the right adrenal (mean and SD: 6.49 ± 2.77 ml versus 5.25 ± 1.87 ml for the right adrenal; p < 0.001). Concordance between volumetry and AVS in subtyping was 58.8%, versus 51.8% between conventional CT results and AVS (p = NS). The volumes of the contralateral adrenals in the patients with unilateral disease (right 4.78 ± 1.37 ml; left 6.00 ± 2.73 ml) were higher than those of healthy controls reported in the literature (right 3.62 ± 1.23 ml p < 0.001; left 4.84 ± 1.67 ml p = 0.02). In a multivariable analysis the contralateral volume was not associated with biochemical or clinical success, nor with the defined daily doses of antihypertensive agents at 1 year follow-up. CONCLUSIONS: Volumetry of the adrenal glands is not superior to current assessment of adrenal size by CT for subtyping patients with PA. Furthermore, in patients with unilateral disease the size of the contralateral adrenal is enlarged but its size is not associated with outcome.
PubMed-ID: 33666874
http://dx.doi.org/10.1007/s40618-021-01540-5

SDHC phaeochromocytoma and paraganglioma: A UK-wide case series.
Clin Endocrinol (Oxf), 96(4):499-512.
S. T. Williams, P. Chatzikyriakou, P. V. Carroll, B. M. McGowan, A. Velusamy, G. White, R. Obholzer, S. Akker, N. Tufton, R. T. Casey, E. R. Maher, S. M. Park, M. Porteous, R. Dyer, T. Tan, F. Wernig, A. F. Brady, M. Kosicka-Slawinska, B. C. Whitelaw, H. Dorkins, F. Lalloo, P. Brennan, J. Carlow, R. Martin, A. L. Mitchell, R. Harrison, L. Hawkes, J. Newell-Price, A. Kelsall, R. Igbokwe, J. Adlard, S. Schirwani, R. Davidson, P. J. Morrison, T. T. Chung, C. Bowles and L. Izatt. 2022.
OBJECTIVE: Phaeochromocytomas and paragangliomas (PPGL) are rare, but strongly heritable tumours. Variants in succinate dehydrogenase (SDH) subunits are identified in approximately 25% of cases. However, clinical and genetic information of patients with SDHC variants are underreported. DESIGN: This retrospective case series collated data from 18 UK Genetics and Endocrinology departments. PATIENTS: Both asymptomatic and disease-affected patients with confirmed SDHC germline variants are included. MEASUREMENTS: Clinical data including tumour type and location, surveillance outcomes and interventions, SDHC genetic variant assessment, interpretation, and tumour risk calculation. RESULTS: We report 91 SDHC cases, 46 probands and 45 non-probands. Fifty-one cases were disease-affected. Median age at genetic diagnosis was 43 years (range: 11-79). Twenty-four SDHC germline variants were identified including six novel variants. Head and neck paraganglioma (HNPGL, n = 30, 65.2%), extra-adrenal paraganglioma (EAPGL, n = 13, 28.2%) and phaeochromocytomas (PCC) (n = 3, 6.5%) were present. One case had multiple PPGLs. Malignant disease was reported in 19.6% (9/46). Eight cases had non-PPGL SDHC-associated tumours, six gastrointestinal stromal tumours (GIST) and two renal cell cancers (RCC). Cumulative tumour risk (95% CI) at age 60 years was 0.94 (CI: 0.79-0.99) in probands, and 0.16 (CI: 0-0.31) in non-probands, respectively. CONCLUSIONS: This study describes the largest cohort of 91 SDHC patients worldwide. We confirm disease-affected SDHC variant cases develop isolated HNPGL disease in nearly 2/3 of patients, EAPGL and PCC in 1/3, with an increased risk of GIST and RCC. One fifth developed malignant disease, requiring comprehensive lifelong tumour screening and surveillance.
PubMed-ID: 34558728
http://dx.doi.org/10.1111/cen.14594

Preoperative mineralocorticoid receptor antagonist reduces postoperative hyperkalaemia in patients with Conn syndrome.
Clin Endocrinol (Oxf), 96(1):40-6.
J. Zhang, R. Libianto, J. C. Lee, S. Grodski, J. Shen, P. J. Fuller and J. Yang. 2022.
BACKGROUND: The preoperative use of mineralocorticoid receptor antagonists (MRA) in patients with unilateral forms of primary aldosteronism (PA) is not standardized. The current Endocrine Society Guidelines do not specifically recommend MRA treatment before surgery. It is unclear whether preoperative MRA can optimize perioperative blood pressure and potassium control, and reduce the incidence of postoperative hyperkalaemia. OBJECTIVE: This study aimed to investigate the effect of MRA on the incidence of postoperative hyperkalaemia in addition to perioperative blood pressure and potassium concentration in patients undergoing unilateral adrenalectomy for the treatment of PA. DESIGN: Retrospective cohort study. SETTING: Tertiary referral centres, Victoria, Australia. PATIENTS: A total of 96 patients who were diagnosed with unilateral forms of PA: 73 patients ('MRA' group) received preoperative MRA while 23 patients ('No-MRA' group) did not. RESULTS: The prevalence of postoperative hyperkalaemia was significantly higher in the 'No-MRA' group at 2-4 weeks after surgery, compared to the 'MRA' group (35% vs. 11%, p = .014). In a logistic regression, the use of MRA significantly predicted a lower incidence of postoperative hyperkalaemia after adjusting for age, sex, baseline aldosterone-to-renin ratio, potassium and preoperative eGFR. Before surgery, patients in the 'MRA' group had normalized blood pressure and potassium concentration requiring fewer antihypertensive medications and no potassium supplements. CONCLUSION: Preoperative MRA use was associated with optimal perioperative blood pressure and normalized serum potassium in addition to a lower incidence of postoperative hyperkalaemia. MRA should be considered standard treatment for patients awaiting surgery for PA.
PubMed-ID: 34743353
http://dx.doi.org/10.1111/cen.14630

Letter to the Editor from Rui Zhu et al: "Performance of the Aldosterone-to-Renin Ratio as a Screening Test for Primary Aldosteronism: A Systematic Review and Meta-Analysis".
J Clin Endocrinol Metab, 106(10):e4292-e3.
R. Zhu, T. Shagjaa, T. M. Seccia and G. P. Rossi. 2021.
PubMed-ID: 34197581
http://dx.doi.org/10.1210/clinem/dgab485

NET

Meta-Analyses

Head-to-head comparison between (18) F-DOPA PET/CT and (68) Ga-DOTA peptides PET/CT in detecting intestinal neuroendocrine tumours: A systematic review and meta-analysis.
Clin Endocrinol (Oxf), 95(4):595-605.
A. Piccardo, F. Fiz, G. Bottoni, M. Ugolini, W. Noordzij and P. Trimboli. 2021.
PURPOSE: The imaging of intestinal neuroendocrine tumours (NETs) relies on functional positron emission tomography (PET) tracers; these tumours can be studied by means of both (68) Ga-DOTA peptides and (18) F-fluorodihydroxyphenyl- l-alanine ((18) F-DOPA) PET/computed tomography (CT). As yet, it is unclear which of these two modalities offers the better sensitivity. We therefore conducted a meta-analysis to assess the available data. METHODS: PubMed, CENTRAL, Scopus and Web of Science were searched for studies comparing the sensitivity of (68) Ga-DOTA peptides and (18) F-DOPA PET/CT; papers up to February 2021 were considered. In each study, we considered sensitivity in terms of patient-based analysis (PBA), region-based analysis (RBA) and lesion-based analysis (LBA), and pooled the results yielded by each tracer. Multidisciplinary follow-up served as the standard of truth. RESULTS: Of the 636 records identified, 6 articles published between 2008 and 2021 were finally selected, and 112 intestinal NETs patients were included. The pooled sensitivity of (18) F-DOPA PET/CT was 83%, 89% and 95% on PBA, RBA and LBA, respectively. (68) Ga-DOTA peptides PET/CT showed sensitivity of 88%, 92% and 82% on PBA, RBA and LBA, respectively. No significant differences were found between the two tracers on PBA and RBA. By contrast, a clear trend towards significance in favour of (18) F-DOPA PET/CT was identified on LBA. The presence of a significant difference in favour of (18) F-DOPA PET/CT was confirmed in a subgroup analysis conducted only on the most recent and largest studies. In all three analyses, mild-to-high heterogeneity was found; however, no publication bias was observed. CONCLUSION: Both (18) F-DOPA PET/CT and (68) Ga-DOTA-peptides PET/CT are reliable diagnostic procedures in patients with intestinal NETs. However, in terms of lesion detection, a non-negligible difference in favour of (18) F-DOPA PET/CT was observed. Thus, the use of (18) F-DOPA PET/CT could be considered as a first-line molecular procedure in intestinal NETs.
PubMed-ID: 34018606
http://dx.doi.org/10.1111/cen.14527

