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
Cancer	6.860	Langenbecks Arch Surg	3.445
Chirurg	0.955	Laryngoscope	3.325
Clin Endocrinol Oxf	3.478	N Engl J Med	91.245
Clin Nucl Med	7.794	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	43.330
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
Endocr Rev	19.871	Neuroendocrinology	4.914
Eur Arch Otorhinolaryngol	2.503	Oncologist	5.550
Eur J Endocrinol	6.664	Otolaryngol Head Neck Surg	3.497
Eur J Surg Oncol	4.424	Surg Clin North Am	2.741
Gland Surg	2.953	Surg Endosc	4.584
Head Neck	3.147	Surg Laparosc Endosc Percutan Tech	1.719
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

Long-term efficacy and safety of percutaneous ethanol injection (PEI) in cystic thyroid nodules: A systematic review and meta-analysis.
Clin Endocrinol (Oxf), 96(2):97-106.
R. Cesareo, G. Tabacco, A. M. Naciu, A. Crescenzi, S. Bernardi, F. Romanelli, M. Deandrea, P. Trimboli, A. Palermo and M. Castellana. 2022.
BACKGROUND: Percutaneous ethanol injection (PEI) is used for the treatment of benign cystic thyroid nodules. This systematic review and meta-analysis aimed to obtain strong evidence of its long-term efficacy and safety. METHODS: PubMed, CENTRAL, Scopus and Web of Science databases were searched until November 2020 for studies reporting data on volume reduction rate (VRR), compressive symptoms and cosmetic concerns. Associated complications were assessed. A random-effects model was designed to pool the data. RESULTS: Out of 385 papers, nine studies evaluating 1667 nodules were finally included. Overall, VRR at 6, 12, 24, 36, 60 and 120 months was 77%, 81%, 72%, 68%, 74% and 69%, respectively. Significant reductions in the compressive symptoms and cosmetic concerns were observed. No permanent complications were observed. CONCLUSIONS: The present meta-analysis showed that PEI could significantly reduce the volume of benign cystic thyroid nodules. This reduction was already effective at 6 months post-treatment, and the effect was stable over time.
PubMed-ID: 34028855
http://dx.doi.org/10.1111/cen.14530

The influence of incidental detection of thyroid nodule on thyroid cancer risk and prognosis-A systematic review.
Clin Endocrinol (Oxf), 96(2):246-54.
J. E. Chooi, A. Ravindiran and S. P. Balasubramanian. 2022.
BACKGROUND: Clinically inapparent thyroid nodules discovered serendipitously on imaging for nonthyroid indications are termed as thyroid incidentalomas. It is unclear whether these incidentalomas have a lower prevalence of malignancy or slower tumour progression compared to symptomatic nodules. The aims of this systematic review were to determine the impact of incidental detection of thyroid nodules on both the risk of malignancy and on prognosis in patients with thyroid cancer. METHOD: PubMed and MEDLINE(r) on Web of Science databases were searched from inception to March 2020 for English language articles reporting on human studies of thyroid cancer risk and/or prognosis in incidental and nonincidental nodules. RESULTS: Eighteen observational studies published between 1998 and 2020 were eligible for analysis; four studies reported on risk, nine on prognosis and five studies reported on both risk and prognosis. When comparing the incidental and nonincidental groups in the risk study, the odds of incidental detection in the cancer and benign groups ranged from 0.16 to 0.5 and 0.06 to 0.38, respectively (odds ratio [OR] = 0.64-2.86) in case-control studies (n = 6); the risk of malignancy for thyroid nodules ranged from 4% to 23.5% in the incidental and 3.8% to 28.7% in the nonincidental groups (relative risk = 0.13-6.27) in the cohort studies (n = 3). A meta-analysis of the eligible case-control studies (n = 3) showed a nonsignificant summated OR of 1.04 (95% confidence interval = 0.63-1.70; p = .88). In the prognosis study, five direct and thirteen indirect markers of prognosis were compared between the incidental and nonincidental groups. A meta-analysis was not possible but incidentally detected thyroid cancer had better progression-free and overall survival. CONCLUSION: Current evidence suggests that investigation and management of thyroid nodules should not be influenced by the mode of detection.
PubMed-ID: 34378225
http://dx.doi.org/10.1111/cen.14575

ERAS Protocols for Thyroid and Parathyroid Surgery: A Systematic Review and Meta-analysis.
Otolaryngol Head Neck Surg, 166(3):425-33.
K. Chorath, N. Luu, B. C. Go, A. Moreira and K. Rajasekaran. 2022.
OBJECTIVE: Enhanced recovery after surgery (ERAS) protocols are evidenced-based multidisciplinary programs implemented in the perioperative setting to improve postoperative recovery and attenuate the surgical stress response. However, evidence on their effectiveness in thyroid and parathyroid surgery remains sparse. Therefore, our goal was to investigate the clinical benefits and cost-effectiveness of ERAS protocols for the perioperative management of thyroidectomy and parathyroidectomy. DATA SOURCE: A systematic review of Medline, Scopus, Embase, and gray

literature was performed to identify studies of ERAS or clinical care protocols for thyroidectomy and parathyroidectomy. REVIEW METHODS: Two reviewers screened studies using predetermined inclusion criteria. Our primary outcomes included hospital length of stay and hospital costs. Readmission and postoperative complication rates composed our secondary outcomes. Meta-analysis was performed to compare outcomes for patients enrolled in the ERAS protocol versus standard of care. RESULTS: A total of 450 articles were identified; 7 (1.6%) met inclusion criteria with a total of 3082 patients. Perioperative components in ERAS protocols varied across the studies. Nevertheless, patients enrolled in ERAS protocols had reduced hospital length of stay (mean difference, -0.64 days [95% CI, -0.92 to -0.37]) and hospital costs (in US dollars; mean difference, -307.70 [95% CI, -346.49 to -268.90]), without an increase in readmission (odds ratio, 0.75 [95% CI, 0.29-1.94]) or complication rates (odds ratio, 1.14 [95% CI, 0.82-1.57]). CONCLUSION: There is growing literature supporting the role of ERAS protocols for the perioperative management of thyroidectomy and parathyroidectomy. These protocols significantly reduce hospital length of stay and costs without increasing complications or readmission rates.
PubMed-ID: 34126805
http://dx.doi.org/10.1177/01945998211019671

Active Surveillance Versus Thyroid Surgery for Differentiated Thyroid Cancer: A Systematic Review.
Thyroid, 32(4):351-67.
R. Chou, T. Dana, M. Haymart, A. M. Leung, R. P. Tufano, J. A. Sosa and M. D. Ringel. 2022.
Background: Active surveillance has been proposed as an appropriate management strategy for low-risk differentiated thyroid cancer (DTC), due to the typically favorable prognosis of this condition. This systematic review examines the benefits and harms of active surveillance vs. immediate surgery for DTC, to inform the updated American Thyroid Association guidelines. Methods: A search on Ovid MEDLINE, Embase, and Cochrane Central was conducted in July 2021 for studies on active surveillance vs. immediate surgery. Studies of surgery vs. no surgery for DTC were assessed separately to evaluate relevance to active surveillance. Quality assessment was performed, and evidence was synthesized narratively. Results: Seven studies (five cohort studies [N = 5432] and two cross-sectional studies [N = 538]) of active surveillance vs. immediate surgery, and seven uncontrolled treatment series of active surveillance (N = 1219) were included. One cross-sectional study was rated fair quality, and the remainder were rated poor quality. In patients with low risk (primarily papillary), small (primarily =1 cm) DTC, active surveillance, and immediate surgery were associated with similar, low risk of all-cause or cancer-specific mortality, distant metastasis, and recurrence after surgery. Uncontrolled treatment series reported no cases of mortality in low-risk DTC managed with active surveillance. Among patients managed with active surveillance, rates of tumor growth were low; rates of subsequent surgery varied and primarily occurred due to patient preference rather than tumor progression. Four cohort studies (N = 88,654) found that surgery associated with improved all-cause or thyroid cancer mortality compared with nonsurgical management, but findings were potentially influenced by patient age and tumor risk category and highly susceptible to confounding by indication; eligibility for, and receipt of, active surveillance; and timing of surgery was unclear. Conclusions: In patients with small low-risk (primarily papillary) DTC, active surveillance and immediate surgery may be associated with similar mortality, risk of recurrence, and other outcomes, but methodological limitations preclude strong conclusions. Studies of no surgery vs. surgery are difficult to interpret due to clinical heterogeneity and potential confounding factors and are unsuitable for assessing the utility of active surveillance. Research is needed to clarify the benefits and harms of active surveillance and determine outcomes in nonpapillary DTC, larger (>1 cm) cancers, and older patients.
PubMed-ID: 35081743
http://dx.doi.org/10.1089/thy.2021.0539

Suboptimal accuracy of ultrasound and ultrasound-based risk stratification systems in detecting medullary thyroid carcinoma should not be overlooked. Findings from a systematic review with meta-analysis.
Clin Endocrinol (Oxf),
G. Ferrarazzo, C. Camponovo, M. Deandrea, A. Piccardo, L. Scappaticcio and P. Trimboli. 2022.
OBJECTIVE: Ultrasound (US) is the pivotal procedure during the diagnostic work-up of thyroid nodule and several US-based risk stratification systems (RSSs) have been recently developed. Since the performance of RSSs in detecting medullary thyroid carcinoma (MTC) has been rarely investigated, the present systematic review aimed to achieve high evidence about (1) how MTC is classified according to RSSs; (2) if RSSs correctly classify MTC at high risk/suspicion, and (3) if MTC is classified as suspicious at US when RSSs are not used. DESIGN: The review was performed according to MOOSE. The online search was performed by specific algorithm on January 2022. A random-effects model was used for statistical analysis. RESULTS: Twenty-five papers were initially included and their risk of bias was generally low. According to ATA system, 65% of MTCs was assessed at high suspicion and 25% at intermediate suspicion. Considering all RSSs, a 54.8% of MTCs was put in a high-risk/suspicion category. Pooling data from studies without data of RSS the prevalence of ultrasonographically

suspicious MTCs was 60%. CONCLUSIONS: As conclusion, MTC presentation according to RSSs is partially known and it is classified in a high-risk/suspicion category of RSSs in just over a half of cases. This advises for further studies, ideally supported by international societies, to better define the US presentation of MTC.
PubMed-ID: 35419855
http://dx.doi.org/10.1111/cen.14739

Near-infrared autofluorescence-based parathyroid glands identification in the thyroidectomy or parathyroidectomy: a systematic review and meta-analysis.
Langenbecks Arch Surg, 407(2):491-9.
D. H. Kim, S. Lee, J. Jung, S. Kim, S. W. Kim and S. H. Hwang. 2022.
PURPOSE: To evaluate the diagnostic accuracy of near-infrared autofluorescence-based identification in the identification of parathyroid glands during thyroidectomy or parathyroidectomy. METHODS: The clinical studies were retrieved from PubMed, the Cochrane Central Register of Controlled Trials, Embase, Web of Science, SCOPUS, and Google Scholar. The study protocol was registered on Open Science Framework (https://osf.io/um8rj/). The search period ranged from the date of each database's inception to May 2021. Cohort studies dealing with patients of whom parathyroid glands were detected by near-infrared autofluorescence and confirmed clinically or pathologically during thyroidectomy or parathyroidectomy were included. Editorials, letters, "how-I-do-it" descriptions, other site head and neck tumors, and articles with lack of diagnostic identification data were excluded. True positive, true negative, false positive, and false negative were extracted. The QUDAS ver. 2 was used to evaluate the methodological quality. RESULTS: Seventeen studies with 1198 participants were evaluated in this analysis. Near-infrared autofluorescence-based identification of parathyroid glands showed a diagnostic odds ratio of 228.8759 (95% confidence interval, 134.1099; 390.6063). The area under the summary receiver operating characteristic curve was 0.967. The sensitivity, specificity, negative predictive value, and positive predictive value were 0.9693 (0.9491; 0.9816), 0.9248 (0.8885; 0.9499), 0.9517 (0.8981; 0.9778), and 0.9488 (0.9167; 0.9689), respectively. Subgroup analyses were performed to compare two autofluorescence detection methods, because there was high heterogeneity in the outcomes. The diagnostic accuracy was higher in probe-based detection than in image-based detection. CONCLUSIONS: Near-infrared autofluorescence-based identification is valuable for identifying the parathyroid glands of patients during thyroidectomy or parathyroidectomy.
PubMed-ID: 34322746
http://dx.doi.org/10.1007/s00423-021-02269-8

Parathyroid allotransplantation for the treatment of permanent hypoparathyroidism: A systematic review.
Am J Surg, 223(4):652-61.
E. Kim, K. M. Ramonell, N. Mayfield and B. Lindeman. 2022.
BACKGROUND: Hypoparathyroidism is the most common complication of bilateral operations in the central neck. No formal guidelines exist for the management of permanent hypoparathyroidism. Current treatment involving medical supplementation increases resource utilization and patient morbidity while decreasing quality of life. Parathyroid allotransplant (PA) offers a promising therapy; however, the optimal technique and role of immunosuppression (IS) in PA remain unclear. METHODS: We performed a systematic search of the Embase, MEDLINE, and Cochrane Library databases to identify studies investigating PA for treatment of hypoparathyroidism. RESULTS: A total of 24 studies including 186 individual allograft transplants in 146 patients were identified. Pooled graft survival for allotransplants in transplant-naïve vs prior transplant recipients was 29.9% and 80%, respectively. CONCLUSIONS: PA using normocellular, fresh parathyroid donor tissue that is ABO-compatible, with induction and, at minimum, short-term maintenance IS presents a potentially safe and effective therapeutic option for permanent hypoparathyroidism in patients tolerating IS.
PubMed-ID: 34304848
http://dx.doi.org/10.1016/j.amjsurg.2021.07.025

Letter to the editors on 'Clinical efficacy of lenvatinib for the treatment of radioiodine-refractory thyroid carcinoma: A systematic review and meta-analysis of clinical trials'.
Clin Endocrinol (Oxf),
Y. R. Li, S. Y. Wang and C. N. Yeh. 2021.
PubMed-ID: 34288014
http://dx.doi.org/10.1111/cen.14565

Current therapeutic options for low-risk papillary thyroid carcinoma: Scoping evidence review.
Head Neck, 44(1):226-37.
A. Sanabria, P. Pinillos, R. B. Lira, J. P. Shah, R. P. Tufano, M. E. Zafereo, I. J. Nixon, G. W. Randolph, R. Simo, V. Vander Poorten, A. Rinaldo, J. E. Medina, A. Khafif, P. Angelos, A. A. Mäkitie, A. R. Shaha, J. P. Rodrigo, D. M. Hartl, L. P. Kowalski and A. Ferlito. 2022.
Most cases of thyroid carcinoma are classified as low risk. These lesions have been treated with open surgery, remote access thyroidectomy, active surveillance, and percutaneous ablation. However, there is lack of consensus and clear indications for a specific treatment selection. The objective of this study is to review the literature regarding the indications for management selection for low-risk carcinomas. Systematic review exploring inclusion and exclusion criteria used to select patients with low-risk carcinomas for treatment approaches. The search found 69 studies. The inclusion criteria most reported were nodule diameter and histopathological confirmation of the tumor type. The most common exclusions were lymph node metastasis and extra-thyroidal extension. There was significant heterogeneity among inclusion and exclusion criteria according to the analyzed therapeutic approach. Alternative therapeutic approaches in low-risk carcinomas can be cautiously considered. Open thyroidectomy remains the standard treatment against which all other approaches must be compared.
PubMed-ID: 34590380
http://dx.doi.org/10.1002/hed.26883

Predictive factors of radioiodine therapy failure in Graves' Disease: A meta-analysis.
Am J Surg, 223(2):287-96.
M. Shalaby, D. Hadedeya, E. A. Toraih, M. A. Razavi, G. S. Lee, M. H. Hussein, M. C. Weidenhaft, M. J. Serou, K. Ibraheem, M. Abdelgawad and E. Kandil. 2022.
BACKGROUND: I-131 therapy is a common treatment modality for adults with Graves' Disease (GD). Utilizing meta-analysis, we examined patient specific factors that predict I-131 therapy failure. METHODS: Literature search followed PRISMA. Comprehensive Meta-analysis (version 3.0) was used. Mantel-Haenszel test with accompanying risk ratio and confidence intervals evaluated categorical variables. Continuous data was analyzed using inverse variance testing yielding mean difference or standardized mean difference. Decision tree algorithms identified variables of high discriminative performance. RESULTS: 4822 collective patients across 18 studies were included. Male sex (RR = 1.23, 95%CI = 1.08-1.41, p = 0.002), I-131 therapy 6 months after GD diagnosis (RR = 2.10, 95%CI = 1.45-3.04, p < 0.001) and history of anti-thyroid drugs (RR = 2.05, 95%CI = 1.49-2.81, p < 0.001) increased the risk of I-131 therapy failure. Elevated free thyroxine, 24-h radioactive iodine uptake scan =60.26% and thyroid volume =35.77 mL were also associated with failure. CONCLUSION: Patient characteristics can predict the likelihood of I-131 therapy failure in GD. Definitive surgical treatment may be a reasonable option for those patients.
PubMed-ID: 33865565
http://dx.doi.org/10.1016/j.amjsurg.2021.03.068

Reply: Clinical efficacy of lenvatinib for the treatment of radioiodine-refractory thyroid carcinoma: A systematic review and meta-analysis of clinical trials.
Clin Endocrinol (Oxf),
J. Su, Y. Fu, M. Wang and S. Lin. 2022.
PubMed-ID: 35261050
http://dx.doi.org/10.1111/cen.14718

Trainee participation does not adversely affect the safety of thyroid surgery: Systematic review and meta-analysis.
Head Neck, 44(1):262-74.
B. K. J. Tan, J. Raghupathy, H. Song, B. S. Y. Yeo, M. Samuel, A. See and R. Parameswaran. 2022.
Surgical traineeship is essential but must be safe for patients. In thyroid surgery, surgeon volume correlates with improved clinical/economic outcomes. However, it is presently unclear how far does trainee participation affect post-thyroidectomy complication rates in real-world and randomized data. We systematically searched four databases for associations of trainee participation with any post-thyroidectomy outcome. We conducted univariate meta-analyses, sensitivity analyses, and assessed publication bias qualitatively and quantitatively. We included 1 randomized and 15 observational studies from 3755 records, comprising 34 774 thyroid surgical patients. Trainee participation was associated with 12 min longer operative time, but not higher complication rates (hypoparathyroidism, recurrent laryngeal nerve palsy, hematoma, blood loss, return to operating room, hospitalization duration, readmission, and mortality). Sensitivity, publication bias, and multivariate analyses did not change our findings. Real-world and limited randomized data suggest that trainee

participation in thyroid surgery is safe, given adequate consultant supervision and appropriate case selection.
PubMed-ID: 34708904
http://dx.doi.org/10.1002/hed.26900

Transoral thyroidectomy vestibular approach versus non-transoral endoscopic thyroidectomy: a comprehensive systematic review and meta-analysis.
Surg Endosc, 36(3):1739-49.
D. Wang, Y. Wang, S. Zhou, X. Liu, T. Wei, J. Zhu and Z. Li. 2022.
BACKGROUND: To conduct a meta-analysis to compare the short-term outcomes of transoral thyroidectomy vestibular approach (TOTVA) with non-transoral endoscopic thyroidectomy (NTET). METHODS: MEDLINE, EMBASE, science citation index expanded, and the Cochrane Central Register of Controlled Trials in the Cochrane Library from January 2007 to January 2021 were searched for relevant literature. The evaluated endpoints were intra-operative and post-operative outcomes. RESULTS: Ten eligible, non-randomized comparative studies involving 1677 patients were included. Meta-analysis results revealed that TOTVA was associated with significantly longer operative time [weighted mean differences (WMD), 22.60; 95%confidence interval (CI), 7.51-37.69; P = 0.003]. No significant differences were found between TOTVA group and NTET group in terms of post-operative outcomes. CONCLUSION: TOTVA appears to be an equally feasible and safe surgical procedure as NTET for patients with benign thyroid nodules and selected differentiated thyroid carcinomas.
PubMed-ID: 34750702
http://dx.doi.org/10.1007/s00464-021-08836-w

Randomized controlled trials

TSH receptor specific monoclonal autoantibody K1-70(TM) targeting of the TSH receptor in subjects with Graves' disease and Graves' orbitopathy-Results from a phase I clinical trial.
Clin Endocrinol (Oxf), 96(6):878-87.
J. Furmaniak, J. Sanders, P. Sanders, Y. Li and B. Rees Smith. 2022.
OBJECTIVES: In Graves' disease (GD), autoantibodies to the thyroid stimulating hormone receptor (TSHR) cause hyperthyroidism. The condition is often associated with eye signs including proptosis, oedema, and diplopia (collectively termed Graves' orbitopathy [GO]). The safety profile of K1-70(TM) (a human monoclonal TSHR specific autoantibody, which blocks ligand binding and stimulation of the receptor) in patients with GD was evaluated in a phase I clinical trial. PATIENTS AND STUDY DESIGN: Eighteen GD patients stable on antithyroid drug medication received a single intramuscular (IM) or intravenous (IV) dose of K1-70(TM) during an open label phase I ascending dose, safety, tolerability, pharmacokinetic and pharmacodynamic (PD) study. Immunogenic effects of K1-70(TM) were also determined. RESULTS: K1-70(TM) was well-tolerated in all subjects at all doses and no significant immunogenic response was observed. There were no deaths or serious adverse events. Increased systemic exposure to K1-70(TM) was observed following a change to IV dosing, indicating this was the correct dosage route. Expected PD effects occurred after a single IM dose of 25 mg or single IV dose of 50 mg or 150 mg with fT3, fT4, and TSH levels progressing into hypothyroid ranges. There were also clinically significant improvements in symptoms of both GD (reduced tremor, improved sleep, improved mental focus, reduced toilet urgency) and GO (reduced exophthalmos measurements, reduced photosensitivity). CONCLUSIONS: K1-70(TM) was safe, well tolerated and produced the expected PD effects with no immunogenic responses. It shows considerable promise as a new drug to block the actions of thyroid stimulators on the TSHR.
PubMed-ID: 35088429
http://dx.doi.org/10.1111/cen.14681

Consensus Statements/Guidelines

- None -

Other Articles

Corrigendum to: Predicting Malignancy in Pediatric Thyroid Nodules: Early Experience With Machine Learning for Clinical Decision Support.
J Clin Endocrinol Metab, 107(6):e2659.
2022.
PubMed-ID: 35134190
http://dx.doi.org/10.1210/clinem/dgac027

The prevalence and significance of nonuniform thyroid radio-isotope uptake in patients with Graves' disease.
Clin Endocrinol (Oxf), 97(1):100-5.
A. Abdalaziz, R. Vanka, P. Bartholomew, N. Vennart, J. Vernazza, K. Stewart, V. Tsatlidis, K. Narayanan, J. U. Weaver and S. Razvi. 2022.
OBJECTIVE: To evaluate the prevalence and clinical significance of nonuniform technetium ((99m) Tc) uptake among patients with Graves' disease (GD). DESIGN, PATIENTS AND MEASUREMENTS: Patients with GD, referred between July 2005 and March 2018, had Tc(99) - uptake scans and TSH-receptor antibody (TRAb) measured before antithyroid drug (ATD) therapy. Risk of relapse after ATD cessation was monitored until June 2021 and compared between GD patients based on uptake patterns. RESULTS: Of the 276 GD patients (mean age, 49.8 years; 84% female), 25 (9.0%) had nonuniform Tc(99) uptake. At diagnosis, individuals with nonuniform uptake were older (mean age of 61.8 vs. 48.5 years, $p < .001$), had lower mean thyroid hormone levels (free thyroxine: 36.3 vs. 45.4 pmol/L, $p = .04$ and free triiodothyronine: 10.0 vs. 17.8 pmol/L, $p < .001$) and median TRAb levels (4.2 vs. 6.6 U/L, $p = .04$) compared with those with a uniform uptake. Older age was a significant predictor for the presence of nonuniform uptake in GD patients; odds ratio (95% confidence intervals) of 1.07 (1.03 - 1.10). The risk of relapse was similar in both groups after a median (IQR) follow-up of 41 (13-74) months after ATD cessation (56.0% vs. 46.3%, respectively); hazard ratio (95% confidence intervals) of 1.74 (0.96-3.15). CONCLUSIONS: Nonuniform radio-isotope uptake is seen in 1 in 11 patients with GD which could be misdiagnosed as toxic multinodular goitre if TRAb levels are not measured. Treatment of GD patients with nonuniform radio-isotope uptake with ATD therapy as first-line appears to be equally effective as compared with those with uniform uptake. TRAb testing should be the main diagnostic test for patients with suspected GD with radio-labelled uptake scans being reserved for those who are TRAb negative.
PubMed-ID: 35244288
http://dx.doi.org/10.1111/cen.14709

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

A prospective randomized controlled trial to assess the efficacy and safety of prophylactic central compartment lymph node dissection in papillary thyroid carcinoma.
Surgery, 171(1):182-9.
J. H. Ahn, J. H. Kwak, S. G. Yoon, J. W. Yi, H. W. Yu, H. Kwon, S. J. Kim and K. E. Lee. 2022.
BACKGROUND: The efficacy of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma remains controversial. We performed a randomized controlled trial to evaluate the efficacy and safety of prophylactic central compartment lymph node dissection in patients with papillary thyroid carcinoma. METHODS: In this parallel-group randomized controlled trial, we assessed 101 patients aged 20 to 70 years with small/noninvasive papillary thyroid carcinoma and no clinical metastases or history of cervical surgery/radiation exposure. Randomization ran from April 2015 to November 2017. Data were collected between April 2015 and October 2020. Of the 101 enrolled patients, 50 underwent total thyroidectomy (TTx group) and 51 underwent total thyroidectomy as well as prophylactic central compartment lymph node dissection (TTx+pCND group). Surgical completeness, local recurrence, successful ablation, postoperative complication, and papillary thyroid carcinoma upstaging were compared between the 2 groups. RESULTS: No patient showed structural recurrence after 46.6 ± 9.1 months of follow-up. Both groups had similar rates of surgical completeness and successful ablation. There was no difference in the incidence of complications. More patients were upstaged to pN1a in the TTx+pCND group compared to those in the TTx group ($P < .05$). CONCLUSIONS: Prophylactic central compartment lymph node dissection detected more lymph node metastases but did not affect recurrence. The 2 groups showed similar outcomes with regard to surgical completeness, successful ablation, and complications. In conclusion, for small/noninvasive papillary thyroid carcinoma without clinical evidence of lymph node metastases, prophylactic central compartment lymph node dissection may not be required if total thyroidectomy is planned.
PubMed-ID: 34391573
http://dx.doi.org/10.1016/j.surg.2021.03.071

Identifying and Addressing Health Disparities in Thyroid Cancer Care.
J Clin Endocrinol Metab, 107(5):e2190-e1.
E. O. Asamoah, G. Caraballo and M. R. Castro. 2022.
PubMed-ID: 34871424
http://dx.doi.org/10.1210/clinem/dgab875

How to manage Graves' disease in women of childbearing potential.
Clin Endocrinol (Oxf),
C. Ashkar, S. Sztal-Mazer and D. J. Topliss. 2022.
The management of Graves' disease (GD) in women of childbearing potential has multiple specific complexities. Many factors are involved, which differ at the various stages from preconception, conception, first trimester, later pregnancy, postpartum and lactation, with both maternal and foetal considerations. The incidence and significance of the risks incurred from antithyroid drugs (ATDs) in pregnancy have been re-evaluated recently and must be balanced against the risks of uncontrolled hyperthyroidism during childbearing years. Contraception is advised until hyperthyroidism is controlled. ATD cessation should be considered in those who are well controlled on low dose therapy before conception and in early pregnancy. Advice on iodine supplementation does not generally differ in those with GD. Radioiodine (RAI) is contraindicated from 6 months preconception until completion of breastfeeding. In all women who have a history of GD, monitoring of TSH receptor antibodies (TRAb) is strongly recommended during pregnancy, and if elevated, foetal monitoring and assessment of thyroid function in the neonate are required. Of note, RAI increases TRAb for up to a year, making this treatment option even less attractive in this patient group. A small amount of ATD is transferred into breast milk but low doses are safe during lactation. Routine periodic thyroid function testing is recommended in remission to detect postpartum GD recurrence. We present our approach to the Clinical Question 'How to manage GD in women of childbearing potential?'.
PubMed-ID: 35192205
http://dx.doi.org/10.1111/cen.14705

Secondary thyroid carcinoma in survivors of childhood cancer: A need to revise current screening recommendations.
Clin Endocrinol (Oxf), 97(1):137-9.
G. Atlas, S. Farrell and M. Zacharin. 2022.
PubMed-ID: 35460104
http://dx.doi.org/10.1111/cen.14746

Intraoperative Mapping Angiograms of the Parathyroid Glands Using Indocyanine Green During Thyroid Surgery: Results of the Fluogreen Study.
World J Surg, 46(2):416-24.
F. Benmiloud, G. Penaranda, L. Chiche and S. Rebaudet. 2022.
BACKGROUND: During thyroid surgery, preservation of parathyroid gland (PG) feeding vessels is often impossible. The aim of the Fluogreen study was to determine the feasibility of using indocyanine green (ICG)-based intraoperative mapping angiograms of the PG (iMAP) to improve vascular preservation. STUDY DESIGN: This prospective study enrolled all patients undergoing thyroid lobectomy or total thyroidectomy at the Hôpital Européen Marseille between September and December 2018. After exploring the thyroid lobe by autofluorescence to locate the PGs, ICG solution was injected intravenously to locate the PG feeding vessels and guide dissection. A second ICG injection was administered at the end of the lobectomy to assess perfusion of the PGs. The primary outcome was the quality of the angiogram, scaled as iMAP 0 (not informative), iMAP 1 (general vascular pattern visible but no clear vascular pedicle flowing into the PG), or iMAP 2 (clear vascular pedicle flowing into the PG). The secondary outcome was the PG perfusion score at the end of surgery, scaled from ICG 0 (no perfusion) to ICG 2 (intense uptake). RESULTS: A total of 47 adult patients were analyzed, including 34 total thyroidectomies and 13 lobectomies. ICG angiography assessed 76 PGs, which were scored as iMAP 2 in 24 cases (31.6%), iMAP 1 in 46 (60.5%) and iMAP 0 in six (7.9%). At the end of dissection, the ICG perfusion score was significantly better for the PGs with informative angiography (iMAP 1 or 2), than for the PGs with uninformative angiography (iMAP 0), or the PGs not evaluated by vascular angiography ($p < 0.05$). CONCLUSION: iMAP is feasible and provides direct vascular information in one-third of the cases. Further improvements to this technology are necessary, and the influence of this technique on patient outcomes during thyroidectomy will need to be further evaluated.
PubMed-ID: 34743241
http://dx.doi.org/10.1007/s00268-021-06353-4

Weight-based thyroid dosing vs fixed dosing during pregnancy for subclinical hypothyroidism: A retrospective cohort study.
Clin Endocrinol (Oxf), 96(2):263-9.
B. Bohlega, A. Zahedi, G. Tomlinson and D. S. Feig. 2022.
OBJECTIVE: Thyroid hormones play a crucial role in foetal growth and neurocognitive development. Our aim was to compare a weight-based dosing method of starting thyroxine to a fixed-dose method in newly diagnosed women with subclinical hypothyroidism during pregnancy. DESIGN: We performed a retrospective cohort study of consecutive women with newly diagnosed subclinical hypothyroidism during pregnancy seen at Mount Sinai Hospital and Women's College Hospital, Toronto, Canada 2015-2018. PATIENTS: We identified women that were treated based on pre-pregnancy weight and those that were given a fixed dose of 50 mcg/day. MEASUREMENTS: The percent of women who reached the target TSH of <2.5 mIU/L within 4-8 weeks was compared using a chi-squared test and a logistic regression model, adjusting for age, initial TSH and gestational age treatment was started. RESULTS: 393 women were included: 252 treated using a fixed-dose approach; 141 treated based on pre-pregnancy weight. In the unadjusted analysis, there was no difference between the groups in the percentage of women in the target range within 4-8 weeks (89.6% in the fixed-dose group vs 88.8% in the weight-based group ($p = .954$)). However, after adjustment for between-group differences in age, initial TSH and gestational age treatment was started, there was a significantly greater odds of achieving the target range using the weight-based dosing (OR 4.26 (1.60-11.7), $p = .004$). CONCLUSIONS: Treating women with newly diagnosed subclinical hypothyroidism during pregnancy with a weight-based strategy increased the odds of reaching the target TSH range within 4-8 weeks. Clinicians caring for these women should consider this approach when starting treatment during pregnancy.
PubMed-ID: 33891710
http://dx.doi.org/10.1111/cen.14488

Characterization of Subtypes of BRAF-Mutant Papillary Thyroid Cancer Defined by Their Thyroid Differentiation Score.
J Clin Endocrinol Metab, 107(4):1030-9.
L. Boucai, V. Seshan, M. Williams, J. A. Knauf, M. Saqcena, R. A. Ghossein and J. A. Fagin. 2022.
CONTEXT: The BRAFV600E mutation has been associated with more advanced clinical stage in papillary thyroid cancer (PTC) and decreased responsiveness to radioiodine (RAI). However, some BRAF mutant PTCs respond to RAI and have an indolent clinical behavior suggesting the presence of different subtypes of BRAF mutant tumors with distinct prognosis. OBJECTIVE: To characterize the molecular and clinical features of 2 subtypes of BRAF-mutant PTCs defined by their degree of expression of iodine metabolism genes. DESIGN: 227 BRAF-mutant PTCs from the Cancer Genome Atlas Thyroid Cancer study were divided into 2 subgroups based on their thyroid differentiation score (TDS): BRAF-TDShi and BRAF-TDSlo. Demographic, clinico-pathological, and molecular characteristics of the 2 subgroups were compared. RESULTS: Compared

to BRAF-TDShi tumors (17%), BRAF-TDSlo tumors (83%) were more frequent in blacks and Hispanics (6% vs 0%, P = 0.035 and 12% vs 0%, P = 0.05, respectively), they were larger (2.95 ± 1.7 vs 2.03 ± 1.5, P = 0.002), with more tumor-involved lymph nodes (3.9 ± 5.8 vs 2.0 ± 4.2, P = 0.042), and a higher frequency of distant metastases (3% vs 0%, P = 0.043). Gene set enrichment analysis showed positive enrichment for RAS signatures in the BRAF-TDShi cohort, with corresponding reciprocal changes in the BRAF-TDSlo group. Several microRNAs (miRs) targeting nodes in the transforming growth factor ß (TGFß)-SMAD pathway, miR-204, miR-205, and miR-144, were overexpressed in the BRAF-TDShi group. In the subset with follow-up data, BRAF-TDShi tumors had higher complete responses to therapy (94% vs 57%, P < 0.01) than BRAF-TDSlo tumors. CONCLUSION: Enrichment for RAS signatures, key genes involved in cell polarity and specific miRs targeting the TGFß-SMAD pathway define 2 subtypes of BRAF-mutant PTCs with distinct clinical characteristics and prognosis.
PubMed-ID: 34897468
http://dx.doi.org/10.1210/clinem/dgab851

Letter to the Editor From Boucai and Tuttle: "BRAF V600E Status Sharply Differentiates Lymph Node Metastasis-Associated Mortality Risk in Papillary Thyroid Cancer".
J Clin Endocrinol Metab, 107(6):e2638-e9.
L. Boucai and R. M. Tuttle. 2022.
PubMed-ID: 35262726
http://dx.doi.org/10.1210/clinem/dgac127

A Randomized Study of Lenvatinib 18 mg vs 24 mg in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 107(3):776-87.
M. S. Brose, Y. Panaseykin, B. Konda, C. de la Fouchardiere, B. G. M. Hughes, A. G. Gianoukakis, Y. Joo Park, I. Romanov, M. K. Krzyzanowska, S. Leboulleux, T. A. Binder, C. Dutcus, R. Xie and M. H. Taylor. 2022.
BACKGROUND: Lenvatinib is a multikinase inhibitor approved to treat radioiodine-refractory differentiated thyroid cancer (RR-DTC) at a starting dose of 24 mg/day. This study explored, in a double-blinded fashion, whether a starting dose of 18 mg/day would provide comparable efficacy with reduced toxicity. METHODS: Patients with RR-DTC were randomized to lenvatinib 24 mg/day or 18 mg/day. The primary efficacy endpoint was objective response rate as of week 24 (ORRwk24); the odds ratio noninferiority margin was 0.4. The primary safety endpoint was frequency of grade =3 treatment-emergent adverse events (TEAEs) as of week 24. Tumors were assessed using RECIST v1.1. TEAEs were monitored and recorded. RESULTS: The ORRwk24 was 57.3% (95% CI 46.1, 68.5) in the lenvatinib 24-mg arm and 40.3% (95% CI 29.3, 51.2) in the lenvatinib 18-mg arm, with an odds ratio (18/24 mg) of 0.50 (95% CI 0.26, 0.96). As of week 24, the rates of TEAEs grade =3 were 61.3% in the lenvatinib 24-mg arm and 57.1% in the lenvatinib 18-mg arm, a difference of -4.2% (95% CI -19.8, 11.4). CONCLUSION: A starting dose of lenvatinib 18 mg/day did not demonstrate noninferiority compared to a starting dose of 24 mg/day as assessed by ORRwk24 in patients with RR-DTC. The results represent a clinically meaningful difference in ORRwk24. The safety profile was comparable, with no clinically relevant difference between arms. These results support the continued use of the approved starting dose of lenvatinib 24 mg/day in patients with RR-DTC and adjusting the dose as necessary.
PubMed-ID: 34664662
http://dx.doi.org/10.1210/clinem/dgab731

Adjuvant Rituximab-Exploratory Trial in Young People With Graves Disease.
J Clin Endocrinol Metab, 107(3):743-54.
T. D. Cheetham, M. Cole, M. Abinun, A. Allahabadia, T. Barratt, J. H. Davies, P. Dimitri, A. Drake, Z. Mohamed, R. D. Murray, C. A. Steele, N. Zammitt, S. Carnell, J. Prichard, G. Watson, S. Hambleton, J. N. S. Matthews and S. H. S. Pearce. 2022.
CONTEXT: Remission rates in young people with Graves hyperthyroidism are less than 25% after 2 years of thionamide antithyroid drug (ATD). OBJECTIVE: We explored whether rituximab (RTX), a B-lymphocyte-depleting agent, would increase remission rates when administered with a short course of ATD. METHODS: This was an open-label, multicenter, single-arm, phase 2 trial in young people (ages, 12-20 years) with Graves hyperthyroidism. An A'Hern design was used to distinguish an encouraging remission rate (40%) from an unacceptable rate (20%). Participants presenting with Graves hyperthyroidism received 500 mg RTX and 12 months of ATD titrated according to thyroid function. ATDs were stopped after 12 months and primary outcome assessed at 24 months. Participants had relapsed at 24 months if thyrotropin was suppressed and free 3,5,3'-triiodothyronine was raised; they had received ATD between months 12 and 24; or they had thyroid surgery/radioiodine. RESULTS: A total of 27 participants were recruited and completed the trial with no serious

side effects linked to treatment. Daily carbimazole dose at 12 months was less than 5 mg in 21 of 27 participants. Thirteen of 27 participants were in remission at 24 months (48%, 90% one-sided CI, 35%-100%); this exceeded the critical value (9) for the A'Hern design and provided evidence of a promising remission rate. B-lymphocyte count at 28 weeks, expressed as a percentage of baseline, was related to likelihood of remission. CONCLUSION: Adjuvant RTX, administered with a 12-month course of ATD, may increase the likelihood of remission in young people with Graves hyperthyroidism. A randomized trial of adjuvant RTX in young people with Graves hyperthyroidism is warranted.
PubMed-ID: 34687316
http://dx.doi.org/10.1210/clinem/dgab763

