EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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Contents

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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)

blue underline: Hyperlink to PubMed entry or web site of publisher. Clicking on hyperlink opens the corresponding web site in browser (in Vista: CTRL-click).

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Preliminary

This collection is special interest for all of us there are some papers with the consensus guidelines achieved in ESES Mainz Conference in 2023

Enjoin the reading

Merry Christmas and happy new year

paola

Journals covered

Journal	Journal
Acta Cytol	J Bone Miner Res
Am J Kidney Dis	J Clin Endocrinol Metab
Am J Nephrol	J Clin Oncol
Am J Surg	J Endocrinol
Am Surgeon	J Endocrinol Invest
Ann Surg	J Nephrol
Ann Surg Oncol	J Nucl Med
ANZ J Surg	J Surg Oncol
Br J Surg	Lancet
Cancer	Langenbecks Arch Surg
Chirurgie (formerly: Chirurg)	Laryngoscope
Clin Endocrinol Oxf	N Engl J Med
Clin Nucl Med	Nat Rev Endocrinol
Curr Opin Oncol	Nat Rev Clin Oncol
Endocr Relat Cancer	Nephrol Dial Transplant
Endocr Rev	Neuroendocrinology
Eur Arch Otorhinolaryngol	Oncologist
Eur J Endocrinol	Otolaryngol Head Neck Surg
Eur J Surg Oncol	Surg Clin North Am
Gland Surg	Surg Endosc
Head Neck	Surg Laparosc Endosc Percutan Tech
Horm Metab Res	Surg Oncol
JAMA Otolaryngol Head Neck Surg	Surg Oncol Clin N Am
JAMA Surg	Surgery
Int J Cancer	Thyroid
J Am Coll Surg	Updates In Surgery
J Am Soc Nephrol	World J Surg
J Bone Miner Metab	

Journal names are links to the journal's homepage!,

Thyroid

Meta-Analyses

Effectiveness of Different Treatment Modalities in Initial and Chronic Phases of Thyroid Eye Disease: A Systematic Review With Meta-analysis.
J Clin Endocrinol Metab, 109(11):2997-3009.
J. M. Alves Junior, W. Bernardo and D. Villagelin. 2024.
BACKGROUND: Thyroid eye disease (TED), a common extrathyroidal manifestation of Graves disease, poses significant management challenges due to potential disfigurement, visual impairment, and decreased quality of life. Uncertainties remain about the optimal treatment approach, especially regarding TED duration and its impact on outcomes. OBJECTIVE: This meta-analysis evaluates the effects of various treatments on inflammatory markers and severity endpoints in TED, stratified by disease duration, distinguishing between treatments initiated within the first 6 months (initial phase) and those initiated thereafter (subacute/chronic phase). METHODS: Following PRISMA guidelines, a systematic search of multiple electronic databases yielded 26 studies meeting predefined inclusion criteria. Methodological quality was assessed, and data were meticulously extracted and analyzed. RESULTS: In the initial phase, treatments like corticosteroids and teprotumumab showed significant improvements in clinical activity score, proptosis, and diplopia. In the subacute/chronic phase, the efficacy of methylprednisolone and teprotumumab is reduced. A "critical window" effect was observed, with treatments showing diminished efficacy after 6 months of TED duration. CONCLUSION: This meta-analysis highlights the importance of tailoring treatment strategies based on TED duration, emphasizing early interventions to maximize benefits. The findings guide clinicians in selecting optimal treatments and underscore the need for further research to refine evidence-based approaches, ultimately enhancing patient outcomes and quality of life.
PubMed-ID: 39076015
DOI: 10.1210/clinem/dgae526

Malignancy Risk of Follicular Neoplasm (Bethesda IV) With Variable Cutoffs of Tumor Size: A Systemic Review and Meta-Analysis.
J Clin Endocrinol Metab, 109(5):1383-92.
Y. Y. Cho, S. H. Ahn, E. K. Lee, Y. J. Park, D. Choi, B. Y. Kim, C. H. Jung, J. O. Mok, C. H. Kim and S. W. Kim. 2024.
CONTEXT: The decision on diagnostic lobectomy for follicular neoplasms (FN) is challenging. OBJECTIVE: This meta-analysis investigates whether an appropriate size cutoff exists for recommending surgery for thyroid nodules diagnosed as FN by fine needle aspiration. METHODS: The Ovid-Medline, EMBASE, Cochrane, and KoreaMed databases were searched for studies reporting the malignancy rate of FN/suspicious for FN (FN/SFN) according to tumor size, using search terms "fine needle aspiration," "follicular neoplasm," "lobectomy," "surgery," and "thyroidectomy." RESULTS: Fourteen observational studies comprising 2016 FN/SFN nodules with postsurgical pathologic reports were included, and 2 studies included malignancy rates with various tumor sizes. The pooled malignancy risk of FN/SFN nodules according to size was: odds ratio (OR) 2.29 (95% CI, 1.68-3.11) with cutoff of 4 cm (9 studies), OR 2.39 (95% CI, 1.45-3.95) with cutoff of 3 cm (3 studies), and OR 1.81 (95% CI, 0.94-3.50) with cutoff of 2 cm (5 studies). However, tumors >/=2 cm also showed a higher risk (OR 2.43; 95% CI, 1.54-3.82) based on the leave-one-out meta-analysis after removal of 1 influence study. When each cutoff size was evaluated by summary receiver operating characteristic (sROC) curves, the cutoff of 4 cm showed the highest summary area under the curve (sAUC, 0.645) compared to other cutoffs (sAUC, 0.58 with 2 cm, and 0.62 with 3 cm), although there was no significant difference. CONCLUSION: Although the risk of malignancy increases with increasing tumor size, the risk remains significant at all tumor sizes and no cutoff limit can be recommended as a decision-making parameter for diagnostic surgery in Bethesda IV thyroid nodules.
PubMed-ID: 38113188
DOI: 10.1210/clinem/dgad684

Transoral endoscopic thyroidectomy submental vestibular approach for early-stage papillary thyroid carcinoma: a systematic review and meta-analysis.
Langenbecks Arch Surg, 409(1):204.
M. D. Hindawi, A. H. G. Ali, R. M. Qafesha, W. Soliman, H. Salem, E. Bali and A. Elrosasy. 2024.
PURPOSE: Our study aimed to compare the effectiveness and complications of the transoral endoscopic thyroidectomy submental vestibular approach (TOETSMVA) versus the transoral endoscopic thyroidectomy vestibular approach (TOETVA)

or conventional open thyroidectomy (COT) in patients with early-stage papillary thyroid carcinoma (PTC). METHODS: We searched online databases up to January 2024. The outcomes were analyzed using RevMan 5.4 and inverse variance. RESULTS: Seven studies (two RCTs and five retrospective cohort studies) were included. We established higher significance differences for TOETSMVA in comparison with TOETVA in terms of all primary outcomes; operation time, hospital stay, number of resected lymph nodes [MD -21.05, 95% CI= -30.98, -11.12; p < 0.0001], [MD -1.76, 95% CI= -2.21, -1.32, p < 0.00001], [MD -2.99, 95% CI= -19.75, 13.76, p < 0.73], [MD -0.83, 95% CI = -1.19 to -0.47; p < 0.00001], respectively, except the drainage volume, it showed no difference [MD -2.99, 95% CI= -19.75, 13.76, p < 0.73]. In secondary outcomes, it was favored only in mandibular numbness and return to normal diet outcomes. Additionally, TOETSMVA compared with COT showed a significant difference in drainage volume, pain, cosmetic effect, and satisfaction score. CONCLUSIONS: TOETSMVA showed a significant improvement compared to the TOETVA in operation time, hospital stay, number of resected lymph nodes, mandibular numbness, and return to normal diet but did not show a difference in drainage volume. However, TOETSMVA was better in cosmetic effect, drainage volume, satisfaction, and pain scores compared with COT. Further RCTs with larger sample size, multicentral, and longer follow-up are necessary to evaluate the limitations.
PubMed-ID: 38963576
DOI: 10.1007/s00423-024-03377-x
PMCID: PMC11224072

Efficacy and Safety of Multikinase Inhibitors for Patients With Refractory Thyroid Cancer: Systematic Review and Network Meta-Analysis.
J Clin Endocrinol Metab, 109(10):2658-72.
R. Jing, N. Wu, Y. Wu, Q. Zhang, Q. Liang, P. Huang and S. Yi. 2024.
CONTEXT: Multikinase inhibitors (MKIs) improve the treatment of refractory thyroid cancer, including radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) and advanced medullary thyroid carcinoma (aMTC). OBJECTIVE: This study aims to compare the efficacy of MKIs in improving survival outcomes and safety. DATA SOURCES: Comprehensive database searches of MEDLINE via PubMed, EMBASE, and Cochrane were performed from inception to December 2023. STUDY SELECTION: Three independent authors selected these studies. Randomized controlled trials that compared the use of a MKI to other MKIs or placebo were included. DATA EXTRACTION AND SYNTHESIS: This review followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Risk of bias was analyzed using the Cochrane risk of bias 2 tool. Bayesian network meta-analysis was performed. Treatments were grouped into common nodes based on the type of MKI. MAIN OUTCOMES AND MEASURES: Primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes included objective response rate, disease control rate, clinical benefit rate, and adverse events. RESULTS: Cabozantinib 60 mg/day (CAB60) was associated with the highest prolonged PFS in RAIR-DTC patients, followed by lentivatinib 18 or 24 mg/day (LEN18 or LEN24), and apatinib. PFS was also improved in aMTC patients who received CAB 140 mg/day (CAB140), CAB60, or anlotinib. A significantly greater improvement on the performance of OS was seen in CAB60, LEN24, anlotinib, and sorafenib in RAIR-DTC patients, but in aMTC patients there were lack of statistical differences. Compared with the low-dose MKIs, high-dose MKIs such as CAB, LEN, and vandetanib increased the incidence of adverse events. CONCLUSION: CAB60, LEN, and apatinib are promising topical MKIs with statistically significant primary outcomes in RAIR-DTC patients, while CAB and anlotinib are effective in prolonging PFS in aMTC patients.
PubMed-ID: 38970485
DOI: 10.1210/clinem/dgae454