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Laparoscopic Enucleation of a Deep Neuroendocrine Tumor of the Pancreatic Head Avoiding Pancreatoduodenectomy.
Ann Surg Oncol, 28(11):6319-20.
J. Dembinski, D. Hammoud, A. Lemaire, F. S. Ftériche, B. Aussilhou, A. Sauvanet and S. Dokmak. 2021.
PubMed-ID: 33683526
http://dx.doi.org/10.1245/s10434-021-09723-3

Prognosis for Poorly Differentiated, High-Grade Rectal Neuroendocrine Carcinomas.
Ann Surg Oncol, 29(4):2539-48.
D. J. Erstad, A. Dasari, M. W. Taggart, H. Kaur, T. Konishi, B. K. Bednarski and G. J. Chang. 2022.
INTRODUCTION: Rectal neuroendocrine carcinomas (rNECs) are poorly characterized and, given their aggressive nature, optimal management is not well-established. We therefore sought to describe clinicopathologic traits, treatment details, and survival patterns for patients with rNECs. METHODS: Patients captured in the National Cancer Database (NCDB; 2004-2016) with rNECs managed with observation, chemotherapy, or proctectomy ± chemotherapy were considered for analysis. RESULTS: The inclusion criteria were met by 777 patients. Mean age was 62.4 years, 45% were male, 80% were Caucasian, 40% presented with lymph nodes metastases, and 49% presented with distant metastases. Chemotherapy and surgical resection were administered in 72 and 19% of cases, respectively. Median overall survival (OS) was 0.83 years (1 year, 41%; 3 years, 13%; 5 years, 10%). During the study interval, 659 (85%) patients died, with a median follow-up of 0.79 years. On multivariable analysis, age =60 years, male sex, and distant metastases were associated with worse survival; surgical resection and administration of chemotherapy were associated with a reduced risk of death. Among non-metastatic patients treated with surgical resection, administration of chemotherapy was protective, while a positive lymph node ratio (LNR) =42% (median value) was associated with an increased risk of death. There was no difference in the number of examined lymph nodes between LNR cohorts. CONCLUSIONS: Patients with rNECs experience dismal survival outcomes, including those with non-metastatic disease treated with curative-intent surgical resection. Neoadjuvant therapy can serve as a useful biologic test, and surgical resection should be judiciously employed.
PubMed-ID: 34787737
http://dx.doi.org/10.1245/s10434-021-11016-8

A Blood-based Polyamine Signature Associated With MEN1 Duodenopancreatic Neuroendocrine Tumor Progression.
J Clin Endocrinol Metab, 106(12):e4969-e80.
J. F. Fahrmann, A. R. Wasylishen, C. R. C. Pieterman, E. Irajizad, J. Vykoukal, E. Murage, R. Wu, J. B. Dennison, H. Krishna, C. B. Peterson, G. Lozano, H. Zhao, K. A. Do, D. M. Halperin, S. K. Agarwal, J. E. Blau, J. Del Rivero, N. Nilubol, M. F. Walter, J. M. Welch, L. S. Weinstein, M. R. Vriens, R. S. van Leeuwaarde, M. J. C. van Treijen, G. D. Valk, N. D. Perrier and S. M. Hanash. 2021.
CONTEXT: Duodenopancreatic neuroendocrine tumors (dpNETs) frequently occur in patients with multiple endocrine neoplasia type 1 (MEN1), and metastatic dpNET is the primary cause of disease-related mortality. There is a need for biomarkers that can identify patients with MEN1-related dpNETs that are at high risk of developing distant metastasis. Polyamines have tumor-promoting roles in several cancer types. OBJECTIVE: We hypothesized that MEN1-dpNET-related disease progression is associated with elevated levels of circulating polyamines. METHODS: Through an international collaboration between The University of Texas MD Anderson Cancer Center, the National Institutes of Health, and the University Medical Center Utrecht, plasma polyamine levels were assessed using mass spectrometry in 84 patients with MEN1 (20 with distant metastatic dpNETs [patients] and 64 with either indolent dpNETs or no dpNETs [controls]). A mouse model of MEN1-pNET, Men1fl/flPdx1-CreTg, was used to test time-dependent changes in plasma polyamines associated with disease progression. RESULTS: A 3-marker plasma polyamine signature (3MP: N-acetylputrescine, acetylspermidine, and diacetylspermidine) distinguished patients with metastatic dpNETs from controls in an initial set of plasmas from the 3 participating centers. The fixed 3MP yielded an area under the curve of 0.84 (95% CI, 0.62-1.00) with 66.7% sensitivity at 95% specificity for distinguishing patients from controls in an independent test set from MDACC. In Men1fl/flPdx1-CreTg mice, the 3MP was elevated early and remained high during disease progression. CONCLUSION: Our findings provide a basis for prospective testing of blood-based polyamines as a potential means for monitoring patients with MEN1 for harboring or developing aggressive disease.
PubMed-ID: 34318891
http://dx.doi.org/10.1210/clinem/dgab554

Secretin stimulation test and early diagnosis of gastrinoma in MEN1 syndrome: Survey on the MEN1 Florentine database.
J Clin Endocrinol Metab,
F. Giusti, F. Cioppi, C. Fossi, F. Marini, L. Masi, F. Tonelli and M. L. Brandi. 2021.
CONTEXT: Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited endocrine cancer syndrome. Multiple gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) affect 30-80% of MEN1 patients, with the most common functioning GEP-NET being gastrinoma. Biochemical identification of hypergastrinemia may help to recognize the presence of gastrinomas before they are detectable by instrumental screening, enabling early diagnosis and start of therapy, preferably before tumor progression and metastases occurrence. OBJECTIVE: Evaluate the effectiveness of secretin

stimulation test to precociously diagnose the presence of gastrin-secreting tumors. DESIGN: Results of secretin stimulation tests, performed between 1991 and February 2020, were retrospectively analyzed, as aggregate, in a cohort of MEN1 patients with GEP-NETs. SETTING: Data were extracted from the MEN1 Florentine database. PATIENTS: The study included 72 MEN1 patients with GEP-NETs who underwent a secretin stimulation test for the evaluation of gastrin secretion. OUTCOMES: A positive secretin stimulation test was assumed with a difference between basal fasting serum gastrin (FSG) and the maximum stimulated value of gastrin over 120 pg/ml. RESULTS: The secretin stimulation test showed a secretin-induced hypergastrinemia in 27.8% (20/72) of patients with GEP-NETs, and a positive test in 18 cases. The test allowed the identification of a positively stimulated hypergastrinemia in 75.0% (3/4) of patients who presented a basal FSG within the normal range. CONCLUSIONS: Diagnosis of gastrinoma is complex, difficult and controversial. Results of this study confirm that a positive secretin stimulation test allows early diagnosis of gastrinomas, even in the presence of borderline or normal levels of non-stimulated FSG.
PubMed-ID: 34922358
http://dx.doi.org/10.1210/clinem/dgab903