Association of Total Thyroidectomy or Thyroid Lobectomy With the Quality of Life in Patients With Differentiated Thyroid Cancer With Low to Intermediate Risk of Recurrence.
JAMA Surg, 157(3):200-9.
W. Chen, J. Li, S. Peng, S. Hong, H. Xu, B. Lin, X. Liang, Y. Liu, J. Liang, Z. Zhang, Y. Ye, F. Liu, C. Lin, H. Xiao and W. Lv. 2022.
IMPORTANCE: Owing to the good prognosis of differentiated thyroid cancer (DTC), guidelines recommend total thyroidectomy (TT) or thyroid lobectomy (TL) as surgical treatment for DTC with low to intermediate risk of recurrence. However, the association of these surgeries with the health-related quality of life (HRQOL) of patients with DTC with low to intermediate risk of recurrence is unclear. OBJECTIVE: To longitudinally compare the HRQOL of patients with DTC undergoing different surgeries. DESIGN, SETTING, AND PARTICIPANTS: This prospective observational longitudinal cohort study enrolled patients diagnosed with DTC with low to intermediate risk of recurrence at the First Affiliated Hospital, Sun Yat-sen University, China, from October 1, 2018, to September 31, 2019. Eligible patients were categorized into TL and TT groups according to the surgery they underwent. They were evaluated preoperatively and followed up at 1, 3, 6, and 12 months postoperatively using 3 HRQOL-related questionnaires (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version 3.0; Hospital Anxiety and Depression Scale; and Thyroid Cancer-Specific Quality of Life Questionnaire); serum thyrotropin levels, complications, and patient satisfaction were also monitored. Data were analyzed to compare the HRQOL of patients undergoing different surgeries at different time points. EXPOSURES: Total thyroidectomy or TL. MAIN OUTCOMES AND MEASURES: The primary end point was HRQOL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version 3.0; Hospital Anxiety and Depression Scale; and Thyroid Cancer-Specific Quality of Life Questionnaire) at different time points, and the secondary end points were postoperative complications, thyrotropin level, and patient satisfaction. RESULTS: Of the 1060 eligible patients, 563 underwent TL (438 women [77.8%]; median [IQR] age, 38 [31-45] years), and 497 underwent TT (390 women [78.5%]; median [IQR] age, 38 [32-48] years). Compared with the TL group, including the 1- to 4-cm tumor subgroup, the TT group experienced more postoperative HRQOL problems at 1 and 3 months postoperatively. However, nearly all the differences disappeared at 6 and 12 months postoperatively. CONCLUSIONS AND RELEVANCE: Results of this study suggest that HRQOL of patients with DTC with low to intermediate risk of recurrence is not associated with the extent of surgery, and HRQOL may not be an important consideration when making surgical decisions. If better HRQOL is requested in the short term, TL may be preferred.
PubMed-ID: 34935859
http://dx.doi.org/10.1001/jamasurg.2021.6442

Trans-oral endoscopic thyroidectomy vestibular approach (TOETVA) for the pediatric population: a multicenter, large case series.
Surg Endosc, 36(4):2507-13.
O. Cohen, R. P. Tufano, A. Anuwong, J. O. Russell, N. Assadi, G. Dionigi, H. Y. Kim, A. Bertelli and A. Khafif. 2022.
INTRODUCTION: A cervical scar has been shown to have an impact on the quality of life of children undergoing thyroid surgery. Transoral endoscopic vestibular thyroidectomy via the vestibular approach (TOETVA) offers the absence of a cutaneous incision, and has not been described to date in the pediatric population. OBJECTIVE: To describe the first series of TOETVA in a pediatric population. PATIENTS AND METHODS: A retrospective, multicenter study, including all patients > 18 years old who underwent TOETVA. Data was prospectively collected and included demographics, preoperative ultrasound, cytology and indications for surgery. Intraoperative parameters included length of surgery and complications, with final pathology and postoperative course also reviewed. TOETVA surgical success was defined as completion of surgery via this approach. RESULTS: Forty-eight children were included. Of these, 43 (89.5%) were girls. The median age was 16 years (range 10-17). The most common indication for surgery was a benign thyroid nodule (n = 26, 54.1%). Eleven patients (22.9%) had papillary thyroid carcinoma on final pathology, of which 90.9% (10/11) were diagnosed pre-operatively based on FNA cytology. Hemithyroidectomy was performed in 36 patients (75%). All surgeries were completed endoscopically. The mean malignant tumor size was 1.4 ± 0.4 cm and all tumors were completely excised with clean

margins. No permanent complications were documented. A single patient (2.1%) had transient RLN injury (1.6%, 1/60 nerves at risk). Transient hypocalcemia was documented in 4 of the 12 patients undergoing total thyroidectomy (33.3%). Transient mental nerve injury/chin hypoesthesia was documented in 2 patients (4.2%). CONCLUSIONS: TOETVA appears to be a feasible and safe approach for thyroidectomy in the pediatric population in carefully selected cases, and may be discussed with patients and parents as an alternative for the trans-cervical approach.
PubMed-ID: 34031742
http://dx.doi.org/10.1007/s00464-021-08537-4

Low-Iodine Diet of 4 Days Is Sufficient Preparation for 131I Therapy in Differentiated Thyroid Cancer Patients.
J Clin Endocrinol Metab, 107(2):e604-e11.
B. L. Dekker, M. H. Links, A. C. Muller Kobold, L. G. Swart-Busscher, M. Kars, J. A. P. Bons, A. H. Brouwers, T. P. Links and A. N. A. van der Horst-Schrivers. 2022.
CONTEXT: No consensus exists about the optimal duration of the low-iodine diet (LID) in the preparation of 131I therapy in differentiated thyroid cancer (DTC) patients. OBJECTIVE: This work aimed to investigate if a LID of 4 days is enough to achieve adequate iodine depletion in preparation for 131I therapy. In addition, the nutritional status of the LID was evaluated. METHODS: In this prospective study, 65 DTC patients treated at 2 university medical centers were included between 2018 and 2021. The patients collected 24-hour urine on days 4 and 7 of the LID and kept a food diary before and during the LID. The primary outcome was the difference between the 24-hour urinary iodine excretion (UIE) on both days. RESULTS: The median 24-hour UIE on days 4 and 7 of the LID were not significantly different (36.1 mcg [interquartile range, 25.4-51.2 mcg] and 36.5 mcg [interquartile range, 23.9-47.7 mcg], respectively, P = .43). On day 4 of the LID, 72.1% of the DTC patients were adequately prepared (24-hour UIE < 50 mcg), and 82.0% of the DTC patients on day 7 (P = .18). Compared to the self-reported regular diet, DTC patients showed a significantly (P < .01) lower percentage of nutrient intake (calories, protein, calcium, iodine, and water) during the LID. CONCLUSION: The 24-hour UIE on day 4 of the LID did not differ from day 7, and therefore shortening the LID from 7 to 4 days seems justified to prepare DTC patients for 131I therapy in areas with sufficient iodine intake and may be beneficial to maintain a sufficient nutritional intake during DTC treatment.
PubMed-ID: 34534327
http://dx.doi.org/10.1210/clinem/dgab691

Which Is the Best Endoscopic Procedure for Thyroid Gland?
Ann Surg Oncol, 29(5):3093-4.
G. Dionigi, L. Boni, L. Fugazzola, H. Y. Kim and P. Miccoli. 2022.
PubMed-ID: 35275328
http://dx.doi.org/10.1245/s10434-022-11604-2

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

Outcomes after radioiodine ablation in patients with thyroid cancer: Long-term follow-up of a Chinese randomized clinicaltrial.
Clin Endocrinol (Oxf), 95(5):782-9.
P. Dong, Y. Qu, L. Yang, L. Xiao, R. Huang and L. Li. 2021.
OBJECTIVE: Two large randomized trials of patients with differentiated thyroid cancer (DTC) reported recently (HiLo and ESTIMABL1) found that the recurrence rate among patients who underwent 1.1 GBq radioactive iodine (RAI) ablation was not higher than that of patients who underwent 3.7 GBq radioactive iodine (RAI) ablation. However, no similar studies have been conducted in China. We aimed to report clinical outcomes in Chinese patients with low/intermediate risk of recurrence DTC after long-term follow-up, and evaluate the risk factors that influence the presence or absence of incomplete response at the final follow-up. DESIGN: A long-term follow-up of a Chinese randomized clinical trial (October 2014 and February 2021) was conducted. PATIENTS: A total of 506 DTC patients at low/intermediate risk of recurrence who were randomized into two groups to receive 1.1 (n = 251) or 3.7 GBq (n = 255) RAI ablation following thyroid hormone withdrawal were followed on levothyroxine treatment for a median of 4.5 years (range: 1.6-6.3). MEASUREMENTS: Suppressed serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) levels were determined,

and neck ultrasonography was performed. RESULTS: At the final follow-up, 499 (98.6%) patients showed an excellent response. The other seven patients (two patients underwent 1.1 GBq and five patients underwent 3.7 GBq RAI ablation, respectively) showed either structural incomplete response (lymph node metastasis, n = 1), biochemical incomplete response (increased serum Tg = 1 ng/ml, or increased positive TgAb levels, n = 5), or indeterminate response (stable positive TgAb levels, n = 1). The risk of incomplete response at the final follow-up was significantly increased in patients with stimulated serum Tg = 10 ng/ml at ablation (p = .003) and in patients with unsuccessful ablation (p = .008). CONCLUSION: Our findings indicated that there was no difference in the long-term outcomes with RAI ablation using either 1.1 or 3.7 GBq in patients with low/intermediate risk of recurrence DTC, and 1.1 GBq RAI might be suitable for patients who are recommended for ablation.
PubMed-ID: 34368999
http://dx.doi.org/10.1111/cen.14563

Predictive factors for thyroid complications after radiation therapy-data from a cohort of cancer patients closely followed since they were irradiated.
Clin Endocrinol (Oxf), 96(5):728-33.
V. Duarte, J. Maciel, D. Cavaco, S. Donato, I. Damásio, S. Pinheiro, A. Figueiredo, A. Ferreira and J. S. Pereira. 2022.
INTRODUCTION: Cancer survivors are at an increased risk of adverse outcomes, including thyroid neoplasms, given the high radiosensitivity of this gland. The aim of this study is to assess the incidence and timeframe of thyroid complications in cancer patients, followed systematically since their radiation therapy, and to identify risk factors for the development of hypothyroidism and thyroid cancer. METHODS: We performed a retrospective study, including 282 subjects, who received neck, craniospinal, or total body irradiation (TBI). Patients were grouped into four primary diagnostic clusters: leukaemia, Hodgkin's disease, central nervous system, and head and neck tumours. RESULTS: Hypothyroidism was observed in 56.7% of patients, on average 6.8 ± 5.9 years after the treatment. Neck and craniospinal irradiation presented a 3.5-fold increased risk for the development of hypothyroidism compared to TBI. Papillary thyroid cancer was diagnosed in 8.5% of the patients, on average, 18.5 ± 4.9 years after radiotherapy (RT). Female gender, younger age, and lower irradiation doses were independently associated with thyroid cancer development. CONCLUSION: Our study provides useful information about the risk of hypothyroidism and thyroid cancer after RT, as it was performed in a cohort of patients closely followed since the oncological therapies, and, thus, may give new insights into the follow-up management of these patients.
PubMed-ID: 34978354
http://dx.doi.org/10.1111/cen.14665

Long-Term Efficacy of Ethanol Ablation as Treatment of Metastatic Lymph Nodes From Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 107(5):e2141-e7.
P. S. Frich, E. Sigstad, A. E. Berstad, K. H. Fagerlid, T. H. Paulsen, T. Bjøro and L. I. Flinder. 2022.
CONTEXT: Ethanol ablation (EA) is considered an alternative to surgery for metastatic lymph nodes from papillary thyroid carcinoma (PTC) in selected patients. OBJECTIVE: The aim of this study was to evaluate the long-term efficacy and safety of this treatment. DESIGN AND SETTING: Adult patients with PTC who had received EA in lymph node metastasis at a tertiary referral center, and were included in a published study from 2011, were invited to participate in this follow-up study. METHODS: Radiologic and medical history were reviewed. Ultrasound examination of the neck was performed by radiologists, and clinical examination was performed by an endocrine surgeon. Response was reported according to predefined criteria for satisfactory EA treatment. Adverse events associated with EA were evaluated. Cause of death was reported for deceased patients. RESULTS: From the 2011 study, 51 of 63 patients were included. Forty-four patients were reexamined (67/109 lesions) and 7 patients were deceased. Median follow-up time from primary surgery was 14.5 years. Median follow-up from the latest performed EA in the 2011 study was 11.3 years. Local control was permanently achieved in most patients (80%). Recurrence within an ablated node was registered in 13 metastases in 10 patients. Seven of these patients also had recurrent disease elsewhere in the neck. No major side effects were reported. CONCLUSION: EA is a minimally invasive procedure with a low risk of complications. Our data suggest that EA is a safe and efficient treatment, providing excellent results for a large group of patients in the long term.
PubMed-ID: 34922379
http://dx.doi.org/10.1210/clinem/dgab907

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

Young Children Are not the Same as Adolescents When it Comes to Treating Thyroid Cancer.
J Clin Endocrinol Metab, 107(3):e1308-e9.
M. Goldfarb, E. Christison-Lagay, J. Rastatter and J. Wasserman. 2022.
PubMed-ID: 34610121
http://dx.doi.org/10.1210/clinem/dgab711

Letter to the Editor From Green and Gosmanov: "Tall Cell Percentage Alone in PTC Without Aggressive Features Should Not Guide Patients' Clinical Management".
J Clin Endocrinol Metab, 107(6):e2647-e8.
M. Green and A. R. Gosmanov. 2022.
PubMed-ID: 35100609
http://dx.doi.org/10.1210/clinem/dgac053

Incidental T1 stage medullary thyroid carcinoma: The effect of tumour diameter on prognosis and therapeutic implications.
Clin Endocrinol (Oxf), 97(3):355-62.
Z. Gui, Z. Wang, J. Xiang, W. Sun, L. He, W. Dong, J. Huang, D. Zhang, C. Lv, T. Zhang, L. Shao, P. Zhang and H. Zhang. 2022.
OBJECTIVE: The definition of the tumour diameter of micro-medullary thyroid carcinoma (micro-MTC) is insufficient. It is controversial to perform a completion thyroidectomy immediately for incidental T1 stage MTC. DESIGN: We used the Surveillance, Epidemiology and End Results (SEER) registry to retrospectively analyze all patients with T1 stage MTC diagnosed between 2004 and 2015. The tumour diameter 1.0 and 0.5 cm were used as the cut-off points to group and analyze the differences of clinicopathological features. We analyzed the prognosis of patients with less than total thyroidectomy. METHODS: The disease-specific survival was the main outcome. Survival was estimated with Kaplan-Meier curves and Cox regression models estimated hazard ratios for tumour characteristics. RESULTS: A total of 908 patients diagnosed with T1 stage MTC in the SEER database were included. Our study found that tumour diameter 1.0 cm is a key point affecting the prognosis of T1 stage MTC patients, although patients with tumour diameter = 0.5 cm had a lower rate of lymph node metastasis and no distant metastasis. Cox proportional hazard multivariate analysis showed that distant metastasis was the only risk factor for survival in patients with T1 stage MTC. Kaplan-Meier survival analysis showed that, regardless of tumour diameter, there was no significant difference between less than total thyroidectomy and total thyroidectomy in T1 stage patients. CONCLUSIONS: For incidental MTC with tumour diameter = 1.0 cm and without distant metastasis, if there is no significant increase in serum calcitonin level after surgery and ret proto-oncogene (RET) gene mutation is negative, it may be not necessary to perform completion thyroidectomy immediately.
PubMed-ID: 35192214
http://dx.doi.org/10.1111/cen.14702

What Is the Role of Radiofrequency Ablation for Benign Thyroid Nodules?
Laryngoscope, 132(1):1-2.
P. Horwich, B. A. Chang, A. A. Asarkar, G. W. Randolph and C. O. Nathan. 2022.
PubMed-ID: 33656181
http://dx.doi.org/10.1002/lary.29498

Appraising the Effect of Potential Risk Factors on Thyroid Cancer: A Mendelian Randomization Study.
J Clin Endocrinol Metab, 107(7):e2783-e91.
L. Huang, X. Feng, W. Yang, X. Li, K. Zhang, S. Feng, F. Wang and X. Yang. 2022.
CONTEXT: Various risk factors have been associated with the risk of thyroid cancer in observational studies. However, the causality of the risk factors is not clear given the susceptibility of confounding and reverse causation. OBJECTIVE: A 2-sample Mendelian randomization approach was used to estimate the effect of potential risk factors on thyroid cancer risk. METHODS: Genetic instruments to proxy 55 risk factors were identified by genome-wide association studies (GWAS). Associations of these genetic variants with thyroid cancer risk were estimated in GWAS of the FinnGen Study (989 cases and 217 803 controls). A Bonferroni-corrected threshold of P = 9.09 × 10-4 was considered significant, and P < 0.05 was considered to be suggestive of an association. RESULTS: Telomere length was significantly associated with increased thyroid cancer risk after correction for multiple testing (OR 4.68; 95% CI, 2.35-9.31; P = 1.12 × 10-5). Suggestive associations with increased risk were noted for waist-to-hip ratio (OR 1.85; 95% CI, 1.02-3.35; P = 0.042) and diastolic blood pressure (OR 1.60; 95% CI, 1.08-2.38; P = 0.019). Suggestive associations were noted between hemoglobin A1c (HbA1c) (OR 0.20; 95% CI, 0.05-0.82; P = 0.025) and decreased risk of thyroid cancer. Risk of thyroid cancer was not associated with sex hormones and reproduction, developmental and growth, lipids, diet and lifestyle, or inflammatory factors (All P > 0.05). CONCLUSION: Our study identified several potential targets for primary prevention of thyroid cancer, including central obesity, diastolic blood pressure, HbA1c, and telomere length, which should inform public health policy.
PubMed-ID: 35366326
http://dx.doi.org/10.1210/clinem/dgac196

Age increased the cancer-specific mortality risk of thyroid cancer with lung metastasis.
Clin Endocrinol (Oxf), 96(5):719-27.
X. Huang, Q. Xia, Y. Huang, A. Peng and J. Yang. 2022.
OBJECTIVE: To investigate the relationship between age and cancer-specific mortality in thyroid cancer (TC) with lung-metastasis. PATIENTS AND METHODS: A total of 1418 patients with initial distant metastases from Surveillance, Epidemiology, and End Results databases were investigated. Patients with a median follow-up time of 8 months (interquartile range [IQR]: 2-27] and a median age of 66 years (IQR: 55-76) were divided into five groups by age and the association between age and TC-specific mortality was analysed. RESULTS: The TC-specific mortality rates were 32.78% (118/360), 46.71% (156/334), 53.93% (199/369), 58.96% (158/268) and 82.76% (72/87) in patients aged =55 years, >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years. Kaplan-Meier curves showed that TC-specific mortality rate was associated with increased age (p < .001). Compared with patients =55 years, patients aged >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years had significantly higher hazard ratios (HRs) of 1.69 (1.26-2.26), 1.97 (1.47-2.64), 2.18 (1.59-2.99) and 3.24 (2.08-5.06) after adjustments for sex, tumour size and radiation therapy (all p < .001). In TC with initial lung-metastasis, compared with patients =55 years, patients aged >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years had significantly higher adjusted HRs of 1.68 (1.20-2.36; p = .003), 2.18 (1.57-3.02), 2.16 (1.51-3.08) and 2.91 (1.79-4.75; p < .001). Similar results were obtained in papillary TC. CONCLUSIONS: The TC-specific mortality was increased with age in TC patients with initial lung-metastasis, indicating that further risk stratification based on age was necessary for TC over 55 years with lung-metastasis. Individual treatment strategies maybe recommended for such patients.
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http://dx.doi.org/10.1111/cen.14675

Response to Letter to the Editor From Raven: Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine.
J Clin Endocrinol Metab, 107(4):e1773-e4.
B. G. Iremli, S. N. Sendur and U. Ünlütürk. 2022.
PubMed-ID: 34752630
http://dx.doi.org/10.1210/clinem/dgab823

ASO Author Reflection: Optimizing Lateral Neck Dissection Extent of PTC by FNA-Tg.
Ann Surg Oncol, 29(1):97-8.
X. Jia, R. Tao, Y. Yang, Y. Wang, Y. Liu, A. Yang and R. Gao. 2022.
PubMed-ID: 34383193
http://dx.doi.org/10.1245/s10434-021-10636-4

Thyroglobulin Measurement Through Fine-Needle Aspiration for Optimizing Neck Node Dissection in Papillary Thyroid Cancer.
Ann Surg Oncol, 29(1):88-96.
X. Jia, Y. Wang, Y. Liu, X. Wang, X. Yao, R. Tao, H. Liu, A. Yang and R. Gao. 2022.
BACKGROUND: Thyroglobulin measurement in fine-needle aspiration (FNA-Tg) is an additional diagnostic tool of lymph node metastasis (LNM) in papillary thyroid carcinoma (PTC). However, its performance as a preoperative indicator of lateral neck LNM in PTC is unclear. We evaluated the use of FNA cytology and FNA-Tg to detect neck LNM presurgery using a simple methodology, and established a cut-off value for diagnosing LNM in PTC. METHODS: We performed a retrospective cohort study based on hospital records, including 299 FNA-Tg measurements from 228 patients with PTC. The cut-off value for FNA-Tg was obtained through a receiver operating characteristic (ROC) curve analysis. The relationships between various parameters and FNA-Tg were analyzed using Spearman's correlation. RESULTS: Of 299 lymph nodes (LNs) from 228 patients following surgery, 151 were malignant and 148 were benign. The median FNA-Tg levels were 414.40 ng/mL and 6.36 ng/mL in the metastatic and benign LNs, respectively. An FNA-Tg cut-off value of 28.3 ng/mL had the best diagnostic performance (93.38% sensitivity, 70.27% specificity, area under the ROC curve [AUC] 0.868) in the whole cohort. The diagnostic value performed better in the lateral neck group (level II-V, n = 163) than in the central neck group (level VI, n = 136); in the lateral neck group, the sensitivity and specificity of the FNA-Tg cut-off (16.8 ng/mL) were 96.25% and 96.36%, respectively. CONCLUSIONS: FNA-Tg is a useful technique for the diagnosis of LNM before surgery, especially in lateral neck dissection. CLINICAL TRIAL REGISTRATION NUMBER: ChiCTR1900028547.
PubMed-ID: 34386915
http://dx.doi.org/10.1245/s10434-021-10549-2

Extension of Prophylactic Surgery in Medullary Thyroid Carcinoma. Differences Between Sporadic and Hereditary Tumours According to Calcitonin Levels and Lymph Node Involvement.
World J Surg, 46(4):820-8.
L. D. Juez, E. Mercader, I. Amunategui, B. Febrero, J. M. Rodríguez and J. Gómez-Ramírez. 2022.
INTRODUCTION: Currently, there is no consensus on the indication of prophylactic surgery of the nodal compartments in the treatment of medullary thyroid carcinoma (MTC). The aim of our study was to perform a correlation study between preoperative calcitonin (basalCT) values and lymph node involvement to establish a criterion on which to base prophylactic surgery in these patients. MATERIAL AND METHODS: We conducted an observational, retrospective and multicentre study with 29 hospitals. Patients over 18 years of age with a diagnosis of MTC with a pre-surgical calcitonin registry were included. The minimum surgery in all patients had to have been total thyroidectomy (TT) with central compartment lymph node dissection (CCLND). Receiver operating characteristic (ROC) curve analysis was used to establish basalCT cut-off values as predictors of postoperative lymph node involvement. RESULTS: A total of 244 patients were included. Baseline calcitonin (basalCT) was a good predictor of nodal involvement (AUC 0.718 and 95%CI 0.66-0.978). Heritability was identified as a preoperative factor correlated with baseline tumour CT values (p = 0.000). With a probability of lymph node involvement below 10%, new cut-off points were established. A prophylactic bilateral lateral lymph node dissection in sporadic tumours should be performed at a basalCT > 600 pg/mL; in the case of RET-mutated tumours this value would be 200 pg/mL. CONCLUSION: The baseline CT value is a good predictor of postoperative lymph node involvement in MTC, however, cut-off points should depent on the hereditary nature of the tumour.
PubMed-ID: 35089388
http://dx.doi.org/10.1007/s00268-022-06448-6

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

PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism.
J Clin Endocrinol Metab, 107(1):e372-e85.
A. A. Khan, L. Rejnmark, M. Rubin, P. Schwarz, T. Vokes, B. Clarke, I. Ahmed, L. Hofbauer, C. Marcocci, U. Pagotto, A. Palermo, E. Eriksen, M. Brod, D. Markova, A. Smith, S. Pihl, S. Mourya, D. B. Karpf and A. D. Shu. 2022.
CONTEXT: Hypoparathyroidism is characterized by insufficient levels of parathyroid hormone (PTH). TransCon PTH is an investigational long-acting prodrug of PTH(1-34) for the treatment of hypoparathyroidism. OBJECTIVE: This work aimed to investigate the safety, tolerability, and efficacy of daily TransCon PTH in adults with hypoparathyroidism. METHODS: This phase 2, randomized, double-blind, placebo-controlled 4-week trial with open-label extension enrolled 59 individuals with hypoparathyroidism. Interventions included TransCon PTH 15, 18, or 21 µg PTH(1-34)/day or placebo for 4 weeks, followed by a 22-week extension during which TransCon PTH dose was titrated (6-60 µg PTH[1-34]/day). RESULTS: By Week 26, 91% of participants treated with TransCon PTH achieved independence from standard of care (SoC, defined as active vitamin D = 0 µg/day and calcium [Ca] = 500 mg/day). Mean 24-hour urine Ca (uCa) decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 (n = 44) while normal serum Ca (sCa) was maintained and serum phosphate and serum calcium-phosphate product fell within the normal range. By Week 26, mean scores on the generic 36-Item Short Form Health Survey domains increased from below normal at baseline to within the normal range. The Hypoparathyroidism Patient Experience Scale symptom and impact scores improved through 26 weeks. TransCon PTH was well tolerated with no treatment-related serious or severe adverse events. CONCLUSION: TransCon PTH enabled independence from oral active vitamin D and reduced Ca supplements (= 500 mg/day) for most participants, achieving normal sCa, serum phosphate, uCa, serum calcium-phosphate product, and demonstrating improved health-related quality of life. These results support TransCon PTH as a potential hormone replacement therapy for adults with hypoparathyroidism.
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http://dx.doi.org/10.1210/clinem/dgab577

Does Radioactive Iodine Therapy for Hyperthyroidism Cause Cancer?
J Clin Endocrinol Metab, 107(2):e448-e57.
B. W. Kim. 2022.
Radioactive iodine has been considered a safe and effective therapeutic option for hyperthyroidism secondary to Graves disease and autonomously functioning thyroid nodules since the mid-20th century. The question of whether I-131 at the doses used for hyperthyroidism might increase the risk of cancer has been investigated in a number of observational cohort studies over the years, with the preponderance of evidence being reassuring as to its safety. In particular, the 1998 Cooperative Thyrotoxicosis Therapy Follow-up Study (CTTFUS) has been widely cited as compelling evidence that I-131 is safe in hyperthyroidism therapy with respect to carcinogenesis. However, in 2019, a study by Kitahara and colleagues re-analyzed the CTTFUS cohort, extending the follow-up time and applying a novel dosimetric model for estimating tissue absorbed doses of radiation. This new analysis concluded that radioactive iodine was associated with an increased risk for mortality from overall cancer, breast cancer, and non-breast solid cancers. Reaction to this study was vociferous and particularly negative in the nuclear medicine literature. This mini-review was inspired by the 2019 CTTFUS controversy, and it is intended to provide the necessary context for clinicians to provide nuanced advice to their patients on the subject. To that end, the pre-2019 literature is surveyed, the 2019 CTTFUS study and a 2020 follow-up are discussed, and lessons from the literature and critical commentaries are considered.

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Single-port transaxillary robotic thyroidectomy (START): 200-cases with two-step retraction method.
Surg Endosc, 36(4):2688-96.
J. K. Kim, S. H. Choi, S. M. Choi, H. R. Choi, C. R. Lee, S. W. Kang, J. J. Jeong, K. H. Nam and W. Y. Chung. 2022.
BACKGROUND: This study aims to report the results of a pioneering clinical study using the single-port transaxillary robotic thyroidectomy (START) for 200 patients with thyroid tumor and to introduce our novel two-step retraction method. METHODS: START was performed on consecutive 200 patients using the da Vinci Single-Port (SP) robot system from January 2019 to September 2020 at the Yonsei University Health System, Seoul, Korea. The novel two-step retraction technique, in which a 3.5 cm long incision is made along the natural skin crease, was used for the latter 164 patients. The surgical outcome and invasiveness of the SP two-step retraction method were analyzed. RESULTS: Among the 200 cases who underwent START, 198 were female and 2 were male, with a mean age of 34.7 (range: 13-58 years). Thyroid lobectomy was performed for 177 patients and total thyroidectomy was performed for 23 patients. Ten patients had benign thyroid nodules, whereas the other 190 had thyroid malignancy. The mean body mass index (BMI) was 22.2 ± 3.7 kg/m(2) (range: 15.9-37.0 kg/m(2)). All of the operations were performed successfully without any open conversions, and patients were discharged on postoperative day 3 or 4 without significant complication. The mean operative time for thyroid lobectomy with the two-step retraction method was 116.69 ± 23.23 min, which was similar to that in the conventional robotic skin flap method (115.33 ± 17.29 min). We could minimize the extent of the robotic skin flap dissection with the two-step retraction method. CONCLUSIONS: START is a practical surgical method. By employing the new two-step retraction method, we can maximize the cosmetic and functional benefits for patients and reduce the workload fatigue of surgeons by increasing robotic dependency.
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http://dx.doi.org/10.1007/s00464-021-08837-9

Comparison of a Handheld Device vs Endotracheal Tube-Based Neuromonitoring for Recurrent Laryngeal Nerve Stimulation.
Otolaryngol Head Neck Surg, 166(2):260-6.
D. K. Kong, A. M. Kong and R. L. Chai. 2022.
OBJECTIVE: To measure the effect of thyroidectomy difficulty on intraoperative neuromonitoring false loss of signal (LOS) and to compare intraoperative endotracheal tube-based neuromonitoring (ETNM) and Checkpoint palpation-based direct stimulation (pDS) signals with postoperative laryngoscopy. We hypothesized that pDS has higher a positive predictive value for postdissection confirmation of recurrent laryngeal nerve function than ETNM and that this difference is accentuated with increasing thyroidectomy difficulty. STUDY DESIGN: Prospective single-arm cross-sectional study comparing ETNM and pDS for patients undergoing hemi-, total, or completion thyroidectomy from July 2018 to March 2020. SETTING: Single-surgeon series at a tertiary care hospital. METHODS: Percentage concordance and positive and negative predictive values were measured. Each thyroidectomy was assigned a validated thyroidectomy difficulty score, and recorded recurrent laryngeal nerve signals were compared with postoperative vocal fold mobility. RESULTS: Percentage concordance was 90.09%. Positive and negative predictive values were 0.19 (95% CI, 0.09-0.31) and 1.0 for ETNM and 0.59 (95% CI, 0.35-0.82) and 1.0 for pDS. The difference in positive predictive value was significant (0.40 [95% CI, 0.33-0.47], P < .001). False LOS rates for ETNM and pDS were 13.19% versus 3.30% (9.89% [95% CI, 1.80%-18.62%], P = .0155), 44.11% versus 0% (44.11% [95% CI, 25.80%-60.54%], P < .001), and 73.33% versus 13.33% (60% [95% CI, 24.76%-78.46%], P = .001) for the second through fourth thyroidectomy difficulty score quartiles, respectively. False LOS with ETNM was linearly correlated with increasing difficulty (R(2) = 0.97). CONCLUSION: ETNM was subject to high rates of postdissection false LOS that increased with thyroidectomy difficulty score. pDS is a reliable alternative that has higher positive predictive value than ETNM, particularly in more challenging cases such as those with posteriorly fixed thyroid cancers and fibrotic glands. EVIDENCE LEVEL: 2.
PubMed-ID: 34030499
http://dx.doi.org/10.1177/01945998211013753

Predictive Value of Gross Extranodal Extension for Differentiated Thyroid Carcinoma Persistence/Recurrence.
Otolaryngol Head Neck Surg, 166(4):643-51.
Y. Kou, G. Shen, Z. Cheng and A. Kuang. 2022.
OBJECTIVE: We systematically investigated the predictive value of gross extranodal extension (gENE) for differentiated thyroid carcinoma persistence/recurrence. STUDY DESIGN: Retrospective study. SETTING: A tertiary care hospital.

METHODS: This study was divided into 2 groups according to gENE status: the gENE group and non-gENE group. We compared the disease persistence/recurrence rates of these 2 groups in the entire cohort and by individual risk group (intermediate/high risk), analyzed whether gENE was an independent risk factor for disease persistence/recurrence, and explored the impact of gENE-specific features on disease persistence/recurrence. RESULTS: There were 989 patients who satisfied the inclusion criteria: 57 patients in the gENE group and 932 in the non-gENE group. The disease persistence/recurrence rate of the gENE group was higher than that of the non-gENE group in the entire cohort and by individual risk group ($P < .05$ for each). Unexpectedly, the outcomes of the gENE group with intermediate risk were similar to those of the non-gENE group with high risk ($P = .72$). For the entire cohort, gENE was an independent predictor for disease persistence/recurrence (odds ratio, 2.89; 95% CI, 1.39-6.00; $P = .005$). Specific features of gENE ($P > .05$ for each) were not related to disease persistence/recurrence. CONCLUSION: Patients with gENE and intermediate risk might be regraded as high risk. Specific features of gENE have no impact on disease persistence/recurrence.
PubMed-ID: 34182831
http://dx.doi.org/10.1177/01945998211023177

Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer.
N Engl J Med, 386(10):923-32.
S. Leboulleux, C. Bournaud, C. N. Chougnet, S. Zerdoud, A. Al Ghuzlan, B. Catargi, C. Do Cao, A. Kelly, M. L. Barge, L. Lacroix, I. Dygai, P. Vera, D. Rusu, O. Schneegans, D. Benisvy, M. Klein, J. Roux, M. C. Eberle, D. Bastie, C. Nascimento, A. L. Giraudet, N. Le Moullec, S. Bardet, D. Drui, N. Roudaut, Y. Godbert, O. Morel, A. Drutel, L. Lamartina, C. Schvartz, F. L. Velayoudom, M. J. Schlumberger, L. Leenhardt and I. Borget. 2022.
BACKGROUND: In patients with low-risk differentiated thyroid cancer undergoing thyroidectomy, the postoperative administration of radioiodine (iodine-131) is controversial in the absence of demonstrated benefits. METHODS: In this prospective, randomized, phase 3 trial, we assigned patients with low-risk differentiated thyroid cancer who were undergoing thyroidectomy to receive ablation with postoperative administration of radioiodine (1.1 GBq) after injections of recombinant human thyrotropin (radioiodine group) or to receive no postoperative radioiodine (no-radioiodine group). The primary objective was to assess whether no radioiodine therapy was noninferior to radioiodine therapy with respect to the absence of a composite end point that included functional, structural, and biologic abnormalities at 3 years. Noninferiority was defined as a between-group difference of less than 5 percentage points in the percentage of patients who did not have events that included the presence of abnormal foci of radioiodine uptake on whole-body scanning that required subsequent treatment (in the radioiodine group only), abnormal findings on neck ultrasonography, or elevated levels of thyroglobulin or thyroglobulin antibodies. Secondary end points included prognostic factors for events and molecular characterization. RESULTS: Among 730 patients who could be evaluated 3 years after randomization, the percentage of patients without an event was 95.6% (95% confidence interval [CI], 93.0 to 97.5) in the no-radioiodine group and 95.9% (95% CI, 93.3 to 97.7) in the radioiodine group, a difference of -0.3 percentage points (two-sided 90% CI, -2.7 to 2.2), a result that met the noninferiority criteria. Events consisted of structural or functional abnormalities in 8 patients and biologic abnormalities in 23 patients with 25 events. Events were more frequent in patients with a postoperative serum thyroglobulin level of more than 1 ng per milliliter during thyroid hormone treatment. Molecular alterations were similar in patients with or without an event. No treatment-related adverse events were reported. CONCLUSIONS: In patients with low-risk thyroid cancer undergoing thyroidectomy, a follow-up strategy that did not involve the use of radioiodine was noninferior to an ablation strategy with radioiodine regarding the occurrence of functional, structural, and biologic events at 3 years. (Funded by the French National Cancer Institute; ESTIMABL2 ClinicalTrials.gov number, NCT01837745.).
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http://dx.doi.org/10.1056/NEJMoa2111953

Audit of long-term treatment outcomes of thyrotoxicosis in a single-centre virtual clinic: The utility of long-term antithyroid drugs.
Clin Endocrinol (Oxf),
M. J. Levy, N. Reddy, D. Price, R. Bhake, E. Bremner, M. Barrowcliffe, V. Kieffer, C. Robinson, F. Zaccardi and T. A. Howlett. 2022.
OBJECTIVE: To investigate the long-term outcomes and prognosis of thyrotoxicosis in a large number of patients in a single UK county (Leicestershire). DESIGN: Retrospective cohort analysis of 56,741 thyroid function test (TFT) results, treatment modalities and outcomes in a well-established virtual thyrotoxicosis clinic database. PATIENTS: One thousand four hundred and eighty-nine patients were included with a median length of follow-up of 10.9 years. The aetiology of thyrotoxicosis was autoimmune (85.9%), nodular (9.1%) and mixed (5.0%). Treatment modalities included antithyroid

drugs (ATDs), radioiodine (RAI; 555 MBq fixed dose) and thyroidectomy. METHODS: We analysed both individual TFTs and groups of sequential TFTs on or after the same thyroid treatment(s), which we describe as 'phase of thyroid care' (POTC). Patients studied entered the virtual clinic between 1 January 1995 and 1 January 2010; we exported data on every TFT sample up to April 2020. RESULTS: ATD had been used in 99.2% (median 2, maximum seven courses) with long-term ATD (>2 years) in 48%. RAI and thyroidectomy were used more commonly with nodular and mixed aetiology. Overall, T4 was more often controlled than thyroid-stimulating hormone (TSH), and at the latest follow-up, T4 was normal in >96%, TSH in >79% and both in >76% of different aetiologies. The mean percentage control of T4 was 85% and TSH 50%; in long-term ATD courses, this improved to 89% and 62%, respectively. In the latest POTC, control of T4 and TSH was best in cases off treatment (95%/87%) and on T4 without ablative therapy (94%/72%), but was broadly similar in patients on long-term ATD (90%/68%), after RAI (92%/60%) or after thyroidectomy (91%/58%). After the first course of ATD, remission or hypothyroidism was seen in 47.3% autoimmune, 20.9% nodular and 32.5% mixed, with 90% relapses seen within 4 years. Relapse was more common in patients with ophthalmopathy, but there was no difference between the sexes. CONCLUSIONS: Thyrotoxicosis can be well controlled with minimal specialist clinic attendance using a software-supported virtual shared-care scheme. Long-term ATD appears to be a valid patient choice achieving TFT control comparable to that seen after RAI or surgery. In patients with autoimmune disease, relapse is more common in patients with ophthalmopathy, and hypothyroidism is common after RAI. In nodular disease, we found that spontaneous remission may occur.
PubMed-ID: 35274339
http://dx.doi.org/10.1111/cen.14721

CAR-T Cells Targeting TSHR Demonstrate Safety and Potent Preclinical Activity Against Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 107(4):1110-26.
H. Li, X. Zhou, G. Wang, D. Hua, S. Li, T. Xu, M. Dong, X. Cui, X. Yang, Y. Wu, M. Cai, X. Liao, T. Zhang, Z. Yang, Y. Du and X. Li. 2022.
BACKGROUND: Chimeric antigen receptor T cells (CAR-Ts) have demonstrated remarkable efficacy in hematological cancers but have not yet translated in treating solid tumors. The significant hurdles limiting CAR-T therapy were from a paucity of differentially expressed cell surface molecules on solid tumors that can be safely targeted. Here, we present TSH receptor (TSHR) as a putative target for CAR-T therapy of differentiated thyroid cancer (DTC). METHODS: We undertook a large-scale screen on thyroid cancer tissues and multiple internal organs through bioinformatical analysis and immunohistochemistry to date TSHR expression. Using 3 previously described monoclonal antibodies, we generated 3 third-generation CAR-Ts. We tested anti-TSHR CAR-T in vitro activity by T-cell function and killing assay. Then we tested preclinical therapeutical efficacy in a xenograft mouse model of DTC and analyzed mice's physical conditions and histological abnormalities to evaluate anti-TSHR CAR-T's safety. RESULTS: TSHR is highly and homogeneously expressed on 90.8% (138/152) of papillary thyroid cancer, 89.2% (33/37) of follicular thyroid cancer, 78.2% (18/23) of cervical lymph node metastases, and 86.7% of radioactive iodine resistance diseases. We developed 3 novel anti-TSHR CAR-Ts from monoclonal antibodies M22, K1-18, and K1-70; all 3 CAR-Ts mediate significant antitumor activity in vitro. Among these, we demonstrate that K1-70 CAR-T can have therapeutical efficacy in vivo, and no apparent toxicity has been observed. CONCLUSION: TSHR is a latent target antigen of CAR-T therapy for DTC. Anti-TSHR CAR-T could represent a therapeutic option for patients with locoregional relapsed or distant metastases of thyroid cancer and should be tested in carefully designed clinical trials.
PubMed-ID: 34751400
http://dx.doi.org/10.1210/clinem/dgab819