Systematic review and meta-analysis of the use of high-energy devices for thyroid surgery.
Langenbecks Arch Surg, 409(1):217.
G. Montori, E. Botteri, M. Ortenzi, C. Gerardi, E. Allocati, A. Giordano, N. Vettoretto, A. Arezzo, B. Huo, C. Bergamini, M. Podda and F. Agresta. 2024.
BACKGROUND: We conducted a systematic review and meta-analysis to evaluate the role of High Energy Devices (HEDs) versus conventional clamp and tie technique in thyroidectomy. This work is endorsed by the Italian Society of Surgical Endoscopy (Italian Society of Endoscopic Surgery and new technologies-SICE) in the broader project on the evaluation of the role of HEDs in different surgical settings with the full health technology assessment report. MEHODS: Inclusion criteria were adult patients (>/= 18 years old) undergoing Thyroidectomy/Parathyroidectomy conducted with High Energy Devices (as ultrasonic (US), radiofrequency (RF), and hybrid energy (H-US/RF)) in the setting of thyroid surgery (both partial and total) for benign and malign diseases. However, some variability was found in included studies and described in the text. This systematic review and meta-analysis were performed according to the Cochrane handbook for systematic reviews, and the recommendations of the 2020 updated Preferred Reporting Items for Systematic reviews and Meta-

analyses (PRISMA) guidelines were pursuit. Selection of abstracts was performed in Ryyan system by 2 independent reviewers, and doubts were solved by another independent reviewer. At the end of literature research, Randomized controlled trials and observational studies were included. Risk of Bias was assessed with ROB2 for RCTs, and New Castle Ottawa Scale for Observational studies. RESULTS: The literature search yielded 47 studies, including 29 RCTs and 18 observational studies. Meta-analysis was performed for 29 randomized clinical trials. Outcomes included in the comparison between High Energy Devise and conventional technique groups were operative time, operative blood loss, overall post-operative drainage volume, length of stay, complications, and costs. HED significantly reduced operative time (28 studies, 3097patients; MD -128.8; 95% CI -34.4 to -23.20; I2 = 96%, p < 0.00001, Random-effect), intra-operative blood loss (13 studies, 642 vs 519 patients; SMD -0.82; 95% CI -1.33 to -0.32; I2 = 93%, p < 0.00001, Random-effect), LOS (22 studies, 2808 vs 2789 patients; MD -0.38, 95% CI -0.59 to -0.17; I2 = 98%, p < 0.00001 Random-effect), and healthcare costs (8 studies, 1138 vs 1129 patients, SMD 1.05; 95% CI -0.06 to 2.16; I2 = 99%, p < 0.00001 Random-effect). The rate of overall intraoperative complications was significantly different between both groups (25 studies, 2804 vs 2775 patients; RR 0.88, 95% CI 0.80 to 0.97; I2 = 38%, p = 0.03 Random-effect), but the sensitivity analysis did not find a statistically significant difference (6 studies, 605 vs 594 patients, RR; 95% CI to; I2 = 0%, p = 0.50, Random-effect). There was no difference in the subgroup analysis for the occurrence of transient and permanent RLN palsy, nor hematoma formation and hypocalcaemia. DISCUSSION: Though findings of our systematic review and metanalysis are limited by heterogeneous data, surgeons, hospital managers, and policymakers should note that the use of High Energy Devices compared to conventional clamp and tie technique have reduced operative times, intra-operative blood loss, length of stay, and hospital costs in patients underwent to tyroid surgery. Future work must explore issues of equity to mitigate barriers to patient access to safe thyroid surgical care and define better this initial results.
PubMed-ID: 39017727
DOI: 10.1007/s00423-024-03399-5

Feasibility of remote-access and minimally invasive video-assisted approaches in lateral neck dissection for papillary thyroid carcinoma: A systematic review and network meta-analysis.
Eur J Surg Oncol, 50(9):108469.
V. C. Nguyen, C. M. Song, Y. B. Ji, J. K. Myung, J. S. Park and K. Tae. 2024.
BACKGROUND: This study was conducted to evaluate the feasibility and surgical outcomes of minimally invasive video-assisted thyroidectomy (MIVAT) and three remote-access approaches, namely the robotic bilateral axillo-breast approach (BABA-R), endoscopic breast-chest approach (BCA-E), and robotic gasless transaxillary approach (GTAA-R) in lateral neck dissection for papillary thyroid carcinoma, compared with conventional transcervical approach (CTA). METHODS: The literature search was conducted in the PubMed, EMBASE, and Cochrane Library databases, covering the period January 2000 to February 2024. A systematic review and network meta-analysis were performed to compare surgical feasibility, safety, and oncologic outcomes between approaches. RESULTS: Fourteen articles on lateral neck dissection in patients with papillary thyroid carcinoma were included after systematic screening. The number of removed and metastatic lateral lymph nodes, the extent of lateral neck dissection, the rate of transient recurrent laryngeal nerve palsy and hypoparathyroidism, serum-stimulated thyroglobulin levels, and recurrence were not significantly different between the MIVAT and three remote-access approaches. Additionally, these were comparable to those of the CTA. However, the MIVAT and remote-access approaches took a longer operative time but provided superior cosmetic outcomes compared to the CTA. CONCLUSION: Lateral neck dissection using the MIVAT and three remote-access approaches was feasible and comparable to CTA in the number of lymph nodes removed, complications, stimulated thyroglobulin level, and recurrence. The MIVAT and remote-access approaches lasted longer but provided significantly superior cosmetic outcomes compared to the CTA.
PubMed-ID: 38865930
DOI: 10.1016/j.ejso.2024.108469

From Bench-to-Bedside: How Artificial Intelligence is Changing Thyroid Nodule Diagnostics, a Systematic Review.
J Clin Endocrinol Metab, 109(7):1684-93.
V. R. Sant, A. Radhachandran, V. Ivezic, D. T. Lee, M. J. Livhits, J. X. Wu, R. Masamed, C. W. Arnold, M. W. Yeh and W. Speier. 2024.
CONTEXT: Use of artificial intelligence (AI) to predict clinical outcomes in thyroid nodule diagnostics has grown exponentially over the past decade. The greatest challenge is in understanding the best model to apply to one's own patient population, and how to operationalize such a model in practice. EVIDENCE ACQUISITION: A literature search of PubMed and IEEE Xplore was conducted for English-language publications between January 1, 2015 and January 1, 2023, studying diagnostic tests on suspected thyroid nodules that used AI. We excluded articles without prospective or external

validation, nonprimary literature, duplicates, focused on nonnodular thyroid conditions, not using AI, and those incidentally using AI in support of an experimental diagnostic outside standard clinical practice. Quality was graded by Oxford level of evidence. EVIDENCE SYNTHESIS: A total of 61 studies were identified; all performed external validation, 16 studies were prospective, and 33 compared a model to physician prediction of ground truth. Statistical validation was reported in 50 papers. A diagnostic pipeline was abstracted, yielding 5 high-level outcomes: (1) nodule localization, (2) ultrasound (US) risk score, (3) molecular status, (4) malignancy, and (5) long-term prognosis. Seven prospective studies validated a single commercial AI; strengths included automating nodule feature assessment from US and assisting the physician in predicting malignancy risk, while weaknesses included automated margin prediction and interobserver variability. CONCLUSION: Models predominantly used US images to predict malignancy. Of 4 Food and Drug Administration-approved products, only S-Detect was extensively validated. Implementing an AI model locally requires data sanitization and revalidation to ensure appropriate clinical performance.
PubMed-ID: 38679750
DOI: 10.1210/clinem/dgae277
PMCID: PMC11180510

Three-year follow-up results of radiofrequency ablation for low-risk papillary thyroid microcarcinomas: Systematic review and meta-analysis.
Eur J Surg Oncol, 50(9):108470.
X. Xu, Y. Peng and G. Han. 2024.
OBJECTIVES: Confidence in long-term treatment results of radiofrequency ablation (RFA) for papillary thyroid microcarcinoma (PTMC) is required in comparison with surgery and active surveillance (AS). The objective of this meta-analysis is to report more than three years of follow-up results of radiofrequency ablation for PTMCs. METHODS: Ovid PUBMED, COCHRANE, and EMBASE databases were searched through Nov 19, 2023, for studies reporting outcomes in patients with PTMC treated with radiofrequency ablation and followed up for more than 3 years. The standard mean difference of the tumor volume before and after therapy, tumor recurrence, lymph node (LN) metastasis, distant metastasis, complications, and the pooled volume reduction rates (VRRs) at 1, 3, 6, 12, 24, 36, and 48 months after radiofrequency ablation were assessed. Data were extracted and methodological quality was assessed independently by two radiologists according to the PRISMA guidelines. RESULTS: Eight studies, involving 2131 patients, met the inclusion criteria through database searches. The overall VRR was 99.81 % (95 % CI: 99.68, 99.95) in the last follow-up. During a mean pooled follow-up of 46.59 months, 69 patients experienced local PTMC recurrence, with 8 cases within the ablation area. Additionally, 44 patients were diagnosed with newly discovered PTMC, and 17 patients exhibited lymph node metastases. Among the patients with PTMC recurrence, 3 were under active surveillance while 59 underwent additional RFA. The pooled mean complication rate was 2.80 %, with no instances of life-threatening or delayed complications. CONCLUSIONS: Radiofrequency ablation proves to be an effective local tumor control method for low-risk PTMC patients, resulting in clinically significant and enduring volume reduction. The rate of regrowth and retreatment requirement post-RFA was notably lower, positioning RFA as a compelling alternative to existing treatment options.
PubMed-ID: 38870871
DOI: 10.1016/j.ejso.2024.108470

Randomized controlled trials

Vandetanib in locally advanced or metastatic differentiated thyroid cancer refractory to radioiodine therapy.
Endocr Relat Cancer, 31(8)
M. S. Brose, J. Capdevila, R. Elisei, L. Bastholt, D. Fuhrer-Sakel, S. Leboulleux, I. Sugitani, M. H. Taylor, Z. Wang, L. J. Wirth, F. P. Worden, J. Bernard, P. Caferra, R. M. Colzani, S. Liu and M. Schlumberger. 2024.
The VERIFY study aimed to determine the efficacy of vandetanib in patients with differentiated thyroid cancer (DTC) that is either locally advanced or metastatic and refractory to radioiodine (RAI) therapy. Specifically, VERIFY is a randomized, double-blind, multicenter phase III trial aimed to determine the efficacy and safety of vandetanib in tyrosine kinase inhibitor-naive patients with locally advanced or metastatic RAI-refractory DTC with documented progression (NCT01876784). Patients were randomized 1:1 to vandetanib or placebo. The primary endpoint was progression-free survival (PFS). Secondary endpoints included best objective response rate, overall survival (OS), safety, and tolerability. Patients continued to receive randomized treatment until disease progression or for as long as they were receiving clinical benefit unless criteria for treatment discontinuation were met. Following randomization, 117 patients received

vandetanib, and 118 patients received a placebo. Median PFS was 10.0 months in the vandetanib group and 5.7 months in the placebo group (hazard ratio: 0.75; 95% CI: 0.55-1.03; P = 0.080). OS was not significantly different between treatment arms. Common Terminology Criteria for Adverse Events (CTCAE) of grade >/=3 were reported in 55.6% of patients in the vandetanib arm and 25.4% in the placebo arm. Thirty-three deaths (28.2%; one related to study treatment) occurred in the vandetanib arm compared with 16 deaths (13.6%; two related to treatment) in the placebo arm. No statistically significant improvement was observed in PFS in treatment versus placebo in patients with locally advanced or metastatic, RAI-refractory DTC. Moreover, active treatment was associated with more adverse events and more deaths than placebo, though the difference in OS was not statistically significant.
PubMed-ID: 38828895
DOI: 10.1530/ERC-23-0354
PMCID: PMC11301419