ASO Author Reflections: How Important is Type in the Management of Gastric Neuroendocrine Tumors?
Ann Surg Oncol, 28(13):8847-8.
A. Hanna and R. E. Roses. 2021.
PubMed-ID: 34142291
http://dx.doi.org/10.1245/s10434-021-10333-2

Surgical resection of high-grade nonfunctional pancreatic neuroendocrine carcinoma is associated with improved survival.
J Surg Oncol, 124(8):1373-80.
J. Jiang, J. Park, S. Kim, A. Daan, T. Donahue and M. D. Girgis. 2021.
BACKGROUND AND OBJECTIVES: The role of surgery in the treatment of nonfunctional pancreatic neuroendocrine carcinomas (PNEC) is not well defined. This study investigated the effect of surgical resection on cause-specific survival compared with nonoperative management. METHODS: The Surveillance, Epidemiology, and End Results Program (SEER) database was utilized to identify patients with nonfunctional pancreatic neuroendocrine carcinoma diagnosed between January 1, 2004 and December 31, 2015. Survival was modeled using Kaplan-Meier analysis and multivariable Cox proportional hazards models. RESULTS: Of the 488 patients identified, 137 (29%) underwent surgical resection of the primary site. Patients who underwent surgery had a median CSS of 31 months compared with 5 months in those who did not ($p < 0.01$). A survival benefit was observed when the cohort was stratified into local, nodal, and metastatic disease. CONCLUSION: Resection of the primary site in the cohort of PNEC patients compiled by SEER is associated with improved survival. Further consideration be placed on primary surgical resection for PNEC while additional studies that can select specifically for high-grade, poorly differentiated carcinomas need to be undertaken.
PubMed-ID: 34406651
http://dx.doi.org/10.1002/jso.26644

Initiating Pancreatic Neuroendocrine Tumor (pNET) Screening in Young MEN1 Patients: Results From the DutchMEN Study Group.
J Clin Endocrinol Metab, 106(12):3515-25.
M. J. Klein Haneveld, M. J. C. van Treijen, C. R. C. Pieterman, O. M. Dekkers, A. van de Ven, W. W. de Herder, W. T. Zandee, M. L. Drent, P. H. Bisschop, B. Havekes, M. R. Vriens, A. A. Verrijn Stuart, G. D. Valk and R. S. van Leeuwaarde. 2021.
CONTEXT: Nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) are highly prevalent and constitute an important cause of mortality in patients with multiple endocrine neoplasia type 1 (MEN1). Still, the optimal age to initiate screening for pNETs is under debate. OBJECTIVE: The aim of this work is to assess the age of occurrence of clinically relevant NF-pNETs in young MEN1 patients. METHODS: Pancreatic imaging data of MEN1 patients were retrieved from the DutchMEN Study Group database. Interval-censored survival methods were used to describe age-related penetrance, compare survival curves, and develop a parametric model for estimating the risk of having clinically relevant NF-pNET at various ages. The primary objective was to assess age at occurrence of clinically relevant NF-pNET (size = 20 mm or rapid growth); secondary objectives were the age at occurrence of NF-pNET of any size and pNET-associated metastasized disease. RESULTS: Five of 350 patients developed clinically relevant NF-pNETs before age 18 years, 2 of whom subsequently developed lymph node metastases. No differences in clinically relevant NF-pNET-free survival were found for sex, time frame, and type of MEN1 diagnosis or genotype. The estimated ages (median, 95% CI) at a 1%, 2.5%, and 5% risk of having developed a clinically relevant tumor are 9.5 (6.5-12.7), 13.5 (10.2-16.9), and 17.8 years (14.3-21.4), respectively.

CONCLUSION: Analyses from this population-based cohort indicate that start of surveillance for NF-pNETs with pancreatic imaging at age 13 to 14 years is justified. The psychological and medical burden of screening at a young age should be considered.
PubMed-ID: 34333645
http://dx.doi.org/10.1210/clinem/dgab569

Clinical Characteristics and Incidences of Benign and Malignant Insulinoma Using a National Inpatient Database in Japan.
J Clin Endocrinol Metab, 106(12):3477-86.
K. I. Kurakawa, A. Okada, K. Manaka, T. Konishi, T. Jo, S. Ono, K. Uda, N. Michihata, H. Matsui, K. Fushimi, S. Yamaguchi, T. Yamauchi, M. Nangaku, H. Yasunaga and T. Kadowaki. 2021.
CONTEXT: Insulinoma is the most common pancreatic functional neuroendocrine neoplasm, yet little information on recent clinical practice in patients with insulinoma, especially malignant insulinoma, is available. OBJECTIVE: This work aims to clarify the characteristics and practice patterns in patients with insulinoma using a national inpatient database. METHODS: Using the Japanese Diagnosis Procedure Combination database, we retrospectively identified patients with insulinoma admitted between 2010 and 2018. We compared background characteristics and therapeutic interventions between patients with benign and malignant insulinoma. We also estimated the incidence of insulinoma using the number of patients with newly diagnosed insulinoma in 2012. RESULTS: We identified 844 patients with benign insulinoma and 102 patients with malignant insulinoma. Patients with malignant insulinoma were younger (median, 55.5 vs 66.0 years, P < .001) and less likely to be female (55.9% vs 65.3%, P = .061) than patients with benign insulinoma. Analysis of therapeutic interventions revealed that patients with malignant insulinoma more frequently received medications (71.6% vs 49.6%, P < .001) but less frequently underwent pancreatic surgery (57.8% vs 72.0%, P = .003). Older patients were a smaller proportion of those undergoing surgery and a larger proportion of those managed with medications without surgery (P < .001). The incidence of insulinoma was estimated to be 3.27 (95% CI, 2.93-3.61) individuals per million Japanese adult population per year. CONCLUSION: The present study using a nationwide database had a larger sample size than previous studies and revealed definitive differences in patient characteristics and therapeutic patterns between benign and malignant insulinoma.
PubMed-ID: 34343300
http://dx.doi.org/10.1210/clinem/dgab559

Long-term effect of everolimus in recurrent thymic neuroendocrine neoplasia.
Clin Endocrinol (Oxf), 95(5):744-51.
M. Lang, T. Hackert and C. Anamaterou. 2021.
PURPOSE: Neuroendocrine neoplasia (NEN) of the thymus is a very rare entity with a poor prognosis. None of the treatments was proofed by studies. Usually, therapy protocols for bronchopulmonary carcinoids are used. So far no data exist on the effect of mammalian target of rapamycin (mTOR) inhibitors. We describe our long-term experience with everolimus and give a thorough review of the therapeutic strategies used so far. PATIENTS AND METHODS: Four patients (mean age 46 years, range 37-55) with progressing thymic NEN (t-NEN) (two well-differentiated atypical carcinoids and two atypical carcinoids with large cell characteristics) were treated with everolimus 10 mg/day after the failure of at least one previous medical therapy. Everolimus was applied after a mean interval of 32.4 months (range 5-56) after the first diagnosis. The follow-up included clinical examination, imaging and chromogranin A testing in 3 or 6 monthly intervals. RESULTS: We observed stable disease for a mean of 20.8 months. Both patients with large cell characteristics t-NEN (Ki-67 of 20%) had rapid progress after 7 and 10 months and had more previous therapies (three and six) than the patients with well-differentiated t-NEN (Ki-67 5% and 10%, progress after 24 and 42 months, one and two previous therapies). No severe side effects occurred. In three of four patients, everolimus led to stable disease for the longest compared to the other nonsurgical therapies used. CONCLUSION: Comparing the sparse data available everolimus is a promising treatment for t-NEN at least in second-line therapy. A low Ki-67 index was associated with a better outcome.
PubMed-ID: 34323309
http://dx.doi.org/10.1111/cen.14572