Preoperative prediction of central lymph node metastasis in cN0T1/T2 papillary thyroid carcinoma: A nomogram based on clinical and ultrasound characteristics.
Eur J Surg Oncol, 48(6):1272-9.
J. Li, P. Sun, T. Huang, L. Li, S. He, X. Ai, H. Xiao and G. Xue. 2022.
BACKGROUND: Preoperative status of central lymph nodes is a key determinant of the initial surgical extent for papillary thyroid carcinoma (PTC). We aimed to develop and validate a nomogram based on preoperative clinical characteristics and ultrasound features to predict central lymph node status in patients with clinically lymph node-negative (cN0) T1/T2 PTC. METHODS: This retrospective study included 729 patients with cN0T1/T2 PTC who were treated between January 2015 and March 2020. Based on the ratio of 6:4, 431 patients who underwent surgeries relatively earlier comprised the training set to develop the nomogram, while the other 298 who underwent surgeries relatively later comprised validation set to validate the performance of nomogram. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression were used to identify predictors of central lymph node metastasis (CLNM). These variables

were used to construct a nomogram for predicting the risk of CLNM. The predictive performance, discriminative ability, calibration, and clinical utility of the nomogram model were evaluated in both sets. RESULTS: A total of 313 (42.9%) PTC patients were identified with CLNM. On multivariate logistic regression analyses, malegender, younger age, larger maximum diameter, multifocality, capsular invasion, infiltrative margins, intra-nodular vascularity, and aspect ratio >1 were independent risk factors for CLNM. Nomogram integrating these 8 factors showed excellent discrimination in the training [area under the curve (AUC): 0.788] and validation (AUC: 0.829) sets, and obtained well-fitted calibration curves. The cut-off value of this nomogram was 0.410 (~245 points). Decision curve analysis confirmed the clinical utility of the nomogram. CONCLUSION: The CLNM-predicting nomogram can facilitate stratification of cN0T1/T2 PTC patients. Prophylactic central neck lymph node dissection can be considered for those with high nomogram scores.
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Multimodal Assessments of Altered Sensation after Transoral Endoscopic Thyroidectomy.
World J Surg, 46(3):600-9.
T. J. Liang, K. C. Wang, S. I. Liu, I. S. Chen and N. Y. Wang. 2022.
BACKGROUND: Transoral endoscopic thyroidectomy, a novel technique, uses oral vestibule as the entry point and leaves no scar on the body surface. However, because the incisions are close to the mental nerve, nerve damage and the associated sensory impairment are concerning. Herein, we evaluated sensory alteration after transoral endoscopic thyroidectomy and determined factors associated with the prolonged sensory alteration. METHODS: Patients who underwent transoral endoscopic thyroidectomy were enrolled. Sensation over the lower lip, chin, and neck was evaluated before and after the surgery. A self-assessment questionnaire, Semmes-Weinstein monofilament test, and two-point discrimination test were used to subjectively and objectively evaluate sensory changes. RESULTS: Fifty-one patients were enrolled; most of them reported altered sensation, with chin (72.5%) being the most common site, followed by lower lip (52.9%), upper neck (33.3%), and lower neck (5.9%) on postoperative day 2. The sensory disturbance resolved within 3 months. Factors associated with prolonged sensory alteration are male sex and old age. Fourteen patients (27.5%) experienced mild drooling from the mouth, which was usually self-limiting in 1 month. Sensory impairments in light touch pressure threshold and two-point discrimination were significant in the chin and neck on postoperative day 2 and at 1 week. The ability to discern two-point was also compromised in the lower lip on postoperative day 2. All these significant changes normalized to preoperative baseline at 1 month. CONCLUSIONS: There was an altered sensation after transoral endoscopic thyroidectomy with the most common and disturbed in the chin. Sensory impairment was usually transient and recovered in 3 months.
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http://dx.doi.org/10.1007/s00268-021-06356-1

Long-term outcome of patients treated with antithyroid drugs, radioactive iodine or surgery for persistent or relapsed Graves' disease.
Br J Surg, 109(4):381-9.
X. Liu, C. K. H. Wong, W. W. L. Chan, E. H. M. Tang, Y. C. Woo, S. Y. W. Liu, C. L. K. Lam and B. H. H. Lang. 2022.
BACKGROUND: The aim of this study was to compare long-term mortality, morbidity, and cumulative healthcare costs between antithyroid drugs, radioactive iodine, and surgical treatment for patients with persistent or relapsed Graves' disease. METHODS: Data on patients with persistent or relapsed Graves' disease between 2006 and 2018 were retrieved from the Hong Kong Hospital Authority. Hazard ratios (HRs) estimated by Cox proportional hazards regression models were used to compare the risks of all-cause mortality, cardiovascular disease, atrial fibrillation, psychological disease, Graves' ophthalmopathy, and cancer across treatment groups. The 10-year healthcare cost and change in co-morbidity status were also estimated. RESULTS: Over a median follow-up of 79 months (22 636 person-years), a total of 3443 patients (antithyroid drug 2294, radioactive iodine 755, surgery 394) were analysed. Compared with antithyroid drug treatment, surgery was associated with significantly lower risks of all-cause mortality (HR 0.40, 95 per cent c.i. 0.36 to 0.45), cardiovascular disease (HR 0.54, 0.48 to 0.60), atrial fibrillation (HR 0.11, 0.09 to 0.14), psychological disease (HR 0.85, 0.79 to 0.92), Graves' ophthalmopathy (HR 0.09, 0.08 to 0.10), and cancer (HR 0.56, 0.50 to 0.63). Patients who underwent surgery also had a lower risk of all outcome events than those in the radioactive iodine group. The 10-year direct cumulative healthcare cost was €14 754 for surgery compared with €17 390 for antithyroid drugs, and €17 918 for the radioactive iodine group. CONCLUSION: Patients who underwent surgery for persistent or relapsed Graves' disease had lower risks of all-cause mortality and analysed morbidities. The 10-year cumulative healthcare cost in the surgery group was lowest among the three treatment alternatives.

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http://dx.doi.org/10.1093/bjs/znab474

Concurrent Use of Thyroid Hormone Therapy and Interfering Medications in Older US Veterans.
J Clin Endocrinol Metab, 107(7):e2738-e42.
R. Livecchi, A. B. Coe, D. Reyes-Gastelum, M. Banerjee, M. R. Haymart and M. Papaleontiou. 2022.
CONTEXT: Thyroid hormone management in older adults is complicated by comorbidities and polypharmacy. OBJECTIVE: Determine the prevalence of concurrent use of thyroid hormone and medications that can interfere with thyroid hormone metabolism (amiodarone, prednisone, prednisolone, carbamazepine, phenytoin, phenobarbital, tamoxifen), and patient characteristics associated with this practice. DESIGN: Retrospective cohort study between 2004 and 2017 (median follow-up, 56 months). SETTING: Veterans Health Administration Corporate Data Warehouse. PARTICIPANTS: A total of 538 137 adults = 65 years prescribed thyroid hormone therapy during the study period. MAIN OUTCOME MEASURE: Concurrent use of thyroid hormone and medications interfering with thyroid hormone metabolism. RESULTS: Overall, 168 878 (31.4%) patients were on at least 1 interfering medication while on thyroid hormone during the study period. In multivariable analyses, Black/African-American race (odds ratio [OR], 1.25; 95% CI, 1.21-1.28, compared with White), Hispanic ethnicity (OR, 1.12; 95% CI, 1.09-1.15, compared with non-Hispanic), female (OR, 1.11; 95% CI, 1.08-1.15, compared with male), and presence of comorbidities (eg, Charlson/Deyo Comorbidity Score = 2; OR, 2.50; 95% CI, 2.45-2.54, compared with 0) were more likely to be associated with concurrent use of thyroid hormone and interfering medications. Older age (eg, = 85 years; OR, 0.48; 95% CI, 0.47-0.48, compared with age 65-74 years) was less likely to be associated with this practice. CONCLUSIONS AND RELEVANCE: Almost one-third of older adults on thyroid hormone were on medications known to interfere with thyroid hormone metabolism. Our findings highlight the complexity of thyroid hormone management in older adults, especially in women and minorities.
PubMed-ID: 35396840
http://dx.doi.org/10.1210/clinem/dgac216

Airway injury from transoral endoscopic thyroidectomy vestibular approach.
Head Neck, 44(2):E6-E10.
S. M. Long, K. Ali, R. P. Tufano and V. E. Banuchi. 2022.
BACKGROUND: The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a novel technique that eliminates a cervical scar. This procedure carries unique risks, and data on outcomes are needed as more cases are performed. METHODS: We describe two cases of airway injury during the TOETVA. A description of the procedure and management of the injuries is outlined. RESULTS: In one case, a 3-mm injury in the thyrohyoid membrane was identified. The TOETVA was converted to an open approach due to significant inflammation in the setting of Graves' and the repair was performed while open. In the second case, a fracture occurred from the thyroid notch to Broyle's ligament without avulsion. A primary repair was endoscopically performed. CONCLUSIONS: Airway injury is a possible complication of both open thyroidectomy and TOETVA. For TOETVA, trauma is most likely to occur in the midline during Hegar dilation and trocar placement through the central incision.
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http://dx.doi.org/10.1002/hed.26909

Outcomes in Pediatric Thyroidectomy: Results From a Multinational, Multi-institutional Database.
Otolaryngol Head Neck Surg:1945998221076065.
M. Maksimoski, A. J. Bauer, K. Kazahaya, S. C. Manning, S. R. Parikh, J. P. Simons, J. D'Souza, J. Maddalozzo, M. R. Purkey, K. Rychlik, B. Ho, M. J. Rutter, W. Jiang, J. D. Prager, G. Diercks, E. J. Propst, R. C. Miyamoto, B. C. Stack, G. W. Randolph and J. C. Rastatter. 2022.
OBJECTIVE: Traditionally, data regarding thyroidectomy were extracted from billing databases, but information may be missed. In this study, a multi-institutional pediatric thyroidectomy database was used to evaluate recurrent laryngeal nerve (RLN) injury and hypoparathyroidism. STUDY DESIGN: Retrospective multi-institutional cohort study. SETTING: Tertiary care pediatric hospital systems throughout North America. METHODS: Data were individually collected for thyroidectomies, then entered into a centralized database and analyzed using univariate and multivariable regression models. RESULTS: In total, 1025 thyroidectomies from 10 institutions were included. Average age was 13.9 years, and 77.8% were female. Average hospital stay was 1.9 nights and 13.5% of patients spent at least 1 night in the pediatric intensive care unit. The most frequent pathology was papillary thyroid carcinoma (42%), followed by Graves' disease (20.1%) and follicular adenoma (18.2%). Overall, 1.1% of patients experienced RLN injury (0.8% permanent), and 7.2% experienced hypoparathyroidism (3.3% permanent). Lower institutional volume (odds ratio [OR], 3.57; 95% CI, 1.72-7.14)

and concurrent hypoparathyroidism (OR, 3.51; 95% CI, 1.64-7.53) correlated with RLN injury on multivariable analysis. Graves' disease (OR, 2.27; 95% CI, 1.35-3.80), Hashimoto's thyroiditis (OR, 4.67; 95% CI, 2.39-9.09), central neck dissection (OR, 3.60; 95% CI, 2.36-5.49), and total vs partial thyroidectomy (OR, 7.14; 95% CI, 4.55-11.11) correlated with hypoparathyroidism. CONCLUSION: These data present thyroidectomy information and complications pertinent to surgeons, along with preoperative risk factor assessment. Multivariable analysis showed institutional volume and hypoparathyroidism associated with RLN injury, while hypoparathyroidism associated with surgical indication, central neck dissection, and extent of surgery. Low complication rates support the safety of thyroidectomy in pediatric tertiary care centers.
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http://dx.doi.org/10.1177/01945998221076065

Pregnancy-associated plasma protein A mRNA expression as a marker for differentiated thyroid cancer: results from a "surgical" and a "cytological" series.
J Endocrinol Invest, 45(2):369-78.
C. Marzocchi, M. Capezzone, A. Sagnella, A. Cartocci, M. Caroli Costantini, L. Brindisi, V. Mancini, S. Cantara and M. G. Castagna. 2022.
PURPOSE: Pregnancy-associated plasma protein A (PAPPA) is a metalloproteinase initially described for its role during pregnancy. PAPPA regulates IGF ligands 1 (IGF1) bioavailability through the degradation of IGF-binding protein 4 (IGFBP4). After the cleavage of IGFBP4, free IGF1 is able to bind IGF1 receptors (IGF1R) triggering the downstream signaling. Recently, PAPPA expression has been linked with development of several cancers. No data have been published on thyroid cancer, yet. METHODS: We evaluated PAPPA, insulin-like growth factor (IGF1), IGF1 receptors (IGF1R) and IGF-binding protein 4 (IGFBP4) mRNA expression levels in a "Surgical series" of 94 thyroid nodules (64 cancers, 16 follicular adenomas and 14 hyperplastic nodules) and in a "Cytological series" of 80 nodules from 74 patients underwent to fine-needle aspiration cytology (FNAC). In tissues, PAPPA was also evaluated by western blot. RESULTS: We found that PAPPA expression was increased in thyroid cancer specimen at mRNA and protein levels and that, adenomas and hyperplastic nodules had an expression similar to normal tissues. When applied on thyroid cytologies, PAPPA expression was able to discriminate benign from malignant nodules contributing to pre-surgical classification of the nodules. We calculated a cut-off with a good specificity (91%) which reached 100% when combined with molecular biology. CONCLUSION: These results show that PAPPA could represent a promising diagnostic marker for differentiated thyroid cancer.
PubMed-ID: 34350538
http://dx.doi.org/10.1007/s40618-021-01655-9

Mutation based approaches to the treatment of anaplastic thyroid cancer.
Clin Endocrinol (Oxf), 96(5):734-42.
H. C. McCrary, J. Aoki, Y. Huang, B. Chadwick, K. Kerrigan, B. Witt, J. P. Hunt and D. Abraham. 2022.
OBJECTIVE: The treatment of anaplastic thyroid cancer (ATC) has continued to rapidly evolve over time. Increased utilization of novel, personalized therapies based upon the tumour's somatic mutation status has recently been integrated. The aim of this case series is to describe a series of patients that underwent rapid genomic testing upon their diagnosis of ATC, allowing for the early integration of novel therapies. DESIGN: A fast track pathway for genomic tumour analysis of patients with ATC was implemented at a single academic cancer hospital in January of 2020. PATIENTS: All patients were evaluated by head and neck surgery, endocrinology, and medical oncology upon diagnosis of ATC. MEASUREMENTS: Genetic work-up was completed, which prompted a recommendation for dual BRAF/MEK inhibition with dabrafenib and trametinib for tumours with BRAF V600E mutation. For patients whose tumours were BRAF V600E wild-type, pembrolizumab with lenvatinib was offered. RESULTS: A total of four patients were included in this series. Two patients (50%) had tumours that were BRAF V600E positive. Among patients that were BRAF V600E positive, both patients initiated urgent dabrafenib and trametinib dual tyrosine kinase inhibitor (TKI) therapy; with one patient demonstrating near-complete clinical response allowing for posttreatment surgery, while the other demonstrated decreased tumour burden. Among patients who were BRAF V600E wild-type, lenvatinib and pembrolizumab were recommended off-label; one patient demonstrated decreased tumour burden, but developed severe pure red cell aplasia, while the other patient is demonstrating an early clinical response. CONCLUSIONS: The integration of early genomic analysis and personalized neoadjuvant TKI therapy into the treatment of ATC can greatly benefit patient care outcomes and optimize tumour control.
PubMed-ID: 35067961
http://dx.doi.org/10.1111/cen.14679

Heavier Weight of Resected Thyroid Specimen Is Associated With Higher Postoperative Morbidity in Benign Goiter.
J Clin Endocrinol Metab, 107(7):e2762-e9.
I. Mintziras, R. Ringelband, J. Jähne, C. Vorländer, C. Dotzenrath, A. Zielke, C. Klinger and K. Holzer. 2022.
OBJECTIVE: The impact of heavier weight of resected thyroid specimen on postoperative morbidity after total thyroidectomy for multinodular benign goiter remains unclear. METHODS: Data from the prospective StuDoQ|Thyroid registry of the German Society of General and Visceral Surgery were analyzed regarding the weight of the resected thyroid specimen and perioperative morbidity (vocal cord palsy, hemorrhage, surgical site infection, and hypocalcemia). To achieve a homogeneous patient population, only patients with total thyroidectomy for multinodular benign goiter were included. RESULTS: A total of 7911 patients from 105 departments underwent total thyroidectomy for benign conditions (January 2017-July 2020). The median resected weight of the thyroid specimen in all patients was 53 g (interquartile range 32-92). In 1732 patients, the specimen weight exceeded 100 g. Intraoperative neuromonitoring was used in 99.5% of patients. Postoperative laryngoscopy revealed vocal cord dysfunction in 480 of 15 822 (3.03%) nerves at risk, with unilateral dysfunction in 454 (2.87%) of patients and bilateral dysfunction in 13 patients (0.08%). In multivariable analysis, a thyroid weight >100 g was an independent predictor of early postoperative vocal cord dysfunction [odds ratio (OR) 1.462, 95% CI 1.108-1.930, P = 0.007). Heavier (>100 g) thyroid weight was an independent predictor of surgical site infection (OR 1.861, 95% CI 1.203-2.880, P = 0.005) and also predicted postoperative hemorrhage in the univariate analysis (OR 1.723, 95% CI 1.027-2.889, P = 0.039). On the contrary, postoperative parathyroid function was not affected. CONCLUSIONS: Heavier (>100 g) resected thyroid weight independently predicts higher postoperative morbidity, including early vocal cord palsy and surgical site infection after total thyroidectomy for benign multinodular goiter.
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http://dx.doi.org/10.1210/clinem/dgac214

Restratification of Patients with Intermediate-Risk Papillary Thyroid Carcinoma.
Ann Surg Oncol,
G. Moon, S. W. Jang, K. T. Nam, J. H. Park, H. J. Kwon and J. H. Yoon. 2022.
BACKGROUND: Long-term management and follow-up strategies in patients with intermediate-risk papillary thyroid carcinoma (PTC) according to the American Thyroid Association (ATA) are still controversial due to the paucity of data on unique risk factors or a risk stratification system predictive of long-term outcomes. PATIENTS AND METHODS: This study included 649 patients with PTC who underwent an initial surgical treatment. Retrospectively enrolled patients were categorized according to the ATA risk stratification system. Intermediate-risk patients were further categorized into subgroups by the number of ATA intermediate risk factors. The recurrence-free survival (RFS) rates of these subgroups were compared with those of low- and high-risk patient groups. Additionally, the patients were classified according to their response to the initial therapy using the dynamic risk stratification (DRS) system, and the percentages of patients in each category were compared among the subgroups. RESULTS: The median follow-up period was 102 months. Structural recurrence occurred in 9.2% of all enrolled patients (60/649) and in 13.0% of intermediate-risk patients (40/308). Patients with two or more current intermediate risk factors had a poorer RFS than patients with only one risk factor ($p < 0.001$) and showed a comparable RFS to high-risk patients ($p > 0.050$). The percentages of patients with an excellent response category for DRS significantly decreased with an increase in the number of intermediate risk factors. CONCLUSION: Subclassification according to the number of intermediate risk factors may be useful to better predict the RFS and the response to initial therapy in patients with intermediate-risk PTC.
PubMed-ID: 35169978
http://dx.doi.org/10.1245/s10434-022-11414-6

Intraoperative Indocyanine Green Angiography of Parathyroid Glands and the Prevention of Post-Thyroidectomy Hypocalcemia.
World J Surg, 46(1):121-7.
P. Moreno Llorente, A. García Barrasa, J. M. Francos Martínez, M. Alberich Prats and M. Pascua Solé. 2022.
BACKGROUND: We compared the reliability of indocyanine green (ICG) angiography and intraoperative PTH levels for predicting early post-thyroidectomy hypocalcemia. METHODS: Prospective study of 94 patients (71% women, mean age 53.7 years) undergoing total thyroidectomy. An ICG score of 2 (white) indicated a well-vascularized gland. PTH preoperative levels-PTH postresection levels divided by preoperative PTH × 100 was used to determine the PTH decline percentage. A decrease of at least 62.5% or <17.1 pg/mL in ioPTH was the criterion for predicting hypocalcemia. RESULTS: At surgery, the four parathyroid glands were identified in 50 (53.2%) patients and <4 glands in 44. Calcium supplements were needed by 22 patients (23.4%) postoperatively, 11 patients in each group of 4 and <4 parathyroid glands identified. The diagnostic accuracy of ICG angiography (0.883, 95% confidence interval [CI] 0.800-0.940) and ioPTH (0.862, 95% CI

0.775-0.92) was similar. When all four parathyroid glands were identified, ICG angiography showed a slightly higher diagnostic accuracy, specificity and positive predictive than ioPTH levels, but when < 4 glands were identified, the ioPTH showed a slightly higher diagnostic accuracy, specificity and positive predictive value. Differences were not statistically significant for any of the comparisons. CONCLUSIONS: The presence of one well-perfused parathyroid gland (ICG score 2) using ICG angiography or ioPTH decline, measured before and after completion of thyroid surgery, is both reliable methods in prediction of early post-thyroidectomy hypocalcemia independently of the number of glands identified intraoperatively.
PubMed-ID: 34561745
http://dx.doi.org/10.1007/s00268-021-06322-x

Radiofrequency Ablation and Autonomous Functioning Thyroid Nodules: Review of the Current Literature.
Laryngoscope, 132(4):906-14.
H. Muhammad, A. Tehreem, J. O. Russell and R. P. Tufano. 2022.
OBJECTIVE: Autonomously functioning thyroid nodules (AFTNs) have long been treated with either surgery or radioactive iodine (RAI). Being an invasive procedure, even thyroid lobectomy for this condition is associated with complications such as anesthesia side effects, scarring, iatrogenic hypothyroidism, and injury to other structures. Similarly, RAI is associated with hypothyroidism and may require multiple courses. Therefore, minimally invasive techniques such as radiofrequency ablation (RFA) are being advocated as an alternative treatment for AFTNs. To date, only few studies have been published on this topic and are largely on European and Asian populations. The aim of this review is to assess the efficacy and safety of RFA as a potential alternative for treatment of AFTNs compared to conventional surgery and radioiodine. METHODS/STUDY DESIGN: Comprehensive PubMed and Embase searches were performed using the following terms such as (autonomously functioning thyroid nodules and radiofrequency ablation), (radiofrequency ablation and hyperthyroidism), and (radiofrequency ablation and toxic thyroid nodule). Both prospective and retrospective studies were included based on the inclusion and exclusion criteria specified in the text. RESULTS: Initially, 57 studies were identified and after excluding 47 studies, finally 10 studies were included in the review. CONCLUSION: Although surgery remains the first line treatment for AFTN. However, RFA is a safe option compared to RAI or surgery, especially in patients who are high-risk surgical candidates or have absolute contraindications to RAI. Currently, trials with follow-up greater than or equal to 5 years are warranted. It will aid in formulating a standardized surveillance protocol and also generalize RFA's use for AFTN. Laryngoscope, 132:906-914, 2022.
PubMed-ID: 34375454
http://dx.doi.org/10.1002/lary.29811

Clinicopathological indicators for TERT promoter mutation in papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 97(1):106-15.
H. Y. Na, H. W. Yu, W. Kim, J. H. Moon, C. H. Ahn, S. I. Choi, Y. K. Kim, J. Y. Choi and S. Y. Park. 2022.
OBJECTIVE: Mutations in the telomerase reverse transcriptase (TERT) promoter have been reported as a convincing prognostic factor in papillary thyroid carcinomas (PTCs). We aimed to investigate the frequency of TERT promoter mutations in patients with thyroid cancer and identify the clinicopathological factors associated with them in PTCs. DESIGN: A total of 1086 consecutive cases of thyroid cancer composed of mostly PTCs were included in this study. TERT promoter and BRAF mutations were detected by pyrosequencing and their associations with clinicopathological features of tumour were analyzed. RESULTS: TERT promoter mutations were observed in 1.9% of PTCs, 6.7% of follicular thyroid carcinomas, 8.3% of Hurthle cell carcinomas and 25.0% of poorly differentiated thyroid carcinomas and in a single case of anaplastic thyroid carcinoma. In PTCs, aggressive clinicopathological features, higher stage and BRAF V600E mutation were all found to be associated with TERT promoter mutations. Distant metastasis and disease recurrence were more frequent in TERT promoter-mutated PTCs. In multivariate analysis, age =55 years, tall cell variant, mitoses =3/10 high-power fields, tumour necrosis, and gross extrathyroidal extension (ETE) were identified as independent factors associated with TERT promoter mutations in PTCs. CONCLUSIONS: This study revealed a relatively low frequency of TERT promoter mutations in Korean patients with PTC. Certain clinicopathological features including old age, tall cell variant, increased mitoses, tumour necrosis and gross ETE were found to be indicative of TERT promoter mutations in PTCs, suggesting that mutational analysis in a particular group of PTCs can be effective in regions with low mutation rates.
PubMed-ID: 35343605
http://dx.doi.org/10.1111/cen.14728

Preoperative detection of the TERT promoter mutations in papillary thyroid carcinomas.
Clin Endocrinol (Oxf), 95(5):790-9.
T. Nakao, M. Matsuse, V. Saenko, T. Rogounovitch, A. Tanaka, K. Suzuki, M. Higuchi, H. Sasai, T. Sano, M. Hirokawa, A. Miyauchi, A. Kawakami and N. Mitsutake. 2021.
OBJECTIVE: Telomerase reverse transcriptase promoter (TERT-p) mutations are strongly associated with tumour aggressiveness and worse prognosis in papillary thyroid carcinomas (PTCs). Since the TERT-p mutations have been reported to be subclonal, it is unclear how accurately they can be detected by preoperative fine-needle aspiration (FNA). The objective of this study was to analyse the concordance rate of the TERT-p mutations between preoperative FNA and corresponding postoperative surgical specimens. DESIGN AND PATIENTS: Ninety-six cases of PTC aged 55 years or older were studied. The mutational status of TERT-p was detected by droplet digital polymerase chain reaction assay. RESULTS: The mutational status of the TERT-p in FNA samples was highly concordant with that in postoperative formalin-fixed and paraffin-embedded (FFPE) specimens. The TERT-p mutation was significantly associated with age, tumour size, extrathyroidal extension and the Ki-67 labelling index in multivariate analysis in both FNA and FFPE samples. CONCLUSIONS: The detection of the TERT-p mutations using FNA samples has a good ability to predict disease aggressiveness and, therefore, could be clinically useful in the determination of PTC management.
PubMed-ID: 34322882
http://dx.doi.org/10.1111/cen.14567

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

ASO Author Reflections: Central Neck Dissection Can Be Performed Via Transoral Approach.
Ann Surg Oncol, 29(3):1975-6.
D. Q. Ngo, D. T. Le, Q. X. Ngo and Q. Van Le. 2022.
PubMed-ID: 34988832
http://dx.doi.org/10.1245/s10434-021-11167-8

Recurrence of Papillary Thyroid Cancer: A Systematic Appraisal of Risk Factors.
J Clin Endocrinol Metab, 107(5):1392-406.
H. R. Nieto, C. E. M. Thornton, K. Brookes, A. Nobre 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. 2022.
CONTEXT: 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 personalized and improved patient care. OBJECTIVE: We aimed to perform a comprehensive bioinformatic and experimental analysis of 3 levels of genetic change (mRNA, microRNA, and somatic mutation) apparent in recurrent tumors and construct a new combinatorial prognostic risk model. METHODS: We analyzed The Cancer Genome Atlas data (TCGA) to identify differentially expressed genes (mRNA/microRNA) in 46 recurrent vs 455 nonrecurrent thyroid tumors. 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 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 utilized genes with a validated functional role and identified a 5-gene risk score classifier as an independent predictor of thyroid cancer recurrence. CONCLUSION: 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 posttreatment surveillance.
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http://dx.doi.org/10.1210/clinem/dgab836

"Cutting the Support" to Improve Treatment Efficacy in Thyroid Cancer by Targeting Tumor Microenvironment.
J Clin Endocrinol Metab, 107(4):e1758-e9.
N. Nilubol. 2022.
PubMed-ID: 34668970
http://dx.doi.org/10.1210/clinem/dgab685

SARS-CoV-2 Vaccine-induced Thyroiditis: Safety of Revaccinations and Clinical Follow-up.
J Clin Endocrinol Metab, 107(5):e1823-e34.
S. H. Oguz, S. N. Sendur, B. G. Iremli, A. Gürlek, T. Erbas and U. Ünlütürk. 2022.
CONTEXT: The number of reported cases with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine-induced subacute thyroiditis (SAT) and Graves' disease (GD) is growing. However, active debate continues about managing such side effects and the safety of repeat or booster doses of the vaccines in such cases. OBJECTIVES: This study aims to present long-term clinical follow-up of SARS-CoV-2 vaccine-induced SAT or GD cases and provide data regarding the safety of revaccinations. METHODS: Patients diagnosed with SARS-CoV-2 vaccine-induced SAT or GD were included. Data regarding the long-term clinical follow-up of SARS-CoV-2 vaccine-induced SAT and GD cases and outcomes of repeat or booster SARS-CoV-2 vaccinations were documented. The literature, including cases of SARS-CoV-2 vaccine-induced SAT or GD, was reviewed. RESULTS: Fifteen patients with SARS-CoV-2 vaccine-induced SAT and 4 with GD were included. Pfizer/BioNTech COVID-19 vaccine (BNT162b2) was associated with symptoms in a majority of cases with SAT and all with GD. Median time from vaccination to symptom onset was 7 and 11.5 days, respectively, while 7 and 2 patients required medical treatment in SAT and GD groups, respectively. Remission was documented in 10 SAT patients, with a median time to remission of 11.5 weeks. No exacerbation/recurrence of SAT occurred in 7 of 9 patients who received a repeat vaccination dose, while symptoms of SAT worsened following the second vaccination in 2 cases. None of the patients experienced severe side effects that could be associated with revaccinations. CONCLUSIONS: Revaccinations appear to be safe in patients with SARS-CoV-2 vaccine-induced SAT cases, while more evidence is needed regarding SARS-CoV-2 vaccine-induced GD.
PubMed-ID: 35100622
http://dx.doi.org/10.1210/clinem/dgac049

Large, Slowly Growing, Benign Thyroid Nodules Frequently Coexist With Synchronous Thyroid Cancers.
J Clin Endocrinol Metab, 107(8):e3474-e8.
R. D. Paparodis, E. Karvounis, D. Bantouna, C. Chourpiliadis, H. Hourpiliadi, S. Livadas, S. Imam and J. C. Jaume. 2022.
CONTEXT: Thyroid nodules' size should not be the sole criterion for thyroidectomy; however, many patients undergo surgery for large or slowly growing nodules. OBJECTIVE: We evaluated risk for clinically significant thyroid cancer in patients with large or slowly growing nodules. METHODS: We reviewed data from 2 prospectively collected databases of patients undergoing thyroidectomies in tertiary referral centers in the USA and Greece over 14 consecutive years. We collected data on the preoperative surgical indication, FNA cytology, and surgical pathology. We included subjects operated solely for large or growing thyroid nodules, without any known or presumed thyroid cancer or high risk for malignancy, family history of thyroid cancer, or prior radiation exposure. RESULTS: We reviewed 5523 consecutive cases

(USA: 2711; Greece: 2812). After excluding 3059 subjects, we included 2464 subjects in the present analysis. Overall, 533 thyroid cancers were identified (21.3%): 372 (69.8%) microcarcinomas (<1 cm) and 161 (30.2%) macrocarcinomas (=1 cm). The histology was consistent with papillary cancer (n = 503), follicular cancer (n = 12), Hürthle cell cancer (n = 9), medullary cancer (n = 5), and mixed histology cancers n = 4. Only 47 (1.9%) of our subjects had any form of thyroid cancer in the nodule that originally led to surgery. The cancers were multifocal in 165 subjects; had extrathyroidal extension in 61, capsular invasion in 80, lymph node involvement in 35, and bone metastasis in 2 subjects. CONCLUSION: The risk of synchronous, clinically important thyroid cancers is small, but not null in patients with large or slow growing thyroid nodules. Therefore, more precise preoperative evaluation is needed to separate the patients who would clearly benefit from thyroid surgery from the vast majority of those who do not need to be operated.
PubMed-ID: 35436327
http://dx.doi.org/10.1210/clinem/dgac242

Repeat Fine-Needle Aspiration With Molecular Analysis in Management of Indeterminate Thyroid Nodules.
Otolaryngol Head Neck Surg:1945998221093527.
M. R. Papazian, J. C. Dublin, K. N. Patel, T. Oweity, A. S. Jacobson, T. C. Brandler and B. Givi. 2022.
OBJECTIVE: To analyze clinical outcomes in a series of indeterminate thyroid nodules (ITNs) with repeat fine-needle aspiration (FNA) biopsy and results of genomic classifier. STUDY DESIGN: Historical chart review. SETTING: Tertiary care center. METHODS: We reviewed FNA samples from subjects with Bethesda III or IV diagnoses from January 2015 to December 2018 at a single institution and selected those with repeat FNA and ThyroSeq testing of the same nodule. Patient demographics, Bethesda classifications, ThyroSeq results, treatment detail, and surgical pathology, when available, were analyzed. RESULTS: Ninety-six patients with cytologic diagnosis of ITN, repeat FNA, and ThyroSeq testing were identified. Following repeat FNA, 55 nodules (57%) remained ITN; 40 (42%) were reclassified as benign; and 1 (1%) was reclassified as suspicious for malignancy. In 31 patients with ThyroSeq analysis accompanying initial and repeat FNA, 26 (84%) had the same result on each, while 5 (16%) tested ThyroSeq positive following an initially negative result (? = 0.24). Most nodules that were downgraded to Bethesda II on repeat FNA (37/40, 93%) were managed nonsurgically. Patients with ThyroSeq-positive results were treated with surgery more often (25/28, 89%) than patients with ThyroSeq-negative results (11/68, 16%; P < .0001). In excised nodules, the prevalence of malignancy and noninvasive follicular thyroid neoplasm with papillary-like nuclear features was 28% (n = 10) and 22% (n = 8), respectively, and all malignancies were low risk. CONCLUSION: In this case series, repeat FNA helped patients with ITNs avoid diagnostic surgery through reclassification to benign cytology. The risk of high-risk malignancy in ThyroSeq-positive nodules with repeat indeterminate cytology was low.
PubMed-ID: 35412868
http://dx.doi.org/10.1177/01945998221093527

Thyroid Nodule Shape Independently Predicts Risk of Malignancy.
J Clin Endocrinol Metab, 107(7):1865-70.
T. Pappa, S. Ahmadi, A. Bikas, S. Hwang, A. Coleman, I. Lobon, P. Xiang, M. Kim, E. Marqusee, D. M. Richman, S. M. Durfee, E. H. Asch, C. B. Benson, M. C. Frates, I. Landa and E. K. Alexander. 2022.
CONTEXT: Predictive models of thyroid nodule cancer risk are presently based upon nodule composition, echogenicity, margins, and the presence of microcalcifications. Nodule shape has shown promise to be an additive factor helping determine the need for nodule biopsy. OBJECTIVE: We sought to determine if calculation of a nodule's spherical shape independently associates with cancer risk. METHODS: This prospective cohort study, conducted at a single large academic healthcare system in the United States, included patients with 1 or 2 clinically relevant thyroid nodules (predominantly solid and over 1 cm) presenting for diagnostic evaluation. Thyroid ultrasound, cytological evaluation with fine-needle biopsy, and/or histopathological examination on occasion of thyroid surgery were performed. We calculated the nodule's long to short ratio (spherical shape), and its association with tissue proven benign or malignant endpoints. RESULTS: The long to short nodule ratio was significantly lower in malignant compared to benign nodules indicating greater risk of malignancy in more spherical nodules (1.63 ± 0.38 for malignant nodules vs 1.74 ± 0.47 for benign, P < 0.0001). The risk of malignancy continually increased as the long to short ratio approached a purely spherical ratio of 1.0 (ratio > 2.00, 14.6% cancer; ratio 1.51-2.00, 19.7%; ratio 1.00-1.50, 25.5%, P < 0.0001). In multiple regression analysis, younger age, male sex, and nodule's spherical shape were each independently associated with cancer risk. CONCLUSION: The more a thyroid nodule is spherically shaped, as indicated by a long to short ratio approaching 1.0, the greater its risk of malignancy. This was independent of age, sex, and nodule size. Incorporating a nodule's sphericity in the risk stratification systems may improve individualized clinical decision making.