Impact of autofluorescence-guided surgery of parathyroid glands during total thyroidectomy in experienced surgeons: A randomized clinical trial.
World J Surg, 48(7):1710-20.
J. L. Carrillo Lizarazo, S. Bakkar, C. Zerrweck, M. M. Onofre Ramos, J. L. Kraimps and G. Donatini. 2024.
INTRODUCTION: Post-surgical hypoparathyroidism often occurs after total thyroidectomy (TT). The aim of this study is to investigate whether the use of near-infrared autofluorescence (NIRAF) of parathyroid glands (PGs) can aid experienced surgeons in identifying more PGs during surgery, potentially reducing unintended resection, and assessing its impact on post-surgical hypoparathyroidism. MATERIALS AND METHODS: All patients undergoing at least a TT by two experienced surgeons, between 2020 and 2021, were enrolled and randomized into two cohorts: NIRAF group (NG) and CONTROL group (CG). Transient hypoparathyroidism was defined by serum concentration of PTH<12 ng/mL at the 1st post-operative day and permanent by the need of calcium-active vitamin D treatment >6 months from the surgery with still undetectable PTH or <12 ng/m. RESULTS: Among 236 patients (111 in NG, 125 in CG), the number of PGs identified was higher in NG (93.9%, 417/444) compared to CG (81.4%, 407/500) ($p < 0.001$), with a mean of 3.76 +/- 0.44 PGs per patient in NG and 3.25 +/- 0.79 in CG. The number of unintendedly resected PGs was 14 in NG and 42 in CG ($p < 0.0001$). Transient hypoparathyroidism was observed in 18 patients (16.2%) in NG and 40 patients (32.0%) in CG ($p = 0.004$). Permanent hypoparathyroidism affected 1 patient in NG and 7 patients in CG ($p = 0.06$). The mean operative time was longer in NG (104.3 +/- 32.08 min) compared to CG (85.5 +/- 40.62 min) ($p < 0.001$). CONCLUSIONS: NIRAF enhances the identification of PGs, preventing their inadvertent resection and reducing the overall incidence of post-surgical hypoparathyroidism.
PubMed-ID: 38797994
DOI: 10.1002/wjs.12236

Role of Lugol solution before total thyroidectomy for Graves' disease: randomized clinical trial.
Br J Surg, 111(8):undefined-undefined.
D. Schiavone, F. Crimi, G. Cabrelle, G. Pennelli, D. Sacchi, C. Mian, F. Torresan and M. Iacobone. 2024.
BACKGROUND: Lugol solution is often administered to patients with Graves' disease before surgery. The aim is to reduce thyroid vascularization and surgical morbidity, but its real effectiveness remains controversial. The present study was designed to evaluate the effects of preoperative Lugol solution on thyroid vascularization and surgical morbidity in patients with Graves' disease undergoing total thyroidectomy. METHODS: Fifty-six patients undergoing total thyroidectomy for Graves' disease were randomly assigned to receive 7 days of Lugol treatment (Lugol+ group, 29) or no Lugol treatment (LS- group, 27) before surgery in this single-centre and single-blinded trial. Preoperative hormone and colour Doppler ultrasonographic data for assessing thyroid vascularization were collected 8 days before surgery (T0) and on the day of surgery (T1). The primary outcome was intraoperative and postoperative blood loss. Secondary outcomes included duration of surgery, thyroid function, morbidity, vascularization, and microvessel density at final pathology. RESULTS: No differences in demographic, preoperative hormone or ultrasonographic data were found between LS+ and LS- groups at T0. At T1, free tri-iodothyronine (FT3) and free thyroxine (FT4) levels were significantly reduced compared with T0 values in the LS+ group, whereas no such variation was observed in the LS- group. No differences between T0 and T1 were found for ultrasonographic vascularization in either group, nor did the histological findings differ. There were no significant differences between the LS+ and LS- groups concerning intraoperative/postoperative blood loss (median 80.5 versus 94 ml respectively), duration of surgery (75 min in both groups) or postoperative morbidity. CONCLUSION: Lugol solution significantly reduces FT3 and FT4 levels in patients undergoing surgery for Graves' disease, but does not decrease intraoperative/postoperative blood loss, thyroid vascularization, duration of surgery or postoperative morbidity. REGISTRATION NUMBER: NCT05784792 (https://www.clinicaltrials.gov).

PubMed-ID: 39129619
DOI: 10.1093/bjs/znae196

Effects of low-dose methotrexate with MMI in patients with Graves' disease: results of a randomized clinical trial.
J Clin Endocrinol Metab,
P. Xie, L. Shen, R. Peng, Y. Wang, Q. Yin, X. Chen, Z. Jin, G. Ning, W. Wang, S. Wang and Y. Zhou. 2024.
CONTEXT: Supplemental methotrexate (MTX) may affect the clinical course of Graves' disease (GD). OBJECTIVE: Evaluate efficacy of add-on MTX on medical treatment in GD. DESIGN: Prospective, open-label, randomized supplementation controlled trial. SETTING: Academic endocrine outpatient clinic. PATIENTS: One hundred and fifty-three untreated hyperthyroid patients with GD. INTERVENTION: Patients received MTX 10 mg/d with methimazole (MMI) or MMI only. MTX and MMI were discontinued at months 12-18 in euthyroid patients. MAIN OUTCOME MEASURES: Discontinuation rate at months 18 in each group. RESULTS: In the MTX with MMI group, the discontinuation rate was higher than the MMI group at months 15-18 (50.0 vs. 33.3%, P=0.043, 95% CI 1.020 to 3.922; and 55.6 vs 38.9%, P=0.045, 95%CI 1.011 to 3.815, respectively). The decrease in TRAb levels in the MTX with MMI group was significant from baseline to months 6 compared to the MMI alone group [MTX+MMI 67.22% (43.12-80.32), MMI 54.85% (33.18-73.76), P= 0.039) and became more significant from months 9 [MTX+MMI 77.79% (62.27-88.18), MMI 69.55% (50.50-83.22), P= 0.035] to months 18 (P < 0.01 in 15-18 months). A statistically significant difference between the levels of TRAb in the MTX with MMI group and the MMI group at 9-18 months. There were no significant differences in the levels of FT3, FT4 and TSH between two groups. No serious drug-related adverse events were observed in both groups(P=0.771). CONCLUSIONS: Supplemental MTX with MMI resulted in higher discontinuation rate and improvement in decreased TRAb levels to homeostatic levels faster than methimazole treatment alone at months 12-18.
PubMed-ID: 38994582
DOI: 10.1210/clinem/dgae472

Consensus Statements/Guidelines

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management.
Br J Surg, 111(8):undefined-undefined.
M. Raffaelli, N. Voloudakis, M. Barczynski, K. Brauckhoff, C. Durante, J. Gomez-Ramirez, I. Koutelidakis, K. Lorenz, O. Makay, G. Materazzi, R. Pandev, G. W. Randolph, N. Tolley, M. Vriens and T. Musholt. 2024.
PubMed-ID: 39158073
DOI: 10.1093/bjs/znae199
PMCID: PMC11331340

Other Articles

Cost-effectiveness of molecular testing for thyroid nodules with indeterminate cytology.
J Clin Endocrinol Metab,
S. Ahmadi and J. A. Sipos. 2024.
PubMed-ID: 38981077
DOI: 10.1210/clinem/dgae470

Nonoperative, Active Surveillance of Larger Malignant and Suspicious Thyroid Nodules.
J Clin Endocrinol Metab, 109(8):1996-2002.
B. Altshuler, A. Bikas, T. Pappa, E. Marqusee, N. L. Cho, M. A. Nehs, J. B. Liu, G. M. Doherty, I. Landa, S. Ahmadi and E. K. Alexander. 2024.
CONTEXT: Active surveillance for papillary thyroid cancer (PTC) meeting criteria for surgical resection is uncommon. Which patients may prove reasonable candidates for this approach is not well defined. OBJECTIVE: This work aimed to examine the feasibility and safety of active surveillance for patients with known or suspected intrathyroidal PTC up to 4 cm in

diameter. METHODS: A retrospective review was conducted of all consecutive patients who underwent nonoperative active surveillance of suspicious or malignant thyroid nodules over a 20-year period from 2001 to 2021. We included patients with an initial ultrasound-fine-needle aspiration confirming either (a) Bethesda 5 or 6 cytology or (b) a "suspicious" Afirma molecular test. The primary outcomes and measures included the rate of adverse oncologic outcomes (mortality and recurrence), as well as the cumulative incidence of size/volume growth. RESULTS: Sixty-nine patients were followed with active surveillance for 1 year or longer (average 55 months), with 26 patients (38%) having nodules 2 cm or larger. No patients were found to develop new-incident occurrence of lymph node or distant metastasis. One patient, however, demonstrated concern for progression to a dedifferentiated cancer on repeat core biopsy 17 years after initial start of nonoperative selection. A total of 21% of patients had an increase in maximum diameter more than 3 mm, while volume increase of 50% or greater was noted in 25% of patients. Thirteen patients ultimately underwent delayed (rescue) surgery, and no disease recurrence was noted after such treatment. Age and initial nodule size were not predictors of nodule growth. CONCLUSION: These data expand consideration of active surveillance of PTC in select patients with intrathyroidal suspected malignancy greater than 1 cm in diameter. Rescue surgery, if required at a later time point, appears effective.
PubMed-ID: 38349208
DOI: 10.1210/clinem/dgae082

The effect of adrenalectomy on overall survival in metastatic adrenocortical carcinoma.
J Clin Endocrinol Metab,
A. Assad, R. B. Incesu, S. Morra, L. Scheipner, A. Baudo, C. Siech, M. De Angelis, Z. Tian, S. Ahyai, N. Longo, F. K. H. Chun, S. F. Shariat, D. Tilki, A. Briganti, F. Saad and P. I. Karakiewicz. 2024.
CONTEXT: Although complete surgical resection provides the only means of cure in adrenocortical carcinoma (ACC), the magnitude of the survival benefit of adrenalectomy in metastatic ACC (mACC) is unknown. OBJECTIVE: To assess the effect of adrenalectomy on survival outcomes in patients with mACC in a real-world setting. DESIGN AND SETTING: Patients with mACC were identified within the Surveillance, Epidemiology, and End Results database (SEER 2004-2020) and we tested for differences according to adrenalectomy status. PATIENTS: Patients aged >/=18 years with metastatic ACC at initial presentation who were treated between 2004-2020. INTERVENTION: Primary tumor resection status (Adrenalectomy vs no-adrenalectomy). MAIN OUTCOME AND MEASURES: Kaplan-Meier plots, multivariable Cox regression models and landmark analyses were used. Sensitivity analyses focused on use of systemic therapy, contemporary (2012-2020) vs. historical (2004-2011), single vs. multiple metastatic sites and assessable specific solitary metastatic sites (lung only and liver only). RESULTS: Of 543 patients with mACC, 194 (36%) underwent adrenalectomy. In multivariable analyses, adrenalectomy was associated with lower overall mortality without (hazard ratio [HR]: 0.39; p<0.001), as well as with three months' landmark analyses (HR: 0.57, p=0.002). The same association effect with three months' landmark analyses was recorded in patients exposed to systemic therapy (HR: 0.49, p<0.001), contemporary patients (HR: 0.57, p=0.004), historical patients (HR: 0.42 , p<0.001), and in those with lung only solitary metastasis (HR: 0.50, p=0.02). In contrast, no significant association was recorded in patients naive to systemic therapy (HR: 0.68, p=0.3), those with multiple metastatic sites (HR: 0.55, p=0.07) and those with liver only solitary metastasis (HR: 0.98, p=0.9). CONCLUSIONS: The current results indicate a potential protective effect of adrenalectomy in mACC, particularly in patients exposed to systemic therapy and those with lung-only metastases.
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DOI: 10.1210/clinem/dgae571