Two distinct classes of thymic tumors in patients with MEN1 show LOH at the MEN1 locus.
Endocr Relat Cancer, 28(11):L15-L9.
A. Mandl, J. M. Welch, G. Kapoor, V. I. Parekh, D. S. Schrump, R. T. Ripley, M. F. Walter, J. Del Rivero, S. Jha, W. F. Simonds, R. T. Jensen, L. S. Weinstein, J. E. Blau and S. K. Agarwal. 2021.
Patients with the multiple endocrine neoplasia type 1 (MEN1) syndrome carry germline heterozygous loss-of-function

mutations in the MEN1 gene which predisposes them to develop various endocrine and non-endocrine tumors. Over 90% of the tumors show loss of heterozygosity (LOH) at chromosome 11q13, the MEN1 locus, due to somatic loss of the wild-type MEN1 allele. Thymic neuroendocrine tumors (NETs) or thymic carcinoids are uncommon in MEN1 patients but are a major cause of mortality. LOH at the MEN1 locus has not been demonstrated in thymic tumors. The goal of this study was to investigate the molecular aspects of MEN1-associated thymic tumors including LOH at the MEN1 locus and RNA-sequencing (RNA-Seq) to identify genes associated with tumor development and potential targeted therapy. A retrospective chart review of 294 patients with MEN1 germline mutations identified 14 patients (4.8%) with thymic tumors (12 thymic NETs and 2 thymomas). LOH at the MEN1 locus was identified in 10 tumors including the 2 thymomas, demonstrating that somatic LOH at the MEN1 locus is also the mechanism for thymic tumor development. Unsupervised principal component analysis and hierarchical clustering of RNA-Seq data showed that thymic NETs formed a homogenous transcriptomic group separate from thymoma and normal thymus. KSR2 (kinase suppressor of Ras 2), that promotes Ras-mediated signaling, was abundantly expressed in thymic NETs, a potential therapeutic target. The molecular insights gained from our study about thymic tumors combined with similar data from other MEN1-associated tumors may lead to better surveillance and treatment of these rare tumors.
PubMed-ID: 34515662
http://dx.doi.org/10.1530/ERC-21-0226

Value of somatostatin receptor PET/CT in MEN1 patients at various stages of their disease.
J Clin Endocrinol Metab,
C. Mennetrey, M. Le Bras, A. Bando-Delaunay, L. Al-Mansour, M. Haissaguerre, M. Batisse-Lignier, E. Ouvrard, C. Ansquer, T. Walter, L. de Mestier, A. Kelly, G. Tlili, S. Giraud, M. O. North, M. F. Odou, B. Goichot, T. Cuny, A. Loundou, P. Romanet, A. Imperiale and D. Taïeb. 2021.
CONTEXT: Despite the growing evidence of the clinical value of somatostatin receptor (SSTR) PET in the evaluation of neuroendocrine tumors/NET, its role remains to be clarified at different time points in the MEN1 patient journey. The rareness of the disease is however a significant impediment to prospective clinical trials. OBJECTIVES: The goals of the study were to assess the indications and value of SSTR PET/CT in MEN1 patients. METHODS: We retrospectively included patients from 7 French expert centres for whom data on SSTR PET/CT and morphological imaging performed at the same period were available. Detection rates of PET study were analysed. RESULTS: One hundred eight patients were included. SSTR PET/CT was performed at screening (n=33), staging (n=34), restaging (n=37) and for PRRT selection (n=4). PET detected positive pancreatic lesions in 91% of cases at screening, with comparable results to MRI but superiority to CT (P=0.049). Metastases (mostly LN) were present at the screening phase in 28% of cases, possibly due to the suboptimal value of screening morphological imaging in the assessement of nodal metastases and/or a long delay between imaging studies. SSTR PET/CT was considered as superior or complementary to the reference standard in the assessment of LN or distant metastases in the vast majority of cases and regardless of the clinical scenario. CONCLUSION: This study shows the potential added value of SSTR PET in the assessment of MEN1-associated NETs and provides a great impetus towards its implementation in the evaluation of MEN1 patients.
PubMed-ID: 34940846
http://dx.doi.org/10.1210/clinem/dgab891

Molecular Genomic Assessment Using a Blood-based mRNA Signature (NETest) is Cost-effective and Predicts Neuroendocrine Tumor Recurrence With 94% Accuracy.
Ann Surg, 274(3):481-90.
I. M. Modlin, M. Kidd, A. Frilling, M. Falconi, P. L. Filosso, A. Malczewska and A. Kitz. 2021.
INTRODUCTION: Identification of residual disease after neuroendocrine tumor (NET) resection is critical for management. Post-surgery imaging is insensitive, expensive, and current biomarkers ineffective. We evaluated whether the NETest, a multigene liquid biopsy blood biomarker, correlated with surgical resection and could predict recurrence. METHODS: Multicenter evaluation of NET resections over 24 months (n = 103): 47 pancreas, 26 small bowel, 26 lung, 2 appendix, 1 duodenum, 1 stomach. Surgery: R0 (83), R1/R2 (20). One millilitre of blood was collected at D0 and posroperative day (POD) 30. Transcript quantification by polymerase chain reaction (normal: =20), CgA by NEOLISA (normal =108 ng/mL). Standard-of-care (SoC) follow-up costs were calculated and compared to POD30 NETest-stratification approach. Analyses: Wilcoxon-paired test, Chi-square test. D BIOMARKERS: NETest: 103 of 103 (100%)-positive, whereas 23 of 103 (22%) were CgA-positive (Chi-square = 78, P < 0.0001).In the R0 group, the NETest decreased 59 ± 28 to 26 ± 23 (P < 0.0001); 36% (30/83) remained elevated. No significant decrease was evident for CgA. In the R1/R2 group the NETest decreased but 100% remained elevated. CgA levels did not decrease.An elevated POD30 NETest was present in R0 and 25 (83%) developed radiological recurrences. Normal score R0 s (n = 53) did not develop recurrence (Chi-square = 56, P < 0.0001).

Recurrence prediction was 94% accurate with the NETest. COST EVALUATION: Using the NETest to stratify postoperative imaging resulted in a cost-savings of 42%. CONCLUSION: NETest diagnosis is more accurate than CgA (100% vs 22%). Surgery significantly decreased NETest. An elevated POD30 NETest predicted recurrence with 94% accuracy and post-surgical POD30 NETest follow-up stratification decreased costs by 42%. CgA had no surgical utility. Further studies would define the accuracy and cost-effectiveness of the NETest in the detection of postoperative recurrent disease.
PubMed-ID: 34183517
http://dx.doi.org/10.1097/SLA.0000000000005026