PubMed-ID: 35439309
http://dx.doi.org/10.1210/clinem/dgac246

Bone-density testing interval and transition to osteoporosis in differentiated thyroid carcinoma patients on TSH suppression therapy.
Clin Endocrinol (Oxf), 97(1):130-6.
H. Park, J. Park, H. Yoo, S. Kim, J. H. Koh, J. H. Jee, Y. K. Min, J. H. Chung, T. H. Kim, M. Kang and S. W. Kim. 2022.
OBJECTIVE: Thyrotropin (TSH) suppression therapy is a standard treatment after surgery for differentiated thyroid carcinoma (DTC). It may be associated with osteoporosis in postmenopausal women. However, there are no guidelines for bone mineral density (BMD) testing intervals to screen for osteoporosis in these patients. Therefore, we evaluated the timing of repeated BMD testing in DTC patients with TSH suppression according to baseline T-scores. DESIGN, PATIENTS, AND MEASUREMENT: We retrospectively evaluated 658 DTC patients who underwent BMD testing more than twice between January 2007 and January 2020. A 1:3 propensity score matching was conducted to compare the timing of repeated BMD tests between the DTC and non-DTC groups. We stratified the participants into four groups based on their baseline T-scores: normal (-1.00 or higher), mild osteopenia (-1.01 to -1.49), moderate osteopenia (-1.50 to -1.99), and severe osteopenia (-2.00 to -2.49). Additionally, the 10% of patients in each group that transitioned to osteoporosis were analysed. RESULTS: The estimated BMD testing interval for 10% of patients who developed osteoporosis was 85 months for patients with initially mild osteopenia, 65 months for those with moderate osteopenia, and 15 months for those with severe osteopenia in the DTC group. In the non-DTC group, the testing intervals for mild, moderate, and severe osteopenia were 98, 57, and 13 months, respectively. On multivariate analysis, baseline T-score (mild osteopenia: hazard ratio [HR] 5.91, p = .105; moderate osteopenia: HR, 25.27, p = .02; and severe osteopenia: HR, 134.82, p < .001) and duration of TSH suppression (tertile 2: HR, 2.25, p = .005; Tertile 3: 1.78, p = .033) were independent risk factors for osteoporosis in the DTC group. CONCLUSION: This study provides guidance for the timing of repeated BMD tests in women over 50 years of age with TSH suppression. The rescreening interval for BMD testing can be modified based on the baseline T-score. The appropriate BMD testing intervals in female DTC patients were similar to those in non-DTC females.
PubMed-ID: 35174522
http://dx.doi.org/10.1111/cen.14698

Molecular Testing for Thyroid Nodules Including Its Interpretation and Use in Clinical Practice.
Ann Surg Oncol, 28(13):8884-91.
S. G. Patel, S. E. Carty and A. J. Lee. 2021.
Despite advances in imaging and biopsy techniques, the management of thyroid nodules often remains a diagnostic and clinical challenge. In particular, patients with cytologically indeterminate nodules often undergo diagnostic thyroidectomy although only a minority of patients are found to have thyroid malignancy on final pathology. More recently, several molecular testing platforms have been developed to improve the stratification of cancer risk for patients with cytologically indeterminate thyroid nodules. Based on numerous studies demonstrating its accuracy, molecular testing has been incorporated as an important diagnostic adjunct in the management of indeterminate thyroid nodules in the National Comprehensive Cancer Network Guidelines as well as in the American Thyroid Association (ATA) and American Association of Endocrine Surgeons (AAES) guidelines. This overview describes the currently available molecular testing platforms and highlights the published data to date on the clinical validity and utility of molecular testing in the contemporary management of thyroid nodules.
PubMed-ID: 34275048
http://dx.doi.org/10.1245/s10434-021-10307-4

Postradioiodine Graves' management: The PRAGMA study.
Clin Endocrinol (Oxf),
P. Perros, A. Basu, K. Boelaert, C. Dayan, B. Vaidya, G. R. Williams, J. H. Lazarus, J. Hickey, W. M. Drake, A. Crown, S. M. Orme, A. Johnson, D. W. Ray, G. P. Leese, T. H. Jones, P. Abraham, A. Grossman, A. Rees, S. Razvi, F. W. Gibb, C. Moran, A. Madathil, M. P. Žarkovic, Z. Plummer, S. Jarvis, A. Falinska, A. Velusamy, V. Sanderson, N. Pariani, S. L. Atkin, A. A. Syed, T. Sathyapalan, S. Nag, J. Gilbert, H. Gleeson, M. J. Levy, C. Johnston, N. Sturrock, S. Bennett, B. Mishra, I. Malik and N. Karavitaki. 2022.
OBJECTIVE: Thyroid status in the months following radioiodine (RI) treatment for Graves' disease can be unstable. Our objective was to quantify frequency of abnormal thyroid function post-RI and compare effectiveness of common management strategies. DESIGN: Retrospective, multicentre and observational study. PATIENTS: Adult patients with Graves' disease treated with RI with 12 months' follow-up. MEASUREMENTS: Euthyroidism was defined as both serum

thyrotropin (thyroid-stimulating hormone [TSH]) and free thyroxine (FT4) within their reference ranges or, when only one was available, it was within its reference range; hypothyroidism as TSH = 10 mU/L, or subnormal FT4 regardless of TSH; hyperthyroidism as TSH below and FT4 above their reference ranges; dysthyroidism as the sum of hypo- and hyperthyroidism; subclinical hypothyroidism as normal FT4 and TSH between the upper limit of normal and <10 mU/L; and subclinical hyperthyroidism as low TSH and normal FT4. RESULTS: Of 812 patients studied post-RI, hypothyroidism occurred in 80.7% and hyperthyroidism in 48.6% of patients. Three principal post-RI management strategies were employed: (a) antithyroid drugs alone, (b) levothyroxine alone, and (c) combination of the two. Differences among these were small. Adherence to national guidelines regarding monitoring thyroid function in the first 6 months was low (21.4%-28.7%). No negative outcomes (new-onset/exacerbation of Graves' orbitopathy, weight gain, and cardiovascular events) were associated with dysthyroidism. There were significant differences in demographics, clinical practice, and thyroid status postradioiodine between centres. CONCLUSIONS: Dysthyroidism in the 12 months post-RI was common. Differences between post-RI strategies were small, suggesting these interventions alone are unlikely to address the high frequency of dysthyroidism.
PubMed-ID: 35274331
http://dx.doi.org/10.1111/cen.14719

Quality of Life, Patient-Reported Outcomes, and Extent of Surgery for Patients With Low- and Intermediate-Risk-Differentiated Thyroid Cancer.
JAMA Surg, 157(3):209-10.
S. C. Pitt. 2022.
PubMed-ID: 34935879
http://dx.doi.org/10.1001/jamasurg.2021.6443

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

Physician Specialties Involved in Thyroid Cancer Diagnosis and Treatment: Implications for Improving Health Care Disparities.
J Clin Endocrinol Metab, 107(3):e1096-e105.
A. Radhakrishnan, D. Reyes-Gastelum, P. Abrahamse, B. Gay, S. T. Hawley, L. P. Wallner, D. W. Chen, A. S. Hamilton, K. C. Ward and M. R. Haymart. 2022.
CONTEXT: Little is known about provider specialties involved in thyroid cancer diagnosis and management. OBJECTIVE: Characterize providers involved in diagnosing and treating thyroid cancer. DESIGN/SETTING/PARTICIPANTS: We surveyed patients with differentiated thyroid cancer from the Georgia and Los Angeles County Surveillance, Epidemiology and End Results registries (N = 2632, 63% response rate). Patients identified their primary care physicians (PCPs), who were also surveyed (N = 162, 56% response rate). MAIN OUTCOME MEASURES: (1) Patient-reported provider involvement

(endocrinologist, surgeon, PCP) at diagnosis and treatment; (2) PCP-reported involvement (more vs less) and comfort (more vs less) with discussing diagnosis and treatment. RESULTS: Among thyroid cancer patients, 40.6% reported being informed of their diagnosis by their surgeon, 37.9% by their endocrinologist, and 13.5% by their PCP. Patients reported discussing their treatment with their surgeon (71.7%), endocrinologist (69.6%), and PCP (33.3%). Physician specialty involvement in diagnosis and treatment varied by patient race/ethnicity and age. For example, Hispanic patients (vs non-Hispanic White) were more likely to report their PCP informed them of their diagnosis (odds ratio [OR]: 1.68; 95% CI, 1.24-2.27). Patients =65 years (vs <45 years) were more likely to discuss treatment with their PCP (OR: 1.59; 95% CI, 1.22-2.08). Although 74% of PCPs reported discussing their patients' diagnosis and 62% their treatment, only 66% and 48%, respectively, were comfortable doing so. CONCLUSIONS: PCPs were involved in thyroid cancer diagnosis and treatment, and their involvement was greater among older patients and patients of minority race/ethnicity. This suggests an opportunity to leverage PCP involvement in thyroid cancer management to improve health and quality of care outcomes for vulnerable patients.
PubMed-ID: 34718629
http://dx.doi.org/10.1210/clinem/dgab781

Indication for radioactive iodine in patients with papillary thyroid carcinoma without apparent disease after total thyroidectomy but with elevated antithyroglobulin antibodies.
Clin Endocrinol (Oxf), 96(1):82-8.
F. Ramos da Silva, P. W. Rosario and G. F. Mourão. 2022.
OBJECTIVE: To evaluate a criterion for the selective indication of radioactive iodine (RAI) based on the short-term behaviour of antithyroglobulin antibodies (TgAb) in patients with papillary thyroid carcinoma (PTC) who have negative thyroglobulin (Tg) and neck ultrasonography (US) without abnormalities after total thyroidectomy but elevated TgAb. DESIGN: This was a prospective study that evaluated 216 patients with low- or intermediate-risk PTC who had nonstimulated Tg = 0.2 ng/ml and no US abnormalities but elevated TgAb 3 months after thyroidectomy. RAI was not indicated in patients with negative TgAb or a >50% reduction in TgAb concentrations 6 months after initial assessment followed by a negative test or an additional reduction (also >50%) after 12 months. RESULTS: Only two of the 114 patients who did not receive RAI developed recurrences; another 108 patients met the criterion of an excellent response to therapy in the last assessment and TgAb persisted in four patients but there was an additional reduction in their concentration during follow-up. Among the 102 patients who received RAI, post-therapy whole-body scanning (RxWBS) detected persistent disease in 8 (8%). Two of the 94 patients without persistent disease on RxWBS developed recurrences. In the last assessment, in the absence of additional treatment, 54/92 patients (58.7%) without structural recurrence had negative TgAb. CONCLUSIONS: The indication for RAI can be based on the short-term behaviour of TgAb in patients with PTC and elevated TgAb after thyroidectomy who are not high risk and who do not have apparent disease (nonstimulated Tg = 0.2 ng/ml and no US abnormalities).
PubMed-ID: 34323308
http://dx.doi.org/10.1111/cen.14570

Letter to the Editor From Raven et al: "Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine".
J Clin Endocrinol Metab, 107(4):e1767-e8.
L. M. Raven, A. I. McCormack and J. R. Greenfield. 2022.
PubMed-ID: 34752614
http://dx.doi.org/10.1210/clinem/dgab822

Vascular invasion predicts advanced tumor characteristics in papillary thyroid carcinoma.
Am J Surg, 223(3):487-91.
J. Reilly, E. Faridmoayer, M. Lapkus, J. Pastewski, F. Sun, H. Elassar, D. M. Studzinski, R. E. Callahan, P. Czako and S. Nagar. 2022.
BACKGROUND: The clinical impact of vascular invasion in Papillary Thyroid Carcinoma (PTC) is not well understood. Our aim was to determine if there was an association between vascular invasion and other tumor characteristics and patient outcomes in PTC. METHODS: A retrospective chart review was performed of 536 patients with PTC between January 2007-December 2011. Patient demographics, comorbidities, tumor characteristics, and outcomes were collected. RESULTS: Vascular invasion was associated with lymphatic invasion, capsular invasion, extrathyroidal extension, and the presence of positive lymph nodes. Logistic regression revealed that tumor size was a predictor of vascular invasion. Vascular invasion in PTC tumors was associated with higher tumor recurrence rates, but there were no differences in mortality. CONCLUSION: This study indicates that vascular invasion in PTC is associated with other aggressive pathologic features and

an increased recurrence rate. For these reasons, vascular invasion should be an important tumor characteristic when determining extent of treatment.
PubMed-ID: 34952686
http://dx.doi.org/10.1016/j.amjsurg.2021.11.038

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

Association between number of parathyroid glands identified during total thyroidectomy and functional parathyroid preservation.
Langenbecks Arch Surg, 407(1):297-303.
F. Riordan, M. S. Murphy, L. Feeley and P. Sheahan. 2022.
PURPOSE: Systematic identification of all 4 parathyroid glands has been recommended during total thyroidectomy (TT); however, it is unclear whether this strategy necessarily translates into optimized functional parathyroid preservation. We wished to investigate the association between number of parathyroids identified intraoperatively during TT, and incidence of incidental parathyroidectomy, and postoperative hypoparathyroidism. METHODS: Retrospective review of prospectively maintained database of 511 consecutive patients undergoing TT at an academic teaching hospital. The association between number of parathyroid glands identified intraoperatively and incidence of biochemical hypocalcaemia (defined as any calcium < 2 mmol/L n first 48 h after surgery), symptomatic hypocalcaemia; permanent hypoparathyroidism (defined as any hypocalcaemia or need for calcium or vitamin D > 6 months after surgery), and incidental parathyroidectomy, was investigated. The association between number of parathyroid glands visualized and postoperative parathyroid hormone (PTH) levels was investigated in a subset of 454 patients. RESULTS: Patients in whom a greater number of parathyroids had been identified had a significantly higher incidence of biochemical and symptomatic hypocalcaemia, and significantly lower postoperative PTH levels, than patients with fewer glands identified. There were no significant differences in incidence of permanent hypoparathyroidism or incidental parathyroidectomy. On multivariate analysis, malignancy, Graves disease, and identification of 3-4 parathyroids were independent predictors of biochemical hypocalcaemia. For symptomatic hypocalcaemia, identification of 2-4 parathyroids, and identification of 3-4 parathyroids, were significant. CONCLUSIONS: Systematic identification of as many parathyroid glands as possible during TT is not necessary for functional parathyroid preservation.
PubMed-ID: 34406491
http://dx.doi.org/10.1007/s00423-021-02287-6

Graves' Disease in the Young: Could We Change the Weather?
J Clin Endocrinol Metab, 107(5):e2186-e7.
P. Rodien. 2022.
PubMed-ID: 34928376
http://dx.doi.org/10.1210/clinem/dgab909

Increased Risk of Type 2 Diabetes in Patients With Thyroid Cancer After Thyroidectomy: A Nationwide Cohort Study.
J Clin Endocrinol Metab, 107(3):e1047-e56.
E. Roh, E. Noh, S. Y. Hwang, J. A. Kim, E. Song, M. Park, K. M. Choi, S. H. Baik, G. J. Cho and H. J. Yoo. 2022.
CONTEXT: Abnormal thyroid function after thyroidectomy and subsequent thyroid-stimulating hormone suppression can have detrimental effects on glucose homeostasis in patients with thyroid cancer. OBJECTIVE: To investigate whether thyroidectomy increases the risk of type 2 diabetes in patients with thyroid cancer and to explore the association between levothyroxine dosage and type 2 diabetes risk. METHODS: A retrospective population-based cohort study using the Korean National Health Insurance database. We included 36 377 thyroid cancer patients without known diabetes who underwent thyroidectomy between 2004 and 2013. Matched subjects with nonthyroid cancer were selected using 1:1 propensity score matching. The main outcome measure was newly developed type 2 diabetes mellitus. RESULTS: Patients with thyroid cancer who underwent thyroidectomy had a higher risk of developing type 2 diabetes mellitus than the matched controls (hazard ratio [HR] 1.43, 95% CI 1.39-1.47). Among patients with thyroid cancer, when the second quartile group (in terms of the mean levothyroxine dosage; 101-127 μg/day) was considered the reference group, the risk of type 2 diabetes mellitus increased in the first quartile (<101 μg/day; HR 1.45, 95% CI 1.36-1.54) and fourth quartile groups (=150 μg/day; HR 1.37, 95% CI 1.29-1.45); meanwhile, the risk decreased in the third quartile group (128-149 μg/day; HR 0.91, 95% CI 0.85-0.97). CONCLUSION: Patients with thyroid cancer who underwent thyroidectomy were more likely to develop type 2 diabetes mellitus than the matched controls. There was a U-shaped dose-dependent relationship between the levothyroxine dosage and type 2 diabetes mellitus risk.
PubMed-ID: 34718625
http://dx.doi.org/10.1210/clinem/dgab776

Symptoms of thyrotoxicosis, bone metabolism, and occult atrial fibrillation in older women with mild endogenous subclinical hyperthyroidism: A reassessment after 5 years.
Clin Endocrinol (Oxf), 96(6):914-5.
P. W. Rosario. 2022.
PubMed-ID: 34369606
http://dx.doi.org/10.1111/cen.14579

Outcomes of 756 patients with differentiated thyroid cancer and excellent response to treatment: An evidence-based paradigm for long-term surveillance strategies.
Clin Endocrinol (Oxf), 96(3):395-401.
K. Seejore, O. Mulla, G. E. Gerrard, V. M. Gill, A. Al-Qaissi, J. W. Moor and R. D. Murray. 2022.
BACKGROUND: The 2014 British Thyroid Association thyroid cancer guidelines recommend lifelong follow-up of all thyroid cancer patients. This is probably unnecessary, particularly for differentiated thyroid cancer (DTC) patients with an excellent response to treatment and places significant demand on health service resources. DESIGN: Single centre retrospective cohort analysis of patients diagnosed and treated at the Leeds Cancer Centre between 2001 and 2014. PATIENTS: A total of 756 patients were dynamically risk-stratified (DRS) as having 'excellent response to treatment' after total thyroidectomy and radioiodineremnant ablation (RRA) for DTC. RESULTS: Median follow-up was 11.2 (range: 6.5-18.5) years. Radiological recurrence occurred in 15/756 (2.0%) patients and was always preceded by a raised thyroglobulin or thyroglobulin antibody level. The vast majority of tumour recurrences (13/15, 85%) were identifiable within 5 years of diagnostic surgery. Patients classified as having high-risk disease as per American Thyroid Association (ATA) guidelines had an almost threefold higher recurrence rate (2/34 [5.9%] vs. 13/722 [1.8%]) than those with ATA low-risk or intermediate-risk disease. Tumour histology subtype was a significant contributing factor, with Hürthle cell cancer having a worse prognosis than papillary thyroid cancer (PTC) (5/68 [7.4%] vs. 9/582 [1.5%]; relative risk: 4.76 [95% confidence interval: 1.64-13.8]). CONCLUSIONS: The recurrence rate of DRS patients with excellent response to treatment is low. It is reasonable to consider discharge of ATA low-risk or intermediate-risk patients with PTC who remain disease-free after 5 years of secondary care follow-up. Lifelong follow-up, however, currently remains the standard for subgroups at greater risk.

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Response to Letter to the Editor From Bonnema et al: "Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine + Liothyronine in Hypothyroidism".
J Clin Endocrinol Metab, 107(3):e1327-e8.
M. K. M. Shakir, D. I. Brooks, E. A. McAninch, T. L. Fonseca, V. Q. Mai, A. C. Bianco and T. D. Hoang. 2022.
PubMed-ID: 34718640
http://dx.doi.org/10.1210/clinem/dgab779

Preoperative comprehensive malignancy risk estimation for thyroid nodules: Development and verification of a network-based prediction model.
Eur J Surg Oncol, 48(6):1264-71.
G. Shao, B. Sun, M. Shi, Y. Song, Z. Sun, X. Hao, L. Li and Z. Fu. 2022.
BACKGROUND: In order to avoid excessive treatment of thyroid nodules in the clinic, it is necessary to find a simple and practical analysis method to comprehensively and accurately reflect benign or malignant thyroid nodules. This study aimed to construct and validate a comprehensive and reliable network-based predictive model using a variety of imaging and laboratory criteria for thyroid nodules to stratify the risk of malignancy prior to surgery. METHODS: We retrospectively analyzed data from patients who underwent surgical treatment for thyroid nodules at the Thyroid and Breast Diagnosis and Treatment Center of Weifang Hospital of Traditional Chinese Medicine between January 2018 and December 2020. Binary logical regression analysis was performed to predict whether nodules were malignant or benign. The developmental dataset included 457 patients (January 2018-December 2020). The validation set included separate data points (n = 225, January 2018-December 2020). RESULTS: In this study, criteria that showed significant predictive value for malignant nodules included TI-RADS: 4b (p = 0.065); Bethesda IV, Bethesda V, Bethesda VI (P < 0.0001); BRAF(V600E) mutation (P < 0.0001); Calcitonin>5 pg/ml (p = 0.0037); and FNA-Tg>30 ng/ml (p = 0.0003). A 10-grade risk scoring system was developed. The risk of malignancy risk ranged from 2.06% to 100% and was positively associated with increasing risk grade. The areas under the receiver-operating characteristic curve of the development and validation sets were 0.972 and 0.946, respectively. CONCLUSION: A simple, comprehensive and reliable web-based predictive model was designed using a variety of imaging and laboratory criteria to stratify thyroid nodules by probability of malignancy.
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http://dx.doi.org/10.1016/j.ejso.2022.03.016

Development and pilot testing of a conversation aid to support the evaluation of patients with thyroid nodules.
Clin Endocrinol (Oxf), 96(4):627-36.
N. M. Singh Ospina, D. Bagautdinova, I. Hargraves, D. Barb, S. Subbarayan, A. Srihari, S. Wang, S. Maraka, C. L. Bylund, D. Treise, V. Montori and J. P. Brito. 2022.
OBJECTIVE: To support patient-centred care and the collaboration of patients and clinicians, we developed and pilot tested a conversation aid for patients with thyroid nodules. DESIGN, PATIENT AND MEASUREMENTS: We developed a web-based Thyroid NOdule Conversation aid (TNOC) following a human-centred design. A proof of concept observational pre-post study was conducted (TNOC vs. usual care [UC]) to assess the impact of TNOC on the quality of conversations. Data sources included recordings of clinical visits, post-encounter surveys and review of electronic health records. Summary statistics and group comparisons are reported. RESULTS: Sixty-five patients were analysed (32 in the UC and 33 in the TNOC cohort). Most patients were women (89%) with a median age of 57 years and were incidentally found to have a thyroid nodule (62%). Most thyroid nodules were at low risk for thyroid cancer (71%) and the median size was 1.4 cm. At baseline, the groups were similar except for higher numeracy in the TNOC cohort. The use of TNOC was associated with increased involvement of patients in the decision-making process, clinician satisfaction and discussion of relevant topics for decision making. In addition, decreased decisional conflict and fewer thyroid biopsies as the next management step were noted in the TNOC cohort. No differences in terms of knowledge transfer, length of consultation, thyroid cancer risk perception or concern for thyroid cancer diagnosis were found. CONCLUSION: In this pilot observational study, using TNOC in clinical practice was feasible and seemed to help the collaboration of patients and clinicians.
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Surgical Case Volume has an Impact on Outcomes for Patients with Lateral Neck Disease in Thyroid Cancer.
Ann Surg Oncol, 29(2):1141-50.
J. Siu, R. Griffiths, C. W. Noel, P. C. Austin, J. Pasternak, D. Urbach, E. Monteiro, D. P. Goldstein, J. C. Irish, A. M. Sawka and A. Eskander. 2022.
BACKGROUND: This study aimed to assess whether surgical case volume for lateral neck dissection has an impact on the survival of patients who have well-differentiated thyroid cancer (WDTC) with lateral cervical node metastases. The authors used a population-based cohort study design. METHODS: The study cohort consisted of WDTC patients in Ontario Canada who underwent thyroidectomy and lateral neck dissection. These patients were identified using both hospital- and surgeon-level administrative data between 1993 and 2017 (n = 1832). Surgeon and hospital volumes were calculated based on the number of cases managed in the year before the procedure by the physician and at the institution managing each case, respectively, and divided into tertiles. Multilevel Cox regression models were used to estimate the effect of volume on disease-free survival (DFS). RESULTS: A crude model without patient or treatment characteristics demonstrated that DFS was associated with both higher surgeon volume tertiles ($p < 0.01$) and higher hospital volume tertiles ($p < 0.01$). After control for clustering, patient/treatment covariates, and hospital volume, the lowest surgeon volume tertile (range, 0-20/year; mean, 6.5/year) remained an independent statistically significant negative predictor of DFS (hazard ratio, 1.71; 95 % confidence interval, 1.22-2.4; $p < 0.01$). CONCLUSION: Surgeon lateral neck dissection case volume is a predictor of better DFS for thyroid cancer patients, with the lowest surgeon volume tertile (<20 neck dissections per year) demonstrating poorer DFS.
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http://dx.doi.org/10.1245/s10434-021-10923-0

Patterns of Occult Metastasis to Level Va and Vb in Clinically Lateral Node-Positive Papillary Thyroid Carcinoma.
Ann Surg Oncol, 29(4):2550-6.
K. Song, Y. Jin, M. Kim, S. Moon, D. B. Heo, H. R. Won, J. W. Chang and B. S. Koo. 2022.
BACKGROUND: The optimal extent of therapeutic lateral neck dissection (ND) in papillary thyroid carcinoma (PTC) continues to be debated. We analyzed the frequency, patterns, and predictive factors of occult level Va and Vb metastasis in clinically lateral node-positive PTC patients. METHODS: We reviewed the data of PTC patients who underwent thyroidectomy and therapeutic lateral ND from level II to V between May 2008 and August 2020. In our study, 46 patients without clinically positive metastatic lymph nodes (LNs) at level V on the preoperative evaluation were included to analyze occult metastasis at level Va and Vb, respectively. Patient demographics, including age, sex, distribution of pathologic LNs, and characteristics of the primary tumors, were reviewed. In addition, clinicopathologic factors associated with occult level Va and Vb metastasis were analyzed. RESULTS: Of the 46 patients, 14 (30.4%) patients had occult metastases at level Vb. No occult metastases were found at level Va. Clinically positive level II metastasis ($p = 0.015$) and simultaneous level II, III, and IV metastases ($p = 0.010$) in the preoperative evaluation were significantly associated with occult level Vb metastasis. Patients without LN metastasis at level IV or with three or fewer metastatic LNs in the lateral neck never had occult LN metastases at level Vb. CONCLUSIONS: Occult metastasis at level Va is rare in PTC with lateral LN metastasis. Occult metastasis at level Vb may occur in PTC patients with multilevel involvement, including level II and/or four or more lateral LN metastases.
PubMed-ID: 34792697
http://dx.doi.org/10.1245/s10434-021-11085-9

ASO Author Reflections: Patterns and Predictors of Occult Level V Lymph Node Metastasis in Papillary Thyroid Carcinoma.
Ann Surg Oncol, 29(4):2557-8.
K. Song, Y. Jin, M. Kim, S. Moon, D. B. Heo, H. R. Won, J. W. Chang and B. S. Koo. 2022.
PubMed-ID: 35001234
http://dx.doi.org/10.1245/s10434-021-11118-3

Level IIb neck dissection guided by fine-needle aspiration for N1b papillary thyroid carcinoma.
Surg Oncol, 40:101705.
Y. Song, G. Xu, Y. Bai, T. Wang, K. Fei and B. Zhang. 2022.
BACKGROUND: The extent of neck dissection for patients with papillary thyroid carcinoma (PTC) metastasis in lateral cervical lymph nodes is still debated. Studies aiming to omit level IIb were generally based on postoperative histopathologic information. The purpose of this study was to evaluate the predictive value of fine-needle aspiration (FNA) for level II lymph nodes in identifying candidates for neck dissection sparing level IIb before surgery. METHODS: We

prospectively enrolled 156 consecutive previously untreated PTC patients with lateral neck metastases who were subjected to 178 therapeutic lateral neck dissections (including level IIa, IIb, III, IV, and Vb) between June 2018 and August 2021. Ultrasound-guided FNA of suspicious lymph nodes at level II was preoperatively performed. The cytology of FNA and thyroglobulin (Tg) washout concentration with other clinical predictors was analyzed for lymph node metastases at level IIb. RESULTS: Preoperative ultrasonography revealed suspicious lymph nodes at level II in 118 cases, and fifty were positive on FNA results. Metastasis at level IIb was seen in 17 (9.6%) of the postoperative specimens. By univariate analysis, the rate of level IIb metastasis was significantly higher in patients with FNA-positive lymph nodes at level II (P<0.001, odds ratio = 16.899). The tumor sizes of the two FNA-negative level IIb metastatic lymph nodes were 0.4 mm and 3 mm. CONCLUSIONS: Level IIb lymph node dissection may be omitted in the treatment of N1b PTC patients if FNA to level II lymph nodes is negative.
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http://dx.doi.org/10.1016/j.suronc.2021.101705

Nonsurgical Management of Thyroid Nodules: The Role of Ablative Therapies.
J Clin Endocrinol Metab, 107(5):1417-30.
M. N. Stan, M. Papaleontiou, J. J. Schmitz and M. R. Castro. 2022.
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 surgery or radioactive iodine (RAI) (if toxic) are the treatments of choice. Both interventions can lead to hypothyroidism and other adverse outcomes (eg, 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 concern (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. CONCLUSION: 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

The Effects of Common Genetic Variation in 96 Genes Involved in Thyroid Hormone Regulation on TSH and FT4 Concentrations.
J Clin Endocrinol Metab, 107(6):e2276-e83.
R. Sterenborg, T. E. Galesloot, A. Teumer, R. T. Netea-Maier, D. Speed, M. E. Meima, W. E. Visser, J. W. A. Smit, R. P. Peeters and M. Medici. 2022.
OBJECTIVE: While most of the variation in thyroid function is determined by genetic factors, single nucleotide polymorphisms (SNPs) identified via genome-wide association analyses have only explained ~5% to 9% of this variance so far. Most SNPs were in or nearby genes with no known role in thyroid hormone (TH) regulation. Therefore, we performed a large-scale candidate gene study investigating the effect of common genetic variation in established TH regulating genes on serum thyrotropin [thyroid-stimulating hormone (TSH)] and thyroxine (FT4) concentrations. METHODS: SNPs in or within 10 kb of 96 TH regulating genes were included (30 031 TSH SNPs, and 29 962 FT4 SNPs). Associations were studied in 54 288 individuals from the ThyroidOmics Consortium. Linkage disequilibrium-based clumping was used to identify independently associated SNPs. SNP-based explained variances were calculated using SumHer software. RESULTS: We identified 23 novel TSH-associated SNPs in predominantly hypothalamic-pituitary-thyroid axis genes and 25 novel FT4-associated SNPs in mainly peripheral metabolism and transport genes. Genome-wide SNP variation explained ~21% (SD 1.7) of the total variation in both TSH and FT4 concentrations, whereas SNPs in the 96 TH regulating genes explained 1.9% to 2.6% (SD 0.4). CONCLUSION: Here we report the largest candidate gene analysis on thyroid function, resulting in a substantial increase in the number of genetic variants determining TSH and FT4 concentrations. Interestingly, these candidate gene SNPs explain only a minor part of the variation in TSH and FT4 concentrations, which substantiates the need for large genetic studies including common and rare variants to unravel novel, yet unknown, pathways in TH regulation.

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http://dx.doi.org/10.1210/clinem/dgac136

Delayed Tracheal Perforation Following Total Thyroidectomy.
Laryngoscope, 132(1):17-9.
M. N. Stevens, A. Bolduan and A. Gelbard. 2022.
Delayed tracheal rupture following total thyroidectomy (TT) is rare and represents a potential airway emergency. A 34-year-old female with Felty Syndrome underwent TT for Hashimoto's thyroiditis. On post-operative day 10, she presented with subcutaneous emphysema and an anterolateral tracheal perforation on CT scan. Urgent operative exploration revealed transmural tracheal necrosis and a 5 mm perforation. This was oversewn with non-absorbable suture and a strap muscle flap rotated over the defect to promote healing. Repeat direct laryngoscopy at 72 hours revealed healing tissue. Tracheal necrosis and perforation following TT constitutes a potential airway emergency and should be promptly explored and repaired. Laryngoscope, 132:17-19, 2022.
PubMed-ID: 33782958
http://dx.doi.org/10.1002/lary.29534

Medullary thyroid cancer: What is the optimal management of the lateral neck in a node negative patient at index operation?
Surgery, 171(1):177-81.
T. Szabo Yamashita, R. T. Rogers, T. R. Foster, M. L. Lyden, J. C. Morris, G. B. Thompson, T. McKenzie and B. M. Dy. 2022.
BACKGROUND: Medullary thyroid cancer is a neuroendocrine malignancy that can occur sporadically or as the result of genomic rearranged during transfection mutations. Medullary thyroid cancer has a higher rate of metastasis than well-differentiated thyroid cancer. Lateral neck dissection is often performed, and its prophylactic use is controversial. METHODS: Single-center, retrospective review (2000-2017) of patients undergoing primary surgical treatment for medullary thyroid cancer who had negative lateral neck imaging preoperatively. Demographics, genetic associations, clinical, and imaging findings were analyzed. Locoregional recurrence, overall recurrence, and overall survival were examined. RESULTS: A total of 110 patients were identified, of which 18 underwent prophylactic lateral neck dissection and 92 did not. Age, sex distribution, preoperative calcitonin levels, and follow-up were similar among groups. Overall recurrence was 20% for no prophylactic lateral neck dissection and 39% for prophylactic lateral neck dissection (P = .46). Most recurrences were locoregional recurrence, 7.6% for no prophylactic lateral neck dissection versus 22% for prophylactic lateral neck dissection (P = .08), half of it being to the lateral neck in both groups. A total of 7 patients from the no prophylactic lateral neck dissection group required treatment for recurrences versus 4 patients in prophylactic lateral neck dissection group (P = .57). Overall survival at 5 years was similar, 43% the no prophylactic lateral neck dissection group and 31% for prophylactic lateral neck dissection group (P = .52). CONCLUSION: Lateral neck dissection has no effect in decreasing locoregional or overall recurrences in medullary thyroid cancer and has no effect in overall survival when performed prophylactically at index surgical intervention.
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http://dx.doi.org/10.1016/j.surg.2021.04.052

Utility of mutational analysis for risk stratification of indeterminate thyroid nodules in a real-world setting.
Clin Endocrinol (Oxf), 96(4):637-45.
V. Torrecillas, A. Sharma, K. Neuberger and D. Abraham. 2022.
OBJECTIVE: American Thyroid Association (ATAn) 2015 guidelines recommend repeat fine-needle aspiration with molecular marker profiling (MMP) or diagnostic lobectomy in thyroid nodules yielding atypia of unknown significance/follicular lesion of unknown significance (AUS/FLUS) or follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) cytology. Our objective is to describe the molecular profiles and histological correlates of these cytologically indeterminate nodules (CIN) to aid risk stratification. DESIGN: Retrospective chart review. PATIENTS: Adults with CIN that underwent MMP from 2017 to 2020. MEASUREMENTS: Pearsons' ?(2) , Fisher's exact test, nonparametric testing and multiple regression analysis were performed. RESULTS: A total of 89 CIN underwent mutational analysis. Of 55% (n = 49) were Bethesda class III AUS/FLUS and 45% (n = 40) were Bethesda class IV FN/SFN. The US phenotype of a CIN was isoechoic (53%) or hypoechoic (32%) with well-defined margins (98%), absence of calcifications (75%) and mildly increased internal vascularity (70%). A total of 84% and 87% of nodules were classified as mild/moderate or low/intermediate risk per the Thyroid Imaging Reporting and Data System and ATA classifications, respectively. Based on the Thyroseq patient management resource, 6.7% (n = 6) of nodules had a high predicted probability of cancer (=95%), 41.6% (n = 37) were intermediate probability (40%-94%) and 51.7% (n = 46) were low probability (<40%). MMP revealed positive mutations in

45% (n = 40) of nodules, with 71% demonstrating RAS mutations. Of the nodules that underwent resection (n = 38), 39% (n = 15) had malignant pathology. Increasing the threshold to recommend surgical resection to a Thyroseq predicted probability of cancer to =50%, had a 100% sensitivity and 65% specificity for detecting malignant nodules (area under the ROC curve: 0.86). The positive predictive value was 37% and the negative predictive value was 100%. CONCLUSION: US phenotypes of CIN nodules were variable and did not aid in differentiating malignant from benign nodules. Of the CIN nodules with a positive MMP, most were RAS and had a benign pathology. With the exception of high-risk genetic markers for malignancy, the threshold to recommend surgical resection should be raised for CIN. Further studies to improve risk stratification in these nodules are required.
PubMed-ID: 34605038
http://dx.doi.org/10.1111/cen.14601

Isolated Lateral Neck Nodal Metastases in Patients With Papillary Thyroid Cancer: Does Cervical Compartment Matter?
J Clin Endocrinol Metab, 107(8):e3534-e5.
T. M. Ullmann and Q. Y. Duh. 2022.
PubMed-ID: 35413110
http://dx.doi.org/10.1210/clinem/dgac219

RET Fusion-Positive Papillary Thyroid Cancers are Associated with a More Aggressive Phenotype.
Ann Surg Oncol,
T. M. Ullmann, J. W. Thiesmeyer, Y. J. Lee, S. Beg, J. M. Mosquera, O. Elemento, T. J. Fahey, 3rd, T. Scognamiglio and Y. Houvras. 2022.
BACKGROUND: It is unclear if different genetic drivers in papillary thyroid cancer (PTC) confer different phenotypic tumor behavior leading to more aggressive disease. We hypothesized that RET-driven cancers are more aggressive. PATIENTS AND METHODS: We reviewed records of consecutive patients treated for newly diagnosed PTC at this single institution from 2015 to 2016. Tumor samples from these patients were genotyped to identify RET-translocated, BRAF(V600E) mutant, and HRAS, KRAS, and NRAS mutant tumors. Patient demographic, clinicopathologic, and outcomes data were compared to identify genotype-specific patterns of disease. RESULTS: Of the 327 patients who underwent initial surgery for PTC during the study period, 192 (58.7%) had BRAF(V600E) mutant tumors (BRAF), 14 (4.3%) had RET-rearranged tumors (RET), 46 (14.1%) had RAS mutant tumors (RAS), and 75 (22.9%) had BRAF, RET, and RAS wildtype tumors. RET-driven tumors were more likely to have extrathyroidal extension (50.0% versus 27.0% for BRAF and 2.2% for RAS, P < 0.001), multifocal disease (85.7% versus 60.3%, and 44.4%, respectively, P = 0.017), and distant metastases (14.3% versus 1.1%, and 0%, respectively, P = 0.019). RET and BRAF patients also had worse disease-free survival than RAS patients (Kaplan-Meier log rank, P = 0.027). CONCLUSIONS: Patients with RET-driven PTCs had higher rates of extrathyroidal extension, multifocal disease, and distant metastases than patients whose tumors had BRAF(V600E) or RAS mutations. Patients with RET-rearranged tumors had similar disease-free survival to patients with BRAF(V600E) mutant tumors. RET rearrangement may confer an aggressive phenotype in PTC.
PubMed-ID: 35230579
http://dx.doi.org/10.1245/s10434-022-11418-2

Establishing a Multicenter Network for Patients With Thyroid Nodules and Cancer: Effects on Referral Patterns.
Otolaryngol Head Neck Surg:1945998221086203.
S. P. J. van Dijk, I. Loncar, E. van Veen-Berkx, W. Edward Visser, R. P. Peeters, C. van Noord, E. T. Massolt, M. Castro Cabezas, M. Schouten, E. M. von Meyenfeldt and T. M. van Ginhoven. 2022.
OBJECTIVE: To perform a qualitative evaluation of the Thyroid Network, with a quantitative analysis of second opinion referrals for patients in the southwestern part of the Netherlands who have thyroid nodules and cancer. METHODS: This prospective observational study registered all patients with thyroid nodules and cancer who were referred to the academic hospital from 2 years before and 4 years after the foundation of the Thyroid Network. We implemented biweekly regional multidisciplinary tumor boards using video conference and a regional patient care pathway for patients with thyroid nodules and cancer. For qualitative evaluation, interviews were conducted with a broad selection of stakeholders via maximum variation sampling. The primary outcome was the change in second opinions after the foundation of the Thyroid Network. RESULTS: Second opinions from Thyroid Network hospitals to the academic hospital decreased from 10 (30%) to 2 (7%) two years after the start of the Thyroid Network (P = .001), while patient referrals remained stable (n = 108 to 106). Qualitative evaluation indicated that the uniform care pathway and the regional multidisciplinary tumor board were valued high. DISCUSSION: Establishing a regional network, including multidisciplinary tumor boards and a care pathway for patients with thyroid nodules and cancer, resulted in a decrease in second opinions

of in-network hospitals and high satisfaction of participating specialists. IMPLICATIONS FOR PRACTICE: The concept of the Thyroid Network could spread to other regions as well as to other specialties in health care. Future steps would be to assess the effect of regional collaboration on quality of care and patient satisfaction.
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http://dx.doi.org/10.1177/01945998221086203

Endoscopic cephalic access thyroid surgery (EndoCATS) using the retroauricular approach - a single centre retrospective data analysis.
Surg Endosc, 36(1):117-25.
T. von Ahnen, U. Wirth, M. von Ahnen, J. Kroenke, P. Busch, H. M. Schardey and S. Schopf. 2022.
BACKGROUND: Due to improvements in endoscopic as well as robotic technology, and a request for better cosmetic results, there was a significant increase in thyroid surgery using these methods during the past decade. METHODS: The aim of our study is to evaluate the perioperative short- and long-term outcome as well as the learning curve of EndoCATS and the Quality of Life (QoL). RESULTS: A total of 150 patients with 152 hemithyroidectomies who underwent endoscopic thyroid surgery by EndoCATS between 2010 and 2016 were enrolled in this study. The mean specimen volume was 15.04 g ± 7.89 g. The mean operation time was 132.79 ± 50.52 min. There is a significant reduction of the operation time after the 53th case. ($p < 0.05$) There was no acute rebleeding or permanent hypoparathyroidism. Permanent RLN palsy occurred in 3 nerves at risk (NAR) 1.97%. There were no cases of pneumothorax, postoperative infections or skin flap ischemia. 94.11% of the patients describe their state of general health as good as or better than before the surgery. CONCLUSIONS: EndoCATS is a safe and effective, but a demanding single port access procedure; therefore, extensive training is required. An advantage is the near ideal visualization of the RLN and the parathyroid glands as well as the ability to recover even large specimens without difficulties.
PubMed-ID: 33427912
http://dx.doi.org/10.1007/s00464-020-08244-6

Extended En Bloc Reoperation for Recurrent or Persistent Parathyroid Carcinoma: Analysis of 31 Cases in a Single Institute Experience.
Ann Surg Oncol, 29(2):1208-15.
B. Wei, T. Zhao, H. Shen, M. Jin, Q. Zhou, X. Liu, J. Wang and Q. Wang. 2022.
BACKGROUND: Parathyroid carcinoma (PC) is a rare malignancy that is difficult to eradicate completely after recurrence. We assessed the efficiency of extended en bloc resection (EEBR) in the management of recurrent or persistent PC. METHODS: In this observational cohort study, 31 patients who underwent reoperations for recurrent or persistent PC were enrolled after 2-9 surgeries by other medical teams. EEBRs, which provided the oncologic resection by removing all possible tumor-bearing scar tissues, were adopted in 25 patients. The other 6 with gross infiltration into the upper aerodigestive tract (UAT) underwent less radical procedures for unwillingness to sacrifice laryngeal function. RESULTS: The 5-year overall survival (OS) rate after EEBR was 59.6% compared with 16.7% after less radical procedures, with an improved median expected survival time of 90.0 months compared with 13.0 months after local excision. EEBR exhibited a favorable local control of relapses in 84.0% of patients after a median follow-up period of 27.0 months, 40.0% even achieved disease-free survival, although 56.0% had subsequent distant metastases (DMs) and suffered a worse 5-year OS of 36.7% in contrast with 100.0% in the absence of DM ($p = 0.011$). UAT invasion, rather than age, number of previous operations, or preoperative PTH levels, was the unique independent factor associated with both DM (HR = 5.466, $p = 0.006$) and mortality (HR = 7.606, $p = 0.011$). CONCLUSION: EEBRs provide better outcomes than other conventional surgical approaches and might offer a second chance of cure for patients with recurrent or persistent PC in the absence of DM.
PubMed-ID: 34694522
http://dx.doi.org/10.1245/s10434-021-10962-7