The relation of recurrent laryngeal nerve to inferior thyroid artery and extralaryngeal nerve branching may increase the risk of vocal cord paralysis in thyroidectomy.
Langenbecks Arch Surg, 409(1):198.
N. Aygun, M. T. Unlu, O. Caliskan, M. Kostek, A. Isgor and M. Uludag. 2024.
PURPOSE: The anatomical variations of the recurrent laryngeal nerve (RLN) are common during thyroidectomy. We aimed to evaluate the risk of RLN paralysis in case of its anatomical variations, retrospectively. METHODS: The patients with primary thyroidectomy between January 2016 and December 2019 were enrolled. The effect of age, gender, surgical intervention, neuromonitorisation type, central neck dissection, postoperative diagnosis, neck side, extralaryngeal branching, non-RLN, relation of RLN to inferior thyroid artery (ITA), grade of Zuckerkandl tubercle on vocal cord paralysis (VCP) were investigated. RESULTS: This study enrolled 1070 neck sides. The extralaryngeal branching rate was 35.5%. 45.9% of RLNs were anterior and 44.5% were posterior to the ITA, and 9.6% were crossing between the branches of the ITA. The rate of total VCP was 4.8% (transient:4.5%, permanent: 0.3%). The rates of total and transient VCP were significantly higher in extralaryngeal branching nerves compared to nonbranching nerves (6.8% vs. 3.6%, p = 0.018; 6.8%

vs. 3.2%, p = 0.006, respectively). Total VCP rates were 7.2%, 2.5%, and 2.9% in case of the RLN crossing anterior, posterior and between the branches of ITA, respectively (p = 0.003). The difference was also significant regarding the transient VCP rates (p = 0.004). Anterior crossing pattern increased the total and transient VCP rates 2.8 and 2.9 times, respectively. CONCLUSION: RLN crossing ITA anteriorly and RLN branching are frequent anatomical variations increasing the risk of VCP in thyroidectomy that cannot be predicted preoperatively. This study is the first one reporting that the relationship between RLN and ITA increased the risk of VCP.
PubMed-ID: 38935142
DOI: 10.1007/s00423-024-03392-y
PMCID: PMC11211155

Approach to the Patient Considering Long-term Antithyroid Drug Therapy for Graves' Disease.
J Clin Endocrinol Metab, 109(10):e1881-e8.
F. Azizi, L. Mehran, H. Abdi and A. Amouzegar. 2024.
Antithyroid drugs (ATD) are the treatment of choice for the majority of patients with Graves' hyperthyroidism worldwide. However, relapse of hyperthyroidism after withdrawal of arbitrarily chosen conventional 12 to 18 months of therapy is very common. In the last 2 decades, many studies have shown that treatment with long-term ATD (LT-ATD) is effective and safe in the maintenance of euthyroidism. In addition, it has been reported that serum TSH receptor antibody may not decrease permanently before 5 to 6 years of ATD treatment, and clinical trials have shown that >/=5 years of ATD treatment is accompanied by remission in the majority of patients with Graves' hyperthyroidism. The objective of this article is to discuss the optimal time to withdraw of conventional ATD therapy, to illustrate the decision-making of the management of recurrent hyperthyroidism, to review the proper management of LT-ATD, and to generate suggestions for lifelong ATD treatment by discussing 4 scenarios of decision-making in patients with Graves' disease.
PubMed-ID: 39018185
DOI: 10.1210/clinem/dgae456

Hemithyroidectomy, does the indication influence the outcome?
Langenbecks Arch Surg, 409(1):1.
E. Beka, H. Hanna, P. Olofsson and O. Gimm. 2023.
PURPOSE: Hemithyroidectomies are mainly performed for two indications, either therapeutically to relieve compression symptoms or diagnostically for suspicious nodule(s). In case of the latter, one could consider the approach to be rather extensive since the majority of patients have no symptoms and will have benign disease. The aim of this study is to investigate the complication rates of diagnostic hemithyroidectomy and to compare it with the complication rates of compressive symptoms hemithyroidectomy. METHODS: Data from patients who had undergone hemithyroidectomy either for compression symptoms or for excluding malignancy were extracted from a well-established Scandinavian quality register (SQRTPA). The following complications were analyzed: bleedings, wound infections, and paresis of the recurrent laryngeal nerve (RLN). Risk factors for these complications were examined by univariable and multivariable logistic regression. RESULTS: A total of 9677 patients were included, 3871 (40%) underwent surgery to exclude malignancy and 5806 (60%) due to compression symptoms. In the multivariable analysis, the totally excised thyroid weight was an independent risk factor for bleeding. Permanent (6-12 months after the operation) RLN paresis were less common in the excluding malignancy group (p = 0.03). CONCLUSION: A range of factors interfere and contribute to bleeding, wound infections, and RLN paresis after hemithyroidectomy. In this observational study based on a Scandinavian quality register, the indication "excluding malignancy" for hemithyroidectomy is associated with less permanent RLN paresis than the indication "compression symptoms." Thus, patients undergoing diagnostic hemithyroidectomy can be reassured that this procedure is a safe surgical procedure and does not entail an unjustified risk.
PubMed-ID: 38062331
DOI: 10.1007/s00423-023-03168-w
PMCID: PMC10703970

Prognostic Analysis of 131I Efficacy After Papillary Thyroid Carcinoma Surgery Based on CT Radiomics.
J Clin Endocrinol Metab, 109(12):3036-45.
H. Cao, L. Shangguan, H. Zhu, C. Hu, T. Zhang, Z. Han and P. Wei. 2024.
OBJECTIVE: To develop and validate a radiomics-clinical combined model combining preoperative computed tomography (CT) and clinical data from patients with papillary thyroid carcinoma (PTC) to predict the efficacy of initial postoperative 131I treatment. METHODS: A total of 181 patients with PTC who received total thyroidectomy and initial 131I treatment were divided into training and testing sets (7:3 ratio). Univariate analysis and multivariate logistic regression were used to

screen clinical factors affecting the therapeutic response to 131I treatment and construct a clinical model. Radiomics features extracted from preoperative CT images of PTCs were dimensionally reduced through recursive feature elimination and least absolute shrinkage and selection operator. Logistic regression was used to establish a radiomics model, and a radiomics-clinical combined model was developed by integrating the clinical model. The area under the curve (AUC), sensitivity, and specificity were used to evaluate the prediction performance of each model. RESULTS: Multivariate analysis revealed that pre-131I treatment serum thyroglobulin was an independent clinical risk factor affecting the efficacy of initial 131I treatment (P = .002), and the AUC, sensitivity, and specificity for predicting the efficacy of initial 131I treatment were 0.895, 0.899, and 0.816, respectively. After dimensionality reduction, 14 key CT radiomics features of PTCs were included. The established radiomics model predicted the efficacy of 131I treatment in the training and testing sets with AUCs of 0.825 and 0.809, sensitivities of 0.828 and 0.636, and specificities of 0.745 and 0.944, respectively. The combined model improved the AUC, sensitivity, and specificity in both sets. CONCLUSION: The preoperative CT-based radiomics model can effectively predict the efficacy of initial postoperative 131I treatment in patients with intermediate- or high-risk PTC, and the radiomics-clinical combined model exhibits better predictive performance.
PubMed-ID: 38801437
DOI: 10.1210/clinem/dgae364
PMCID: PMC11570395

Pediatric Papillary Thyroid Carcinoma: Outcomes After Surgery Without Adjuvant Radioactive Iodine.
J Clin Endocrinol Metab,
L. E. Castellanos, M. E. Zafereo, E. M. Sturgis, J. R. Wang, A. K. Ying and S. G. Waguespack. 2024.
CONTEXT: Pediatric papillary thyroid carcinoma (PTC) is usually treated with total thyroidectomy followed by radioactive iodine (RAI). Recently, RAI is being used more selectively based on surgical pathology and postoperative dynamic risk stratification (DRS). OBJECTIVE: To describe patients with pediatric PTC not initially treated with RAI and their disease outcomes. METHODS: This was an ambispective study at a tertiary cancer center of patients < 19 years diagnosed from 1/1/1990 to 12/31/2021 with stage I PTC who intentionally were not treated with RAI within a year of diagnosis. We assessed clinical characteristics, management, and disease outcomes using DRS. RESULTS: Of 490 PTC patients, we identified 93 eligible patients (median age at diagnosis 16y; 87% female), including 46 (49%) with cervical lymph node metastases. Initial management included: total thyroidectomy +/- neck dissection (n=69, 75%), lobectomy +/- neck dissection (n=20, 21%), or a Sistrunk procedure for ectopic PTC (n=4, 4%). After a median follow-up of 5.5 years (range 1-26), most patients (85/93; 91%) remained disease-free with no further therapy. Persistent (n=5) or recurrent (n=3) disease was found in 9% of the entire cohort. Four patients ultimately received RAI, of which only one clearly benefited, and additional surgery was performed or planned in four patients, two of whom had an excellent response at last follow-up. CONCLUSIONS: Selected pediatric PTC patients, even those with lymph node metastases, may not require therapeutic 131I and can avoid the unnecessary risks of RAI while still benefitting from the excellent long-term outcomes that are well-described for this disease.
PubMed-ID: 39163248
DOI: 10.1210/clinem/dgae576

Paediatric thyroid disease.
Clin Endocrinol (Oxf), 101(3):223-33.
T. Cheetham and C. Wood. 2024.
The spectrum of thyroid disorders presenting to paediatricians is different to that seen by adult physicians. Referrals reflect cases detected by the neonatal screening programme for congenital hypothyroidism and many of the inherited defects of thyroid hormone generation or action will be manifest in early life. Autoimmune thyroid disease can be particularly challenging to manage in the young and the potential impact of thyroid status on neurodevelopment and schooling are key considerations throughout childhood and adolescence.
PubMed-ID: 39072866
DOI: 10.1111/cen.15110