Early Identification of Residual Disease After Neuroendocrine Tumor Resection Using a Liquid Biopsy Multigenomic mRNA Signature (NETest).
Ann Surg Oncol, 28(12):7506-17.
I. M. Modlin, M. Kidd, K. Oberg, M. Falconi, P. L. Filosso, A. Frilling, A. Malczewska, R. Salem, C. Toumpanakis, F. M. Laskaratos, S. Partelli, M. Roffinella, C. von Arx, B. K. Kudla, L. Bodei, I. A. Drozdov and A. Kitz. 2021.
INTRODUCTION: Surgery is the only cure for neuroendocrine tumors (NETs), with R0 resection being critical for successful tumor removal. Early detection of residual disease is key for optimal management, but both imaging and current biomarkers are ineffective post-surgery. NETest, a multigene blood biomarker, identifies NETs with >90% accuracy. We hypothesized that surgery would decrease NETest levels and that elevated scores post-surgery would predict recurrence. METHODS: This was a multicenter evaluation of surgically treated primary NETs (n = 153). Blood sampling was performed at day 0 and postoperative day (POD) 30. Follow-up included computed tomography/magnetic resonance imaging (CT/MRI), and messenger RNA (mRNA) quantification was performed by polymerase chain reaction (PCR; NETest score: 0-100; normal =20). Statistical analyses were performed using the Mann-Whitney U-test, Chi-square test, Kaplan-Meier survival, and area under the receiver operating characteristic curve (AUROC), as appropriate. Data are presented as mean ± standard deviation. RESULTS: The NET cohort (n = 153) included 57 patients with pancreatic cancer, 62 patients with small bowel cancer, 27 patients with lung cancer, 4 patients with duodenal cancer, and 3 patients with gastric cancer, while the surgical cohort comprised patients with R0 (n = 102) and R1 and R2 (n = 51) resection. The mean follow-up time was 14 months (range 3-68). The NETest was positive in 153/153 (100%) samples preoperatively (mean levels of 68 ± 28). In the R0 cohort, POD30 levels decreased from 62 ± 28 to 22 ± 20 ($p < 0.0001$), but remained elevated in 30% (31/102) of patients: 28% lung, 29% pancreas, 27% small bowel, and 33% gastric. By 18 months, 25/31 (81%) patients with a POD30 NETest >20 had image-identifiable recurrence. An NETest score of >20 predicted recurrence with 100% sensitivity and correlated with residual disease (Chi-square 17.1, $p < 0.0001$). AUROC analysis identified an AUC of 0.97 ($p < 0.0001$) for recurrence-prediction. In the R1 (n = 29) and R2 (n = 22) cohorts, the score decreased (R1: 74 ± 28 to 45 ± 24, $p = 0.0012$; R2: 72 ± 24 to 60 ± 28, p = non-significant). At POD30, 100% of NETest scores were elevated despite surgery ($p < 0.0001$). CONCLUSION: The preoperative NETest accurately identified all NETs (100%). All resections decreased NETest levels and a POD30 NETest score >20 predicted radiologically recurrent disease with 94% accuracy and 100% sensitivity. R0 resection appears to be ineffective in approximately 30% of patients. NET mRNA blood levels provide early objective genomic identification of residual disease and may facilitate management.
PubMed-ID: 34008138
http://dx.doi.org/10.1245/s10434-021-10021-1

Impact of Specific Bowel Symptoms on Quality of Life in Patients with Midgut Neuroendocrine Tumours.
World J Surg, 45(9):2793-803.
H. Ohlsson, G. Wahlberg, M. Malmström, R. Gustafsson, A. Sundlöv, E. Nordenström and M. Almquist. 2021.
INTRODUCTION: Patients with midgut neuroendocrine tumours (NETs) suffer from decreased health-related quality of life (HRQoL), in large part due to bowel symptoms. However, it is unknown which bowel symptoms affect HRQoL the most. An enhanced understanding of this is essential to better focus treatment on this aspect of the disease. This study aimed to determine which bowel symptoms affect HRQoL the most in patients with midgut NETs. METHODS: Consenting patients with midgut NET completed the Memorial Sloan Kettering Bowel Function Instrument and the HRQoL questionnaire (EORTC QLQ-C30). The correlation between bowel symptoms and HRQoL was analysed using multiple linear regression, adjusting for age, Charlson Comorbidity Index score, presence of metastatic disease, chromogranin A, and BMI yielding ß-coefficients with 95% confidence intervals. RESULTS: Totally, 119 patients with midgut NET completed the questionnaires and were included in the study. Loose stool and bowel frequency = 3/day were the most common bowel symptoms, reported by 47% and 56% of patients, respectively. However, sensitivity to certain types of food and beverages, a feeling of incomplete emptying of the bowel, and soiling were the symptoms most strongly correlated with decreased HRQoL, especially within domains concerning role and social function, with ß-coefficients for the strongest correlated symptoms of 15.0 and 14.6, respectively. DISCUSSION: While symptoms concerning stool consistency and frequency are common in

patients with midgut NET, our study suggests that other, more socially stigmatising symptoms affect patients' HRQoL more. Our findings could help caregivers understand patients' perceptions of the disease and provide avenues for more directed therapies.
PubMed-ID: 33969447
http://dx.doi.org/10.1007/s00268-021-06146-9

Risk of preoperative understaging of duodenal neuroendocrine neoplasms: a plea for caution in the treatment strategy.
J Endocrinol Invest, 44(10):2227-34.
R. E. Rossi, A. C. Milanetto, V. Andreasi, D. Campana, J. Coppa, G. Nappo, M. Rinzivillo, P. Invernizzi, R. Modica, A. David, S. Partelli, G. Lamberti, V. Mazzaferro, A. Zerbi, F. Panzuto, C. Pasquali, M. Falconi and S. Massironi. 2021.
PURPOSE: Pretreatment staging is the milestone for planning either surgical or endoscopic treatment in duodenal neuroendocrine neoplasms (dNENs). Herein, a series of surgically treated dNEN patients was evaluated to assess the concordance between the pre- and postsurgical staging. METHODS: Retrospective analysis of patients with a histologically confirmed diagnosis of dNENs, who underwent surgical resection observed at eight Italian tertiary referral centers. The presurgical TNM stage, based on the radiological and functional imaging, was compared with the pathological TNM stage, after surgery. RESULTS: From 2000 to 2019, 109 patients were included. Sixty-six patients had G1, 26 a G2, 7 a G3 dNEN (Ki-67 not available in 10 patients). In 46/109 patients (42%) there was disagreement between the pre- and postsurgical staging, being it understaged in 42 patients (38%), overstaged in 4 (3%). As regards understaging, in 25 patients (22.9%), metastatic loco-regional nodes (N) resulted undetected at both radiological and functional imaging. Understaging due to the presence of distal micrometastases (M) was observed in 2 cases (1.8%). Underestimation of tumor extent (T) was observed in 12 patients (11%); in three cases the tumor was understaged both in T and N extent. CONCLUSIONS: Conventional imaging has a poor detection rate for loco-regional nodes and micrometastases in the presurgical setting of the dNENs. These results represent important advice when local conservative approaches, such as endoscopy or local surgical excision are considered and it represents a strong recommendation to include endoscopic ultrasound in the preoperative tools for a more accurate local staging.
PubMed-ID: 33651317
http://dx.doi.org/10.1007/s40618-021-01528-1

(68) Ga-DOTATATE PET/CT imaging in endogenous hyperinsulinemic hypoglycemia: A tertiary endocrine centre experience.
Clin Endocrinol (Oxf), 96(2):190-9.
R. Shah, M. Sehemby, R. Garg, N. Purandare, P. Hira, A. Mahajan, V. Lele, G. Malhotra, P. Verma, A. Rojekar, A. Dalvi, S. Uchino, S. Rastogi, A. Lila, V. Patil, N. Shah and T. Bandgar. 2022.
OBJECTIVE: Literature regarding utility of (68) Ga-DOTATATE PET/CT in insulinoma localization across various subgroups [benign/malignant/multiple endocrine neoplasia-1 (MEN-1) syndrome associated] remains scarce. In this study, the performance of (68) Ga-DOTATATE PET/CT was compared with contrast-enhanced computed tomography (CECT) and (68) Ga-NODAGA-Exendin-4 PET/CT (whenever available) in an endogenous hyperinsulinemic hypoglycemia (EHH) cohort. DESIGN: Retrospective audit. PATIENTS: EHH patients [N = 36, lesions (n) = 49, final diagnosis: benign sporadic insulinoma (BSI) (N = 20), malignant insulinoma (N = 4, n = 14), MEN-1 syndrome associated insulinoma (N = 9, n = 15), Munchausen syndrome (N = 2) and drug-induced hypoglycemia (N = 1)] having both preoperative imaging modalities (CECT and (68) Ga-DOTATATE PET/CT). MEASUREMENTS: Per-lesion sensitivity (Sn) and positive predictive value (PPV) for histopathological diagnosis of insulinoma. RESULTS: Sn and PPV of (68) Ga-DOTATATE PET/CT were 67.3% and 89.2%; 55% and 100%; 85.7% and 100%; and 66.7% and 77% for overall EHH, BSI, malignant, and MEN-1 syndrome associated insulinoma cohorts respectively. Despite having comparatively lower sensitivity in BSI cohort, (68) Ga-DOTATATE PET/CT localized a pancreatic tail lesion missed by other modalities. (68) Ga-DOTATATE PET/CT had comparatively higher sensitivity in malignant insulinoma than BSI cohort. (68) Ga-DOTATATE PET/CT also paved the way for successful response to (177) Lu-based peptide receptor radionuclide therapy (PRRT). In MEN-1 cases, lower PPV as compared with BSI was due to uptake in non-insulinoma pancreatic neuroendocrine tumours (Pan-NET). CONCLUSIONS: (68) Ga-DOTATATE PET/CT has supplemental role in selected cases of BSI with negative and/or discordant results with CECT and (68) Ga-NODAGA-Exendin-4 PET/CT. In malignant insulinoma, (68) Ga-DOTATATE-PET/CT has an additional theranostic potential. Interference due to uptake in non-insulinoma Pan-NET in MEN-1 syndrome may hinder insulinoma localization with (68) Ga-DOTATATE-PET/CT.
PubMed-ID: 34498757
http://dx.doi.org/10.1111/cen.14586