Response to Letter to the Editor From Shijie Yang: "Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study".
J Clin Endocrinol Metab, 107(4):e1771-e2.
Y. Wei, Z. L. Zhao, J. Wu, L. L. Peng, Y. Li, N. C. Lu and M. A. Yu. 2022.
PubMed-ID: 34791335
http://dx.doi.org/10.1210/clinem/dgab835

The Prognosis of Skip Metastasis in Papillary Thyroid Microcarcinoma Is Better Than That of Continuous Metastasis.
J Clin Endocrinol Metab, 107(6):1589-98.
H. Y. Weng, T. Yan, W. W. Qiu, Y. B. Fan and Z. L. Yang. 2022.
CONTEXT: A few papillary thyroid microcarcinomas (PTMCs) may have skip metastasis (SLNM), but the risk factors remain controversial and the prognosis is unclear. OBJECTIVES: To investigate the incidence, lymph node metastasis (LNM) patterns, risk factors, and prognosis of SLNM in PTMCs. METHODS: We reviewed the medical records of PTMC patients who underwent thyroid surgery in our institution. Analyses of risk factors were performed for SLNM. Recurrence-free survival (RFS) of SLNM, central lymph node metastasis (CLNM), and continuous metastasis (CLNM and lateral lymph node metastasis [CLNM + LLNM]) were compared after propensity score matching (PSM). RESULTS: SLNM was detected in 1.7% (50/3923) and frequently involved level III (66.7%). Compared with CLNM + LLNM, SLNM had more LNM at a single level (P < 0.01) and less LNM at 2 levels (P < 0.05). A tumor size of 0.5 to 1 cm (odds ratio [OR], 2.26; 95% CI, 1.27-4.00) and location in the upper pole (OR, 3.30; 95% CI, 2.02-5.40) were independent risk factors for SLNM. A total of 910 (23.2%) PTMCs with LNM were included in the prognostic analysis. At a median follow-up of 60 months, the RFS of SLNM did not differ from that of CLNM (P = 0.10) but was significantly higher than that of CLNM + LLNM (P < 0.01) after using PSM. CONCLUSIONS: When the tumor size is 0.5 to 1 cm or its location is in the upper pole, we must remain vigilant to SLNM in PTMC. Because its prognosis is comparable to that of only CLNM and better than that of CLNM + LLNM, less intensive treatment should be considered.
PubMed-ID: 35213704
http://dx.doi.org/10.1210/clinem/dgac107

Quality of life and surgical outcome of ABBA versus EndoCATS endoscopic thyroid surgery: a single center experience.
Surg Endosc, 36(2):968-79.
U. Wirth, T. von Ahnen, J. Hampel, J. Schardey, P. Busch, H. M. Schardey and S. Schopf. 2022.
BACKGROUND: Thyroid surgery is often performed, especially in young female patients. As patient satisfaction become more and more important, different extra-cervical "remote" approaches have evolved to avoid visible scars in the neck for better cosmetic outcome. The most common remote approaches are the transaxillary and retroauricular. Aim of this work is to compare Endoscopic Cephalic Access Thyroid Surgery (EndoCATS) and axillo-bilateral-breast approach (ABBA) to standard open procedures regarding perioperative outcome and in addition to control cohorts regarding quality of life (QoL) and patient satisfaction. METHODS: In a single center, 59 EndoCATS und 52 ABBA procedures were included out of a 2 years period and compared to 225 open procedures using propensity-score matching. For the endoscopic procedures, cosmetic outcome, patient satisfaction and QoL (SF-12 questionnaire) were examined in prospective follow-up. For QoL a German standard cohort and non-surgically patients with thyroid disease were used as controls. RESULT: The overall perioperative outcome was similar for all endoscopic compared to open thyroid surgeries. Surgical time was longer for endoscopic procedures. There were no cases of permanent hypoparathyroidism and no significant differences regarding temporary or permanent recurrent laryngeal nerve (RLN) palsies between open and ABBA or EndoCATS procedures (?(2); p = 0.893 and 0.840). For ABBA and EndoCATS, 89.6% and 94.2% of patients were satisfied with the surgical procedure. Regarding QoL, there was an overall significant difference in distribution for physical, but not for mental health between groups (p < 0.001 and 0.658). Both endoscopic groups performed slightly worse regarding physical health, but without significant difference between the individual groups in post hoc multiple comparison. CONCLUSION: Endoscopic thyroid surgery is safe with comparable perioperative outcome in experienced high-volume centers. Patient satisfaction and cosmetic results are excellent; QoL is impaired in surgical patients, as they perform slightly worse compared to German standard cohort and non-surgical patients.
PubMed-ID: 33683436
http://dx.doi.org/10.1007/s00464-021-08361-w

Is thyroid hormone supplementation avoidable for patients with low-risk papillary thyroid cancer after thyroid lobectomy? A two-center observational study.
Clin Endocrinol (Oxf), 96(3):413-8.
L. Xiao, J. Wu, L. Jiang, Y. Xu and B. Liu. 2022.
OBJECTIVE: Changing insights regarding the extent of surgery for low-risk papillary thyroid cancer (PTC) stir up discussions on the benefits and harms of thyroid lobectomy versus total thyroidectomy. The chance of needing postoperative thyroid hormone supplementation after thyroid lobectomy is still unclear. The purpose of this retrospective two-center study was to identify the incidence and risk factors of postoperative thyroid-stimulating hormone (TSH) elevation (>2.0 μIU/ml) after thyroid lobectomy for low-risk PTC. DESIGN AND METHODS: Medical records of 201 consecutive patients with low-risk PTC from two tertiary centers who underwent thyroid lobectomy between 2015 and 2019 were retrospectively reviewed.

Postoperative thyroid function tests were measured regularly and patients were prescribed levothyroxine if the TSH level was higher than 2.0 µIU/ml. Multivariable regression models were used to evaluate potential risk factors associated with postoperative TSH elevation after thyroid lobectomy. RESULTS: At 6 weeks postoperatively, 85% had TSH level of >2 µIU/ml; this increased to 88% by 3-6 months. Receiver operating characteristic analysis identified preoperative TSH cut-off (>1.7 µIU/ml) to predict postoperative TSH elevation. Multivariate analysis revealed that only a high preoperative TSH level (>1.7 µIU/ml) was an independent risk factor for a postoperative TSH level of >2 µIU/ml (odds ratio = 7.71; p < .001). CONCLUSION: Nearly 90% of the patients who underwent thyroid lobectomy for low-risk PTC had a postoperative TSH level of >2 µIU/ml, necessitating thyroid hormone supplementation in accordance with current guidelines. This finding highlights that preoperative patient counseling should also focus on raising awareness about postoperative thyroid hormone supplementation for low-risk PTC patients seeking thyroid lobectomy.
PubMed-ID: 34398464
http://dx.doi.org/10.1111/cen.14580

Response to Letter to the Editor From Boucai et al: "BRAF V600E Status Sharply Differentiates Lymph Node Metastasis-associated Mortality Risk in Papillary Thyroid Cancer".
J Clin Endocrinol Metab, 107(7):e3103-e4.
M. Xing. 2022.
PubMed-ID: 35262688
http://dx.doi.org/10.1210/clinem/dgac135

Encapsulated Angioinvasive Follicular Thyroid Carcinoma: Prognostic Impact of the Extent of Vascular Invasion.
Ann Surg Oncol,
H. Yamazaki, R. Katoh, K. Sugino, K. Matsuzu, C. Masaki, J. Akaishi, K. Y. Hames, C. Tomoda, A. Suzuki, K. Ohkuwa, W. Kitagawa, M. Nagahama, Y. Rino and K. Ito. 2022.
BACKGROUND: Previous studies have reported an association between four or more foci of vascular invasion (VI) and thyroid cancer prognosis, while the current study aimed to investigate the association between extent of VI and outcome of encapsulated angioinvasive follicular thyroid carcinoma (FTC). METHODS: The records of 303 patients with encapsulated angioinvasive FTC confirmed by surgical specimens at Ito Hospital from January 2005 to December 2014 were retrospectively reviewed. Thirteen patients had distant metastasis at diagnosis and were classified as M1. RESULTS: Among the 290 patients with M0 encapsulated angioinvasive FTC, the 10-year disease-free survival (DFS) rate was 85.6%. Those with a VI of 1 (n = 131) or = 2 (n = 159) had a 10-year DFS rate of 94.9% and 77.9% (p < 0.001), respectively, and those with a VI of 1-3 (n = 211) or = 4 (n = 79) had a 10-year DFS rate of 86.3% and 83.3% (p = 0.311), respectively. Multivariate analysis identified age = 55 years (p = 0.031) and VI = 2 (p = 0.002) as independent negative prognostic factors for DFS. Patients with M0 encapsulated angioinvasive FTC aged = 55 years and VI = 2 had significantly poorer prognosis and a 10-year DFS rate of 66.4% (p < 0.001). CONCLUSIONS: Patients with encapsulated angioinvasive FTC who had two or more foci of VI, especially patients aged = 55 years, should be carefully followed-up.
PubMed-ID: 35169976
http://dx.doi.org/10.1245/s10434-022-11401-x

Visual identification and neuromonitoring vs. no sighting the external branch of the superior laryngeal nerve in thyroid surgery: a randomized clinical trial.
Updates Surg, 74(2):727-34.
Q. Yuan, L. Zheng, J. Hou, R. Zhou, G. Xu, C. Li and G. Wu. 2022.
To evaluate the incidence of external branch of the superior laryngeal nerve (EBSLN) injuries after thyroid surgical procedures with or without the functional and visual identification of the EBSLN before ligation at the superior thyroid pole. Patients with papillary thyroid carcinoma (PTC) enrolled from a single tertiary referral academic medical center were assigned to functional and visual identification of EBSLN group (study group) or no identification of EBSLN group (controlled group). The main outcome measures were the incidence of EBSLN injury detected by the intraoperative neuromonitoring and Voice Handicap Index-10 (VHI-10) and Impairment Index-5 (VII-5) valuation questionnaires. Postoperative complications were recorded. A total of 140 (50.4%) patients were enrolled in study group and 138 (49.6%) in controlled group. In the study group, 110 (39.3%) EBSLNs were direct visual recognized and 170 (60.7%) nerves were visually identified with the help of neuromonitoring. Three patients in the study group and two patients in the controlled group were diagnosed with vocal cord paralysis. Six (4.4%) patients in the identification group and 37 (27.2%) patients in the no identification group presented no response from the stimulation of sternothyroid-laryngeal triangle. The VII-5 scores of the study group were significantly higher than those of the controlled group at one and three months

postoperatively (P = 0.024 and P = 0.034). With significant lower scores of VII-5 and VHI-10, functional and visual identification of EBSLN might be necessary during thyroid surgery to protect the structural integrity and motor activity of the nerve.
PubMed-ID: 34327667
http://dx.doi.org/10.1007/s13304-021-01138-9

The mutation screening in candidate genes related to thyroid dysgenesis by targeted next-generation sequencing panel in the Chinese congenital hypothyroidism.
Clin Endocrinol (Oxf), 96(4):617-26.
R. J. Zhang, G. L. Yang, F. Cheng, F. Sun, Y. Fang, C. X. Zhang, Z. Wang, F. Y. Wu, J. X. Zhang, S. X. Zhao, J. Liang and H. D. Song. 2022.
OBJECTIVE: Congenital hypothyroidism (CH) is known to be due to thyroid dyshormonogenesis (DH), which is mostly inherited in an autosomal recessive inheritance pattern or thyroid dysgenesis (TD), whose inheritance pattern is controversial and whose molecular etiology remains poorly understood. DESIGN AND METHODS: The variants in 37 candidate genes of CH, including 25 genes related to TD, were screened by targeted exon sequencing in 205 Chinese patients whose CH cannot be explained by biallelic variants in genes related to DH. The inheritance pattern of the genes was analyzed in family trios or quartets. RESULTS: Of the 205 patients, 83 patients carried at least one variant in 19 genes related to TD, and 59 of those 83 patients harbored more than two variants in distinct candidate genes for CH. Biallelic or de novo variants in the genes related to TD in Chinese patients are rare. We also found nine probands carried only one heterozygous variant in the genes related to TD that were inherited from a euthyroid either paternal or maternal parent. These findings did not support the monogenic inheritance pattern of the genes related to TD in CH patients. Notably, in family trio or quartet analysis, of 36 patients carrying more than two variants in distinct genes, 24 patients carried these variants inherited from both their parents, which indicated that the oligogenic inheritance pattern of the genes related to TD should be considered in CH. CONCLUSIONS: Our study expanded the variant spectrum of the genes related to TD in Chinese CH patients. It is rare that CH in Chinese patients could be explained by monogenic germline variants in genes related to TD. The hypothesis of an oligogenic origin of the CH should be considered.
PubMed-ID: 34374102
http://dx.doi.org/10.1111/cen.14577

Convolutional Neural Network-Based Computer-Assisted Diagnosis of Hashimoto's Thyroiditis on Ultrasound.
J Clin Endocrinol Metab, 107(4):953-63.
W. Zhao, Q. Kang, F. Qian, K. Li, J. Zhu and B. Ma. 2022.
PURPOSE: This study investigates the efficiency of deep learning models in the automated diagnosis of Hashimoto's thyroiditis (HT) using real-world ultrasound data from ultrasound examinations by computer-assisted diagnosis (CAD) with artificial intelligence. METHODS: We retrospectively collected ultrasound images from patients with and without HT from 2 hospitals in China between September 2008 and February 2018. Images were divided into a training set (80%) and a validation set (20%). We ensembled 9 convolutional neural networks (CNNs) as the final model (CAD-HT) for HT classification. The model's diagnostic performance was validated and compared to 2 hospital validation sets. We also compared the accuracy of CAD-HT against seniors/junior radiologists. Subgroup analysis of CAD-HT performance for different thyroid hormone levels (hyperthyroidism, hypothyroidism, and euthyroidism) was also evaluated. RESULTS: 39 280 ultrasound images from 21 118 patients were included in this study. The accuracy, sensitivity, and specificity of the HT-CAD model were 0.892, 0.890, and 0.895, respectively. HT-CAD performance between 2 hospitals was not significantly different. The HT-CAD model achieved a higher performance (P < 0.001) when compared to senior radiologists, with a nearly 9% accuracy improvement. HT-CAD had almost similar accuracy (range 0.87-0.894) for the 3 subgroups based on thyroid hormone level. CONCLUSION: The HT-CAD strategy based on CNN significantly improved the radiologists' diagnostic accuracy of HT. Our model demonstrates good performance and robustness in different hospitals and for different thyroid hormone levels.
PubMed-ID: 34907442
http://dx.doi.org/10.1210/clinem/dgab870

Recurrent Laryngeal Nerve Injury in Thermal Ablation of Thyroid Nodules-Risk Factors and Cause Analysis.
J Clin Endocrinol Metab, 107(7):e2930-e7.
Z. L. Zhao, Y. Wei, L. L. Peng, Y. Li, N. C. Lu and M. A. Yu. 2022.
CONTEXT: Recurrent laryngeal nerve (RLN) injury is a complication of thermal thyroid nodule treatment. OBJECTIVE: We investigated the influencing factors of RLN injury in patients who underwent thermal ablation of thyroid nodules.

METHODS: The data of 1004 patients (252 male, 752 female; median age 44 years) who underwent thermal thyroid nodule ablation were retrospectively reviewed. Patients were divided into benign cystic, benign solid, and papillary thyroid cancer (PTC) groups. The parameters related to RLN injury were analyzed, including the largest diameter, location of the nodules, and shortest distance of the nodule to thyroid capsule and tracheoesophageal groove (TEG). Univariate and multivariate analyses were performed to select risk factors for RLN injury. RESULTS: The RLN injury rate was higher in PTC (6.3%) than in benign cystic (1.2%, P = 0.019) and solid nodules (2.9%, P = 0.018). PTC subgroup analysis showed that the RLN injury rate was higher in T1b (10.7%) and T2 (28.6%) PTC than in T1a PTC (5.0%, P < 0.05). In the PTC group, TEG distance, anterior capsule distance, median capsule distance, posterior capsule distance, and maximum nodule diameter were risk factors for RLN injury. The logistic regression fitting of the nomogram showed high prediction efficiency (C-Index 0.876). The main cause of RLN injury was insufficient medial isolating fluid (MIF). The safety thicknesses of MIF for benign cystic, benign solid, and PTC nodules were 3.1 mm, 3.7 mm, and 3.9 mm, respectively. CONCLUSION: Several risk factors for RLN injury should be considered before thermal ablation of thyroid nodules. The RLN injury rate could be predicted with the nomogram.
PubMed-ID: 35311971
http://dx.doi.org/10.1210/clinem/dgac177

Can less Be more in the treatment of cN1a papillary thyroid microcarcinoma?
Am J Surg, 223(4):633-4.
P. Zmijewski and L. E. Kuo. 2022.
PubMed-ID: 34756456
http://dx.doi.org/10.1016/j.amjsurg.2021.10.008

Parathyroids

Meta-Analyses

Indocyanine green fluorescence for parathyroid gland identification and function prediction: Systematic review and meta-analysis.
Head Neck, 44(3):783-91.
D. H. Kim, S. H. Kim, J. Jung, S. W. Kim and S. H. Hwang. 2022.
BACKGROUND: To evaluate the diagnostic accuracies of indocyanine green (ICG) fluorescence for identifying parathyroid glands during surgery and predicting the postoperative function. METHODS: From six databases, 21 studies were finally included in the study. True-positive, true-negative, false-positive, and false-negative data were extracted for the analysis. The quality of each study was analyzed using the QUADAS-2 tool. RESULTS: The sensitivity of ICG-based parathyroid gland identification was 0.9380 (95% CI [0.9003, 0.9621]). The diagnostic odds ratio for ICG-based prediction of parathyroid gland function was 54.5652 [13.2059, 225.4570]. The area under the summary receiver operating characteristic curve was 0.909. Fluorescence intensity-based prediction presented higher diagnostic accuracy than that of score-based prediction. The incidence of postoperative hypoparathyroidism was higher in the group with a zero ICG score compared to the high scored group. CONCLUSIONS: Identification of parathyroid gland and prediction of postoperative function using ICG are valuable to patients undergoing thyroidectomy or parathyroidectomy.
PubMed-ID: 34908194
http://dx.doi.org/10.1002/hed.26950

Giant parathyroid tumours in primary hyperparathyroidism: a systematic review.
Langenbecks Arch Surg, 407(2):501-16.
H. K. G. Wong, K. Shipman, K. Allan, A. Ghabbour and F. Borumandi. 2022.
PURPOSE: Giant parathyroid adenoma (GPA) can present with severe biochemical derangement similar to the clinical presentation of parathyroid carcinoma (PC). This study aims to present the current evidence on surgical management of GPAs in primary hyperparathyroidism. METHODS: A systematic review of the literature on GPAs was conducted following the PRISMA guidelines. Data on clinical, biochemical, preoperative diagnostic, and surgical methods were analysed. RESULTS: Sixty-one eligible studies were included reporting on 65 GPAs in eutopic, ectopic mediastinal, and intrathyroidal locations (61.5%, 30.8%, and 7.7%, respectively). A palpable neck mass was present in 58% of GPAs. A total of 90% of patients had symptoms including fatigue, skeletal pain, pathological fracture, nausea, and abdominal pain. Ninety percent of patients had significant hypercalcaemia (mean 3.51 mmol/L; range: 2.59-5.74 mmol/L) and hyperparathyroidism with PTH levels on average 14 times above the upper limit of the normal reference. There was no correlation between the reported GPA size and PTH nor between GPA weight and PTH ($p = 0.892$ and $p = 0.363$, respectively). Twenty-four percent had a concurrent thyroidectomy for suspicious features, intrathyroidal location of GPA, or large goitre. Immunohistochemistry such as Ki-67, parafibromin, and galectin-3 was used in 18.5% of cases with equivocal histology. Ninety-five percent of GPAs were benign with 5% reported as atypical adenomas. CONCLUSION: The reported data on GPAs are sparse and heterogeneous. In GPAs with suspicious features for malignancy, en bloc resection with concurrent thyroidectomy may be considered. In the presence of equivocal histological features, ancillary immunohistochemistry is advocated to differentiate GPAs from atypical adenomas and PCs.
PubMed-ID: 35039921
http://dx.doi.org/10.1007/s00423-021-02406-3

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Erratum to: "Ex Vivo Intact Tissue Analysis Reveals Alternative Calcium-Sensing Behaviors in Parathyroid Adenomas".
J Clin Endocrinol Metab, 107(2):e898.
2022.
PubMed-ID: 34590700
http://dx.doi.org/10.1210/clinem/dgab625

Parathyroidectomy Versus Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients.
World J Surg, 46(4):813-9.
L. Alvarado, N. Sharma, R. Lerma, A. Dwivedi, A. Ahmad, A. Hechanova, F. Payan-Schober, A. Nwosu and E. Alkhalili. 2022.
BACKGROUND: Secondary hyperparathyroidism in patients with end stage renal disease on dialysis is associated with bone pain and fractures in addition to cardiovascular morbidity. Cinacalcet is the most commonly used drug to treat such patients, but it has never been compared to surgery. The goal of this study is to compare the long-term outcomes and survival between cinacalcet and parathyroidectomy in the treatment of secondary hyperparathyroidism in hemodialysis patients. METHODS: Adult patients on hemodialysis who were treated with cinacalcet or parathyroidectomy in the United States Renal Data System were included. Patients treated with surgery (n = 2023) were compared using 1:1 propensity score matching ratio to a cohort of patients treated with cinacalcet. A Cox regression analysis was conducted to compare the overall mortality. RESULTS: The propensity score matching successfully created two groups with similar demographics. Patients in the surgery group had a higher mean peak PTH level prior to therapy (2066.8 vs 1425.4, P < 0.001). No difference was observed in the development of new-onset coronary artery disease (7.7% vs 7.9%, P = 0.8) or cerebrovascular disease (7% vs 6.7%, P = 0.8). Surgical patients had a higher rate of pathologic fractures (27.8% vs 24.9%, P = 0.04). Survival analysis showed that patients undergoing surgery had a better 5-year survival (65.6% vs 57.8%) and were less likely to die within the study period (HR 0.77, 95% CI 0.7-0.85, P < 0.0001). CONCLUSIONS: Patients on dialysis undergoing parathyroidectomy for the treatment of secondary hyperparathyroidism have a better overall survival than those treated with cinacalcet.
PubMed-ID: 35022799
http://dx.doi.org/10.1007/s00268-022-06439-7

A Visual Deep Learning Model to Localize Parathyroid-Specific Autofluorescence on Near-Infrared Imaging : Localization of Parathyroid Autofluorescence with Deep Learning.
Ann Surg Oncol,
S. N. Avci, G. Isiktas and E. Berber. 2022.
BACKGROUND AND PURPOSE: Parathyroid glands may be detected by their autofluorescence on near-infrared imaging. Nevertheless, recognition of parathyroid-specific autofluorescence requires a learning curve, with other unrelated bright signals causing confusion. The aim of this study was to find out whether machine learning could be used to facilitate identification of parathyroid-specific autofluorescence signals on intraoperative near-infrared images in patients undergoing thyroidectomy and parathyroidectomy procedures. METHODS: In an institutional review board-approved study, intraoperative near-infrared images of patients who underwent thyroidectomy and/or parathyroidectomy procedures within a year were used to develop an artificial intelligence model. Parathyroid-specific autofluorescence signals were marked with rectangles on intraoperative near-infrared still images and used for training a deep learning model. A randomly chosen 80% of the data were used for training, 10% for testing, and 10% for validation. Precision and recall of the model were calculated. RESULTS: A total of 466 intraoperative near-infrared images of 197 patients who underwent thyroidectomy and/or parathyroidectomy procedures were analyzed. Procedures included total thyroidectomy in 54 patients, thyroid lobectomy in 24 patients, parathyroidectomy in 108 patients, and combined thyroidectomy and parathyroidectomy procedures in 11 patients. The overall recall and precision of the model were 90.5 and 95.7%, respectively. CONCLUSIONS: To our knowledge, this is the first study that describes the use of artificial intelligence tools to assist in recognition of parathyroid-specific autofluorescence signals on near-infrared imaging. The model developed may have utility in facilitating training and decreasing the learning curve associated with the use of this technology.
PubMed-ID: 35348975
http://dx.doi.org/10.1245/s10434-022-11632-y

Comparison of Parathyroid Autofluorescence Signals in Different Types of Hyperparathyroidism.
World J Surg, 46(4):807-12.
E. Berber, S. Akbulut, S. Avci and G. Isiktas. 2022.
BACKGROUND: There are scant data in the literature regarding whether parathyroid autofluorescence (AF) signal patterns vary based on the etiology of hyperparathyroidism. The aim of this study was to compare AF signals of parathyroid glands across different etiologies of hyperparathyroidism. METHODS: As a prospective institutional review board-approved study between 2016 and 2019, AF intensities and heterogeneity indexes (HIs) of parathyroid glands in patients who underwent parathyroidectomy using AF were calculated and compared using Chi-square, Kruskal Wallis, Mann Whitney U, and logistic regression tests. RESULTS: Of the total of 183 patients, 127 patients had sporadic classic primary hyperparathyroidism, 30 patients had sporadic normohormonal primary hyperparathyroidism, 10 patients had sporadic normocalcemic primary hyperparathyroidism, 12 patients had tertiary hyperparathyroidism, and 4 patients had familial primary hyperparathyroidism related to multiple endocrine neoplasia (MEN) 2A. There were no statistical differences in AF signals of abnormal parathyroid glands in classic, normohormonal or normocalcemic sporadic hyperparathyroidism. Parathyroid glands in patients with tertiary hyperparathyroidism were similar in intensity, but more homogenous compared to those in sporadic primary hyperparathyroidism. CONCLUSIONS: The pattern of AF exhibited by abnormal parathyroid glands was similar across different spectrums of primary hyperparathyroidism, in accordance with observations in the literature. However, parathyroid glands in tertiary hyperparathyroidism were more homogeneous, despite exhibiting a similar intensity of AF compared to those in sporadic primary hyperparathyroidism. These differences should be kept in mind when using the AF pattern as an adjunct to visual assessment in parathyroid exploration.
PubMed-ID: 35006327
http://dx.doi.org/10.1007/s00268-021-06422-8

Novel mutations of the calcium-sensing receptor impede differential diagnosis of primary hyperparathyroidism and familial hypocalciuric hypercalcemia.
Gland Surg, 11(1):12-22.
J. S. Bhangu, S. Baumgartner-Parzer, L. Hargitai, P. Mazal, C. Scheuba and P. Riss. 2022.
BACKGROUND: Familial hypocalciuric hypercalcemia 1 (FHH1) is an autosomal dominant disorder caused by inactivating mutations in the calcium-sensing receptor (CaSR) gene, commonly leading-in contrast to primary hyperparathyroidism (PHPT)-to asymptomatic hypercalcemia. It is important to establish the correct diagnosis, as surgery may be curative in PHPT, but most likely ineffective in FHH. The study aims to evaluate patients with FHH1, initially misinterpreted as PHPT and some even undergone surgery. METHODS: CaSR-genotyping was conducted, various biochemical parameters including twenty-four-hour urinary Ca excretion (24hU CE) and the calculated relation of urinary Ca clearance to creatinine clearance (CCCR), type of surgery and 1-year follow-up data of fourteen patients with proven FHH1 were evaluated retrospectively. RESULTS: Genetic analysis revealed a total of nine novel heterozygous variants in the CaSR gene in our study population. Six of fourteen patients (42.9%) underwent surgery for initially suspected PHPT, showing normalized biochemical parameters immediately after surgery. In 1-year follow-up, however, five of six operated patients (83.3%) showed normal parathyroid hormone (PTH), but elevated serum calcium levels. In contrast, only one of the operated patients (16.7%) presented both PTH and serum calcium in the normal range. Histology showed adenoma in three (50%), hyperplasia in two (33.3%), and normal parathyroid tissue in one (16.7%) of the patients. CONCLUSIONS: We discovered novel heterozygous variants in the CaSR gene, which considerably impede differential diagnosis of PHPT and FHH1. Furthermore, our results indicate that parathyroid surgery fails to provide long-term benefits for patients with FHH1 and suspected PHPT, even though this coincidence seems to exist.
PubMed-ID: 35242665
http://dx.doi.org/10.21037/gs-21-577

European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders.
Eur J Endocrinol, 186(2):R33-R63.
J. Bollerslev, L. Rejnmark, A. Zahn, A. Heck, N. M. Appelman-Dijkstra, L. Cardoso, F. M. Hannan, F. Cetani, T. Sikjær, A. M. Formenti, S. Björnsdottir, C. Schalin-Jantti, Z. Belaya, F. W. Gibb, B. Lapauw, K. Amrein, C. Wicke, C. Grasemann, M. Krebs, E. M. Ryhänen, O. Makay, S. Minisola, S. Gaujoux, J. P. Bertocchio, Z. K. Hassan-Smith, A. Linglart, E. M. Winter, M. Kollmann, H. G. Zmierczak, E. Tsourdi, S. Pilz, H. Siggelkow, N. J. Gittoes, C. Marcocci and P. Kamenicky. 2022.
This European expert consensus statement provides recommendations for the diagnosis and management of primary hyperparathyroidism (PHPT), chronic hypoparathyroidism in adults (HypoPT), and parathyroid disorders in relation to pregnancy and lactation. Specified areas of interest and unmet needs identified by experts at the second ESE Educational

Program of Parathyroid Disorders (PARAT) in 2019, were discussed during two virtual workshops in 2021, and subsequently developed by working groups with interest in the specified areas. PHPT is a common endocrine disease. However, its differential diagnosing to familial hypocalciuric hypercalcemia (FHH), the definition and clinical course of normocalcemic PHPT, and the optimal management of its recurrence after surgery represent areas of uncertainty requiring clarifications. HypoPT is an orphan disease characterized by low calcium concentrations due to insufficient PTH secretion, most often secondary to neck surgery. Prevention and prediction of surgical injury to the parathyroid glands are essential to limit the disease-related burden. Long-term treatment modalities including the place for PTH replacement therapy and the optimal biochemical monitoring and imaging surveillance for complications to treatment in chronic HypoPT, need to be refined. The physiological changes in calcium metabolism occurring during pregnancy and lactation modify the clinical presentation and management of parathyroid disorders in these periods of life. Modern interdisciplinary approaches to PHPT and HypoPT in pregnant and lactating women and their newborns children are proposed. The recommendations on clinical management presented here will serve as background for further educational material aimed for a broader clinical audience, and were developed with focus on endocrinologists in training.
PubMed-ID: 34863037
http://dx.doi.org/10.1530/EJE-21-1044

Preoperative Thoracic Muscle Mass Predicts Bone Density Change After Parathyroidectomy in Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 107(6):e2474-e80.
S. W. Burm, N. Hong, S. Lee, G. J. Kim, S. H. Hwang, J. Jeong and Y. Rhee. 2022.
CONTEXT: Predicting bone mineral density (BMD) gain after parathyroidectomy may influence individualized therapeutic approaches for treating patients with primary hyperparathyroidism (PHPT). OBJECTIVE: This study aimed to assess whether skeletal muscle mass data could predict BMD change after parathyroidectomy in patients with PHPT. METHODS: This retrospective study collected data from 2012 to 2021 at Severance Hospital, Seoul, Korea. A total of 130 patients (mean age, 64.7 years; 81.5% women) with PHPT who underwent parathyroidectomy were analyzed. Thoracic muscle volume (T6-T7 level) was estimated using noncontrast parathyroid single photon emission computed tomography/computed tomography (SPECT/CT) scans and an automated deep-learning-based software. The primary outcome assessed was the change in femoral neck BMD (FNBMD, %) 1 year after parathyroidectomy. RESULTS: The median degree of FNBMD change after parathyroidectomy was + 2.7% (interquartile range: -0.9 to + 7.6%). Elevated preoperative PTH level was associated with lower thoracic muscle mass (adjusted ß: -8.51 cm3 per one log-unit PTH increment, P = .045) after adjusting for age, sex, body mass index (BMI), and baseline FNBMD. One SD decrement in thoracic muscle mass was associated with lesser FNBMD (adjusted ß: -2.35%, P = .034) gain and lumbar spine BMD gain (adjusted ß: -2.51%, P = .044) post surgery after adjusting for covariates. CONCLUSION: Lower thoracic skeletal muscle mass was associated with elevated preoperative PTH levels in patients with PHPT. Lower skeletal muscle mass was associated with lesser BMD gain after parathyroidectomy, independent of age, sex, BMI, preoperative BMD, and PTH level.
PubMed-ID: 35148405
http://dx.doi.org/10.1210/clinem/dgac083

What are predictors of impaired quality of life in patients with hypoparathyroidism?
Clin Endocrinol (Oxf), 97(3):268-75.
M. Büttner, D. Krogh, H. Siggelkow and S. Singer. 2022.
CONTEXT: Hypoparathyroidism (hypoPT) is a rare endocrine disorder. Little is known about what factors are associated with potential quality of life (QOL) impairments. DESIGN: HypoPT patients at a minimum of 6 months' post diagnosis were invited to participate in an online survey through their treating physician or through self-help organisations METHODS: Impairments of clinical importance in QOL were considered present if the score of the respective functioning scale of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 exceeded a pre-defined threshold. Symptom burden was assessed using the HPQ-28. Multivariate logistic regression was used to identify factors associated with impairments in QOL. RESULTS: Data were available for 264 hypoPT patients. Impairments of clinical importance in QOL were reported for 40.4% in role functioning (RF), 40.6% in social functioning (SF), 60.8% in physical functioning (PF), 65.5% in cognitive functioning (CF) and 76.0% in emotional functioning (EF). Higher odds for reporting impaired QOL were seen for higher symptom burden (for almost all domains) and for being unable to work (for PF, RF and SF). Surgery for thyroid cancer being the cause of hypoPT was associated with lower odds in PF for patients and in PF and CF for patients with surgery for other thyroid-related diseases being the hypoPT cause. CONCLUSIONS: HypoPT needs to be recognised as a disease which might be associated with impaired QOL and affect daily living. Symptom management is crucial for improving QOL in hypoPT patients but socioeconomic factors like work-ability need to be considered when treating

hypoPT patients.
PubMed-ID: 35192212
http://dx.doi.org/10.1111/cen.14701

Serum Phosphate: A Neglected Test in the Clinical Management of Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 107(2):e612-e8.
E. Castellano, R. Attanasio, A. Boriano, M. Pellegrino and G. Borretta. 2022.
BACKGROUND: Although the inverse correlation between serum PTH and phosphate (P) levels in patients with primary hyperparathyroidism (PHPT) is well known, the relationship between P levels and the clinical picture of the disease has not been well investigated. This was thus the aim of this paper. PATIENTS: A total of 472 consecutive patients with PHPT attending our center were retrospectively evaluated at diagnosis. RESULTS: P levels lower than 2.5 mg/dL (HypoP) were found in 198/472 patients (41.9%). HypoP was mild (2-2.5 mg/dL), moderate (1-1.9 mg/dL), and severe (<1 mg/dL) in 168 (84.9%), 30 (15.1%), and 0 cases, respectively. P levels were lower in males than females. Patients with more severe bone density impairment at the radial (but not the vertebral or femoral) site had P levels significantly lower than other patients. PHPT severity was worse in HypoP patients, both clinically (higher prevalence of renal stones, but not of osteoporosis) and biochemically (higher serum calcium and PTH levels). All patients in the moderate HypoP group were either symptomatic or asymptomatic reaching surgical indication according to the latest guidelines. CONCLUSIONS: We observed a relationship between P levels and biochemical and clinical features of PHPT severity. In asymptomatic PHPT patients, even moderate HypoP is predictive of surgical indication, regardless of age and hypercalcemia severity.
PubMed-ID: 34519347
http://dx.doi.org/10.1210/clinem/dgab676

Correlation of Preoperative Imaging Findings and Parathyroidectomy Outcomes Support NICE 2019 Guidance.
J Clin Endocrinol Metab, 107(3):e1242-e8.
N. R. Chander, S. Chidambaram, K. Van Den Heede, A. N. DiMarco, N. S. Tolley and F. F. Palazzo. 2022.
CONTEXT: Preoperative localization studies are standard practice in patients undergoing parathyroidectomy for primary hyperparathyroidism (pHPT). The most common modalities are neck ultrasound (US) and sestamibi scanning. However, the nature of pHPT is changing, with imaging increasingly yielding negative results. Numerous studies suggest unlocalized disease is associated with poor outcomes, calling into question whether such patients are best treated conservatively. OBJECTIVE: This study aims to correlate parathyroidectomy outcomes with preoperative imaging in a single, high-volume institution. METHODS: Data from a prospectively maintained departmental database of operations performed from 2017 to 2019 were analyzed. All patients undergoing first-time surgery for sporadic pHPT were included. Data collected included patient demographics, preoperative imaging, surgical strategy, and postoperative outcomes. RESULTS: A total of 609 consecutive parathyroidectomies were included, with a median age of 59 years (range 20-87 years). The all-comer cure rate was 97.5%; this was 97.9% in dual localized patients (those with positive US and sestamibi), compared to 95.8% in the dual unlocalized group (those with negative US and sestamibi) (P = 0.33). Unilateral neck exploration was the chosen approach in 59.9% of patients with double-positive imaging and 5.7% of patients with double-negative imaging (otherwise, bilateral parathyroid visualization was performed). There was no significant difference in postoperative complications between patients undergoing unilateral or bilateral neck exploration. CONCLUSIONS: Patients with negative preoperative imaging who undergo parathyroidectomy are cured in almost 96% of cases, compared to 98% when the disease is localized. This difference does not reach statistical or clinical significance. These findings therefore support current recommendations that all patients with pHPT who are likely to benefit from operative intervention should be considered for parathyroidectomy, irrespective of preoperative imaging findings.
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http://dx.doi.org/10.1210/clinem/dgab740

Preoperative imaging in primary hyperparathyroidism: Are (11) C-Choline PET/CT and (99m) Tc-MIBI/(123) Iodide subtraction SPECT/CT interchangeable or do they supplement each other?
Clin Endocrinol (Oxf), 97(3):258-67.
J. W. Christensen, A. Ismail, S. B. Søndergaard, F. N. Bennedbaek, B. Nygaard, L. T. Jensen, W. Trolle, C. Holst-Hahn, B. Zerahn, B. Kristensen and M. Krakauer. 2022.
OBJECTIVE: Preoperative location of hyperfunctioning parathyroid glands (HPGs) is vital when planning minimally invasive surgery in patients with primary hyperparathyroidism (PHPT). Dual-isotope subtraction scintigraphy with (99m) Tc-MIBI/(123) Iodide using SPECT/CT and planar pinhole imaging (Di-SPECT) has shown high sensitivity, but is challenged by high radiation dose, time consumption and cost. (11) C-Choline PET/CT (faster with a lower radiation dose) is non-inferior

to Di-SPECT. We aim to clarify to what extent the two are interchangeable and how often there are discrepancies. DESIGN: This is a prospective, GCP-controlled cohort study. PATIENTS AND MEASUREMENTS: One hundred patients diagnosed with PHPT were included and underwent both imaging modalities before parathyroidectomy. Clinical implications of differences between imaging findings and negative imaging results were assessed. Surgical findings confirmed by biochemistry and pathology served as reference standard. RESULTS: Among the 90 patients cured by parathyroidectomy, sensitivity was 82% (95% confidence interval [CI]: 74%-88%) and 87% (95% CI: 79%-92%) for Choline PET and Di-SPECT, respectively, p = .88. In seven cases at least one imaging modality found no HPG. Of these, neither modality found any true HPGs and only two were cured by surgery. When a positive finding in one modality was incorrect, the alternative modality was correct in approximately half of the cases. CONCLUSION: Choline PET and Di-SPECT performed equally well and are both appropriate as first-line imaging modalities for preoperative imaging of PHPT. When the first-line modality fails to locate an HPG, additional preoperative imaging with the alternate modality offers no benefit. However, if parathyroidectomy is unsuccessful, additional imaging with the alternate modality has merit before repeat surgery.
PubMed-ID: 35150160
http://dx.doi.org/10.1111/cen.14688