Predicting papillary thyroid microcarcinoma in American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) 3 nodules: radiomics analysis based on intratumoral and peritumoral ultrasound images.
Gland Surg, 13(6):897-909.
Z. Chen, W. Zhan, H. He, H. Yu, X. Huang, Z. Wu and Y. Yang. 2024.
BACKGROUND: A subset of patients undergoing thyroid surgery for presumed benign thyroid disease presented with

papillary thyroid microcarcinoma (PTMC). A non-invasive and precise method for early recognition of PTMC are urgently needed. The aim of this study was to construct and validate a nomogram that combines intratumoral and peritumoral radiomics features as well as clinical features for predicting PTMC in the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) 3 nodules using ultrasonography. METHODS: A retrospective review was conducted on a cohort of 221 patients who presented with ACR TI-RADS 3 nodules. These patients were subsequently pathologically diagnosed with either PTMC or benign thyroid nodules. These patients were randomly divided into a training and test cohort with an 8:2 ratio for developing the clinical model, intratumor-region model, peritumor-region model and the combined-region model respectively. The radiomics features were extracted from ultrasound (US) images of each patient. We employed K-nearest neighbor (KNN) model as the base model for building the radiomics signature and clinical signature. Finally, a radiomics-clinical nomogram that combined intratumoral and peritumoral radiomics features as well as clinical features was developed. The prediction performance of each model was assessed by the area under the curve (AUC), sensitivity, specificity and calibration curve. RESULTS: A total of 23 radiomics features were selected to develop radiomics models. The combined-region radiomics model showed favorable prediction efficiency in both the training dataset (AUC: 0.955) and the test dataset (AUC: 0.923). A radiomics-clinical nomogram was constructed and achieved excellent calibration and discrimination, which yielded an AUC value of 0.950, a sensitivity of 0.950 and a specificity of 0.920. CONCLUSIONS: This study proposed the nomogram that contributes to the accurate and intuitive identification of PTMC in ACR TI-RADS 3 nodules.
PubMed-ID: 39015694
DOI: 10.21037/gs-24-30
PMCID: PMC11247584

PAPP-A as a Potential Target in Thyroid Eye Disease.
J Clin Endocrinol Metab, 109(12):3119-25.
C. A. Conover, L. K. Bale and M. N. Stan. 2024.
CONTEXT: Proptosis in thyroid eye disease (TED) can result in facial disfigurement and visual dysfunction. Treatment with insulin-like growth factor I receptor (IGF-IR) inhibitors has been shown to be effective in reducing proptosis but with side effects. OBJECTIVE: To test the hypothesis that inhibition of IGF-IR indirectly and more selectively with PAPP-A inhibitors attenuates IGF-IR signaling in TED. Informed consent was obtained from patients with TED undergoing surgery, and retro-orbital tissue was collected for fibroblast isolation and culture. Operations were performed in Mayo Clinic operating suites. Cell culture was performed in a sterile tissue culture facility. Retro-orbital tissue was collected from 19 patients with TED. METHODS: Treatment of TED fibroblasts with proinflammatory cytokines. Flow separation of CD34- and CD34+ orbital fibroblasts, the latter representing infiltrating fibrocytes into the orbit in TED. PAPP-A expression and proteolytic activity, IGF-I stimulation of phosphatidylinositol 3 kinase/Akt pathway, and inhibition by immuno-neutralizing antibodies against PAPP-A, CD34+ status, and associated PAPP-A and IGF-IR expression were measured. RESULTS: Proinflammatory cytokines markedly increased PAPP-A expression in TED fibroblasts. IGF-IR expression was not affected by cytokine treatment. Inhibition of PAPP-A's proteolytic activity suppressed IGF-IR activation in orbital fibroblasts from patients with TED. TED fibroblasts that were CD34+ represented approximately 80% of the cells in culture and accounted for approximately 70% of PAPP-A and IGF-IR-expressing cells. CONCLUSION: These results support a role for PAPP-A in TED pathogenesis and indicate the potential for novel therapeutic targeting of the IGF axis.
PubMed-ID: 38752390
DOI: 10.1210/clinem/dgae339
PMCID: PMC11570381

High prevalence of hypercalcitoninemia in a large cohort of adult and paediatric patients with PTH resistance syndromes.
J Clin Endocrinol Metab,
A. Cremaschi, G. Del Sindaco, A. Pagnano, A. Dolci, J. Berkenou, A. Rothenbuhler, A. Contarino, E. Ferrante, M. Arosio, E. Giannetta, A. Linglart and G. Mantovani. 2024.
BACKGROUND: Pseudohypoparathyroidism (PHP) refers to a group of rare hereditary disorders associated with resistance to parathormone (PTH) and other hormones now termed inactivating PTH/PTHrP disorders (iPPSD). Hypercalcitoninemia has been seldom reported in small series. Our aim was to investigate the characteristics of hypercalcitoninemia in paediatric and adult patients with PHP/iPPSD. METHODS: We retrospectively collected data from two cohorts from two European Endocrinology tertiary centers: the paediatric cohort comprised 88 children with available calcitonin (CT) measurements; the adult cohort included 43 individuals with simultaneous CT and PTH measurements. RESULTS: In the paediatric cohort 65.9% had hypercalcitoninemia (median CT 15 ng/L); in the adult cohort 53.5% (mean CT 21.6 ng/L). There was no difference between CT in paediatric and adult population; we observed stable CT levels over a median follow-up of 134.5 months in adults. Notably, no correlations were detected between CT and PTH levels. Other etiologies of hypercalcitoninemia were excluded, adult patients underwent regular thyroid ultrasound (US) to screen for medullary thyroid cancer (MTC). We performed 20 calcium stimulation tests in adult patients. While there was a significant difference in basal and peak CT between our patients, healthy subjects and subjects with MTC, there was no difference with patients with C-cell hyperplasia. CONCLUSIONS: This study underscores the common occurrence of hypercalcitoninemia in both paediatric and adult PHP/iPPSD patients, in particular with subtypes iPPSD2-iPPSD3. Furthermore, these patients show an hyperresponsiveness to calcium stimulation test falling between healthy subjects and patients with MTC. These findings contribute into the understanding of CT dynamics in the context of PHP/iPPSD.
PubMed-ID: 38940443
DOI: 10.1210/clinem/dgae416

The methodological and reporting quality of randomized controlled trials of tyrosine kinase inhibitors for advanced differentiated thyroid cancer: Meta-research study.
Head Neck, 46(7):1683-97.
R. A. Dedivitis, M. A. F. Castro, A. M. D. Boni, A. C. B. Alvares, A. J. P. Tresso, A. D. Oliveira, A. Vieira, F. A. Mendes, G. O. Rossi, G. N. Fava, I. S. Pouza, I. P. Santana, J. G. Laino, L. B. Lima and A. L. C. Martimbianco. 2024.
INTRODUCTION: Clinical trials on tyrosine kinase inhibitors (TKI) treatment have shown an improvement in overall and progression-free survival in patients with advanced differentiated thyroid cancer. However, it is necessary to evaluate these studies to assess methodological biases and inconsistencies that may impact the effects. OBJECTIVE: To map and assess the methodological quality of randomized clinical trials (RCTs) regarding randomization, allocation concealment, blinding, and selective reporting bias. METHODS: RCTs assessing the efficacy and safety of TKI for the treatment of advanced differentiated thyroid cancer were included. The search was performed in the MEDLINE database. The included RCTs were assessed for the adequacy of the methodological steps, as recommended by the Cochrane Risk of Bias tool. RESULTS: Nine studies were analyzed, of which 77.7% were classified as low risk of bias regarding selective reporting and 33.3% as high risk of reporting bias. The mean time between protocol registration and study publication was approximately 5.11 years. Moreover, 66.7% were classified as low risk of bias for randomization and allocation concealment, and 33.3% did not specify the randomization process and allocation concealment in a way that would allow the identification of occurrences of bias. Concerning blinding of participants and outcome assessors, 77.8% of the RCTs reported adequate blinding and were classified as having a low risk of bias, 11.1% had a high risk of bias, and 11.1% had insufficient information and were classified as having unclear risk of bias. Regarding the blinding of the outcome assessors, 33.3% did the blinding correctly, 11.1% did not blind, and 55.6% did not provide enough information. CONCLUSION: Overall, the assessed RCTs were predominantly at low risk of bias. The critical evaluation of these studies is essential to have confidence in the treatment estimated effect that will support clinical decision-making and provide information to preclude future clinical study flaws.
PubMed-ID: 38344932
DOI: 10.1002/hed.27679

Racial-Ethnic Comparison of Treatment for Papillary Thyroid Cancer in the Military Health System.
Ann Surg Oncol, 31(12):8196-205.
Y. L. Eaglehouse, S. Darmon, C. D. Shriver and K. Zhu. 2024.
PURPOSE: We aimed to compare Asian or Pacific Islander, Black, Hispanic, and non-Hispanic White patients in treatment for papillary thyroid cancer (PTC) in the equal access Military Health System to better understand racial-ethnic cancer

health disparities observed in the United States. METHODS: We used the MilCanEpi database to identify a cohort of men and women aged 18 or older who were diagnosed with PTC between 1998 and 2014. Low- or high-risk status was assigned using tumor size and lymph node involvement. Treatment with surgery (e.g., thyroidectomy) overall and treatment by risk status [active surveillance (low-risk) or adjuvant radioactive iodine (RAI) (high-risk)] was compared between racial-ethnic groups using multivariable logistic regression and expressed as adjusted odds ratios (AOR) with 95% confidence intervals (CIs). RESULTS: The study included 598 Asian, 553 Black, 340 Hispanic, and 2958 non-Hispanic White patients with PTC. Asian (AOR = 1.21, 95% CI 0.98, 1.49), Black (AOR = 1.07, 95% CI 0.87, 1.32), and Hispanic (AOR = 0.92, 95% CI 0.71, 1.19) patients were as likely as White patients to receive surgery. By risk status, there were no significant racial-ethnic differences in receipt of active surveillance or thyroidectomy for low-risk PTC or in thyroidectomy or total thyroidectomy with adjuvant RAI for high-risk PTC. CONCLUSIONS: In the Military Health System, where patients have equal access to care, there were no overall racial-ethnic differences in surgical treatment for PTC. As American Thyroid Association guidelines evolve to include more conservative treatment, further research is warranted to understand potential disparities in active surveillance and surgical management in U.S. healthcare settings.
PubMed-ID: 39085551
DOI: 10.1245/s10434-024-15941-2

Tumor microenvironment in thyroid cancer: Immune cells, patterns, and novel treatments.
Head Neck, 46(6):1486-99.
B. Febrero, J. J. Ruiz-Manzanera, I. Ros-Madrid, A. M. Hernandez, E. Orenes-Pinero and J. M. Rodriguez. 2024.
The tumor immune microenvironment of thyroid cancer is the heterogeneous histological space in which tumor cells coexist with host cells. Published data from this review were identified by search and selection database of Pubmed, Elsevier, and Science Direct. Searching was made in two steps using different keywords. In thyroid pathology, the inflammatory response is very important, and might have a key role finding new diagnostic and therapeutic methods, particularly in thyroid cancer. Different immune cells may be more or less present in different types of thyroid cancer and may even have different functions, hence the importance of knowing their presence in different thyroid tumor pathologies. Cancer-related inflammation could be a useful target for new diagnostic and therapeutic strategies by analyzing peritumoral and intratumoral immune cells in different types of thyroid tumors. Moreover, novel strategies for thyroid cancer treatments, such as monoclonal antibodies targeting checkpoint inhibitors, are emerging as promising alternatives.
PubMed-ID: 38380767
DOI: 10.1002/hed.27695