Survival Benefit of Primary Tumor Resection Among Elderly Patients with Pancreatic Neuroendocrine Tumors.
World J Surg, 45(12):3643-51.
J. Toyoda, K. Sahara, D. I. Tsilimigras, K. Miyake, Y. Yabushita, Y. Homma, T. Kumamoto, R. Matsuyama and T. M. Pawlik. 2021.
BACKGROUND: Pancreatectomy is the main curative therapeutic option for pancreatic neuroendocrine tumors (pNETs). Given the indolent behavior of pNETs and the relatively limited lifetime of elderly patients, the impact of primary site surgery (PSS) of pNETs on long-term outcomes among older patients has been a topic of debate. METHODS: Patients aged 70 or older with pNETs were identified in the Surveillance, Epidemiology and the End Results (SEER) database from 1998 to 2016. Propensity score matching was used to compare overall (OS) and cancer-specific survival (CSS) of patients who did versus did not undergo PSS. RESULTS: Among 2,319 elderly patients with pNETs, 942 patients (40.6%) underwent PSS, while 1,377 (59.4%) did not undergo PSS (non-PSS: NPSS). After propensity score matching (n = 433 in each group), PSS group had improved survival compared with the NPSS group (5-year OS: 53.4% vs. 37.3%; 5-year CSS: 77.2% vs. 58.1%, both $p < 0.001$). In contrast, subgroup analysis of individuals aged = 80 revealed no difference in 5-year CSS (PSS: 69.2% vs. NPSS: 67.4%, $p = 0.27$). A subgroup analysis among patients who had small (= 2 cm) non-functional (NF) pNETs noted comparable long-term outcomes among patients who underwent PSS versus NPSS patients (5-year OS: 73.1% vs. 66.5%, $p = 0.19$; 5-year CSS: 98.5% vs. 95.2%, $p = 0.14$). CONCLUSIONS: Approximately 2 in 5 elderly patients with pNETs underwent PSS. While PSS was generally associated with prolonged OS and CSS among older patients, PSS was not associated with improved CSS among a subset of patients aged 80 or older, as well as among patients age = 70 years with NF-pNET less than 2 cm.
PubMed-ID: 34379172
http://dx.doi.org/10.1007/s00268-021-06281-3

ASO Author Reflections: Endoscopic Management is Reasonable for <2 cm Duodenal Neuroendocrine Tumors.
Ann Surg Oncol, 29(1):85-6.
C. G. Tran, S. K. Sherman and J. R. Howe. 2022.
Optimal management of duodenal neuroendocrine tumors (DNETs) has not been well-defined, especially for DNETs 1-2 cm in size. Recent studies comparing endoscopic mucosal resection (EMR) and surgical resection demonstrate EMR is safe and effective for these intermediate-sized DNETs. Expert and consensus guidelines could consider updating recommendations to reflect the outcomes of EMR in DNETs and the importance of endoscopic surveillance in these patients to evaluate for local recurrence.
PubMed-ID: 34608558
http://dx.doi.org/10.1245/s10434-021-10859-5

It's more than just cancer biology: Health disparities in patients with pancreatic neuroendocrine tumors.
J Surg Oncol, 124(8):1390-401.
P. W. Underwood, A. N. Riner, D. Neal, M. E. Cameron, A. Yakovenko, S. Reddy, J. B. Rose, S. J. Hughes and J. G. Trevino. 2021.
BACKGROUND AND OBJECTIVES: Pancreatic neuroendocrine tumors (PNETs) represent a rare form of pancreatic cancer. Racial/ethnic disparities have been documented in pancreatic ductal adenocarcinoma, but health disparities have not been well described in patients with PNETs. METHODS: A retrospective review of patients with PNETs in the National Cancer Database was performed for 2004-2014. Approximately 16 605 patients with PNETs and available vital status were identified. Survival was compared by race/ethnicity and socioeconomic status using Kaplan-Meier methods and Cox regression. RESULTS: There were no significant differences in survival between Non-Hispanic, White; Hispanic, White; or Non-Hispanic, Black patients on univariate analysis. Kaplan-Meier analysis showed that patients from communities with lower median household income and education level had worse survival ($p < 0.001$). Patients age less than 65 without insurance, similarly, had worse survival ($p < 0.001$). Multivariable modeling found no association between race/ethnicity and risk of mortality ($p = 0.37$). Lower median household income and lower education level were associated with increased mortality ($p < 0.001$). CONCLUSIONS: Unlike most other malignancies, race/ethnicity is not associated with survival differences in patients with PNETs. Patients with lower socioeconomic status had worse survival. The presence of identifiable health disparities in patients with PNETs represents a target for intervention and opportunity to improve survival in patients with this malignancy.
PubMed-ID: 34499741
http://dx.doi.org/10.1002/jso.26667

Evaluation of radical surgical treatment in the management of 58 locally advanced rectal neuroendocrine neoplasms, one multicenter retrospective study.
Eur J Surg Oncol, 47(12):3166-74.
Z. Wang, Z. Liu, Z. Wen, R. Li, K. An, S. Mei, J. Chen, H. Shen, J. Li, F. Zhao, F. Wei, T. Xiao and Q. Liu. 2021.
BACKGROUND: Locally advanced rectal neuroendocrine neoplasms (NENs) are rare, and the therapeutic effects of surgery in improving the prognosis have been questioned in previous reports. MATERIALS AND METHODS: The research included 58 consecutive patients with locally advanced rectal NENs from three Chinese medical centers between 2000 and 2020. All have received radical surgical treatment. The clinicopathological and survival data were collected. Kaplan-Meier methods and a Cox proportional hazards regression model were used to evaluate the prognosis and identify independent prognostic factors. RESULTS: All patients were followed up for a median period of 36 (2-125) months. Of the 58 patients, 13 (22.4%) had G1 neuroendocrine tumors (NETs), 15 (25.9%) had G2 NETs, 6 (10.3%) had G3 NETs, and the remaining 24 (41.4%) patients had G3 neuroendocrine carcinomas (NECs). The 1-year and 3-year disease-free survival (DFS) rates were 64.5% and 48.8%, respectively. The 1-year and 3-year overall survival (OS) rates were 90.5% and 75.4%, respectively. Univariate analysis demonstrated that tumor differentiation (p = 0.002), gross morphology (p = 0.009), T stage (p = 0.024), and extramural vascular invasion (p = 0.009) were associated with the OS. The subsequent multivariate analysis confirmed that tumor differentiation [hazard ratio (HR) = 6.002, 95% confidence interval (CI): 1.210-29.767, p = 0.028] and gross morphology (HR = 3.438, 95% CI: 1.038-11.382, p = 0.043) were independent prognostic factors affecting the clinical outcomes. CONCLUSIONS: Rectal NENs are a heterogeneous group of diseases. The survival benefits obtained from surgery vary widely based on the tumor clinicopathological features. Patients with G3 NECs and ulcerative mass are at high risks of poor prognosis.
PubMed-ID: 34294465
http://dx.doi.org/10.1016/j.ejso.2021.07.010