Is Moderate Hypophosphatemia a New Indication for Surgery in Asymptomatic Primary Hyperparathyroidism?
J Clin Endocrinol Metab, 107(4):e1756-e7.
B. L. Clarke. 2022.
PubMed-ID: 34718624
http://dx.doi.org/10.1210/clinem/dgab768

Autofluorescence and Artificial Intelligence: The Future of Parathyroid Surgery?
Ann Surg Oncol,
Q. Y. Duh and S. N. Davis. 2022.
PubMed-ID: 35419754
http://dx.doi.org/10.1245/s10434-022-11732-9

Parathyroidectomy Versus Calcimimetic: The Lower the PTH the Better?
J Clin Endocrinol Metab, 107(8):e3532-e3.
P. Evenepoel and H. S. Jørgensen. 2022.
PubMed-ID: 35427422
http://dx.doi.org/10.1210/clinem/dgac211

The Normohormonal Primary Hyperparathyroidism; a surgical dilemma pre and intra-operatively.
Am J Surg, 223(3):589-91.
T. Fedorova, K. Hagglund and A. Hawasli. 2022.
INTRODUCTION: Normohormonal Primary Hyperparathyroidism (NPHPT), poses a dilemma for surgeons; first in deciding when to operate where the PTH is normal and second at what level should the drop in intra-operative PTH (ioPTH) be considered a successful operation. MATERIALS & METHODS: A retrospective evaluation of all parathyroidectomies performed by a single surgeon from 2009 to 2019 was conducted. RESULTS: In 33 of 349 (9%) parathyroidectomies the indication was NPHPT. Negative pre-operative nuclear localization was found in 17(52%) patients. Intra-operative findings were: 27(82%) single-adenoma, 3(9%) double-adenomas and 3(9%) hyperplasia. In patients with single-adenomas the ioPTH dropped from 57 ± 8 to 23 ± 10 pg./ml. The average size of the adenomas was 403 ± 360 mg. CONCLUSION: NPHPT is uncommon where the disease is diagnosed in its early stages. Over 50% has negative pre-operative nuclear localization test requiring 4-gland surgical exploration. The intra-operative drop in PTH below 30 pg./ml can be utilized as an indicator of a successful operation.
PubMed-ID: 35086696
http://dx.doi.org/10.1016/j.amjsurg.2022.01.002

An Approach to a Patient With Primary Hyperparathyroidism and a Suspected Ectopic Parathyroid Adenoma.
J Clin Endocrinol Metab, 107(6):1706-13.
C. Glasgow, E. Y. C. Lau, L. Aloj, I. Harper, H. Cheow, T. Das, L. Berman, A. S. Powlson, W. A. Bashari, B. G. Challis, A. Marker, P. Moyle, I. A. Mohamed, N. Schoenmakers, J. Broomfield, S. Oddy, C. Moran, M. Gurnell, P. Jani, L. Masterson, B. Fish and R. T. Casey. 2022.
Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia driven by excess parathyroid hormone (PTH)

secretion. PHPT is a common endocrine condition with a prevalence of 1 to 7 cases per 1000 adults. PHPT typically presents in the fifth or sixth decade and shows significant female preponderance. Solitary hyperfunctioning parathyroid adenomas account for 85% to 90% of PHPT cases. The remaining 10% to 15% include cases of multiglandular disease (multiple adenomas or hyperplasia) and, rarely, parathyroid carcinoma (1%). Ectopic parathyroid adenomas may arise due to abnormal embryological migration of the parathyroid glands and can be difficult to localize preoperatively, making surgical cure challenging on the first attempt. The potential existence of multiglandular disease should be considered in all patients in whom preoperative localization fails to identify a target adenoma or following unsuccessful parathyroidectomy. Risk factors for multiglandular disease include underlying genetic syndromes (eg, MEN1/2A), lithium therapy, or previous radiotherapy. In addition to multifocal disease, the possibility of an ectopic parathyroid gland should also be considered in patients requiring repeat parathyroid surgery. In this article, we use illustrative clinical vignettes to discuss the approach to a patient with primary hyperparathyroidism (PHPT) and a suspected ectopic parathyroid adenoma.
PubMed-ID: 35150267
http://dx.doi.org/10.1210/clinem/dgac024

Superior sensitivity of (18)F-fluorocholine: PET localization in primary hyperparathyroidism.
Surgery, 171(1):47-54.
C. E. Graves, T. A. Hope, J. Kim, M. H. Pampaloni, W. Kluijfhout, C. D. Seib, J. E. Gosnell, W. T. Shen, S. A. Roman, J. A. Sosa, Q. Y. Duh and I. Suh. 2022.
BACKGROUND: Preoperative parathyroid imaging guides surgeons during parathyroidectomy. This study evaluates the clinical impact of (18)F-fluorocholine positron emission tomography for preoperative parathyroid localization on patients with primary hyperparathyroidism. METHODS: Patients with primary hyperparathyroidism and indications for parathyroidectomy had simultaneous (18)F-fluorocholine positron emission tomography imaging/magnetic resonance imaging. In patients who underwent subsequent parathyroidectomy, cure was based on lab values at least 6 months after surgery. Location-based sensitivity and specificity of (18)F-fluorocholine positron emission tomography imaging was assessed using 3 anatomic locations (left neck, right neck, and mediastinum), with surgery as the gold standard. RESULTS: In 101 patients, (18)F-fluorocholine positron emission tomography localized at least 1 candidate lesion in 93% of patients overall and in 91% of patients with previously negative imaging, leading to a change in preoperative strategy in 60% of patients. Of 76 patients who underwent parathyroidectomy, 58 (77%) had laboratory data at least 6 months postoperatively, with 55/58 patients (95%) demonstrating cure. (18)F-fluorocholine positron emission tomography successfully guided curative surgery in 48/58 (83%) patients, compared with 20/57 (35%) based on ultrasound and 13/55 (24%) based on sestamibi. In a location-based analysis, sensitivity of (18)F-fluorocholine positron emission tomography (88.9%) outperformed both ultrasound (37.1%) and sestamibi (27.5%), as well as ultrasound and sestamibi combined (47.8%). CONCLUSION: Long-term results in the first cohort in the United States to use (18)F-fluorocholine positron emission tomography for parathyroid localization confirm its utility in a challenging cohort, with better sensitivity than ultrasound or sestamibi.
PubMed-ID: 34301418
http://dx.doi.org/10.1016/j.surg.2021.05.056

Parathyroid Gland Autofluorescence Characteristics in Patients With Primary Hyperparathyroidism.
Laryngoscope, 132(3):715-21.
R. H. Law, K. A. Larrabee, M. Van Harn and M. C. Singer. 2022.
OBJECTIVE: Near-infrared imaging for intraoperative parathyroid gland (PG) detection has recently commanded significant attention. The PTeye (Medtronic, Minneapolis, MN) is a probe-based system for near-infrared autofluorescent evaluation of PGs. This study was designed to evaluate the capabilities of the PTeye in the setting of surgery for primary hyperparathyroidism. STUDY DESIGN: Prospective, Cohort study. METHODS: This single-institution, prospective cohort study included all patients undergoing parathyroidectomy for primary hyperparathyroidism with presumed single gland disease from June 2020 to December 2020. Absolute intensity and intensity ratios, with the thyroid as the control tissue, were obtained for the adenoma, ipsilateral normal PG, and adjacent tissue. The ability of the PTeye to function when not in direct contact with tissue was measured. RESULTS: Twenty-two patients were included. The median intensity ratio for the in situ adenomas was 4.38 (interquartile range [IQR]: 2.03-5.87), ipsilateral normal PGs 6.17 (IQR: 3.83-7.67), strap muscle 0.47 (IQR: 0.30-0.60), and fat 0.20 (IQR: 0.17-0.47). All normal PGs and 21/22 adenomas demonstrated autofluorescence above the detection threshold. The PTeye functioned at a maximum distance of separation of 10 mm through saline medium and 6 mm through clear solid medium. CONCLUSION: This study confirms the PTeye's ability to recognize PGs with a high degree of precision. The device was found to function properly even with the probe not in direct

contact with the tissue. Although adenomatous PGs appear to demonstrate altered autofluorescent properties from normal PGs, additional research is required to determine if these differences are clinically useful. LEVEL OF EVIDENCE: 3 Laryngoscope, 132:715-721, 2022.
PubMed-ID: 34612528
http://dx.doi.org/10.1002/lary.29880

Clinical Presentation, Treatment, and Outcome of Parathyroid Carcinoma: Results of the NEKAR Retrospective International Multicenter Study.
Ann Surg, 275(2):e479-e87.
C. Lenschow, S. Schrägle, S. Kircher, K. Lorenz, A. Machens, H. Dralle, P. Riss, C. Scheuba, A. Pfestroff, C. Spitzweg, A. Zielke, A. Nießen, C. Dotzenrath, B. Riemann, M. Quinkler, C. Vorländer, A. Zahn, F. Raue, C. Chiapponi, K. A. Iwen, T. Steinmüller, M. Kroiss and N. Schlegel. 2022.
OBJECTIVE: In this retrospective cohort study, we describe the clinical presentation and workup of parathyroid carcinoma (PC) and determine its clinical prognostic parameters. Primary outcome was recurrence free survival. SUMMARY BACKGROUND DATA: PC is an orphan malignancy for which diagnostic workup and treatment is not established. METHODS: Eighty-three patients were diagnosed with PC between 1986 and 2018. Disease-specific and recurrence-free survivals were estimated with the Kaplan-Meier method. Risk factors for recurrence were identified by binary logistic regression with adjustment for age and sex. Thirty-nine tumors underwent central histopathological review. RESULTS: Renal (39.8%), gastrointestinal (24.1%), bone (22.9%), and psychiatric (19.3%) symptoms were the most common symptoms. Surgical treatment was heterogeneous [parathyroidectomy [PTx)] alone: 22.9%; PTx and hemithyroidectomy: 24.1%; en bloc resection 15.7%; others 37.3%] and complications of surgery were frequent (recurrent laryngeal nerve palsy 25.3%; hypoparathyroidism 6%). Recurrence of PC was observed in 32 of 83 cases. In univariate analysis, rate of recurrence was reduced when extended initial surgery had been performed (P = 0.04). In multivariate analysis low T status [odds ratio (OR) = 2.65, 95% confidence interval (CI) 1.02-6.88, P = 0.045], N0 stage at initial diagnosis (OR = 6.32, 95% CI 1.33-30.01, P = 0.02), Ki-67 <10% (OR = 14.07, 95% CI 2.09-94.9, P = 0.007), and postoperative biochemical remission (OR = 0.023, 95% CI 0.001-0.52, P = 0.018) were beneficial prognostic parameters for recurrence-free survival. CONCLUSION: Despite a favorable overall prognosis, PC shows high rates of recurrence leading to repeated surgery and postoperative recurrent laryngeal nerve palsy and hypoparathyroidism. In view of the reduced recurrence rate in cases of extended surgery, ipsilateral completion surgery may be considered when PC is confirmed.
PubMed-ID: 32649472
http://dx.doi.org/10.1097/SLA.0000000000004144

Transoral endoscopic parathyroidectomy vestibular approach (TOEPVA) for primary hyperparathyroidism: Turkey's experience.
Surg Endosc, 36(2):1037-43.
Ö. Makay, M. Z. Sabuncuoglu, M. I. Turan, I. C. Sormaz, M. Özdemir, N. Aygün, S. Buldur, Y. Türk, D. Saridemir, A. Sezer, S. Teksöz, M. Uludag, I. Zihni, F. Tunca, M. Haciyanli, C. Arici and Y. Giles Senyürek. 2022.
AIM: Parathyroid surgery has witnessed a significant evolution with the introduction of more efficacious preoperative localization imaging techniques and the use of rapid intraoperative parathormone assays. Parathyroid surgery can now be performed with the minimum of invasion. Through the adaptation of the transoral endoscopic thyroidectomy vestibular approach (TOETVA), the technique has now been adopted for parathyroid surgery, known as the transoral endoscopic parathyroidectomy vestibular approach (TOEPVA). We present here the initial experiences of 11 centers carrying out TOEPVA surgery in Turkey. MATERIALS AND METHODS: Participating in the study were 11 centers, all of which were tertiary care institutions carrying out endocrine surgery. A retrospective review was made of 35 primary hyperparathyroidism patients who underwent the TOEPVA procedure between July 2017 and January 2020. RESULTS: Of the total 35 patients, 32 patients underwent the TOEPVA procedure successfully. All patients but one were female, and the mean age was 47.2 (20-73) years. According to localization studies, 18 of the lesions were lower left, 12 were lower right, 3 were upper right and 2 were upper left. The mean operative time was 116 (30-225) min, and three cases were converted to an open procedure. Simultaneous thyroidectomy was performed in seven cases. The average PTH level dropped to normal within 20 min. after the resection in all cases. The complication rate was 19% (ecchymosis, subcutaneous emphysema, nasal bleeding, surgical site infection and seroma). There were neither recurrent nerve palsies, nor mental nerve root or branch injuries. The average hospital stay was 1 day. No persistence was documented on follow up. CONCLUSION: TOEPVA is a "hidden scar" parathyroidectomy procedure that can be safely performed on parathyroid adenomas, in cases that have scar-related concerns. Having its own procedure-related complications, the procedure provides satisfactory objective results, particularly in centers experienced in endoscopic and endocrine surgery.

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http://dx.doi.org/10.1007/s00464-021-08368-3

Reduced fracture incidence in patients having surgery for primary hyperparathyroidism.
Clin Endocrinol (Oxf), 97(3):276-83.
M. Nilsson, E. Ståhl, K. E. Åkesson, M. Thier, E. Nordenström, M. Almquist and A. Bergenfelz. 2022.
OBJECTIVE: The indication of surgery in primary hyperparathyroidism has been controversial, as many patients experience mild disease. The primary aim was to evaluate fracture incidence in a contemporary population-based cohort of patients having surgery for primary hyperparathyroidism. The secondary aim was to investigate whether preoperative serum calcium, adenoma weight or multiglandular disease influence fracture incidence. DESIGN: A retrospective cohort study with population controls. Primary outcomes, defined by discharge diagnoses and prescriptions, were any fracture and fragility fracture, secondary outcomes were multiple fractures anytime and osteoporosis. Subjects were followed 10 years pre- and up to 10 years postoperatively (or 31 December 2015). Multiple events per subject were allowed. Fracture incidence rate ratios (IRRs) for patients pre- and postoperatively were tabulated and evaluated with mixed-effects Poisson regression. Secondary outcomes were evaluated using conditional logistic regression. PATIENTS: A Swedish nationwide cohort of patients having surgery for primary hyperparathyroidism (n = 5009) from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery between 2003 and 2013 was matched with population controls (n = 14,983). Data were cross-linked with Statistics Sweden and the National Board of Health and Welfare. MEASUREMENTS: Preoperative serum calcium and adenoma weight at pathological examination. RESULTS: Patients had an increased incidence rate of any fracture preoperatively, IRR 1.27 (95% confidence interval: 1.11-1.46), highest in the last year before surgery. Fracture incidence was not increased postoperatively. Serum calcium, adenoma weight and multiglandular disease were not associated with fracture incidence. CONCLUSIONS: Fracture incidence is higher in patients with primary hyperparathyroidism but is normalized after surgery.
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http://dx.doi.org/10.1111/cen.14703

The impact of age on quality of life and frailty outcomes after parathyroidectomy in patients with primary hyperparathyroidism.
J Endocrinol Invest, 45(4):797-802.
T. S. Papavramidis, P. Anagnostis, I. Pliakos, G. Tzikos, A. Chorti, K. Kotsa and A. Michalopoulos. 2022.
OBJECTIVE: Parathyroidectomy (PTx) improves quality of life (QoL) in patients with primary hyperparathyroidism (PHPT). Whether this effect is modified according to the patients' age is unknown. The aim of this study was to evaluate the impact of age on the effect of PTx on QoL and frailty in patients with PHPT, six months post-PTx. METHODS: This was a prospective cohort study, including patients with PHPT, admitted from January 2016 to December 2019, divided into two categories: younger (= 65 years old) and older (> 65 years old). QoL was assessed with the Pasieka questionnaire (PAS-Q) two days pre- and six months post-operatively. Frailty was also assessed at the same time intervals, with the Frailty Index (FI). RESULTS: One hundred and thirty-four patients (younger group: 96 patients, mean age 50.4 ± 9.8 years; older group: 38 patients, mean age 72.1 ± 4.9 years) were included. PTx resulted in a significant reduction in PAS-Q score in both groups. Notably, a greater reduction in "mood swings", "irritability", "itchy skin" and "feeling thirsty" PAS-Q domains was observed in the younger group. In contrast, a greater decrease in "bone pain", "tiredness", "weakness", "joint pain", "getting off chair" and "headaches" items was observed in the older group. Moreover, PTx led to a decrease in FI only in this group. CONCLUSIONS: PTx leads to an improvement in QoL both in older (> 65 years) and younger (= 65 years) patients with PHPT, attributed to a differential effect on PAS-Q items. Frailty improves only in the older group.
PubMed-ID: 34826129
http://dx.doi.org/10.1007/s40618-021-01710-5

Kidney Stone Events Following Parathyroidectomy vs Nonoperative Management for Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 107(7):e2801-e11.
C. D. Seib, C. Ganesan, K. D. Arnow, A. C. Pao, J. T. Leppert, N. B. Barreto, E. Kebebew and M. Kurella Tamura. 2022.
CONTEXT: Primary hyperparathyroidism (PHPT) is associated with an increased risk of kidney stones. Few studies account for PHPT severity or stone risk when comparing stone events after parathyroidectomy vs nonoperative management. OBJECTIVE: Compare the incidence of kidney stone events in PHPT patients treated with parathyroidectomy vs nonoperative management. DESIGN: Longitudinal cohort study with propensity score inverse probability weighting and multivariable Cox proportional hazards regression. SETTING: Veterans Health Administration integrated health care system. PATIENTS: A total of 44 978 patients with > 2 years follow-up after PHPT diagnosis (2000-2018); 5244 patients

(11.7%) were treated with parathyroidectomy. MAIN OUTCOMES MEASURE: Clinically significant kidney stone event. RESULTS: The cohort had a mean age of 66.0 years, was 87.8% male, and 66.4% White. Patients treated with parathyroidectomy had higher mean serum calcium (11.2 vs 10.8mg/dL) and were more likely to have a history of kidney stone events. Among patients with baseline history of kidney stones, the unadjusted incidence of = 1 kidney stone event was 30.5% in patients managed with parathyroidectomy (mean follow-up, 5.6 years) compared with 18.0% in those managed nonoperatively (mean follow-up, 5.0 years). Patients treated with parathyroidectomy had a higher adjusted hazard of recurrent kidney stone events (hazard ratio [HR], 1.98; 95% CI, 1.56-2.51); however, this association declined over time (parathyroidectomy × time: HR, 0.80; 95% CI, 0.73-0.87). CONCLUSION: In this predominantly male cohort with PHPT, patients treated with parathyroidectomy continued to be at higher risk of kidney stone events in the immediate years after treatment than patients managed nonoperatively, although the adjusted risk of stone events declined with time, suggesting a benefit to surgical treatment.
PubMed-ID: 35363858
http://dx.doi.org/10.1210/clinem/dgac193

How and when is multiglandular disease diagnosed in sporadic primary hyperparathyroidism?
Surgery, 171(1):35-9.
U. S. Shah, K. L. McCoy, M. L. Kelley, S. E. Carty and L. Yip. 2022.
BACKGROUND: In total, ~15% of patients with sporadic primary hyperparathyroidism have multiglandular disease, which may be suspected preoperatively but can only be confirmed intra or postoperatively. The study aim is to determine how and when patients are diagnosed with multiglandular disease and to what extent different modalities contribute. METHODS: Consecutive cases of sporadic primary hyperparathyroidism (2013-2019) undergoing initial exploration were reviewed from a single-institution prospective database. Preoperative single-photon emission tomography/computed tomography and neck ultrasound were routinely performed to help direct either bilateral or unilateral exploration guided by intraoperative parathyroid hormone monitoring using the dual criteria. Multiglandular disease was defined as either resection of >1 enlarged parathyroid or hypercalcemia at =6 months after single gland resection. RESULTS: Of 1,890 patients with sporadic primary hyperparathyroidism, multiglandular disease was identified in 254 (13.4%); 244 (96.1%) were diagnosed intraoperatively and 10 (3.9%) postoperatively. In these multiglandular disease patients, single gland disease was suggested on single-photon emission tomography/computed tomography in 54.0%, ultrasound in 49.2%, and both were concordant for single gland disease in 29.4%. Intraoperative multiglandular disease diagnosis was prompted by an inadequate intraoperative parathyroid hormone monitoring drop in 38.5%, by surgeon interpretation of imaging in 38.1%, by observing ipsilateral gland enlargement in 11.0%, by finding an initial gland <200 mg in 10.3%, and 2.0% had unexpected multiglandular disease during thyroidectomy. Multiglandular disease was diagnosed by postoperative hypercalcemia in 10 of 254 patients (4.9%). CONCLUSION: To avoid failure at parathyroidectomy for primary hyperparathyroidism, expert surgeons use multiple approaches to diagnose and manage multiglandular disease. Preoperative localization studies alone are insufficient, missing multiglandular disease in at least 30% of cases. All examined adjuncts are informative, including intraoperative parathyroid hormone monitoring, imaging, and intraoperative visual cues.
PubMed-ID: 34924180
http://dx.doi.org/10.1016/j.surg.2021.09.018

Recurrence after successful parathyroidectomy-Who should we worry about?
Surgery, 171(1):40-6.
A. S. Shirali, S. Y. Wu, Y. J. Chiang, P. H. Graham, E. G. Grubbs, J. E. Lee, N. D. Perrier and S. B. Fisher. 2022.
BACKGROUND: Preventing cervical reoperations is important-especially after parathyroidectomy. We sought to examine early predictors of recurrence of primary hyperparathyroidism after surgical cure. METHODS: Adult patients with sporadic primary hyperparathyroidism treated with parathyroidectomy between September 1, 1997, and September 1, 2019, with confirmed eucalcemia at 6 months postoperatively were identified. Recurrence was defined as hypercalcemia (>10.2 mg/dL) with an elevated or nonsuppressed parathyroid hormone level on subsequent follow-up. RESULTS: Parathyroidectomy was performed in 522 patients (median age, 62.1 years, 77% female) with the majority undergoing planned minimally invasive parathyroidectomy (85.4%, n = 446). After a median follow-up of 30.9 months, 13 patients (2.5%) recurred (median time to recurrence 50.2 months, interquartile range 27.9-66.5), all of whom underwent planned minimally invasive parathyroidectomy (n = 13/446, 2.9%). Recurrence was more common in those with higher (but still normal) 6-month calcium (10.1 vs 9.3 mg/dL, P < .001) or parathyroid hormone values (64 vs 46 pg/mL, P < .01). Multivariate analysis revealed that age >66.5 years, calcium =9.8mg/dL and parathyroid hormone =80 pg/mL at 6 months were associated with increased risk of recurrence. In addition, the presence of at least 1 preoperative imaging study that

conflicted with intraoperative findings among minimally invasive parathyroidectomy patients (n = 446) was associated with increased risk of recurrence (hazard ratio 4.93, 95% confidence interval 1.25-16.53, P = .016). CONCLUSION: Recurrence of sporadic primary hyperparathyroidism after initial surgical cure in the era of minimally invasive parathyroidectomy is 2.5%. Identification of those at risk for recurrence using 6-month serum calcium =9.8 mg/dL, parathyroid hormone =80 pg/mL, and/or potentially conflicting localization studies may inform surveillance strategies.
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Primary Hyperparathyroidism Is Associated With Shorter QTc Intervals, but Not Arrhythmia.
J Clin Endocrinol Metab, 107(4):e1689-e98.
L. A. Stewart, G. K. Steinl, B. L. Huang, C. McManus, J. A. Lee, J. H. Kuo and M. D. Walker. 2022.
CONTEXT: Primary hyperparathyroidism (PHPT) is associated with subclinical cardiovascular disease, but data regarding cardiac conduction abnormalities are limited. OBJECTIVE AND DESIGN: Retrospective cross-sectional comparison of cardiac conduction in patients with PHPT or thyroid disease (TD). PARTICIPANTS AND SETTING: Patients =40 years old who underwent parathyroidectomy or thyroidectomy at a single tertiary institution from 2013 to 2018. METHODS AND OUTCOMES: Demographics and preoperative electrocardiogram (EKG) parameters were compared using the Mann-Whitney U, chi-square test, and linear regression. RESULTS: A total of 1242 patients were included: 49.8% PHPT (n = 619) and 50.2% TD (n = 623). Median age was 60.5 years [interquartile range (IQR) 53.6-67.9]. Compared to controls, PHPT patients had higher median serum calcium [10.7 mg/dL (IQR 10.4-11.1) vs 9.5 mg/dL (IQR 9.3-9.8), P < 0.001] as expected, as well as, a higher prevalence of hyperlipidemia (49% vs 36%, P < 0.001) and hypertension (50.1% vs 42.2%, P < 0.01). Based on EKG, there was no difference in PR interval or the prevalence of arrhythmia, atrioventricular block, ST segment/T wave changes, premature ventricular complexes, right bundle branch block, or left bundle branch block after adjusting for covariates. The PHPT group had a lower mean corrected QT interval (414 ± 24) ms vs 422 ± 24 ms, P < 0.01), adjusted for covariates. Serum calcium predicted QTc independently of age, sex, and other covariates. CONCLUSIONS: In the largest study to date, PHPT patients had shorter QTc intervals compared to TD controls but no increased prevalence of arrhythmia based on preoperative EKG.
PubMed-ID: 34752632
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GCM2 Variants in Familial and Multiglandular Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 107(5):e2021-e6.
S. Vincze, N. V. Peters, C. L. Kuo, T. C. Brown, R. Korah, T. D. Murtha, J. Bellizzi, A. Riccardi, K. Parham, T. Carling, J. Costa-Guda and A. Arnold. 2022.
CONTEXT: Multiglandular and familial parathyroid disease constitute important fractions of primary hyperparathyroidism (PHPT). Germline missense variants of GCM2, a regulator of parathyroid development, were observed in familial isolated hyperparathyroidism and sporadic PHPT. However, as these previously reported GCM2 variants occur at relatively high frequencies in the population, understanding their potential clinical utility will require both additional penetrance data and functional evidence relevant to tumorigenicity. OBJECTIVE: Determine the frequency of GCM2 variants of interest among patients with sporadic multigland or familial parathyroid disease and assess their penetrance. DESIGN AND PATIENTS: DNA-encoding PHPT-associated GCM2 germline variants were polymerase chain reaction-amplified and sequenced from 107 patients with either sporadic multigland or suspected/confirmed familial parathyroid tumors. RESULTS: GCM2 variants were observed in 9 of 107 cases (8.4%): Y282D in 4 patients (6.3%) with sporadic multigland disease; Y394S in 2 patients (11.1%) with familial PHPT and 3 (4.8%) with sporadic multigland disease. Compared with the general population, Y282D was enriched 5.9-fold in multigland disease, but its penetrance was very low (0.02%). Y394S was enriched 79-fold in sporadic multigland disease and 93-fold in familial PHPT, but its penetrance was low (1.33% and 1.04%, respectively). CONCLUSIONS: Observed in vitro-activating GCM2 variant alleles are significantly overrepresented in PHPT patients with multiglandular or familial disease compared to the general population, yet penetrance values are very low; that is, most individuals with these variants in the population have a very low risk of developing PHPT. The potential clinical utility of detecting these GCM2 variants requires further investigation, including assessing their possible role as pathogenic/low-penetrance alleles.
PubMed-ID: 34967908
http://dx.doi.org/10.1210/clinem/dgab929

Proactive exploration of inferior parathyroid gland using a novel meticulous thyrothymic ligament dissection technique.
Eur J Surg Oncol, 48(6):1258-63.
X. Wang, Y. Si, J. Cai, H. Lu, H. Tong, H. Zhang, J. Wen and M. Shen. 2022.
INTRODUCTION: The inferior parathyroid gland (IPTG) is widely distributed; effective techniques for its safe exploration and protection during thyroid surgery have not been documented. The thyrothymic ligament (TTL) is a connective tissue located between the thymic tongue and thyroid. This study aims to introduce a novel meticulous thyrothymic ligament dissection technique and assess its role in proactive exploration and situ preservation of IPTG. MATERIALS AND METHODS: 737 patients undergoing initial thyroid surgery between 2017 and 2021 in the Department of General Surgery of the First Affiliated Hospital of Nanjing Medical University were retrospectively recruited for this clinical study. In 391 of the recruited patients, the TTL was dissected, and the number and location of IPTG were recorded. Among them, 214 patients underwent total/near-total thyroidectomy (TT) plus central neck dissection (CND) were assigned to the observation group. The control group included 346 consecutive patients who underwent conventional TT plus CND. After 1:1 propensity score matching, each group contained 206 patients. The incidence of postoperative hypoparathyroidism was recorded. RESULTS: Among the 391 patients, 596 sides were dissected, out of which 436 sides (73.2%) had TTL, and approximately 90.1% of IPTG were located and identified. A statistically significant difference in incidence of temporary (27.7 vs. 49.0%, P < 0.001) and permanent hypoparathyroidism (0 vs. 8.2%, P = 0.047) was noted between the observation group and the control group. CONCLUSION: The meticulous thyrothymic ligament dissection technique helps to protect IPTG in situ and reduce the incidence of postoperative hypoparathyroidism.
PubMed-ID: 35341610
http://dx.doi.org/10.1016/j.ejso.2022.03.011

ASO Author Reflections: Extended En Bloc Reoperation: A Potential Curative Operation for Recurrent or Persistent Parathyroid Carcinoma.
Ann Surg Oncol, 29(2):1216-7.
B. Wei, T. Zhao, H. Shen, M. Jin, Q. Zhou, X. Liu, J. Wang and Q. Wang. 2022.
PubMed-ID: 34709492
http://dx.doi.org/10.1245/s10434-021-10975-2

Parathyroid Hormone Disturbances in Postmenopausal Women with Distal Forearm Fracture.
World J Surg, 46(1):128-35.
A. Wihlborg, K. Bergström, P. Gerdhem and I. Bergström. 2022.
BACKGROUND: Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a wide range of adverse effects, such as osteoporosis. Many women are not diagnosed due to asymptomatic disease or vague symptoms but are still at risk of severe adverse effects. Early identification of patients with PHPT is therefore of importance. The aim of this study was to determine PHPT prevalence among postmenopausal women with a distal forearm fracture. METHODS: Recruitment was conducted in conjunction with the occurrence of a distal forearm fracture at Karolinska University Hospital. In total, 161 postmenopausal women were included in a cross-sectional study with repeated evaluations. Analyzes of serum calcium, ionized calcium, phosphate, parathyroid hormone (PTH), and vitamin D were performed. Diagnosis of PHPT was based on clinical evaluations and biochemical definitions of serum calcium and PTH in coherence with previous population prevalence reports. RESULTS: Mean age was 64.7 (9.5) years, serum calcium 2.33 (0.10) mmol/L, ionized calcium 1.25 (0.05) mmol/L and PTH 54 (26) ng/L. PTH was elevated in 32 (20%) women. In total, 11 (6.8%) women were diagnosed with PHPT; 6 with classical PHPT and 5 with mild PHPT. The prevalence of PHPT was significantly increased compared to the population prevalence of 3.4% (p = 0.022). CONCLUSION: Screening postmenopausal women in conjunction with low-energy distal forearm fracture revealed a large number of women with parathyroid disturbance. Evaluation of parathyroid hormone and calcium status in this group of patients seems beneficial.
PubMed-ID: 34647149
http://dx.doi.org/10.1007/s00268-021-06331-w

Adrenals

Meta-Analyses

Minimally invasive adrenalectomy: a comprehensive systematic review and network meta-analysis of phase II/III randomized clinical controlled trials.
Langenbecks Arch Surg, 407(1):285-96.
L. Alberici, C. Ingaldi, C. Ricci, S. Selva, G. Di Dalmazi, V. Vicennati, U. Pagotto, R. Casadei and F. Minni. 2022.
PURPOSE: The best approach for minimally invasive adrenalectomy is still under debate. METHODS: A systematic search of randomized clinical trials was carried out. A frequentist random-effects network meta-analysis was made reporting the surface under the cumulative ranking (SUCRA). The primary endpoint regarded both in-hospital mortality and morbidity. The secondary endpoints were operative time (OP), blood loss (BL), length of stay (LOS), conversion, incisional hernia, and disease recurrence rate. RESULTS: Eight studies were included, involving 359 patients clustered as follows: 175 (48.7%) in the TPLA arm; 55 (15.3%) in the RPLA arm; 10 (2.8%) in the Ro-TPLA arm; 25 (7%) in the TPAA arm; 20 (5.6%) in the SILS-LA arm; and 74 (20.6%) in the RPA arm. The RPLA had the highest probability of being the safest approach (SUCRA 69.6%), followed by RPA (SUCRA 63.0%). TPAA, Ro-TPLA, SILS-LA, and TPLA have similar probability of being safe (SUCRA values 45.2%, 43.4%, 43.0%, and 38.5%, respectively). Analysis of the secondary endpoints confirmed the superiority of RPA regarding OP, BL, LOS, and incisional hernia rate. CONCLUSIONS: The best choice for patients with adrenal masses candidate for minimally invasive surgery seems to be RPA. An alternative could be RPLA. The remaining approaches could have some specific advantages but do not represent the first minimally invasive choice.
PubMed-ID: 35022834
http://dx.doi.org/10.1007/s00423-022-02431-w

Composite phaeochromocytomas-a systematic review of published literature.
Langenbecks Arch Surg, 407(2):517-27.
K. Dhanasekar, V. Visakan, F. Tahir and S. P. Balasubramanian. 2022.
INTRODUCTION: Composite phaeochromocytoma is a tumour containing a separate tumour of neuronal origin in addition to a chromaffin cell tumour. This study reports on two cases from a single centre's records and presents a systematic literature review of composite phaeochromocytomas. METHODS: In addition to describing 2 case reports, a systematic search of the Medline database from inception up to April 2020 was done for human case reports on composite phaeochromocytomas. Relevant titles and/or abstracts were screened, and full texts were reviewed to identify appropriate studies. Data was extracted and a descriptive analysis of presentation, clinical features, management strategies and outcomes was performed. The quality of included studies was assessed using a critical appraisal checklist. RESULTS: There were 62 studies included, with a total of 94 patients. Of 91 patients where data was available, the median (range) age of patients was 48 (4-86) years. Of 90 patients where information was provided, 57% were female. In at least 28% of patients, a genetic cause was identified. Common presenting features include abdominal pain, palpable mass, cardiovascular and gastrointestinal symptoms. The most common tumour component with phaeochromocytoma is ganglioneuroma; other components include ganglioneuroblastoma, neuroblastoma and malignant peripheral nerve sheath tumours. In patients with follow-up data (n=48), 85% of patients were alive and well at a median (range) follow-up time of 18 (0.5-168) months. CONCLUSION: Composite phaeochromocytoma is a rare tumour, with a significant genetic predisposition. This review summarises available epidemiological data, which will be useful for clinicians managing this rare condition.
PubMed-ID: 33651160
http://dx.doi.org/10.1007/s00423-021-02129-5

Randomized controlled trials

- None –

Consensus Statements/Guidelines

- None -

Other Articles

Corrigendum to: Autonomous Cortisol Secretion Influences Psychopathological Symptoms in Patients With Primary Aldosteronism.
J Clin Endocrinol Metab, 107(6):e2655.
2022.
PubMed-ID: 35182068
http://dx.doi.org/10.1210/clinem/dgac073

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

Minimally invasive adrenalectomy for large pheochromocytoma: not recommendable yet? Results from a single institution case series.
Langenbecks Arch Surg, 407(1):277-83.
S. Arolfo, G. Giraudo, C. Franco, M. Parasiliti Caprino, E. Seno and M. Morino. 2022.
BACKGROUND: Minimally invasive adrenalectomy represents the treatment of choice of pheochromocytoma (PCC). For large or invasive PCCs, an open approach is currently recommended, in order to ensure complete tumor resection, prevent tumor rupture, avoid local recurrence, and limit perioperative hemodynamic instability. The aim of this study is to analyze perioperative outcomes of laparoscopic adrenalectomies (LAs) for large adrenal PCCs. METHODS: All consecutive LAs for PCC performed at a single institution between 1998 and 2020 were included. Two groups were defined: lesions larger (group 1) and smaller (group 2) than 5 cm. Short-term outcomes were compared in order to find any significant difference between the two groups. OUTCOMES: One hundred fourteen patients underwent LA during the study period: 46 for lesions larger and 68 for lesions smaller than 5 cm. No significant differences were found in patients' characteristics, median operative time, conversion rate, intraoperative hemodynamic and metabolic parameters, postoperative intensive care unit (ICU) admission rate, complications rate, and length of hospital stay. Long-term oncologic outcomes were similar, with a recurrence rate of 5.1% in group 1 vs 3.6% in group 2 ($p = 1$). CONCLUSION: Minimally invasive adrenalectomy seems to be safe and effective even in large PCC. The recommendation to prefer an open approach for large PCCs should probably be reconsidered.