Second Primary Differentiated Thyroid Carcinoma in Adult Cancer Survivors: A SEER Database Analysis.
J Clin Endocrinol Metab,
J. Feng, C. Wu, F. Shen, W. Cai and B. Xu. 2024.
CONTEXT: Adult cancer survivors are at a heightened risk for secondary primary differentiated thyroid carcinoma (2-DTC). The characteristics and outcomes of 2-DTC remain poorly understood. OBJECTIVE: We aim to explore the characteristics and outcomes of 2-DTC. METHODS: We retrospectively analyzed data from the SEER database (2000-2017). 2-DTC was divided into 25 subgroups based on the prior primary malignancies (PPMs). Baseline characteristics were compared using the Chi-square test. Multivariable logistic analysis was used to identified if PPMs associated with aggressive DTC characteristics. DTC-specific and cancer-specific mortality were analyzed using univariable and multivariable competing risk regression model. RESULTS: There were 138,555 1-DTC and 9,253 2-DTC patients were identified. 2-DTC patients were predominantly older, male, and white compared to first primary DTC (1-DTC) (all $P < 0.05$). In multivariable logistic regression analysis, only four types of PPMs were associated with higher rates of DTC aggressive characteristics, while 19 types exhibited lower rates (all $P < 0.05$). In multivariable competing risk analysis, 2-DTC showed no mortality risk in stages I (SHR: 1.16, 95% CI: 0.65-2.07) and II (SHR: 0.67, 95% CI: 0.45-1.01), but a protective role in stages III (SHR: 0.47, 95% CI: 0.27-0.83) and IV (SHR: 0.72, 95% CI: 0.52-0.99). Most PPMs that developed into 2-DTC had a lower risk of DTC-specific death than 1-DTC, but many PPMs had a higher risk of cancer-specific death. CONCLUSIONS: Given the characteristics and outcomes of 2-DTC, aggressive treatment for 2-DTC, particularly for PPM with a high mortality risk, may not be advisable.
PubMed-ID: 39047061
DOI: 10.1210/clinem/dgae501

Association of Free Thyroxine with Progression-Free Survival in Intermediate and High Risk Differentiated Thyroid Cancer.
J Clin Endocrinol Metab,
R. Ghosh, S. Auh, S. Gubbi, P. Veeraraghavan, C. Cochran, L. Shobab, M. L. Urken, K. D. Burman, L. Wartofsky and J. Klubo-Gwiezdzinska. 2024.
CONTEXT: Supraphysiologic thyroxine (T4) doses are used in intermediate and high-risk patients with differentiated thyroid cancer (IR/HR-DTC) to suppress tumor progression by thyrotropin (TSH). However, preclinical data suggest that T4 can also act as a growth stimulus for cancer, but there is no clinical evidence supporting this claim. OBJECTIVE: We analyzed the association between free T4 (FT4) and progression-free survival (PFS) in patients with IR/HR-DTC. METHODS: This longitudinal cohort study, approved by multi-institutional review board, included patients with IR/HR-DTC treated uniformly with total thyroidectomy, radioiodine (RAI), and TSH suppression therapy, with at least three TSH and FT4 values available. Association between FT4 and PFS at landmarks 6, 12, and 18 months was assessed by Kaplan-Meier survival curves, while competing risks were assessed through Cox proportional hazards model. RESULTS: From 739 screened patients 382 met the inclusion criteria and were characterized by a median age of 46 (34-59) years, 64.1% women, treated with a median RAI dosage of 159 (110-410) mCi. During follow up of 7.1 (3.4-12.7) years 34.6% experienced disease progression.Elevated FT4, observed in 29.3% of patients, was not associated with worse PFS (HR 0.9, CI 0.54-1.5, p=0.69), while age (HR 1.02, CI 1.004-1.04, p=0.01), tumor size (HR 1.15, CI 1.04-1.28, p=0.01), and metastases to the lateral neck lymph nodes (HR 2.9, CI 1.7-4.74, p<0.001), bones (HR 4.87, CI 1.79-13.3, p=0.002), and brain (HR 5.56, CI 2.54-12.2, p<0.001) were associated with shorter PFS. CONCLUSIONS: Contrary to preclinical evidence, elevated FT4 levels do not affect PFS in patients with IR/HR-DTC.
PubMed-ID: 39115341
DOI: 10.1210/clinem/dgae537

Racial implications of time to surgery in disparities in thyroid cancer survival.
Am J Surg, 234:85-91.
A. Gillis, P. Zmijewski, M. C. McLeod, B. Lindeman, J. Fazendin, H. Chen and S. Bhatia. 2024.
INTRODUCTION: The influence of time to surgery on racial/ethnic disparities in papillary thyroid carcinoma (PTC) survival remains unstudied. MATERIALS AND METHODS: The National Cancer Database (2004-2017) was queried for patients with localized PTC. Survival data was compared by time to surgery, patient demographics, and multivariable Cox regression was performed. RESULTS: Of 126,708 patients included, 5% were Black, 10% Hispanic. Of all patients, 85% had no comorbidities. Non-Hispanic White (NHW) patients had a shorter median time to surgery than Black and Hispanic patients (36 vs. 43 vs. 42 days, respectively p < 0.001). In multivariable analysis, longer time to surgery (>90 days vs < 30 days) and Black race vs NHW, were associated with worse survival (HR: 1.56, (95%CI, 1.43-1.70), p < 0.001 and HR: 1.21, (1.08-1.36), p = 0.001), respectively. CONCLUSION: Delaying surgery for thyroid cancer is associated with worse survival. However, independent of time to surgery and other confounders, there remains a disparity as black patients have poorer outcomes.
PubMed-ID: 38519403
DOI: 10.1016/j.amjsurg.2024.02.002
PMCID: PMC11585253

Revisiting the Relationship Between Tumor Size and Risk in Well-Differentiated Thyroid Cancer.
Thyroid, 34(8):980-9.
S. P. Ginzberg, J. Sharpe, J. E. Passman, W. Amjad, C. J. Wirtalla, J. M. Soegaard Ballester, C. B. Finn, S. J. Mandel, R. R. Kelz and H. Wachtel. 2024.
Introduction: Large tumor size is associated with poorer outcomes in well-differentiated thyroid cancer, yet it remains unclear whether size >4 cm alone confers increased risk, independent of other markers of aggressive disease. The goal of this study was to assess the relationship between tumor size, other high-risk histopathological features, and survival in well-differentiated thyroid cancer and to evaluate the significance of 4 cm as a cutoff for management decisions. Methods: Patients with well-differentiated thyroid cancer were identified from the National Cancer Database (2010-2015) and categorized by tumor size (i.e., small [</=4 cm] or large [>4 cm]) and presence of high-risk histopathological features (e.g., extrathyroidal extension). First, propensity score matching was used to identify patients who were similar across all other observed characteristics except for small versus large tumor size, and a multivariable Cox proportional hazards model was used to estimate the relationship between tumor size and survival. Second, we assessed whether the presence of high-risk features demonstrates conditional effects on survival based on the presence of tumor size >4 cm using an interaction term. Finally, additional models assessed the relationship between incremental 1 cm increases in tumor size and survival. Analyses were repeated using a validation cohort from the Surveillance, Epidemiology, and End Results

Program (2008-2013). Results: Of 193,133 patients in the primary cohort, 7.9% had tumors >4 cm, and 30% had at least one high-risk feature. After matching, tumor size >4 cm was independently associated with worse survival (HR 1.63, p < 0.001). However, tumor size >4 cm and one or more other high-risk features together yielded worse survival than either size >4 cm alone (MMD: 0.70, p < 0.001) or other high-risk features alone (MMD: 0.49, p < 0.001). When assessed in 1 cm increments, the largest increases in hazard of death occurred at 2 cm and 5 cm, not 4 cm. Results from the validation cohort were largely consistent with our primary findings. Conclusions: Concomitant high-risk features confer worse survival than large tumor size alone, and a 4 cm cutoff is not associated with the greatest increase in risk. These findings support a more nuanced approach to tumor size in the management of well-differentiated thyroid cancer.
PubMed-ID: 38877803
DOI: 10.1089/thy.2023.0327

The Role of Age in the Risk Assessment of Differentiated Thyroid Cancers.
J Clin Endocrinol Metab, 109(8):e1673-e4.
W. Goldner. 2024.
PubMed-ID: 38118019
DOI: 10.1210/clinem/dgad743

The pathologist counts-so many variables in the risk stratification of thyroid cancers.
J Clin Endocrinol Metab,
G. Grani. 2024.
PubMed-ID: 38776230
DOI: 10.1210/clinem/dgae360

Oncocytic carcinoma of the thyroid: Conclusions from a 20-year patient cohort.
Head Neck, 46(8):2042-7.
N. R. Gruszczynski, S. S. Hasan, A. G. Brennan, J. De La Chapa, A. S. Reddy, D. N. Martin, P. P. Batchala, E. B. Stelow, E. M. Dowling, K. L. Fedder, J. C. Garneau and D. C. Shonka, Jr. 2024.
BACKGROUND: Oncocytic carcinoma (OCA) was recently reclassified as a distinct differentiated thyroid carcinoma (DTC). Given its rarity, OCA studies are limited. This study describes the characteristics of OCA in a 20-year cohort. METHODS: Retrospective analysis of patients with OCA at a single tertiary care hospital from 2000 to 2021. RESULTS: Fifty-one OCA patients (22M:29F) were identified. The mean age at diagnosis was 60.3 years; 90% presented as palpable mass; 24% had a family history of thyroid cancer. None had vocal fold paresis. On ultrasound, most tumors were solid and hypoechoic. FNA (n = 14) showed Bethesda-4 lesions in 93%. All were treated surgically. Histologically, 63% demonstrated angioinvasion, 35% had lymphovascular invasion, and 15% had extrathyroidal extension. Radioactive iodine was used as adjunct therapy in 77%. CONCLUSION: OCA has distinct features that distinguish it from other DTCs, and additional focused studies will help clarify the aggressive nature, treatment options, and prognosis of the disease.
PubMed-ID: 38390640
DOI: 10.1002/hed.27700

Young and resilient: Unraveling papillary thyroid cancer outcomes in males under 40.
World J Surg, 48(5):1190-7.
C. Hood, P. V. Zmijewski, M. C. McLeod, B. Herring, D. Bahl, J. Fazendin, B. Lindeman, H. Chen and A. Gillis. 2024.
BACKGROUND: While males present with more adverse clinicopathologic features in papillary thyroid carcinoma (PTC), younger age has previously been shown to be a favorable prognostic factor. We examined the combined effect of male sex and young age on PTC outcomes. METHODS: We conducted a retrospective analysis of a prospectively maintained database of thyroid cancer surgery patients (2000-2020) at a single quaternary care institution. We included papillary thyroid carcinoma cases and excluded those with prior cancer-related thyroid surgery. We examined demographics, cancer stage, surgical outcomes, and complications by age and sex, analyzing groups below and above the age of 40 years. RESULTS: A total of 680 patients with PTC were included. Females constituted 68% (age >/=40 years: 44% and <40 years: 24%) and males 32% (>/=40 years: 24% and <40 years: 8%). A significant difference (p < 0.001) of N1 disease distribution was found between the groups. N1a metastasis was greater in patients younger than 40 regardless of sex ((M < 40 (15%), F < 40 (15%), M >/= 40 (12%), and F >/= 40 (9%)). While, M < 40 had greater N1b metastasis (36%) than all other groups (M >/= 40 (28%), F < 40 (22%), and F >/= 40 (10%)). There was no significant difference in the distribution of T stages between groups. Groups showed no differences in 30-day outcomes, recurrence at 1 year, reoperation, mortality, nerve injury, or hypocalcemia. CONCLUSIONS: Young males with PTC face increased occurrence of nodal metastasis yet experience similar

recurrence rates as their female and older counterparts. Subgroup analysis underscores the predictive role of sex and age in advanced PTC cases.
PubMed-ID: 38517350
DOI: 10.1002/wjs.12151