Peptide Receptor Radionuclide Therapy With 177Lu-DOTATATE for Symptomatic Control of Refractory Carcinoid Syndrome.
J Clin Endocrinol Metab, 106(9):e3665-e72.
W. T. Zandee, T. Brabander, A. Blaževic, N. S. Minczeles, R. A. Feelders, W. W. de Herder and J. Hofland. 2021.
CONTEXT: Peptide receptor radionuclide therapy (PRRT) with [Lutetium-177-DOTA0-Tyr3]octreotate (177Lu-DOTATATE) results in an increase of progression-free survival and quality of life in patients with progressive, well-differentiated neuroendocrine neoplasms (NENs). OBJECTIVE: To study the effect of 177Lu-DOTATATE in patients with carcinoid syndrome and radiologically stable or newly diagnosed disease treated solely for the purpose of symptom reduction. DESIGN: Retrospective cohort study. SETTING: Tertiary care hospital. PATIENTS: Twenty-two patients with a metastatic midgut NEN, elevated urinary 5-hydroxyindolacetic acid excretion, and flushing and/or diarrhea despite treatment with a somatostatin analog, without documented disease progression. INTERVENTION: PRRT with 177Lu-DOTATATE (intended cumulative dose: 29.6 GBq) with a primary aim to reduce symptoms. RESULTS: After PRRT, mean bowel movement frequency (BMF) decreased from 6.1 ± 3.4 to 4.6 ± 3.6 per day (P = 0.009). Flushes decreased from 4.3 ± 2.9 to 2.4 ± 2.7 flushes per day (P = 0.002). A decrease of BMF of more than 30% occurred in 47% of patients with baseline BMF of 4 or more (n = 17). In patients with =2 episodes of flushing a day (n = 15), 67% of patients had more than 50% decrease of daily flushing. A decrease in urinary 5-hydroxyindolacetic acid excretion of more than 30% was seen in 56% of patients. The European Organization for Research and Treatment of Cancer-Core Module diarrhea subscale score showed a trend toward improvement by an average of 16.7 ± 33.3 points (P = 0.11). CONCLUSION: PRRT with 177Lu-DOTATATE effectively reduced diarrhea and flushing in patients with carcinoid syndrome and can be considered for symptomatic treatment of carcinoid syndrome insufficiently controlled with somatostatin analogs.
PubMed-ID: 33942075
http://dx.doi.org/10.1210/clinem/dgab289

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden.
Ann Surg, 274(6):e1202-e8.
M. Annebäck, J. Hedberg, M. Almquist, P. Stålberg and O. Norlén. 2021.
OBJECTIVE: To investigate the prevalence and risk factors for permanent hypoparathyroidism after total thyroidectomy for benign disease in a population-based setting with data independent of input of complication data. SUMMARY OF BACKGROUND DATA: The reported rate of permanent hypoparathyroidism is highly variable and mostly rely on reported complication data from national or institutional registries. METHODS: All patients who underwent total thyroidectomy in Sweden from 2005 to 2015 were identified through Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery and the Swedish National Patient Register. Patients were matched to outcome data from the Swedish Prescribed Drug Register. Permanent hypoparathyroidism was defined as treatment with calcium and/or active vitamin D more than 1 year after surgery. RESULTS: Seven thousand eight hundred fifty-two patients were included and 938 (12.5%) developed permanent hypoparathyroidism. The risk was lower in patients registered in the quality register (11.0% vs 16%, P < 0.001). In a multivariable analysis there was a higher risk of permanent hypoparathyroidism in patients with parathyroid autotransplantation [Odds ratio (OR) 1.72; 95% confidence interval 1.47-2.01], center-volume <100 thyroidectomies per year (OR 1.22; 1.03-1.44), age above 60 year (OR 1.64; 1.36-1.98) and female sex (OR 1.27; 1.05-1.54). Reported data from the quality register only identified 178 of all 938 patients with permanent hypoparathyroidism. CONCLUSION: The risk of permanent hypoparathyroidism after total thyroidectomy was high and associated with parathyroid autotransplantation, higher age, female sex and surgery at a low volume center. Reported follow-up data might underestimate the rate of permanent hypoparathyroidism.
PubMed-ID: 32032086
http://dx.doi.org/10.1097/SLA.0000000000003800

Paraganglioma and other tumour detection rates in individuals with SDHx pathogenic variants by age of diagnosis and after the age of 50.
Clin Endocrinol (Oxf), 95(3):447-52.
S. E. Greenberg, R. Holman, W. Kohlmann, L. Buchmann and A. Naumer. 2021.
OBJECTIVE: Patients with SDHx germline mutations (SDHA, AF2, B, C, D) are at risk for paragangliomas (PGLs), renal cell carcinoma and gastrointestinal stromal tumours. The aim of this study was to evaluate the age of SDHx tumour diagnosis in those with pathogenic variants (PVs), notably tumour detection after the age of 50 years. STUDY DESIGN: Longitudinal retrospective observational analysis. PATIENTS: Individuals with SDHx PVs. MEASUREMENTS: Demographic, clinical, genetic, screening and tumour detection and treatment data were abstracted from the electronic medical record. Descriptive analysis was utilised. RESULTS: A total of 165 patients with SDHx PVs from 34 families were evaluated. Sixty-eight patients (41.2%) had at least one known SDHx-related tumour in their history, identified through symptoms,

screening or incidentally. The average age of SDHx-related tumour diagnosis was 32.0 years. Age of diagnosis varied by the gene. Nine patients (n = 50; 18.0%) were identified with a tumour after the age of 50, identified via baseline screening after PV identification, or due to symptoms before molecular SDHx diagnosis. CONCLUSIONS: Though tumours were identified in individuals above the age of 50; they were all identified on baseline screening or due to symptoms, confirming that baseline screening is essential. Given the slow-growing nature of PGLs, these tumours might have been discovered before age 50 if molecular diagnosis and baseline screening had occurred earlier. Considering discontinuing screening after age 50 may be warranted if baseline screen imaging is negative and the individual does not have a prior tumour history.
PubMed-ID: 34255389
http://dx.doi.org/10.1111/cen.14559

Effect of Medialization on Dyspnea Index in Unilateral Vocal Fold Paralysis.
Otolaryngol Head Neck Surg:1945998211056515.
M. R. Hoffman, B. Vandiver, N. Derise, E. R. Hapner, G. Leverson and C. B. Simpson. 2021.
OBJECTIVE: Patients with unilateral vocal fold paralysis commonly report dysphonia and dysphagia. Dyspnea also occurs, with studies on treatment-related change producing mixed results. Studies including patient-reported outcomes have focused on single-question global scales. The Dyspnea Index (DI) includes 10 questions, is specific to upper airway-related dyspnea, and may better capture these patients' symptoms. We evaluated change in DI after treatment. STUDY DESIGN: Retrospective review. SETTING: Academic medical center. METHODS: Forty-three patients with unilateral vocal fold paralysis underwent injection augmentation (n = 25) or framework surgery (n = 18). DI was recorded preprocedure, 2 to 4 weeks afterward, and at approximately 3 months afterward in 19 patients. Voice Handicap Index-10, Glottal Function Index, Cough Severity Index, and Eating Assessment Tool-10 were also recorded. Change in parameters and correlations were assessed. Obesity, cardiac disease, pulmonary disease, and procedure (injection vs framework surgery) were evaluated for effect on DI. RESULTS: Twenty-four patients had an abnormal baseline DI (>10). DI decreased from 14.9 ± 13.8 to 6.5 ± 9.3 after treatment (P < .001; 95% CI, 4.7-12.1). Twenty-eight scores decreased, 9 remained unchanged, and 6 increased. Change in DI was influenced by the presence of cardiac disease. Decreased DI persisted at 3-month follow-up. Voice Handicap Index-10, Glottal Function Index, Cough Severity Index, and Eating Assessment Tool-10 scores decreased and were correlated with change in DI. CONCLUSION: Upper airway-related dyspnea is common in unilateral vocal fold paralysis, occurring in half of this cohort. Correcting glottic insufficiency may alleviate symptoms. Treatment decision making should consider postprocedural change in dyspnea, especially in patients for whom dyspnea is a motivating factor for seeking treatment.
PubMed-ID: 34752158
http://dx.doi.org/10.1177/01945998211056515