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http://dx.doi.org/10.1007/s00423-021-02312-8

Cancer risk in adrenalectomy: are adrenal lesions equal or more than 4 cm a contraindication for laparoscopy?
Surg Endosc, 36(2):1131-42.
A. Balla, D. Corallino, M. Ortenzi, L. Palmieri, F. Meoli, M. Guerrieri and A. M. Paganini. 2022.
BACKGROUND: Some authors consider adrenal lesions size of less than 4 cm as a positive cut-off limit to set the indications for minimally invasive surgery due to a lower risk of malignancy. Aim of this study is to report the risk of cancer for adrenal lesions measuring 4 cm or more in diameter, assessed as benign at preoperative workup (primary outcome), and to evaluate the feasibility and safety of laparoscopic adrenalectomy (LA) in these cases (secondary outcome). METHODS: From January 1994 to February 2019, 579 patients underwent adrenalectomy. Fifty patients with a preoperative diagnosis of primary adrenal cancer or metastases were excluded. The remaining 529 patients were included and divided in five subgroups based on adrenal lesion size at definitive histology: group A, 4-5.9 cm (137 patients); group B, 6-7.9 cm (64 patients); group C, 8-9.9 cm (13 patients); group D, = 10 cm (11 patients); group E, < 4 cm (304 patients). Each group was further divided based on diagnosis of benign or malignant lesions at definitive histology. RESULTS: Four (2.9%) malignant lesions were observed in group A, 5 (7.8%) in group B, 2 (15.4%) in Groups C and D (18.2%) and 13 (4.3%) in Group E. Comparing the cancer risk among the groups, no statistically significant differences were observed. Operative time increased with increasing lesion size. However, no statistically significant differences were observed between benign and malignant lesions in each group comparing operative time, conversion and complication rates, postoperative hospital stay and mortality rate. CONCLUSIONS: Adrenal lesions measuring 4 cm or more in diameter are not a contraindication for LA neither in terms of cancer risk nor of conversion and morbidity rates, even if the operative time increases with increasing adrenal lesion diameter. Further prospective studies with a larger number of patients are required to draw definitive conclusions.
PubMed-ID: 33650006
http://dx.doi.org/10.1007/s00464-021-08380-7

Plasma Steroid Profiling in Patients With Adrenal Incidentaloma.
J Clin Endocrinol Metab, 107(3):e1181-e92.
K. Berke, G. Constantinescu, J. Masjkur, O. Kimpel, U. Dischinger, M. Peitzsch, A. Kwapiszewska, P. Dobrowolski, S. Nölting, M. Reincke, F. Beuschlein, S. R. Bornstein, A. Prejbisz, J. W. M. Lenders, M. Fassnacht and G. Eisenhofer. 2022.
CONTEXT: Most patients with adrenal incidentaloma have nonfunctional lesions that do not require treatment, while others have functional or malignant tumors that require intervention. The plasma steroid metabolome may be useful to assess therapeutic need. OBJECTIVE: This work aimed to establish the utility of plasma steroid profiling combined with metanephrines and adrenal tumor size for the differential diagnosis of patients with adrenal incidentaloma. METHODS: This retrospective cross-sectional study, which took place at 7 European tertiary-care centers, comprised 577 patients with adrenal incidentaloma, including 19, 77, 65, 104 and 312 respective patients with adrenocortical carcinoma (ACC), pheochromocytoma (PHEO), primary aldosteronism (PA), autonomous cortisol secretion (ACS), and nonfunctional adrenal incidentaloma (NFAI). Mesaures of diagnostic performance were assessed (with [95% CIs]) for discriminating different subgroups of patients with adrenal incidentaloma. RESULTS: Patients with ACC were characterized by elevated plasma concentrations of 11-deoxycortisol, 11-deoxycorticosterone, 17-hydroxyprogesterone, androstenedione, and dehydroepiandrosterone-sulfate, whereas patients with PA had elevations of aldosterone, 18-oxocortisol, and 18-hydroxycortisol. A selection of those 8 steroids, combined with 3 others (cortisol, corticosterone, and dehydroepiandrosterone) and plasma metanephrines, proved optimal for identifying patients with ACC, PA, and PHEO at respective sensitivities of 83.3% (66.1%-100%), 90.8% (83.7%-97.8%), and 94.8% (89.8%-99.8%); and specificities of 98.0% (96.9%-99.2%), 92.0% (89.6%-94.3%), and 98.6% (97.6%-99.6%). With the addition of tumor size, discrimination improved further, particularly for ACC (100% [100%-100%] sensitivity, 99.5% [98.9%-100%] specificity). In contrast, discrimination of ACS and NFAI remained suboptimal (70%-71% sensitivity, 89%-90% specificity). CONCLUSION: Among patients with adrenal incidentaloma, the combination of plasma steroid metabolomics with routinely available plasma free metanephrines and data from imaging studies may facilitate the identification of almost all clinically relevant adrenal tumors.
PubMed-ID: 34665854
http://dx.doi.org/10.1210/clinem/dgab751

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

Laparoscopic adrenalectomy vs. radiofrequency ablation for the treatment of primary aldosteronism. A single center retrospective cohort analysis adjusted with propensity score.
Surg Endosc, 36(3):1970-8.
O. Cano-Valderrama, J. González-Nieto, M. Abad-Cardiel, S. Ochagavía, I. Rünkle, J. V. Méndez, J. A. García-Donaire, M. Cuesta-Hernández, J. E. Armijo, P. Miguel-Novoa, A. J. Torres and N. Martell-Claros. 2022.
BACKGROUND: Laparoscopic adrenalectomy (LA) is the gold standard treatment for unilateral primary aldosteronism. However, satisfactory results have also been published with radiofrequency ablation (RFA). The aim of this study was to compare LA and RFA for the treatment of primary aldosteronism. METHODS: A retrospective cohort study of the patients who underwent LA or RFA in a single center was performed. Morbidity and long-term effectiveness (cure rate and blood pressure control) were analyzed. A multivariate analysis with a propensity score was also performed. RESULTS: Thirty-four patients were included in the study, 24 in the LA group and 10 in the RFA group. Hypertension had been diagnosed a median of 12 years before the intervention. Hypertension was properly controlled before the intervention in 55.9% of the patients. Hypertensive crisis was more common during RFA (4.2% vs. 70.0%, $p < 0.001$), although no patient suffered any complication because of these crises. LA was longer (174.6 vs. 105.5 min, $p = 0.001$) and had a longer length of stay (median 2 vs 1 days, $p < 0.001$). No severe complications were observed in any of the patients. After a median follow-up of 46.2 months, more patients had hypertension cured and blood pressure controlled in the LA group (29.2% vs. 0%, $p = 0.078$ and 95.5% vs. 50.0%, $p = 0.006$, respectively). Also, patients in the LA group were taking less antihypertensive drugs (1.8 vs. 3.0, $p = 0.054$) or mineralocorticoid receptor antagonists (41.7% vs. 90.0%, $p = 0.020$). Multivariate analysis adjusted by propensity score showed that LA had an OR = 11.3 ($p = 0.138$) for hypertension cure and an OR = 55.1 ($p = 0.040$) for blood pressure control. CONCLUSIONS: Although RFA was a less invasive procedure than LA, hypertension was cured and blood pressure was properly controlled in more patients from the LA group. Patients who underwent LA were taking less antihypertensive drugs than patients who had undergone RFA.
PubMed-ID: 33844083
http://dx.doi.org/10.1007/s00464-021-08481-3

Pathological and Genetic Stratification for Management of Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 107(4):1159-69.
M. R. Clay, E. M. Pinto, L. Fishbein, T. Else and K. Kiseljak-Vassiliades. 2022.
CONTEXT: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy that affects patients across the age spectrum. Although the overall survival in patients with ACC is poor, there is significant heterogeneity in terms of outcomes, presentation, and underlying genetic drivers. EVIDENCE ACQUISITION: This review is based on the evidence collected from primary research studies, expert reviews, and published guidelines. The studies were identified through PubMed search with key words "adrenocortical carcinoma," "prognosis," "pathology," and "genetics." The PubMed search was

complemented by authors' expertise, research, and clinical experience in the field of ACC. EVIDENCE SYNTHESIS: Identification of biomarkers has been critical to gain better insight into tumor behavior and to guide therapeutic approach to patients. Tumor stage, resection status, and Ki67 are pathological tumor characteristics that have been identified as prognosticators in patients with ACC. Cortisol excess also correlates with worse prognosis. Clinical and histopathological characteristics help stratify patient outcomes, yet still up to 25% of patients have a different outcome than predicted. To bridge this gap, comprehensive genomic profiling studies have characterized additional profiles that correlate with clinical outcomes. In addition, studies of clinically applicable molecular markers are under way to further stratify outcomes in patients with ACC tumors. CONCLUSIONS: Clinical predictors in combination with pathological markers play a critical role in the approach to patients with ACC. Recent advances in genetic prognosticators will help extend the stratification of these tumors and contribute to a personalized therapeutic approach to patients with ACC.
PubMed-ID: 34850906
http://dx.doi.org/10.1210/clinem/dgab866

Progression of Vertebral Fractures in Patients with Adrenocortical Carcinoma Undergoing Mitotane Therapy.
J Clin Endocrinol Metab, 107(5):e2167-e76.
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. 2022.
CONTEXT: Patients with adrenocortical carcinoma (ACC) are frequently on mitotane therapy for a long time period. The drug exerts adrenolytic activity requiring glucocorticoid supplementation, which can be potentially detrimental for bone. OBJECTIVE: To explore whether mitotane with/without 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; and to explore predictive factors of VF progression and a prognostic role of VF progression. METHODS: 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 2 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 = .04) and French (17.8% vs 35.6%, P = .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. CONCLUSION: The administration of mitotane with/without 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

Temporal Trends in Outcomes in Patients With Adrenocortical Carcinoma: A Multidisciplinary Referral-center Experience.
J Clin Endocrinol Metab, 107(5):1239-46.
M. Daher, J. Varghese, S. K. Gruschkus, C. Jimenez, S. G. Waguespack, S. Bedrose, L. Altameemi, H. Bazerbashi, A. Naing, V. Subaiah, M. T. Campbell, A. Y. Shah, M. Zhang, R. A. Sheth, J. A. Karam, C. G. Wood, N. D. Perrier, P. H. Graham, J. E. Lee and M. A. Habra. 2022.
CONTEXT: Reporting temporal trends in adrenocortical carcinoma (ACC) helps guide management strategies. OBJECTIVE: This work aimed to report the trends in disease burden and clinical outcomes over time that cannot be adequately captured from individual clinical trials. METHODS: A retrospective study was held of ACC patients seen at a referral cancer center between February 1998 and August 2019. Clinical outcomes were compared between an early cohort (February 1998-June 2007) and a late cohort (July 2007-August 2019). RESULTS: A total of 621 patients included with a median age at diagnosis of 49.3 years (range, 0.5-86.6 years). There were 285 (45.9%) patients with hormonal overproduction. More patients in the late cohort had stage IV disease compared to the early cohort (36.8% vs 23.1%; P < .0001). Resection of the primary tumor was performed in 502 patients (80.8%). Complete resection (R0) was more common in the late cohort (165 [60.2%]) than in the early cohort (100 [44.6%]; P = .0005). Of 475 patients with metastatic disease (stage IV or recurrent metastatic disease), 352 (74.1%) received mitotane, 320 (67.4%) received chemotherapy, and 53 (11.2%) received immunotherapy. In the early cohort, 70 (33%) received 2 or more lines of therapy, whereas in the late cohort, 127 (48%) received 2 or more lines of therapy. The 5-year overall survival (OS) rates were 65%, 58%, 45%, and 10% for stage I, II, III, and IV disease, respectively, whereas the 2-year OS rates in patients with stage IV disease was 24% in the early cohort and 46% in the late cohort (P = .01). CONCLUSION: ACC clinical outcomes improved over the past 2 decades as more patients

had complete resection or received more lines of systemic therapy.
PubMed-ID: 35092681
http://dx.doi.org/10.1210/clinem/dgac046

Selective Glucocorticoid Replacement Following Unilateral Adrenalectomy for Hypercortisolism and Primary Aldosteronism.
J Clin Endocrinol Metab, 107(2):e538-e47.
O. M. DeLozier, S. Y. Dream, J. W. Findling, T. B. Carroll, D. B. Evans and T. S. Wang. 2022.
CONTEXT: An institutional study previously demonstrated that cosyntropin stimulation testing on postoperative day 1 (POD1-CST) identified patients at risk for adrenal insufficiency (AI) following unilateral adrenalectomy (UA) for adrenal-dependent hypercortisolism (HC) and primary aldosteronism (PA), allowing for selective glucocorticoid replacement (GR). OBJECTIVE: This study re-evaluates the need for GR following UA for patients with HC and PA in a larger cohort. METHODS: A prospective database identified 108 patients who underwent UA for mild autonomous cortisol excess (MACE) (n = 47), overt hypercortisolism (OH) (n = 27), PA (n = 22), and concurrent PA/HC (n = 12) from September 2014 to October 2020; all underwent preoperative evaluation for HC. MACE was defined by the 1 mg dexamethasone suppression test (cortisol >1.8 µg/dL), with =5 defined as OH. GR was initiated for basal cortisol =5 or stimulated cortisol =14 (=18 prior to April 2017) on POD1-CST. RESULTS: Fifty-one (47%) patients had an abnormal POD1-CST; 54 (50%) were discharged on GR (27 MACE, 20 OH, 1 PA, 6 PA/HC). Median duration of GR was OH: 6.0 months, MACE: 2.1 months, PA: 1 month, PA/HC: 0.8 months. Overall, 26% (n = 7) of patients with OH and 43% (n = 20) of patients with MACE did not require GR. Two (2%) patients with OH had normal POD1-CST but developed AI several weeks postoperatively requiring GR. None experienced life-threatening AI. CONCLUSION: POD1-CST identifies patients with HC at risk for AI after UA, allowing for selective GR. One-quarter of patients with OH and nearly half of patients with MACE can forgo GR after UA. Patients with PA do not require evaluation for AI if concurrent HC has been excluded preoperatively.
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Clinical, Biochemical, Tumoural and Mutation Profile of VHL- and MEN2A-Associated Pheochromocytoma: A Comparative Study.
World J Surg, 46(3):591-9.
M. Dhanda, A. Agarwal, K. Mandal, S. Gupta, M. Sabaretnam, G. Chand, A. Mishra, G. Agarwal and S. K. Mishra. 2022.
OBJECTIVE: To compare clinical, biochemical, tumoural and mutational characteristics of Von Hippel Lindau Syndrome (VHL)-associated pheochromocytoma (PCC) to multiple endocrine neoplasia 2A (MEN2A)-associated pheochromocytoma. DESIGN: Retrospective study design in a tertiary health care centre in Northern India. METHODS: A total of 47 patients with biochemical and histologically proven pheochromocytoma/paraganglioma (PCC/PGL): 29 associated with VHL and 18 with MEN2A, were divided in two cohorts, respectively. Analysis of their medical records along with a prospective follow-up was done. RESULTS: There were more children <19 years in VHL group (13 vs 1). Despite majority of VHL-PCC showing elevation of normetanephrine (NMN) (93%) as compared to MEN2A-PCC (22.2%), 75.8% presented with hypertension as compared to MEN2A (33.3%). The average size of VHL-PCC tumours was 5.66 cm. VHL-PCC as compared to MEN2A-PCC were multifocal (75% vs 61.1%), bilateral synchronous (72.4 vs 61.1%) and extra-adrenal (17.2% vs 0%). Both VHL (24%) and MEN2A-PCC (27.7%) showed multiple nodules, but more MEN2A PCC showed extra-tumoural hyperplasia (44.4% vs. 6.8%). In VHL, the commonest mutation (n = 17) was missense mutation with a hot spot on exon 3, while in MEN2A-PCC majority (66.6%) had 634 mutation in exon 11 and only 2 patients had the rare 611 mutation in exon 10. CONCLUSION: In contrast to world literature, our study suggests Indian VHL-PCC can be symptomatic in spite of noradrenergic phenotype, large in size and multifocal. Multiple nodules in VHL-PCC could increase risk of recurrence following subtotal adrenalectomy.
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http://dx.doi.org/10.1007/s00268-021-06393-w

Clinical, imaging and biochemical presentation of cystic pheochromocytomas.
Clin Endocrinol (Oxf),
P. Dogra, P. J. Navin, T. J. McKenzie, T. Foster, B. Dy, M. Lyden, W. F. Young, Jr. and I. Bancos. 2022.
OBJECTIVE: Cystic adrenal mass is a rare imaging presentation of pheochromocytoma. We aimed to describe the clinical, biochemical and imaging characteristics of patients with cystic pheochromocytoma. DESIGN: Single-centre, retrospective study, 2000-2020. PATIENTS: Consecutive patients with cystic pheochromocytoma were identified from our institutional pathology and adrenal tumour database. RESULTS: Of the 638 patients with pheochromocytomas, 21 (3.2%) had cystic

pheochromocytomas (median age: 57 years, 57% women). Most pheochromocytomas were discovered incidentally (57%) or due to symptoms of catecholamine excess (24%). The median tumour size was 6.4 cm. On imaging, cystic pheochromocytomas were round or oval (90%), heterogeneous lesions (86%) with a thick solid rim (median rim thickness 13.9 mm, unenhanced computed tomography (CT) attenuation 40 Hounsfield units (HU), venous-phase CT attenuation 83 HU), and a median cystic component of 40% (unenhanced CT attenuation 17.6 HU, venous-phase CT attenuation 20.4 HU), and rarely with calcifications (15%). All 20 patients with biochemical testing had functioning tumours (adrenergic in 80%, noradrenergic in 20%). Total urinary metanephrine excretion correlated with the volume of the solid component (R(2) = .75, p < .0001) but not the cystic component (R(2) = .04, p = .4386). All patients underwent adrenalectomy (48% laparoscopic, 52% open), and the median duration of hospital stay was 4 days. CONCLUSIONS: Cystic pheochromocytomas are rare, large tumours with a phenotypic appearance that can masquerade as other adrenal cystic lesions. The degree of biochemical abnormality in cystic pheochromocytomas is associated with the volume of the solid component. All patients with adrenal cysts that have a solid component or an unenhanced attenuation >10 HU should undergo biochemical testing for pheochromocytoma.
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The Socioeconomic Consequences of Cushing's Syndrome: A Nationwide Cohort Study.
J Clin Endocrinol Metab, 107(7):e2921-e9.
A. Ebbehoj, E. Søndergaard, P. Jepsen, K. Stochholm, H. M. L. Svane, M. Madsen, P. L. Poulsen and J. O. L. Jørgensen. 2022.
CONTEXT: The long-term somatic and psychiatric consequences of Cushing's syndrome are well-described, but the socioeconomic consequences are largely unknown. OBJECTIVE: We studied employment status, educational level, risk of depression, and other socioeconomic outcomes of Cushing's syndrome in the years before diagnosis and after surgery. DESIGN: Nationwide register-based cohort study. METHODS: We used a validated algorithm to identify 424 patients operated for adrenal (n = 199) or pituitary Cushing's syndrome (n = 225) in Denmark from January 1, 1986 to December 31, 2017. We obtained socioeconomic registry data from 10 years before diagnosis (year -10) to 10 years after surgery (year +10) and included a sex- and age-matched reference population. We identified prognostic factors for returning to work using modified Poisson regression. RESULTS: Compared to the reference population, the patients' employment was permanently reduced from year -6 [relative risk (RR) 0.92, 95% CI 0.84-0.99] to year +10 (RR 0.66, 95% CI 0.57-0.76). Sick leave (RR 2.15, 95% CI 1.40-3.32) and disability pension (RR 2.60, 95% CI 2.06-3.27) were still elevated in year +10. Annual income, education, parenthood, relationship status, and risk of depression were also negatively impacted, but parenthood and relationship status normalized after surgery. Among patients, negative predictors of full-time employment after surgery included female sex, low education, comorbidity, and depression. CONCLUSION: Cushing's syndrome negatively affects a wide spectrum of socioeconomic variables many years before diagnosis of which only some normalize after treatment. The data underpin the importance of early diagnosis and continuous follow-up of Cushing's syndrome and, not least, the pervasive health threats of glucocorticoid excess.
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http://dx.doi.org/10.1210/clinem/dgac174

The Saline Infusion Test for Primary Aldosteronism: Implications of Immunoassay Inaccuracy.
J Clin Endocrinol Metab, 107(5):e2027-e36.
G. Eisenhofer, M. Kurlbaum, M. Peitzsch, G. Constantinescu, H. Remde, M. Schulze, D. Kaden, L. M. Müller, C. T. Fuss, S. Kunz, S. Kolodziejczyk-Kruk, S. Gruber, A. Prejbisz, F. Beuschlein, T. A. Williams, M. Reincke, J. W. M. Lenders and M. Bidlingmaier. 2022.
CONTEXT: Diagnosis of primary aldosteronism (PA) for many patients depends on positive results for the saline infusion test (SIT). Plasma aldosterone is often measured by immunoassays, which can return inaccurate results. OBJECTIVE: This study aimed to establish whether differences in aldosterone measurements by immunoassay versus mass spectrometry (MS) might impact confirmatory testing for PA. METHODS: This study, involving 240 patients tested using the SIT at 5 tertiary care centers, assessed discordance between immunoassay and MS-based measurements of plasma aldosterone. RESULTS: Plasma aldosterone measured by Liaison and iSYS immunoassays were respectively 86% and 58% higher than determined by MS. With an immunoassay-based SIT cutoff for aldosterone of 170 pmol/L, 78 and 162 patients had, respectivel, negative and positive results. All former patients had MS-based measurements of aldosterone < 117 pmol/L, below MS-based cutoffs of 162 pmol/L. Among the 162 patients with pathogenic SIT results, MS returned nonpathologic results in 62, including 32 under 117 pmol/L. Repeat measurements by an independent MS method confirmed nonpathogenic results in 53 patients with discordant results. Patients with discordant results showed a higher (P < 0.0001) prevalence of nonlateralized than lateralized adrenal aldosterone production than patients with concordant results (83%

vs 28%). Among patients with nonlateralized aldosterone production, 66% had discordant results. Discordance was more prevalent for the Liaison than iSYS immunoassay (32% vs 16%; P = 0.0065) and was eliminated by plasma purification to remove interferents. CONCLUSION: These findings raise concerns about the validity of immunoassay-based diagnosis of PA in over 60% of patients with presumed bilateral disease. We provide a simple solution to minimize immunoassay inaccuracy-associated misdiagnosis of PA.
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http://dx.doi.org/10.1210/clinem/dgab924

Targeting 11-Beta Hydroxylase With [131I]IMAZA: A Novel Approach for the Treatment of Advanced Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 107(4):e1348-e55.
S. Hahner, P. E. Hartrampf, P. W. Mihatsch, M. Nauerz, B. Heinze, H. Hänscheid, C. Teresa Fuß, R. A. Werner, C. Pamporaki, M. Kroiss, M. Fassnacht, A. K. Buck and A. Schirbel. 2022.
CONTEXT: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with limited treatment options. Theranostic approaches with adrenal specific radiotracers hold promise for improved diagnostics and treatment. OBJECTIVE: Here, we report a new theranostic approach to advanced ACC applying (R)-1-[1-(4-[123I]iodophenyl)ethyl]-1H-imidazole-5-carboxylic acid azetidinyl amide ([123I]IMAZA) for diagnostic imaging and [131I]IMAZA for radionuclide therapy. METHODS: Sixty-nine patients with nonresectable, metastatic ACCs were screened using a diagnostic [123I]IMAZA scan. Patients with significant uptake in all tumoral lesions were offered treatment with [131I]IMAZA. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), and adverse effects were assessed by Common Toxicity Criteria (version 5.0). RESULTS: After screening, 13 patients were treated with a median of 25.7 GBq [131I]IMAZA (range 18.1-30.7 GBq). Five individuals received a second treatment course. Best response was a decrease in the RECIST target lesions of -26% in 2 patients. Five patients with disease stabilization experienced a median progression-free survival of 14.3 months (range 8.3-21.9). Median overall survival in all patients was 14.1 months (4.0-56.5) after therapy. Treatment was well tolerated, in other words no severe toxicities (CTCAE grade =3) were observed. CONCLUSION: In patients with advanced ACC refractory to standard therapeutic regimens, [131I]IMAZA treatment was associated with disease stabilization and nonsignificant tumor size reduction in a significant patient fraction and only limited toxicities. High [131I]IMAZA-uptake in tumor lesions was observed in 38.5% of patients with advanced ACC, rendering [131I] IMAZA a potential treatment option in a limited, well-defined patient fraction. Further clinical trials will be necessary to evaluate the full potential of this novel theranostic approach.
PubMed-ID: 34904171
http://dx.doi.org/10.1210/clinem/dgab895

A combination of laparoscopic approach and ERAS pathway optimizes outcomes and cost for adrenalectomy.
Updates Surg, 74(2):519-25.
Z. He, S. Chen, M. Lu, Y. Luo, T. Liu, Y. Xiao and X. Wang. 2022.
Enhanced recovery after surgery (ERAS) pathway comprises a set of comprehensive elements which have been reported to enhance patient postoperative prognosis. In the current study, we aimed to evaluate the effectiveness of the ERAS in patients undergoing laparoscopic adrenal resection. A retrospective review was performed to compare the outcomes of patients undergoing adrenalectomy for primary aldosteronism between the pre-ERAS period and the ERAS era. Data was generated from the traditional surgical period (September 1, 2019, to December 31, 2019) and the ERAS period (September 1, 2020, to December 31, 2020), respectively. Forty-seven adrenalectomy patients were enrolled (pre-ERAS, n = 21; ERAS, n = 26) in analysis. The results revealed that both total length of hospital stay and postoperative length of stay decreased in the ERAS period compared with the pre-ERAS period (14.19 ± 4.96 vs 11.27 ± 4.37, p = 0.015; 5.43 ± 1.08 vs 3.31 ± 0.97, p < 0.001). The medical expenses decreased significantly in the ERAS group (p < 0.05). While, the surgery-related complications, including urinary retention, retroperitoneal effusion and gastrointestinal discomfort, possessed no statistical difference. The ERAS pathway was safe and feasible for adrenalectomy in patients with primary aldosteronism. The ERAS could promote patients to quickly recover from the postoperative status to a physiological state, and decrease the length of hospitalization and medical cost after surgery.
PubMed-ID: 34635985
http://dx.doi.org/10.1007/s13304-021-01188-z

A Modern Assessment of Cancer Risk in Adrenal Incidentalomas: Analysis of 2219 Patients.
Ann Surg, 275(1):e238-e44.
B. Kahramangil, E. Kose, E. M. Remer, J. P. Reynolds, R. Stein, B. Rini, A. Siperstein and E. Berber. 2022.
OBJECTIVE: The aim of this study was to analyze the incidence of and risk factors for adrenocortical carcinoma (ACC) in adrenal incidentaloma (AI). SUMMARY OF BACKGROUND DATA: AI guidelines are based on data obtained with old-generation imaging and predominantly use tumor size to stratify risk for ACC. There is a need to analyze the incidence and risk factors from a contemporary series. METHODS: This is a retrospective review of 2219 AIs that were either surgically removed or nonoperatively monitored for =12 months between 2000 and 2017. Multivariate logistic regression was performed to define risk factors. ROC curves constructed to determine optimal size and attenuation cut-offs for ACC. RESULTS: 16.8% of AIs underwent upfront surgery and rest initial nonoperative management. Of conservatively managed patients, an additional 7.7% subsequently required adrenalectomy. Overall, ACC incidence in AI was 1.7%. ACC rates by size were 0.1%, 2.4%, and 19.5% for AIs of <4, 4 to 6, and >6 cm, respectively. The optimal size cut-off for ACC in AI was 4.6 cm. ACC risks by Hounsfield density were 0%, 0.5%, and 6.3% for lesions of <10, 10 to 20, and >20 HU, with an optimal cut-off of 20 HU to diagnose ACC. 15.5% of all AIs and 19.2% of ACCs were hormonally active. Male sex, large tumor size, high Hounsfield density, and >0.6 cm/year growth were independent risk factors for ACC. CONCLUSION: This contemporary analysis demonstrates that ACC risk per size in AI is less than previously reported. Given these findings, modern management of AIs should not be based just on size, but a combination of thorough hormonal evaluation and imaging characteristics.
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Indices of ACTH-stimulated adrenal venous sampling as predictors of postsurgical outcomes in primary aldosteronism.
Clin Endocrinol (Oxf), 96(4):521-30.
S. H. Lee, J. W. Kim, H. K. Yoon, S. W. Kim, S. J. Kim, K. E. Lee, Y. M. Lee, T. Y. Sung, S. J. Hong, C. S. Shin, J. M. Koh and J. H. Kim. 2022.
OBJECTIVE: This study aimed to investigate the impact of indices of adrenal venous sampling (AVS) on postsurgical outcomes in patients with primary aldosteronism (PA). DESIGN AND PATIENTS: This retrospective study determined biochemical and clinical outcomes based on ACTH-stimulated AVS parameters (lateralisation index [LI], contralateral ratio [CLR], and ipsilateral ratio [ILR]) in 251 patients with PA at 3 months after surgery. RESULTS: Modified complete biochemical success was achieved in 8 of 12 (66.7%) patients with LI = 3-4, 39 of 47 (83.0%) with LI = 4-10, and 155 of 169 (91.7%) with LI = 10 (p = .004 for trend). Modified complete biochemical success was achieved in 29 of 38 (76.3%) patients with CLR = 1 and ILR = 2, 73 of 86 (84.9%) with CLR = 0.25-1 and ILR > 2, and 100 of 104 (96.2%) with CLR < 0.25 and ILR > 2 (p = .001 for trend). After adjusting for confounders, modified complete biochemical success was associated with an LI = 10 (odds ratio [OR] = 6.32; 95% confidence interval [CI] = 1.33-29.93) using LI = 3-4 as a reference and combined CLR < 0.25 and ILR > 2 (OR = 11.49; 95% confidence interval [CI] = 2.49-53.01) using combined CLR = 1 and ILR = 2 as a reference. Using combined CLR = 1 and ILR = 2 as a reference, complete clinical success was associated with combined CLR < 0.25 and ILR > 2 (OR = 3.10; 95% CI = 1.03-9.28) and combined CLR = 0.25-1 and ILR > 2 (OR = 4.92; 95% CI = 1.64-14.76). CONCLUSION: LI = 10 may be appropriate for achieving biochemical success. With ILR > 2, CLR < 0.25, and CLR < 1 may be appropriate for achieving biochemical and clinical success, respectively.
PubMed-ID: 34647340
http://dx.doi.org/10.1111/cen.14610

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.
PubMed-ID: 34486152
http://dx.doi.org/10.1111/cen.14585

Prognostic value of contralateral suppression for remission after surgery in patients with primary aldosteronism.
Clin Endocrinol (Oxf), 96(6):793-802.
S. Mørup, N. Voss, C. Clausen, C. L. Feltoft, M. Andreassen and J. Krogh. 2022.
OBJECTIVE: Primary aldosteronism (PA) is the most common cause of endocrine hypertension and adrenalectomy is the firstline treatment for unilateral PA. Suppression of aldosterone secretion of the nondominant adrenal gland at adrenal venous sampling (AVS), that is, contralateral suppression (CLS) has been suggested as a marker of disease severity. However, whether factors such as CLS, age, gender or comorbidities are associated with remission after surgery is controversial. The objective of this study is to investigate the prognostic value of CLS, age, gender, aldosterone-to-renin ratio, antihypertensives and comorbidities for clinical and biochemical remission following unilateral adrenalectomy in patients with PA. DESIGN AND PATIENTS: A retrospective study of patients with PA referred for AVS at Rigshospitalet from May 2011 to September 2020, who subsequently underwent adrenalectomy. Clinical remission was defined according to the PA surgical outcome criteria, whereas complete biochemical remission was defined as normalization of hypokalaemia without potassium substitution. RESULTS: Eighty-four patients were available for analysis of primary outcome. Among patients with CLS, 28/58 (48.3%) obtained complete clinical remission after surgery compared with 10/26 (38.5%) without CLS (p = .40). Complete biochemical remission was obtained in 55/58 (94.8%) of patients with CLS compared with 25/28 (89.3%) without CLS (p = .44). Female gender and lower number of antihypertensives at baseline were associated with higher odds for complete clinical remission, whereas none of the investigated variables were associated with biochemical remission. CONCLUSION: CLS was not significantly associated with complete clinical or biochemical remission in this cohort. Our results confirmed that female gender and lower number of antihypertensives were predictors of clinical remission.
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http://dx.doi.org/10.1111/cen.14678

Letter to the Editor From Singhania et al: "Increasing Incidence of Primary Aldosteronism in Western Sweden During 3 Decades-Yet an Underdiagnosed Disorder".
J Clin Endocrinol Metab, 107(3):e1315-e6.
P. Singhania and R. Bhattacharjee. 2022.
PubMed-ID: 34734261
http://dx.doi.org/10.1210/clinem/dgab804

Cytoreductive Surgery of the Primary Tumor in Metastatic Adrenocortical Carcinoma: Impact on Patients' Survival.
J Clin Endocrinol Metab, 107(4):964-71.
V. Srougi, I. Bancos, M. Daher, J. E. Lee, P. H. Graham, J. A. Karam, A. Henriquez, T. J. McKenzie, A. Sada, I. Bourdeau, J. Poirier, A. Vaidya, T. Abbondanza, C. M. Kiernan, S. N. Rao, O. Hamidi, N. Sachithanandan, A. O. Hoff, J. L. Chambo, M. Q. Almeida, M. A. Habra and M. Fragoso. 2022.
CONTEXT: The role of cytoreduction of adrenocortical carcinoma (ACC) remains poorly understood. OBJECTIVE: To analyze the impact of cytoreductive surgery of the primary tumor in patients with metastatic ACC. DESIGN AND SETTING: We performed a multicentric, retrospective paired cohort study comparing the overall survival (OS) in patients with metastatic ACC who were treated either with cytoreductive surgery (CR group) or without cytoreductive surgery (no-CR group) of the primary tumor. Data were retrieved from 9 referral centers in the American-Australian-Asian Adrenal Alliance collaborative research group. PATIENTS: Patients aged =18 years with metastatic ACC at initial presentation who were treated between January 1, 1995, and May 31, 2019. INTERVENTION: Performance (or not) of cytoreductive surgery of the primary tumor. MAIN OUTCOME AND MEASURES: A propensity score match was done using age and the number of organs with metastasis (=2 or >2). The main outcome was OS, determined from the date of diagnosis until death or until last follow-up for living patients. RESULTS: Of 339 patients pooled, 239 were paired and included: 128 in the CR group and 111 in the no-CR group. The mean follow-up was 67 months. Patients in the no-CR group had greater risk of death than

did patients in the CR group (hazard ratio [HR] = 3.18; 95% CI, 2.34-4.32). Independent predictors of survival included age (HR = 1.02; 95% CI, 1.00-1.03), hormone excess (HR = 2.56; 95% CI, 1.66-3.92), and local metastasis therapy (HR = 0.41; 95% CI, 0.47-0.65). CONCLUSION: Cytoreductive surgery of the primary tumor in patients with metastatic ACC is associated with prolonged survival.
PubMed-ID: 34850915
http://dx.doi.org/10.1210/clinem/dgab865

Response to Letter to the Editor From de Ponthaud et al: "Cytoreductive Surgery of the Primary Tumor in Metastatic Adrenocortical Carcinoma: Impact on Patients' Survival.".
J Clin Endocrinol Metab, 107(8):e3540.
V. Srougi, M. A. Habra and M. C. B. Villares Fragoso. 2022.
PubMed-ID: 35188202
http://dx.doi.org/10.1210/clinem/dgac097

Risk factors for haemodynamic instability and its prolongation during laparoscopic adrenalectomy for pheochromocytoma.
Clin Endocrinol (Oxf), 95(5):716-26.
T. Takeda, K. Hakozaki, Y. Yanai, T. Masuda, Y. Yasumizu, N. Tanaka, K. Matsumoto, S. Morita, T. Kosaka, R. Mizuno, I. Kurihara, H. Asanuma, H. Itoh and M. Oya. 2021.
OBJECTIVE: Pheochromocytoma is a rare neuroendocrine tumour that secretes catecholamines and originates in the adrenal gland. Although surgical resection is the only curative therapy for pheochromocytoma, it is associated with a risk of haemodynamic instability (HDI), such as extremely high blood pressure and/or post tumour removal hypotension and shock. We investigated the risk factors for HDI during pheochromocytoma surgery. DESIGN AND PATIENTS: Eighty-two patients who underwent laparoscopic adrenalectomy for pheochromocytoma between July 2002 and February 2020 were examined. We excluded 3 patients with bilateral disease and 11 without detailed 24 h urinary data. We defined HDI as systolic blood pressure = 200 or <80 mmHg. We investigated the risk factors for HDI during laparoscopic adrenalectomy for pheochromocytoma. RESULTS: There were 29 males and 39 females with a median age of 50.5 years. Tumours were localised on the right adrenal gland in 28 patients and on the left in 40. The median tumour diameter was 37.5 mm and the median pneumoperitoneum time was 93.5 min. Twenty-five out of sixty-eight patients (37%) developed HDI. A multivariate analysis identified diabetes mellitus (DM; odds ratio: 3.834; 95% confidence interval: 1.062-13.83; p = .04) as an independent predictor of HDI. In terms of hormonal data, median 24 h urinary epinephrine levels (p = .04) and metanephrine levels (p = .01) were significantly higher in the HDI group. DM was also considered as a risk factor for prolonged HDI (p = .02). CONCLUSION: Surgeons and anaesthesiologists need to be aware of the risk of HDI and its prolongation during laparoscopic adrenalectomy for pheochromocytoma for DM patients.
PubMed-ID: 34288003
http://dx.doi.org/10.1111/cen.14557

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.

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ASO Author Reflections: Adrenocortical Carcinoma-All We Need Are Nodes.
Ann Surg Oncol, 29(3):1971.
J. Tseng and M. Jain. 2022.
PubMed-ID: 34802104
http://dx.doi.org/10.1245/s10434-021-11090-y

Clonidine suppression test for a reliable diagnosis of pheochromocytoma: When to use.
Clin Endocrinol (Oxf),
S. Tsiomidou, C. Pamporaki, A. Geroula, L. Van Baal, F. Weber, H. Dralle, K. W. Schmid, D. Führer and N. Unger. 2022.
OBJECTIVE: In clinical practice, false-positive results in biochemical testing for suspected pheochromocytoma/paraganglioma (PPGL) are not infrequent and may lead to unnecessary examinations. We aimed to evaluate the role of the clonidine suppression test (CST) in the era of analyses of plasma-free metanephrines for the diagnosis or exclusion of PPGL in patients with adrenal tumours and/or arterial hypertension. DESIGN AND METHODS: This single-centre, prospective trial investigated the use of CST in 60 patients with suspected PPGL associated with out-patient elevations of plasma normetanephrine (NMN) and/or metanephrine (MN), in most cases accompanied with hypertension or an adrenal mass. Measurements of plasma catecholamines and free metanephrines were performed by liquid chromatography with electrochemical detection and tandem mass spectrometry, respectively. RESULTS: Forty-six patients entered final analysis (n = 20 with PPGL and n = 26 with a nonfunctional adrenal mass and/or hypertension). CST reliably excluded false-positive baseline NMN results with a specificity of 100%. The sensitivity of CST improved from 85% to 94% when tumours with isolated MN increase (n = 3) were not considered. In patients with elevated baseline NMN (n = 24), CST correctly identified all patients without PPGL. Patients with falsely elevated baseline NMN results (n = 7, 26.9%) exhibited increases of baseline NMN up to 1.7-fold above the upper reference limit. CONCLUSION: CST qualifies as a useful diagnostic tool for differential diagnosis of borderline elevated plasma-free NMN in patients with suspected PPGL. In this context, CST helps to correctly identify all false-positive NMN screening results.
PubMed-ID: 35274752
http://dx.doi.org/10.1111/cen.14724

Robot-assisted versus conventional laparoscopic adrenalectomy: Results from the EUROCRINE Surgical Registry.
Surgery, 171(5):1224-30.
S. Vatansever, E. Nordenström, M. Raffaelli, L. Brunaud and Ö. Makay. 2022.
BACKGROUND: Adrenalectomy is routinely performed via the minimally invasive approach. Safety of adrenalectomy using the robot-assisted technique has been widely demonstrated by several series, but the literature is scarce regarding the comparison of conventional laparoscopic versus robot-assisted approach. We decided to carry out a multicenter study to compare clinical and surgical outcomes between laparoscopic and robotic adrenalectomy. METHODS: This is a retrospective case-control study, including data from centers affiliated to the Surgical Registry EUROCRINE. Patients undergoing laparoscopic surgery for adrenal tumors and registered between 2015 and 2018 were included. Robot-assisted versus laparoscopic adrenalectomy was compared. All comparisons were carried out in terms of complication rate, conversion rate and duration of stay. RESULTS: A total of 1,005 patients from 46 clinics underwent robotic or conventional laparoscopic adrenalectomy. Median age was 55 (interquartile range: 45-65) years. Robotic adrenalectomy was performed in 189 (18.8%) patients. According to Clavien-Dindo classification, complication rate was lower in the robotic surgery group (1.6% vs 16.5%, P < .001). Laparoscopic surgery and active hormonal status were significantly correlated with complications, both in univariate and multivariate analysis. There was no significant difference between laparoscopic and robotic surgery groups, in terms of conversion rate (2.1% vs 0.5%, respectively, P = .147). Duration of stay was shorter in the robotic adrenalectomy group (82.1% vs 28.8%, P < .001). CONCLUSION: Analysis of the EUROCRINE database supports that robotic adrenalectomy resulted in a lower complication rate and shorter duration of stay, compared with laparoscopic adrenalectomy. Granular data to support this is warranted.
PubMed-ID: 35027208
http://dx.doi.org/10.1016/j.surg.2021.12.003

Adrenal androgens versus cortisol for primary aldosteronism subtype determination in adrenal venous sampling.
Clin Endocrinol (Oxf), 97(3):241-9.
M. Viukari, E. Kokko, I. Pörsti, H. Leijon, T. Vesterinen, T. Hinkka, M. Soinio, C. Schalin-Jäntti, N. Matikainen and P. I.