Noninvasive monitoring of the vagus nerve during thyroid surgery using cutaneous adhesive and needle electrodes: What is the optimal configuration?
Head Neck, 46(8):1893-901.
A. S. Karcioglu, L. N. Trinh, D. McLlroy, O. C. Okose, B. Wang, I. J. Behr, A. Y. Cheung, A. Srikanthan, M. D. Russell, D. Kamani, A. H. Abdelhamid Ahmed and G. W. Randolph. 2024.
OBJECTIVE: Endotracheal tube (ETT) surface electrodes are used to monitor the vagus nerve (VN), recurrent laryngeal nerve (RLN), and external branch of the superior laryngeal nerve (EBSLN) during thyroid and parathyroid surgery. Alternative nerve monitoring methods are desirable when intubation under general anesthesia is not desirable or possible. In this pilot study, we compared the performance of standard ETT electrodes to four different noninvasive cutaneous recording electrode types (two adhesive electrodes and two needle electrodes) in three different orientations. METHODS: The VN was stimulated directly during thyroid and parathyroid surgery using a Prass stimulator probe. Electromyographic (EMG) responses for each patient were recorded using an ETT plus one of the following four cutaneous electrode types: large-foot adhesive, small-foot adhesive, long-needle and short-needle. Each of the four electrode types was placed in three orientations: (1) bilateral, (2) ipsilateral mediolateral, and (3) ipsilateral craniocaudal. RESULTS: Four surgical cases were utilized for data collection with the repetitive measures obtained in each subject. Bilateral electrode orientation was superior to ipsilateral craniocaudal and ipsilateral mediolateral orientations. Regardless of electrodes type, all amplitudes in the bilateral orientation were >100 muV. When placed bilaterally, the small-foot adhesive and the long-needle electrodes obtained the highest EMG amplitudes as a percentage of ETT amplitudes. CONCLUSION: Cutaneous electrodes could potentially be used to monitor the VN during thyroid and parathyroid procedures. Different electrode types vary in their ability to record amplitudes and latencies. Bilateral orientation improves EMG responses in all electrode types. Additional validation of cutaneous electrodes as an alternative noninvasive method to monitor the VN is needed.
PubMed-ID: 38294128
DOI: 10.1002/hed.27669

Reoperation Rates After Initial Thyroid Lobectomy for Patients with Thyroid Cancer: A National Cohort Study.
Thyroid, 34(8):1007-16.
M. Kheng, A. Manzella, J. C. Chao, A. M. Laird and T. Beninato. 2024.
Introduction: The 2015 American Thyroid Association (ATA) guidelines recommended thyroid lobectomy (TL) as an alternative to total thyroidectomy (TT) for the surgical treatment of low-risk differentiated thyroid cancer. Increasing use of TL has since been reported despite concerns for an increased risk of disease recurrence and need for reoperation. This study sought to compare reoperation rates among patients who underwent initial TL or TT for malignancy, characterize trends at centers based on operative volume, and examine factors associated with reoperation. Methods: We queried the Vizient Clinical Data Base for TL and TT performed preguideline change (pre-GC = 2013-2015) and postguideline change (post-GC = 2016-2021). Reoperations included reoperative thyroid surgery (RTS) and neck dissection (ND); timing was defined as early (</=180 days), thought to indicate inadequacy of initial operative choice, or late (>180 days), suggesting potential disease recurrence. Results: Of 65,627 patients, 31.8% underwent initial TL and 68.2% underwent initial TT; TL increased from 21.4% of total cases pre-GC to 37.0% post-GC ($p < 0.001$). Among TL patients, early RTS declined from 33.9% to 14.2% and ND declined from 0.8% to 0.4% ($p < 0.001$). Among TT patients, early RTS remained 0.2%, while ND increased from 0.4% to 0.7% ($p < 0.001$). TL-associated late RTS declined from 2.0% to 1.7%, while ND increased from 0.6% to 0.8% ($p = 0.17$). In TT patients, both late RTS and ND increased, from 0.2% to 0.3% ($p = 0.04$) and 1.7% to 2.1% ($p < 0.01$), respectively. There was no difference in the late reoperation rate for TL compared with TT post-GC (+0.2%, $p = 0.18$). TL volume grew annually by 12.5% [8.9-16.2%] at high-volume centers (HVCs) and 8.3% [5.6-11.1%] at low-volume centers (LVCs). TL-associated reoperations at HVCs declined annually by 12.6% [5.6-19.0%] and 10.8% [2.7-18.1%] at LVCs. Uninsured status and more recent initial operation were associated with an increased risk of late reoperation (HR = 1.84 [1.06-3.20] and HR = 1.30 [1.24-1.36], respectively). The type of index operation performed, however, was not predictive of late reoperation. Conclusions: The rate of early reoperations declined for TL after the 2015 ATA guideline release, but late reoperations remained unchanged despite a significant shift in practice patterns towards initial lobectomy. Patients appear to be receiving less aggressive, guideline-concordant care without a significant increase in the late reoperation rate for TL compared with TT.

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Longitudinal Changes in Quality of Life Before and After Thyroidectomy in Patients With Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 109(6):1505-16.
B. H. Kim, S. R. Ryu, J. W. Lee, C. M. Song, Y. B. Ji, S. H. Cho, S. H. Lee and K. Tae. 2024.
OBJECTIVE: The objective of this prospective study was to assess longitudinal variations in health-related quality of life (HR-QOL) in patients diagnosed with differentiated thyroid cancer (DTC) before and after thyroidectomy. METHODS: A cohort of 185 DTC patients who underwent thyroidectomy between January 2013 and December 2017 and who completed all necessary questionnaires was evaluated. Their HR-QOL was gauged using the University of Washington Quality of Life questionnaire (UW-QOL) and the City of Hope Quality of Life-Thyroid Version questionnaire (QOL-TV) both prior to surgery and at 3 months, 6 months, 1 year, 2 years, 3 years, and 5 years postoperatively. RESULTS: Out of 185 patients, 150 (81.1%) were female, with an average age of 48.7 +/- 12.9 years. For both UW-QOL and QOL-TV, the total composite QOL scores notably declined from preoperative levels to 3 months postoperatively, then gradually improved over 5 years, ultimately exceeding preoperative scores. Factors such as total thyroidectomy, radioactive iodine (RAI) ablation, and postoperative hypoparathyroidism were associated with lower physical composite QOL scores. Patients who underwent remote-access thyroidectomy expressed significantly higher satisfaction with appearance compared with those who had conventional thyroidectomy. Mood and anxiety were major clinical concerns both before and after surgery, showing considerable improvement postoperatively. CONCLUSION: For DTC patients, HR-QOL experienced a significant drop 3 months postsurgery, subsequently showing gradual improvement, surpassing preoperative QOL by 5 years. Factors contributing to improved physical QOL included the utilization of remote-access thyroidectomy, less extensive thyroidectomy, and the absence of RAI ablation and hypoparathyroidism.
PubMed-ID: 38141213
DOI: 10.1210/clinem/dgad748

The role of the tumor microenvironment in papillary thyroid microcarcinoma nodal metastasis.
Endocr Relat Cancer, 31(8)
M. Kim, C. H. Kwon and B. H. Kim. 2024.
The genetic alterations currently identified in papillary thyroid microcarcinomas (PTMCs) are insufficient for distinguishing tumors with aggressive features. We aimed to identify candidate markers associated with lateral lymph node metastasis (LLNM, N1sb disease) in patients with PTMC using transcriptomic analysis. RNA sequencing was performed on 26 matched tumor and normal thyroid tissue samples (N0, n = 14; N1b, n = 12), followed by functional enrichment analyses of differentially expressed genes (DEGs). EcoTyper was used to explore the distinct tumor microenvironment (TME). We identified 631 DEGs (213 upregulated and 418 downregulated) between N1b and N0 PTMCs. The most significantly upregulated genes in N1b were associated with tumorigenesis, adhesion, migration, and invasion. DEGs were mainly enriched in the pathways of idiopathic pulmonary fibrosis, TME, wound healing, and inhibition of matrix metalloproteases. We predicted the activation of these pathways in N1b PTMCs. N1b PTMCs had a unique TME with abundant fibroblasts and epithelial cells, associated with an increased risk of disease progression. Fibroblast marker genes, including POSTN, MMP11, TNFAIP6,and FN1, and epithelial cell marker genes, including NOX4, MFAP2, TGFVBI,and TNC, were selected. POSTN and FN1, fibroblast cell-specific genes, and NOX4 and TNC, epithelial cell-specific genes, were promising biomarkers for predicting LLNM development and recurrence in patients with PTMC. We delineated the cellular ecotypes within the TME of patients with N1b PTMC and revealed potential markers for predicting LLNM and the prognosis of PTMC. These findings provide valuable insights into the contributions of cancer-associated fibroblasts and epithelial cells to PTMC progression and metastasis.
PubMed-ID: 38768280
DOI: 10.1530/ERC-24-0040

Cabozantinib plus ipilimumab/nivolumab in patients with previously treated advanced differentiated thyroid cancer.
J Clin Endocrinol Metab,
B. Konda, E. J. Sherman, E. Massarelli, J. Nieva, J. Muzaffar, J. C. Morris Iii, M. Ryder, A. L. Ho, M. Agulnik, L. Wei, D. Handley, C. Moses, R. Jacob, J. Wright, H. Streicher, W. Carson and M. H. Shah. 2024.
BACKGROUND: This investigator-initiated phase II trial aimed to evaluate the efficacy of cabozantinib in combination with nivolumab and ipilimumab (CaboNivoIpi) in previously treated patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) (NCT03914300). METHODS: Eligible patients with RAI-refractory DTC who progressed on 1 prior line of VEGFR-targeted therapy received a 2-week run-in of cabozantinib monotherapy followed by CaboNivoIpi

for 4 cycles (cycle length = 6 weeks), followed by cabozantinib plus nivolumab (cycle length = 4 weeks) until disease progression. The primary endpoint was objective response rate (ORR) within the first 6 months of treatment. A Simon optimal 2-stage design allowed for an interim analysis after accrual of 10 evaluable patients. At least 5 responses were needed to proceed to stage 2. RESULTS: Among 11 patients enrolled, the median age was 69 years. Prior VEGFR-targeted therapies included lenvatinib, pazopanib, and sorafenib plus everolimus. Median follow-up was 7.9 months. Among 10 evaluable patients, ORR within the first 6 months of treatment was 10% (1 partial response). Median progression-free survival was 9 months [95% CI: 3.0, not reached] and median overall survival was 19.2 months [(95% CI: 4.6, not reached]. Grade 3/4 treatment-related adverse events (AEs) were noted in 55% (6/11) and grade 5 AEs in 18% (2/11) of patients. The most common treatment-related AE was hypertension. The study did not reach its prespecified efficacy threshold. CONCLUSION: CaboNivoIpi had low ORRs and a high rate of grade >/=3 treatment-related AEs. CLINICAL TRIAL REGISTRATION: NCT03914300.
PubMed-ID: 39133806
DOI: 10.1210/clinem/dgae512