A practical guide to genetic testing in endocrinology.
Clin Endocrinol (Oxf),
L. Izatt, M. M. Owens, H. Pierce, S. Wilcox and S. M. Park. 2021.
Rapid advances in sequencing technology have led to significant improvements in genomic analysis, resulting in increased understanding of the molecular basis of many endocrine conditions. Genomic testing for rare disease is being integrated into everyday clinical practice, as the importance of confirming a genetic diagnosis earlier in a patient's pathway helps direct their clinical care and specialized management. In England, the new nationally commissioned Genomic Medicine Service has started to deliver testing for rare and inherited disease and cancer somatic tissue via seven Genomic Laboratory Hubs. The range of genetic tests, technology employed and eligibility criteria for patient testing are all defined in the National Genomic Test Directory. This review provides practical guidance on how to access genomic testing for endocrine disease, how to interpret and relay results, and details how genetic counselling can help integrate results into ongoing care of the individual and their family. This article discusses general principles as well as specifics related to the process of genomic testing in England. We illustrate mainstream genetic testing with a clinical scenario involving an individual with inherited endocrine neoplasia, followed by a generic description of the different steps involved, including informed consent to proceed to diagnostic testing. Most genetic tests analyse multiple genes simultaneously by next-generation sequencing, and variant interpretation may yield not only pathogenic explanatory results, but also ambiguous outcomes, with variants of unknown significance or incidental findings. Delivery of results and posttest genetic counselling are therefore key components of integrating genetic testing into routine endocrine care.
PubMed-ID: 34528717
http://dx.doi.org/10.1111/cen.14596

Long-term voice changes after thyroidectomy: Results from a validated survey.
Surgery, 170(6):1687-91.
C. Li, B. Lopez, S. Fligor, J. M. Broekhuis, A. Maeda, S. Duncan, H. W. Chen, A. Choudhary, S. Budwani, P. O. Hasselgren, P. Mowschenson, P. S. Mallur and B. C. James. 2021.
BACKGROUND: Long-term dysphonia may persist after thyroid surgery even in the absence of overt nerve injury. Therefore, we evaluated long-term dysphonia after thyroidectomy using a validated survey. METHODS: Patients undergoing thyroidectomy at a single institution from 1990 to 2018 were surveyed via telephone to complete the Voice Handicap Index-10 Survey. Individuals with documented nerve injury were excluded. RESULTS: In total, 308 patients completed the survey (mean age 51 ± 14 years, 78% female). Median time since surgery was 10.7 (interquartile range 2.3-17.5) years. The mean Voice Handicap Index-10 Survey score was 2.6 ± 5.2. Of the 113 (37%) patients who reported subjective dysphonia, the mean Voice Handicap Index-10 Survey score was 7.1 ± 6.5. Twenty-two (7.1%) patients had a Voice Handicap Index-10 Survey score above the empiric normative cutoff of 11, with a mean score of 17.6 ± 6.8. The most frequent complaints included "The clarity of my voice is unpredictable" (N = 71, 23%), "People have difficulty understanding me in a noisy room" (N = 70, 23%), and "I feel as though I have to strain to produce voice" (N = 65, 21%). CONCLUSION: Long-term follow-up of patients after thyroidectomy suggests that more than 30% without nerve injury report dysphonia. Research to further assess the etiology and impact of these changes on quality of life is needed.
PubMed-ID: 34344524
http://dx.doi.org/10.1016/j.surg.2021.04.060

Serum Inflammation-based Scores in Endocrine Tumors.
J Clin Endocrinol Metab, 106(10):e3796-e819.
P. Marques, F. de Vries, O. M. Dekkers, M. Korbonits, N. R. Biermasz and A. M. Pereira. 2021.
CONTEXT: Serum inflammation-based scores reflect systemic inflammatory response and/or patients' nutritional status, and may predict clinical outcomes in cancer. While these are well-described and increasingly used in different cancers, their clinical usefulness in the management of patients with endocrine tumors is less known. EVIDENCE ACQUISITION: A comprehensive PubMed search was performed using the terms "endocrine tumor," "inflammation," "serum inflammation-based score," "inflammatory-based score," "inflammatory response-related scoring," "systemic inflammatory response markers," "neutrophil-to-lymphocyte ratio," "neutrophil-to-platelet ratio," "lymphocyte-to-monocyte ratio," "Glasgow prognostic score," "neutrophil-platelet score," "Systemic Immune-Inflammation Index," and "Prognostic Nutrition Index" in clinical studies. EVIDENCE SYNTHESIS: The neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio are the ones most extensively investigated in patients with endocrine tumors. Other scores have also been considered in some studies. Several studies focused in finding whether serum inflammatory biomarkers may stratify the endocrine tumor patients' risk and detect those at risk for developing more aggressive and/or refractory disease, particularly after endocrine surgery. CONCLUSIONS: In this review, we summarize the current knowledge on the different serum inflammation-based scores and their usefulness in predicting the phenotype, clinical aggressiveness, and disease outcomes and prognosis in patients with endocrine tumors. The value of such serum inflammation-based scores in the management of patients with endocrine tumors has been emerging over the last decade. However, further research is necessary to establish useful markers and their cut-offs for routine clinical practice for individual diseases.
PubMed-ID: 33837783
http://dx.doi.org/10.1210/clinem/dgab238

Children with multiple endocrine neoplasia type 2B: Not tall and marfanoid, but short with normal body proportions.
Clin Endocrinol (Oxf), 95(3):453-9.
M. F. M. van den Broek, H. M. van Santen, G. D. Valk and A. A. Verrijn Stuart. 2021.
OBJECTIVE: Multiple endocrine neoplasia 2B (MEN2B) is characterised by early-onset medullary thyroid carcinoma (MTC), pheochromocytoma and several nonendocrine manifestations. Unfortunately, MEN2B is often diagnosed late, after the development of clinically significant MTC. Marfanoid habitus is considered an important related feature, which may lead to the assumption that patients with MEN2B have tall stature. Here, we describe the longitudinal growth and body proportions of eight MEN2B patients during childhood. DESIGN: It is a retrospective case series. METHODS: Patients were under the care of a Dutch MEN expertise centre. Growth patterns were assessed and interpreted in relation to body mass index (BMI), age at diagnosis and at thyroidectomy, extensiveness of disease manifestations and parental height. RESULTS: Seven patients were short during childhood, of whom four showed growth below target height range (THR) and three at the lowest margin of THR. Only one patient grew well within THR. All patients who attained final height (n = 4) ended within THR, despite short stature during childhood. Arm span/height ratio was not increased and upper segment/lower segment ratio was not reduced in any patient. Short stature in childhood in this study did not seem to be associated with

age at diagnosis, age at thyroidectomy, extensiveness of MTC, endocrine deficiencies or BMI. CONCLUSIONS: This study shows that children with MEN2B may well present with short rather than tall stature. Thereafter, final height within THR was attained in those who already reached adulthood, but none had tall stature. Finally, body proportions were normal in all children and adults in this case series, not underlining a 'marfanoid' body habitus.
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