Nevalainen. 2022.
OBJECTIVE: We examined if measurement of adrenal androgens adds to subtype diagnostics of primary aldosteronism (PA) under cosyntropin-stimulated adrenal venous sampling (AVS). DESIGN: A prospective pre-specified secondary endpoint analysis of 49 patients with confirmed PA, of whom 29 underwent unilateral adrenalectomy with long-term follow-up. METHODS: Concentrations of androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) were measured during AVS in addition to aldosterone and cortisol. Subjects with lateralisation index (LI) of =4 were treated with unilateral adrenalectomy, and the immunohistochemical subtype was determined with CYP11B2 and CYP11B1 stains. The performance of adrenal androgens was evaluated by receiver operating characteristics (ROC) curve analyses in adrenalectomy and medical therapy groups. RESULTS: During AVS, the correlations between cortisol and androstenedione, DHEA and DHEAS for LI and selectivity index (SI) were highly significant. The right and left side SIs for androstenedione and DHEA were higher ($p < .001$) than for cortisol. In ROC analysis, the optimal LI cut-off values for androstenedione, DHEA and DHEAS were 4.2, 4.5 and 4.6, respectively. The performance of these LIs for adrenal androgens did not differ from that of cortisol. CONCLUSIONS: Under cosyntropin-stimulated AVS, the measurement of androstenedione and DHEA did not improve the cannulation selectivity. The performance of cortisol and adrenal androgens are confirmatory but not superior to cortisol-based results in lateralisation diagnostics of PA.
PubMed-ID: 35167715
http://dx.doi.org/10.1111/cen.14691

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

Genetic Characteristics of Incidental Pheochromocytoma and Paraganglioma.
J Clin Endocrinol Metab, 107(5):e1835-e42.
J. Zhang, M. Li, Y. Pang, C. Wang, J. Wu, Z. Cheng, X. Li, Z. Lu, Y. Liu, J. Guo, X. Chen, Y. He, X. Guan, X. Xu, Y. Wang, J. Liu, W. Guo, Y. Hou, L. Liu, J. Jiang and X. Gao. 2022.
CONTEXT: Pheochromocytomas and paragangliomas (PPGLs) are being increasingly discovered by imaging performed for unrelated conditions. The genetic landscape of incidental PPGLs remains to be elucidated. OBJECTIVE: We aimed to describe the genetic characteristics of PPGLs discovered incidentally in a large PPGL cohort. METHODS: This retrospective cross-sectional study included 697 patients with pathology confirmed PPGLs, including 283 incidentalomas and 414 nonincidentalomas, at 2 tertiary care centers in China in 2009-2019. Tumor DNA samples were sequenced by next-generation sequencing. Identified genetic mutations were confirmed by Sanger sequencing and tested in 277 available matched blood DNA samples. RESULTS: There was a lower proportion of patients with mutations identified (53% vs 63.3%; P = 0.0067) in incidental than nonincidental PPGLs. In incidental PPGLs, HRAS (11.7%), FGFR1 (11%), and RET (9.2%) were

the top 3 mutated genes, whereas HRAS (17.9%), VHL (9.2%), and NF-1 (8.7%) exhibited the highest rate of mutations in nonincidental PPGLs. In incidental pheochromocytomas, the most frequently mutated genes were RET (10.9%), HRAS (10.4%), and VHL (8.6%), while in incidental paragangliomas, FGFR1 (32.8%), HRAS (16.4%), and EPAS1 (9.8%) topped the list. The frequency of NF-1 mutations was significantly lower in incidental than nonincidental pheochromocytomas (4.1% vs 11%; P = 0.0042), while FGFR1 mutations were far more common in incidental than nonincidental paragangliomas (32.8% vs 15.3%; P = 0.0076). CONCLUSION: More than half of patients with incidental PPGLs had mutations in common susceptibility genes. The search for susceptibility genes should take both the mode of discovery (incidental vs nonincidental) and tumor location (pheochromocytoma vs paraganglioma) into consideration.
PubMed-ID: 35106577
http://dx.doi.org/10.1210/clinem/dgac058

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

NET

Meta-Analyses

Predictors of disease recurrence after curative surgery for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNENs): a systematic review and meta-analysis.
J Endocrinol Invest, 45(4):705-18.
V. Andreasi, C. Ricci, S. Partelli, G. Guarneri, C. Ingaldi, F. Muffatti, S. Crippa, R. Casadei and M. Falconi. 2022.
PURPOSE: Patients submitted to curative surgery for non-functioning pancreatic neuroendocrine neoplasms (NF-PanNENs) exhibit a variable risk of disease relapse. Aims of this meta-analysis were to estimate the rate of disease recurrence and to investigate the risk factors for disease relapse in patients submitted to curative surgery for NF-PanNENs. METHODS: Medline/Pubmed and Web of Science databases were searched for relevant studies. A meta-regression analysis was performed to investigate the source of recurrence rate heterogeneity. Pooled hazard ratios (HRs) and 95% confidence intervals (95% CI) were used to assess the effect of each possible prognostic factor on disease-free survival. RESULTS: Fifteen studies, involving 2754 patients submitted to curative surgery for NF-PanNENs, were included. The pooled rate of disease recurrence was 21% (95% CI 15-26%). Study quality (Odds ratio, OR 0.94, P = 0.016) and G3-PanNENs rate (OR 2.18, P = 0.040) independently predicted the recurrence rate variability. Nodal metastases (HR 1.63, P < 0.001), tumor grade G2-G3 (G1 versus G2: HR 1.72, P < 0.001, G1 versus G3 HR 2.57, P < 0.001), microvascular (HR 1.25, P = 0.046) and perineural (HR 1.29, P = 0.019) invasion were identified as significant prognostic factors. T stage (T1-T2 versus T3-T4, P = 0.253) and status of resection margins (R0 versus R1, P = 0.173) did not show any significant relationship with NF-PanNENs recurrence. CONCLUSION: Disease relapse occurs in approximately one out of five patients submitted to curative surgery for NF-PanNENs. Nodal involvement, tumor grade, microvascular and perineural invasion are relevant prognostic factors, that should be taken into account for follow-up and for possible trials investigating adjuvant or neoadjuvant treatments.
PubMed-ID: 34773595
http://dx.doi.org/10.1007/s40618-021-01705-2

Effect of primary tumour resection without curative intent in patients with metastatic neuroendocrine tumours of the small intestine and right colon: meta-analysis.
Br J Surg, 109(2):191-9.
K. Van Den Heede, S. Chidambaram, S. Van Slycke, N. Brusselaers, C. F. Warfvinge, H. Ohlsson, E. Nordenström and M. Almquist. 2022.
BACKGROUND: Patients with small intestinal neuroendocrine tumours (siNETs) usually present with advanced disease. Primary tumour resection without curative intent is controversial in patients with metastatic siNETs. The aim of this meta-analysis was to investigate survival after primary tumour resection without curative intent compared with no resection in patients with metastatic siNETs. METHODS: A systematic literature search was performed, using MEDLINE(r) (PubMed), Embase(r), Web of Science, and the Cochrane Library up to 25 February 2021. Studies were included if survival after primary tumour resection versus no resection in patients with metastatic siNETs was reported. Results were pooled in a random-effects meta-analysis, and are reported as hazard ratios (HRs) with 95 per cent confidence intervals. Sensitivity analyses were undertaken to enable comment on the impact of important confounders. RESULTS: After screening 3659 abstracts, 16 studies, published between 1992 and 2021, met the inclusion criteria, with a total of 9428 patients. Thirteen studies reported HRs adjusted for important confounders and were included in the meta-analysis. Median overall survival was 112 (i.q.r. 82-134) months in the primary tumour resection group compared with 60 (74-88) months in the group without resection. Five-year overall survival rates were 74 (i.q.r. 67-77) and 44 (34-45) per cent respectively. Primary tumour resection was associated with improved survival compared with no resection (HR 0.55, 95 per cent c.i. 0.47 to 0.66). This effect remained in sensitivity analyses. CONCLUSION: Primary tumour resection is associated with increased survival in patients with advanced, metastatic siNETs, even after adjusting for important confounders.
PubMed-ID: 34941998
http://dx.doi.org/10.1093/bjs/znab413

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

[Importance of surgery in distant metastatic pancreatic neuroendocrine neoplasms].
Chirurgie (Heidelb), 93(8):758-64.
F. Billmann, A. Nießen and T. Hackert. 2022.
The majority of patients with pancreatic neuroendocrine neoplasms (pNEN) already present with distant metastases at diagnosis. The heterogeneity of pNEN and the broad spectrum of treatment options make adequate patient selection and an evidence-based strategy essential. In metastatic pNEN both primary resection and resection of liver metastases have been shown to improve overall survival. Surgical treatment of liver metastases can also be carried out with palliative intent, especially for symptomatic pNEN and can have a positive effect on disease-free survival and overall survival. Classical hepatectomy techniques and innovative techniques (two-stage resections, liver transplantation) are available to the surgeon. In complex growth types of liver metastases, there is increasing evidence for a combination of surgery and ablative methods. Due to a relevant risk of recurrence following liver resection, pNEN patients need to be included in multimodal treatment concepts. Current areas of interest in the treatment of metastatic pNEN are the use of adjuvant/neoadjuvant chemotherapy and surgery in G3-NEN and G3-NEC patients. The aim of this review is to give an overview on the impact of surgery in the situation of distant metastatic NEN of the pancreas.
PubMed-ID: 35403909
http://dx.doi.org/10.1007/s00104-022-01630-x

Sexual Dimorphism in Small-intestinal Neuroendocrine Tumors: Lower Prevalence of Mesenteric Disease in Premenopausal Women.
J Clin Endocrinol Metab, 107(5):e1969-e75.
A. Blaževic, A. M. Iyer, M. F. van Velthuysen, J. Hofland, L. Oudijk, W. W. de Herder, L. J. Hofland and R. A. Feelders. 2022.
CONTEXT: Small-intestinal neuroendocrine tumors (SI-NETs) have a modest but significantly higher prevalence and worse prognosis in male patients. OBJECTIVE: This work aims to increase understanding of this sexual dimorphism in SI-NETs. PATIENTS AND METHODS: Retrospectively, SI-NET patients treated in a single tertiary center were included and analyzed for disease characteristics. Estrogen receptor 1 (ESR1) and 2 (ESR2), progesterone receptor (PGR), and androgen receptor (AR) messenger RNA (mRNA) expression was assessed in primary tumors and healthy intestine. Estrogen receptor alpha (ERa) and AR protein expression were analyzed by immunohistochemistry in primary tumors and mesenteric metastases. RESULTS: Of the 559 patients, 47% were female. Mesenteric metastasis/fibrosis was more prevalent in men (71% / 46%) than women (58% / 37%; P = 0.001 and P = 0.027, respectively). In women, prevalence of mesenteric metastases increased gradually with age from 41.1% in women <50 years to 71.7% in women >70 years. Increased expression of ESR1 and AR mRNA was observed in primary tumors compared to healthy intestine (both P < 0.001). ERa staining was observed in tumor cells and stroma with a strong correlation between tumor cells of primary tumors and mesenteric metastases (rho = 0.831, P = 0.02), but not in stroma (rho = -0.037, P = 0.91). AR expression was only found in stroma. CONCLUSION: Sexual dimorphism in SI-NETs was most pronounced in mesenteric disease, and the risk of mesenteric metastasis in women increased around menopause. The combination of increased ERa and AR expression in the SI-NET microenvironment suggests a modulating role of sex steroids in the development of the characteristic SI-NET mesenteric metastasis and associated fibrosis.
PubMed-ID: 34999838
http://dx.doi.org/10.1210/clinem/dgac001

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

Neuroendocrine neoplasms of the gallbladder: early detection and surgery is key to improved outcome.
Langenbecks Arch Surg, 407(1):197-206.
S. Gogna, D. Samson, M. Gachabayov, A. Rojas, D. M. Felsenreich, D. Koo, K. Gu, L. Quintero, K. R. Miller, A. Azim and X. Da Eric Dong. 2022.
PURPOSE: Neuroendocrine neoplasms (NENs) of the gallbladder are very rare. As a result, the classification of pathologic specimens from gallbladder NENs, currently classified as gallbladder neuroendocrine tumors (GB-NETs) and carcinomas (GB-NECs), is inconsistent and makes nomenclature, classification, and management difficult. Our study aims to evaluate the epidemiological trend, tumor biology, and outcomes of GB-NET and GB-NEC over the last 5 decades. METHODS: This is a retrospective analysis of the SEER database from 1973 to 2016. The epidemiological trend was analyzed using the age-adjusted Joinpoint regression analysis. Survival was assessed with Kaplan-Meier analysis and Cox regression was used to assess predictors of poor survival. RESULTS: A total of 482 patients with GB-NEN were identified. Mean age at diagnosis was 65.2 ± 14.3 years. Females outnumbered males (65.6% vs. 34.4%). The Joinpoint nationwide trend analysis showed a 7% increase per year from 1973 to 2016. The mean survival time after diagnosis of GB-NEN was 37.11 ± 55.3 months. The most common pattern of nodal distribution was N0 (50.2%) followed by N1 (30.9%) and N2 (19.2%). Advanced tumor spread (into the liver, regional, and distant metastasis) was seen in 60.3% of patients. Patients who underwent surgery had a significant survival advantage (111.0 ± 8.3 vs. 8.3 ± 1.2 months, $p < 0.01$). Cox regression analysis showed advanced age ($p < 0.01$), tumor stage ($P < 0.01$), tumor extension ($p < 0.01$), and histopathologic grade ($p < 0.01$) were associated with higher mortality. CONCLUSION: Gallbladder NENs are a rare histopathological variant of gallbladder cancer that is showing a rising incidence in the USA. In addition to tumor staging, surgical resection significantly impacts patient survival, when patients are able to undergo surgery irrespective of tumor staging. Advanced age, tumor extension, and histopathological grade of the tumor were associated with higher mortality.
PubMed-ID: 34236488
http://dx.doi.org/10.1007/s00423-021-02256-z

Grading Pancreatic Neuroendocrine Tumors via Endoscopic Ultrasound-guided Fine Needle Aspiration: A Multi-Institutional Study.
Ann Surg,
A. A. Javed, A. Pulvirenti, S. Razi, J. Zheng, T. Michelakos, Y. Sekigami, E. Thompson, D. S. Klimstra, V. Deshpande, A. D. Singhi, M. J. Weiss, C. L. Wolfgang, J. L. Cameron, A. C. Wei, A. H. Zureikat, C. R. Ferrone and J. He. 2022.
OBJECTIVES: To identify factors associated with concordance between World Health Organization (WHO) grade on cytological analysis (c-grade) and histopathological analysis (h-grade) of surgical specimen in patients with PanNETs and examine trends in utilization and accuracy of EUS-FNA in preoperatively predicting grade. BACKGROUND: WHO grading system is prognostic in pancreatic neuroendocrine tumors (PanNETs). The concordance between c-grade and h-grade is reported to be between 60% and 80%. METHODS: A multicenter retrospective study was performed on patients

undergoing resection for PanNETs at four high-volume centers. Patients with functional or syndrome-associated tumors, and those receiving neoadjuvant therapy were excluded. Factors associated with concordance between c-grade and h-grade and trends of utilization of EUS-FNA were assessed. RESULTS: Of 1,336 patients included, 682 (51.1%) underwent EUS-FNA; 567 (83.1%) were diagnostic of PanNETs and WHO-grade was reported for 293 (51.7%) patients. The concordance between c-grade and h-grade was 78.2% with moderate inter-rater agreement (Kc=0.48,p<0.001). Significantly higher rates of concordance were observed in patients with smaller tumors (<2 vs. =2 cm, 88.9% vs. 72.7%,p=0.001). Highest concordance (97.9%) was observed in patients with small tumors undergoing assessment between 2015-2019 with near-perfect inter-rater agreement (Kc=0.88,p<0.001)An increase in the utilization of EUS-FNA (46.7% to 62.1%) was observed over the last 2 decades (p<0.001). EUS-FNA was more frequently diagnostic of PanNETs (p<0.001), and WHO-grade was more frequently reported (<0.001). However, concordance between c-grade and h-grade did not change significantly (p=0.056). CONCLUSION: Recently, a trend towards increasing utilization and improved diagnostic accuracy of EUS-FNA has been observed in PanNETs. Concordance between c-grade and h-grade is associated with tumor size with near-perfect agreement when assessing PanNETs >2 cm in size.
PubMed-ID: 35081574
http://dx.doi.org/10.1097/SLA.0000000000005390

Surgical Treatment of Patients with Poorly Differentiated Pancreatic Neuroendocrine Carcinoma: An NCDB Analysis.
Ann Surg Oncol, 29(6):3522-31.
S. R. Kaslow, G. A. Vitiello, K. Prendergast, L. Hani, S. M. Cohen, C. Wolfgang, R. S. Berman, A. Y. Lee and C. Correa-Gallego. 2022.
BACKGROUND: Consensus guidelines discourage resection of poorly differentiated pancreatic neuroendocrine carcinoma (panNEC) given its association with poor long-term survival. This study assessed treatment patterns and outcomes for this rare malignancy using the National Cancer Database (NCDB). METHODS: Patients with non-functional pancreatic neuroendocrine tumors in the NCDB (2004-2016) were categorized based on pathologic differentiation. Logistic and Cox proportional hazard regressions identified associations with resection and overall survival (OS). Survival was compared using Kaplan-Meier and log-rank tests. RESULTS: Most patients (83%) in the cohort of 8560 patients had well-differentiated tumors (panNET). The median OS was 47 months (panNET, 63 months vs panNEC, 17 months; p < 0.001). Surgery was less likely for older patients (odds ratio [OR], 0.97), patients with panNEC (OR, 0.27), and patients with metastasis at diagnosis (OR, 0.08) (all p < 0.001). After propensity score-matching of these factors, surgical resection was associated with longer OS (82 vs 29 months; p < 0.001) and a decreased hazard of mortality (hazard ratio [HR], 0.37; p < 0.001). Surgery remained associated with longer OS when stratified by differentiation (98 vs 41 months for patients with panNET and 36 vs 8 months for patients with panNEC). Overall survival did not differ between patients with panNEC who underwent surgery and patients with panNET who did not (both 39 months; p = 0.294). CONCLUSIONS: Poorly differentiated panNEC exhibits poorer survival than well-differentiated panNET. In the current cohort, surgical resection was strongly and independently associated with improved OS, suggesting that patients with panNEC who are suitable operative candidates should be considered for multimodality therapy, including surgery.
PubMed-ID: 35246811
http://dx.doi.org/10.1245/s10434-022-11477-5

Plasma Polyamines as an Additional to Imaging Biomarker in MEN1 Patients With Duodenopancreatic Neuroendocrine Tumors.
J Clin Endocrinol Metab, 107(2):e880-e2.
E. Kassi and G. Kaltsas. 2022.
PubMed-ID: 34543418
http://dx.doi.org/10.1210/clinem/dgab683

Management of adrenocorticotropic hormone-secreting neuroendocrine tumors and the role of bilateral adrenalectomy in ectopic Cushing syndrome.
Surgery, 172(2):559-66.
J. P. Landry, U. Clemente-Gutierrez, C. R. C. Pieterman, Y. J. Chiang, S. G. Waguespack, C. Jimenez, M. A. Habra, D. M. Halperin, S. B. Fisher, P. H. Graham and N. D. Perrier. 2022.
BACKGROUND: Neuroendocrine tumors can cause ectopic Cushing syndrome, and most patients have metastatic disease at diagnosis. We identified risk factors for outcome, evaluated ectopic Cushing syndrome management, and explored the role of bilateral adrenalectomy in this population. METHODS: This was a retrospective study including patients with diagnosis of ectopic Cushing Syndrome secondary to neuroendocrine tumors with adrenocorticotropic hormone secretion

treated at our quaternary referral center over a 40-year period (1980-2020). RESULTS: Seventy-six patients were included. Mean age at diagnosis was 46.3 ± 15.8 years. Most patients (N = 61, 80%) had metastases at ectopic Cushing syndrome diagnosis. Average follow-up was 2.9 ± 3.7 years (range, 4 months-17.2 years). Patients with neuroendocrine tumors before ectopic Cushing syndrome had more frequent metastatic disease and resistant ectopic Cushing syndrome. Patients with de novo hyperglycemia, poor neuroendocrine tumor differentiation, and metastatic disease had worse survival. Of those with nonmetastatic disease, 8 (53%) had ectopic Cushing syndrome resolution after neuroendocrine tumor resection, 3 (20%) were medically controlled, and 4 (27%) underwent bilateral adrenalectomy. In patients with metastatic neuroendocrine tumors, hypercortisolism was initially medically managed in 92%, 3% underwent immediate bilateral adrenalectomy, 2% had control after primary neuroendocrine tumor debulking, and 2% were lost to follow-up. Medical treatment resulted in hormonal control in 7 (13%) patients. Of the 49 patients with metastatic disease and medically resistant ectopic Cushing syndrome, 23 ultimately had bilateral adrenalectomy with ectopic Cushing syndrome cure in all. CONCLUSION: Patients with neuroendocrine tumors before ectopic Cushing syndrome development were more likely metastatic and had worse survival. De novo hyperglycemia and poor neuroendocrine tumor differentiation were predictive of worse prognosis. Medical control of hypercortisolism is difficult to achieve in patients with neuroendocrine tumors-ectopic Cushing syndrome. Well-selected patients may benefit from bilateral adrenalectomy early in the treatment algorithm, and multidisciplinary management is essential in this complex disease.
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http://dx.doi.org/10.1016/j.surg.2022.03.014

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

Comparison of patient characteristics between East Asian and non-East Asian patients with insulin autoimmune syndrome.
Clin Endocrinol (Oxf), 96(3):328-38.
L. Oest, M. Roden and K. Müssig. 2022.
OBJECTIVE: Insulin autoimmune syndrome (IAS) is the third most common cause of spontaneous hypoglycaemia in Japan but very rare in the rest of the world. We aimed to identify factors, which are associated with the occurrence of IAS and which may differ between East Asian and non-East Asian patients. DESIGN: A PubMed search using the search terms 'insulin autoimmune syndrome' and 'Hirata disease' revealed a total of 287 reports of IAS cases, including one previously unpublished own case. RESULTS: Mean age (±standard deviation) was 52 ± 19 years in East Asian and 54 ± 21 years in non-East Asian patients ($p > .05$). In both groups, there were more females. Mean body mass index was lower in East Asian than in non-East Asian patients (23.0 ± 4.3 vs. 27.1 ± 5.6 kg/m(2) , $p < .0001$). Postprandial hypoglycaemia was more common in non-East Asian patients ($p < .05$). East Asian patients took more frequently antithyroid medications and non-East Asian patients angiotensin-converting enzyme (ACE) inhibitors (both $p < .0001$). Graves' disease and other autoimmune diseases were more frequently observed in East Asian patients (both $p < .01$). Parameters of glucose metabolism were comparable in both groups, independent of diabetes diagnosis ($p > .05$), except for insulin that was higher in East Asian compared to non-East Asian metabolically healthy patients ($p < .01$). Human leukocyte antigen (HLA)-

DRB1*0406 was the most frequent HLA-type in East Asian patients (p < .0001), whereas DRB1*0403 and *0404 were more frequent in non-East Asian patients (both p < .05). Non-East Asian patients received more secondary treatments, including plasmapheresis and rituximab, whereas medication discontinuation was more common in East Asian patients (all p < .05). Outcome was similar in both groups (p > .05). CONCLUSIONS: Factors associated with IAS markedly differ between East Asian and non-East Asian patients, with autoimmune disorders, particularly Graves' disease, antithyroid medications, and HLA-DRB1*0406 more prevalent in East Asian patients and cardiovascular and plasma cell diseases, ACE inhibitors and HLA-DRB1*0403 more prevalent in non-East Asian patients.
PubMed-ID: 34778997
http://dx.doi.org/10.1111/cen.14634

The role of calcium-stimulated venous sampling in the surgical treatment of multiple neuroendocrine neoplasms. Case report.
Clin Endocrinol (Oxf),
V. Panteleev, P. Davydenko, A. Varava, M. Raevskaya and A. Kaldarov. 2021.
PubMed-ID: 34278585
http://dx.doi.org/10.1111/cen.14556

Molecular Imaging of Neuroendocrine Neoplasms.
J Clin Endocrinol Metab, 107(7):e2662-e70.
J. Refardt, J. Hofland, D. Wild and E. Christ. 2022.
The key for molecular imaging is the use of a radiotracer with a radioactive and a functional component. While the functional component targets a specific feature of the tumor, the radioactive component makes the target visible. Neuroendocrine neoplasms (NEN) are a diverse group of rare tumors that arise from neuroendocrine cells found mainly in the gastroenteropancreatic system, lung, thyroid, and adrenal glands. They are characterized by the expression of specific hormone receptors on the tumor cell surface, which makes them ideal targets for radiolabeled peptides. The most commonly expressed hormone receptors on NEN cells are the somatostatin receptors. They can be targeted for molecular imaging with various radiolabeled somatostatin analogs, but also with somatostatin antagonists, which have shown improved imaging quality. 18F-DOPA imaging has become a second-line imaging modality in NENs, with the exception of the evaluation of advanced medullary thyroid carcinoma. Alternatives for NENs with insufficient somatostatin receptor expression due to poor differentiation involve targeting glucose metabolism, which can also be used for prognosis. For the localization of the often-small insulinoma, glucagon-like peptide-1 (GLP-1) receptor imaging has become the new standard. Other alternatives involve metaiodobenzylguanidine and the molecular target C-X-C motif chemokine receptor-4. In addition, new radiopeptides targeting the fibroblast activation protein, the glucose-dependent insulinotropic polypeptide receptor and cholecystokinin-2 receptors have been identified in NENs and await further evaluation. This mini-review aims to provide an overview of the major molecular imaging modalities currently used in the field of NENs, and also to provide an outlook on future developments.
PubMed-ID: 35380158
http://dx.doi.org/10.1210/clinem/dgac207

(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

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

Risk factors for complications after surgery for pancreatic neuroendocrine tumors.
Surgery, 172(1):127-36.
D. J. van Beek, T. J. Takkenkamp, E. M. Wong-Lun-Hing, R. H. J. de Kleine, A. M. E. Walenkamp, J. M. Klaase, M. W. Nijkamp, G. D. Valk, I. Q. Molenaar, J. Hagendoorn, H. C. van Santvoort, I. H. M. Borel Rinkes, F. J. H. Hoogwater and M. R. Vriens. 2022.
BACKGROUND: Surgical resection is the only potentially curative treatment for pancreatic neuroendocrine tumors. The choice for the type of procedure is influenced by the expected oncological benefit and the anticipated risk of procedure-specific complications. Few studies have focused on complications in these patients. This cohort study aimed to assess complications and risk factors after resections of pancreatic neuroendocrine tumors. METHODS: Patients undergoing resection of a pancreatic neuroendocrine tumor were identified within 2 centers of excellence. Complications were assessed according to the Clavien-Dindo classification and the comprehensive complication index. Logistic regression was performed to compare surgical procedures with adjustment for potential confounders (Clavien-Dindo =3). RESULTS: The cohort comprised 123 patients, including 12 enucleations, 50 distal pancreatectomies, 51 pancreatoduodenectomies, and 10 total/combined pancreatectomies. Mortality was 0.8%, a severe complication occurred in 41.5%, and the failure-to-rescue rate was 2.0%. The median comprehensive complication index was 22.6 (0-100); the comprehensive complication index increased after more extensive resections. After adjustment, a pancreatoduodenectomy, as compared to a distal pancreatectomy, increased the risk for a severe complication (odds ratio 3.13 [95% confidence interval 1.32-7.41]). Of the patients with multiple endocrine neoplasia type 1 or von Hippel-Lindau, 51.9% developed a severe complication vs 38.5% with sporadic disease. After major resections, morbidity was significantly higher in patients with multiple endocrine neoplasia type 1/von Hippel-Lindau (comprehensive complication index 45.1 vs 28.9, P = .029). CONCLUSION: Surgery for pancreatic neuroendocrine tumors is associated with a high rate of complications but low failure-to-rescue in centers of excellence. Complications are procedure-specific. Major resections in patients with multiple endocrine neoplasia type 1/von Hippel-Lindau appear to increase the risk of complications.
PubMed-ID: 35341591
http://dx.doi.org/10.1016/j.surg.2022.02.007

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Surveillance Improves Outcomes for Carriers of SDHB Pathogenic Variants: A Multicenter Study.
J Clin Endocrinol Metab, 107(5):e1907-e16.
D. F. Davidoff, D. E. Benn, M. Field, A. Crook, B. G. Robinson, K. Tucker, R. De Abreu Lourenco, J. R. Burgess and R. J. Clifton-Bligh. 2022.
CONTEXT: Carriers of succinate dehydrogenase type B (SDHB) pathogenic variants (PVs) are at risk of pheochromocytoma and paraganglioma (PPGL) from a young age. It is widely recommended carriers enter a surveillance program to detect tumors, but there are limited studies addressing outcomes of surveillance protocols for SDHB PV carriers. OBJECTIVE: The purpose of this study was to describe surveillance-detected (s-d) tumors in SDHB PV carriers enrolled in a surveillance program and to compare their outcomes to probands. METHODS: This was a multicenter study of SDHB PV carriers with at least 1 surveillance episode (clinical, biochemical, imaging) in Australian genetics clinics. Data were collected by both retrospective and ongoing prospective follow-up. Median duration of follow-up was 6.0 years. RESULTS: 181 SDHB PV carriers (33 probands and 148 nonprobands) were assessed. Tumors were detected in 20% of nonprobands undergoing surveillance (age range 9-76 years). Estimated 10-year metastasis-free survival was 66% for probands and 84% for nonprobands with s-d tumors (P = .027). S-d tumors were smaller than those in probands (median 27 mm vs 45 mm respectively, P = .001). Tumor size =40 mm was associated with progression to metastatic disease (OR 16.9, 95% CI 2.3-187.9, P = .001). Patients with s-d tumors had lower mortality compared to probands: 10-year overall survival was 79% for probands and 100% for nonprobands (P = .029). CONCLUSION: SDHB carriers with s-d tumors had smaller tumors, reduced risk of metastatic disease, and lower mortality than probands. Our results suggest that SDHB PV carriers should undertake surveillance to improve clinical outcomes.
PubMed-ID: 35037935
http://dx.doi.org/10.1210/clinem/dgac019

Consensus Conference Statement on the General Use of Near-infrared Fluorescence Imaging and Indocyanine Green Guided Surgery: Results of a Modified Delphi Study.
Ann Surg, 275(4):685-91.
F. Dip, L. Boni, M. Bouvet, T. Carus, M. Diana, J. Falco, G. C. Gurtner, T. Ishizawa, N. Kokudo, E. Lo Menzo, P. S. Low, J. Masia, D. Muehrcke, F. A. Papay, C. Pulitano, S. Schneider-Koraith, D. Sherwinter, G. Spinoglio, L. Stassen, Y. Urano, A. Vahrmeijer, E. Vibert, J. Warram, S. D. Wexner, K. White and R. J. Rosenthal. 2022.
BACKGROUND: In recent decades, the use of near-infrared light and fluorescence-guidance during open and laparoscopic surgery has exponentially expanded across various clinical settings. However, tremendous variability exists in how it is performed. OBJECTIVE: In this first published survey of international experts on fluorescence-guided surgery, we sought to identify areas of consensus and nonconsensus across 4 areas of practice: fundamentals; patient selection/preparation; technical aspects; and effectiveness and safety. METHODS: A Delphi survey was conducted among 19 international experts in fluorescence-guided surgery attending a 1-day consensus meeting in Frankfurt, Germany on September 8th, 2019.

Using mobile phones, experts were asked to anonymously vote over 2 rounds of voting, with 70% and 80% set as a priori thresholds for consensus and vote robustness, respectively. RESULTS: Experts from 5 continents reached consensus on 41 of 44 statements, including strong consensus that near-infrared fluorescence-guided surgery is both effective and safe across a broad variety of clinical settings, including the localization of critical anatomical structures like vessels, detection of tumors and sentinel nodes, assessment of tissue perfusion and anastomotic leaks, delineation of segmented organs, and localization of parathyroid glands. Although the minimum and maximum safe effective dose of ICG were felt to be 1 to 2 mg and >10 mg, respectively, there was strong consensus that determining the optimum dose, concentration, route and timing of ICG administration should be an ongoing research focus. CONCLUSIONS: Although fluorescence imaging was almost unanimously perceived to be both effective and safe across a broad range of clinical settings, considerable further research remains necessary to optimize its use.
PubMed-ID: 33214476
http://dx.doi.org/10.1097/SLA.0000000000004412

Secretin Stimulation Test and Early Diagnosis of Gastrinoma in MEN1 Syndrome: Survey on the MEN1 Florentine Database.
J Clin Endocrinol Metab, 107(5):e2110-e23.
F. Giusti, F. Cioppi, C. Fossi, F. Marini, L. Masi, F. Tonelli and M. L. Brandi. 2022.
CONTEXT: Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited endocrine cancer syndrome. Multiple gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) affect 30% to 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 nonstimulated FSG.
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http://dx.doi.org/10.1210/clinem/dgab903

Noninvasive Prenatal Diagnosis of a Paternally Inherited MEN1 Pathogenic Splicing Variant.
J Clin Endocrinol Metab, 107(4):e1367-e73.
T. Huby, E. Le Guillou, C. Burin des Roziers, L. Pacot, A. Briand-Suleau, A. Chansavang, A. Toussaint, V. Duchossoy, N. Vaucouleur, V. Benoit, L. Lodé, C. Molac, M. O. North, S. Grotto, V. Tsatsaris, A. Jouinot, B. Cochand-Priollet, A. C. Paepegaey, J. Nectoux, L. Groussin and E. Pasmant. 2022.
CONTEXT: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease caused by mutations in the tumor suppressor gene MEN1. The uncertainty of pathogenicity of MEN1 variants complexifies the selection of the patients likely to benefit from specific care. OBJECTIVE: MEN1-mutated patients should be offered tailored tumor screening and genetic counseling. We present a patient with hyperparathyroidism for whom genetic analysis identified a variant of uncertain significance in the MEN1 gene (NM_130799.2): c.654G > T p.(Arg218=). Additional functional genetic tests were performed to classify the variant as pathogenic and allowed prenatal testing. DESIGN: Targeted next generation sequencing identified a synonymous variant in the MEN1 gene in a 26-year-old male with symptomatic primary hyperparathyroidism. In silico and in vitro genetic tests were performed to assess variant pathogenicity. RESULTS: Genetic testing of the proband's unaffected parents showed the variant occurred de novo. Transcript study showed a splicing defect leading to an in-frame deletion. The classification of the MEN1 variant as pathogenic confirmed the diagnosis of MEN1 and recommended an adapted medical care and follow-up. Pathogenic classification also allowed to propose a genetic counseling to the proband and his wife. Noninvasive prenatal diagnosis was performed with a personalized medicine-based protocol by detection of the paternally inherited variant in maternal plasmatic cell free DNA, using digital PCR. CONCLUSION: We showed that functional genetic analysis can help to assess the pathogenicity of a MEN1 variant

with crucial consequences for medical care and genetic counseling decisions.
PubMed-ID: 34897474
http://dx.doi.org/10.1210/clinem/dgab894

Value of Somatostatin Receptor PET/CT in Patients With MEN1 at Various Stages of Their Disease.
J Clin Endocrinol Metab, 107(5):e2056-e64.
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. 2022.
CONTEXT: Despite the growing evidence of the clinical value of somatostatin receptor (SSTR) positron emission tomography (PET) in the evaluation of neuroendocrine tumors (NETs), its role remains to be clarified at different time points in the journey of patients with multiple endocrine neoplasia type 1 (MEN1). The rarity of the disease is however a significant impediment to prospective clinical trials. OBJECTIVE: The goals of the study were to assess the indications and value of SSTR PET/computed tomography (CT) in patients with MEN1. METHODS: We retrospectively included patients from 7 French expert centers for whom data on SSTR PET/CT and morphological imaging performed at the same period were available. Detection rates of PET study were analyzed. RESULTS: One hundred and 8 patients were included. SSTR PET/CT was performed at screening (n = 33), staging (n = 34), restaging (n = 37), and for peptide receptor targeted radiotherapy selection (n = 4). PET detected positive pancreatic lesions in 91% of cases at screening, with results comparable with magnetic resonance imaging but superior to CT (P = .049). Metastases (mostly lymph node [LN]) were present at the screening phase in 28% of cases, possibly due to the suboptimal value of screening morphological imaging in the assessment of nodal metastases and/or a long delay between imaging studies. SSTR PET/CT was considered 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 great impetus toward its implementation in the evaluation of patients with MEN1.
PubMed-ID: 34940846
http://dx.doi.org/10.1210/clinem/dgab891

MEN4, the MEN1 Mimicker: A Case Series of three Phenotypically Heterogenous Patients With Unique CDKN1B Mutations.
J Clin Endocrinol Metab, 107(8):2339-49.
A. Seabrook, A. Wijewardene, S. De Sousa, T. Wong, N. Sheriff, A. J. Gill, R. Iyer, M. Field, C. Luxford, R. Clifton-Bligh, A. McCormack and K. Tucker. 2022.
CONTEXT: Germline CDKN1B pathogenic variants result in multiple endocrine neoplasia type 4 (MEN4), an autosomal dominant hereditary tumor syndrome variably associated with primary hyperparathyroidism, pituitary adenoma, and duodenopancreatic neuroendocrine tumors. OBJECTIVE: To report the phenotype of 3 unrelated cases each with a unique germline CDKN1B variant (of which 2 are novel) and compare these cases with those described in the current literature. DESIGN/METHODS: Three case studies, including clinical presentation, germline, and tumor genetic analysis and family history. SETTING: Two tertiary University Hospitals in Sydney, New South Wales, and 1 tertiary University Hospital in Canberra, Australian Capital Territory, Australia. OUTCOME: Phenotype of the 3 cases and their kindred; molecular analysis and tumor p27kip1 immunohistochemistry. RESULTS: Family A: The proband developed multiglandular primary hyperparathyroidism, a microprolactinoma and a multifocal nonfunctioning duodenopancreatic neuroendocrine tumor. Family B: The proband was diagnosed with primary hyperparathyroidism from a single parathyroid adenoma. Family C: The proband was diagnosed with a nonfunctioning pituitary microadenoma and ectopic Cushing's syndrome from an atypical thymic carcinoid tumor. Germline sequencing in each patient identified a unique variant in CDKN1B, 2 of which are novel (c.179G > A, p.Trp60*; c.475G > A, p.Asp159Asn) and 1 previously reported (c.374_375delCT, p.Ser125*). CONCLUSIONS: Germline CDKN1B pathogenic variants cause the syndrome MEN4. The phenotype resulting from the 3 pathogenic variants described in this series highlights the heterogenous nature of this syndrome, ranging from isolated primary hyperparathyroidism to the full spectrum of endocrine manifestations. We report the first described cases of a prolactinoma and an atypical thymic carcinoid tumor in MEN4.
PubMed-ID: 35323929
http://dx.doi.org/10.1210/clinem/dgac162

A cost-utility analysis of 18F-fluorocholine-positron emission tomography imaging for localizing primary hyperparathyroidism in the United States.

Surgery, 171(1):55-62.

A. Yap, T. A. Hope, C. E. Graves, W. Kluijfhout, W. T. Shen, J. E. Gosnell, J. A. Sosa, S. A. Roman, Q. Y. Duh and I. Suh. 2022.

BACKGROUND: Primary hyperparathyroidism historically necessitated bilateral neck exploration to remove abnormal parathyroid tissue. Improved localization allows for focused parathyroidectomy with lower complication risks. Recently, positron emission tomography using radiolabeled 18F-fluorocholine demonstrated high accuracy in detecting these lesions, but its cost-effectiveness has not been studied in the United States. METHODS: A decision tree modeled patients who underwent parathyroidectomy for primary hyperparathyroidism using single preoperative localization modalities: (1) positron emission tomography using radiolabeled 18F-fluorocholine, (2) 4-dimensional computed tomography, (3) ultrasound, and (4) sestamibi single photon emission computed tomography (SPECT). All patients underwent either focused parathyroidectomy versus bilateral neck exploration, with associated cost ($) and clinical outcomes measured in quality-adjusted life-years gained. Model parameters were informed by literature review and Medicare costs. Incremental cost-utility ratios were calculated in US dollars/quality-adjusted life-years gained, with a willingness-to-pay threshold set at $100,000/quality-adjusted life-year. One-way, 2-way, and threshold sensitivity analyses were performed. RESULTS: Positron emission tomography using radiolabeled 18F-fluorocholine gained the most quality-adjusted life-years (23.9) and was the costliest ($2,096), with a total treatment cost of $11,245 or $470/quality-adjusted life-year gained. Sestamibi single photon emission computed tomography and ultrasound were dominated strategies. Compared with 4-dimentional computed tomography, the incremental cost-utility ratio for positron emission tomography using radiolabeled 18F-fluorocholine was $91,066/quality-adjusted life-year gained in our base case analysis, which was below the willingness-to-pay threshold. In 1-way sensitivity analysis, the incremental cost-utility ratio was sensitive to test accuracy, positron emission tomography using radiolabeled 18F-fluorocholine price, postoperative complication probabilities, proportion of bilateral neck exploration patients needing overnight hospitalization, and life expectancy. CONCLUSION: Our model elucidates scenarios in which positron emission tomography using radiolabeled 18F-fluorocholine can potentially be a cost-effective imaging option for primary hyperparathyroidism in the United States. Further investigation is needed to determine the maximal cost-effectiveness for positron emission tomography using radiolabeled 18F-fluorocholine in selected populations.

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