Tracheal reconstruction using stented aortic matrices in advanced thyroid cancer.
Br J Surg, 111(6):undefined-undefined.
P. Kuczma, D. M. Radu, I. Onorati, C. Ghander, C. Buffet, L. Leenhardt, J. M. Simon, E. Vicaut, C. Tresallet and E. Martinod. 2024.
PubMed-ID: 38875135
DOI: 10.1093/bjs/znae134

Tumour size predicts risk of recurrence in tall cell subtype papillary thyroid carcinoma.
Am J Surg, 234:58-61.
D. Leong, C. Leslie, B. Laurie, L. Hou, J. Keyser, M. K. Yew, S. Ryan, H. Nguyen and D. Lisewski. 2024.
BACKGROUND: The tall cell subtype of papillary thyroid cancer (TCPTC) is the most common aggressive subtype and often treated aggressively. This approach may not be necessary in smaller tumours without adverse histological characteristics. METHODS: 97 patients with TCPTC defined as a height-to-width ratio of >/=3:1 and at least 30% tall cells were compared against 390 classical papillary thyroid carcinoma (CPTC) based on tumour size with recurrence free survival (RFS) as the primary outcome. RESULTS: TCPTC are more likely to present with adverse histological characteristics. In smaller tumours (<2 cm), only central lymph node metastasis (HR7.16 p = 0.03) and multifocality (HR10.11 p = 0.026) increased recurrence risk. In larger tumours, TCPTC histology (HR3.78 p = 0.002), lymphovascular invasion (HR3.02 p = 0.014) and central lymph node metastasis (HR3.24 p < 0.001) significantly increased recurrence risk. CONCLUSION: TCPTC tumours <2 cm without central lymph node metastasis and multifocality are similar in risk of recurrence to classical PTC and could be managed with lobectomy.
PubMed-ID: 38580566
DOI: 10.1016/j.amjsurg.2024.03.022

A Prospective Study of Publicly Funded Molecular Testing of Indeterminate Thyroid Nodules: Canada's Experience.
J Clin Endocrinol Metab,
F. Levesque, R. J. Payne, D. Beaudoin, A. Boucher, P. H. Fortier, M. H. Massicotte, M. Pusztaszeri, G. Rondeau, E. Corriveau, F. El Malt and M. Brassard. 2024.
CONTEXT: Indeterminate thyroid nodules (ITNs) lead to diagnostic surgeries in many countries. Use of molecular testing (MT) is endorsed by several guidelines, but costs are limitative, especially in public healthcare systems like in Canada. OBJECTIVES: Primary objective: evaluate the clinical value of Thyroseq(R) v3 (TSv3) using benign call rate (BCR) in a real-world practice. Secondary objective: assess cost-effectiveness of MT. DESIGN: This is a multicentric prospective study. SETTING: This study was conducted in 5 academic centers in Quebec, Canada. PATIENTS OR OTHER PARTICIPANTS: 500 consecutive patients with Bethesda III (on 2 consecutive cytopathologies) or IV and TIRADS 3 or 4 nodules measuring 1 to 4 cm were included. INTERVENTION: MT was performed between November 2021 and November 2022. Patients with a positive TSv3 were referred to surgery. Patients with a negative TSv3 were planned for follow-up by ultrasonography for a minimum of 2 years. MAIN OUTCOME MEASURE: The BCR, corresponding to the proportion of ITNs with negative TSv3 results, was assessed. RESULTS: 500 patients underwent TSv3 testing, with a BCR of 72.6% (95% CI: 68.5-76.5; p<0.001). 99.7% of patients with a negative result avoided surgery. The positive predictive value of TSv3 was 68.2% (95% CI: 58.5-76.9). The cost-benefit analysis identified that the implementation of MT would yield cost savings of $6.1 million over the next 10 years. CONCLUSIONS: Use of MT (TSv3) in a well-selected population with ITNs led to a BCR of 72.6%. It is cost-effective and prevents unnecessary surgeries in a public healthcare setting.

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DOI: 10.1210/clinem/dgae355

Conformal thyroidectomy is a feasible option in papillary thyroid microcarcinoma: a retrospective cohort study with 10-year follow-up results.
Langenbecks Arch Surg, 409(1):154.
C. Li, J. Cao, G. S. Chen, X. D. Yang, K. W. Jiang and Y. J. Ye. 2024.
BACKGROUND: In recent years, there has been an increasing prevalence of patients with papillary thyroid microcarcinoma (PTMC) without lymph node involvement in medical centers worldwide. For patients who are unable to undergo active surveillance (AS) and are afraid of postoperative complications, conformal thyroidectomy may be a suitable option to ensure both preservation of function and complete removal of the tumor. METHODS: The patients in the cohort during 2010 to 2015 were retrospectively enrolled strictly following the inclusion and exclusion criteria. The observation and control groups were defined based on the surgical approach, with patients in the observation group undergoing conformal thyroidectomy and patients in the control group undergoing lobectomy. Event-free survival (EFS), the interval from initial surgery to the detection of recurrent or metastatic disease, was defined as the primary observation endpoint. RESULTS: A total of 319 patients were included in the study, with 124 patients undergoing conformal thyroidectomy and 195 patients undergoing lobectomy. When compared to lobectomy, conformal thyroidectomy demonstrated reduced hospital stays, shorter operative times, and lower rates of vocal cord paralysis and hypoparathyroidism. Furthermore, the mean bleeding volume during the operation and the rate of permanent hypothyroidism were also lower in the conformal thyroidectomy group than in the lobectomy group. However, there was no statistically significant difference observed in the 5- and 10-year EFS between the two groups. CONCLUSIONS: Conformal thyroidectomy had advantages in perioperative management and short-term complication rates, with an EFS that was not inferior to that of lobectomy. Thus, conformal thyroidectomy is a feasible option for low-risk PTMC patients.
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DOI: 10.1007/s00423-024-03333-9
PMCID: PMC11076371

Association Between a History of Breast Cancer and Decreased Thyroid Cancer-specific Mortality.
J Clin Endocrinol Metab, 109(5):1222-30.
S. Lin, Z. Wang and M. Xing. 2024.
CONTEXT: The clinical relevance of the well-known association between thyroid cancer (TC) and breast cancer (BC) remains to be further defined. OBJECTIVE: This work aimed to investigate the effect of history of BC on the prognosis of TC. METHODS: This was a comparative cohort study of tumor behaviors and TC-specific mortality in 5598 patients with papillary thyroid cancer (PTC) and 604 patients with follicular thyroid cancer (FTC), all with a history of BC (TC-BC patients), and their propensity score-matched TC patients without a history of BC (TCnoBC patients) in Surveillance, Epidemiology and End Results (SEER) 18. The main outcome measure was TC-specific mortality. RESULTS: Lower TC distant metastasis rates of 2.4% vs 3.0% in PTC and 6.1% vs 9.1% in FTC and TC-specific mortality rates of 1.3% vs 2.6% in PTC and 5.8% vs 8.4% in FTC were found in TC-BC patients vs matched TCnoBC patients (all P < .05). Comparing TC-BC patients with matched TCnoBC patients, hazard ratios (HRs) for mortality were 0.472 (95% CI, 0.370-0.601) in PTC and 0.656 (95% CI, 0.461-0.934) in FTC (all P < .05). Such HRs for mortality in PTC were 0.397 (95% CI, 0.268-0.588; P < .001) when TC occurred before BC vs 0.607 (95% CI, 0.445-0.827; P = .002) when BC occurred before TC. CONCLUSION: This study demonstrates a robust protective effect of a history of BC on TC-specific patient survival, which has strong implications for more precise prognostication of TC in such patients.
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DOI: 10.1210/clinem/dgad722
PMCID: PMC11031237

Accurate preoperative prediction of nodal metastasis in papillary thyroid microcarcinoma: Towards optimal management of patients.
Head Neck, 46(5):1009-19.
S. Y. Lin, M. Y. Li, C. P. Zhou, W. Ao, W. Y. Huang, S. S. Wang, J. F. Yu, Z. H. Tang, A. H. Abdelhamid Ahmed, T. Y. Wang, Z. H. Wang, S. Hua, G. W. Randolph, W. X. Zhao and B. Wang. 2024.
OBJECTIVE: To enhance the accuracy in predicting lymph node metastasis (LNM) preoperatively in patients with papillary thyroid microcarcinoma (PTMC), refining the "low-risk" classification for tailored treatment strategies. METHODS: This study involves the development and validation of a predictive model using a cohort of 1004 patients with PTMC

undergoing thyroidectomy along with central neck dissection. The data was divided into a training cohort (n = 702) and a validation cohort (n = 302). Multivariate logistic regression identified independent LNM predictors in PTMC, leading to the construction of a predictive nomogram model. The model's performance was assessed through ROC analysis, calibration curve analysis, and decision curve analysis. RESULTS: Identified LNM predictors in PTMC included age, tumor maximum diameter, nodule-capsule distance, capsular contact length, bilateral suspicious lesions, absence of the lymphatic hilum, microcalcification, and sex. Especially, tumors larger than 7 mm, nodules closer to the capsule (less than 3 mm), and longer capsular contact lengths (more than 1 mm) showed higher LNM rates. The model exhibited AUCs of 0.733 and 0.771 in the training and validation cohorts respectively, alongside superior calibration and clinical utility. CONCLUSION: This study proposes and substantiates a preoperative predictive model for LNM in patients with PTMC, honing the precision of "low-risk" categorization. This model furnishes clinicians with an invaluable tool for individualized treatment approach, ensuring better management of patients who might be proposed observation or ablative options in the absence of such predictive information.
PubMed-ID: 38441255
DOI: 10.1002/hed.27720

US-based, Prospective, Blinded Study of Thyrotropin Receptor Antibody in Autoimmune Thyroid Disease.
J Clin Endocrinol Metab,
M. A. Lupo, P. D. Olivo, M. Luffy, J. Wolf and G. J. Kahaly. 2024.
CONTEXT: Bioassays provide information on the functionality of thyrotropin receptor antibodies (TSH-R-Ab) and thus may offer more clinical utility than binding assays. OBJECTIVE: In this prospective, blinded, US-based study, the clinical performance of several TSH-R-Ab assays was compared. SETTING: US endocrinology clinic. SUBJECTS: One hundred sixty-two unselected, consecutive, well-documented patients with various thyroid diseases and healthy controls. INTERVENTION(S): Blinded TSH-R-Ab measurements. MAIN OUTCOME MEASURE(S): Sensitivity and specificity of 4 TSH-R-Ab assays. RESULTS: The 4 TSH-R-Ab assays were negative in all 42 patients without autoimmune thyroid disease (AITD). In 104 patients with Graves' disease (GD), irrespective of the disease duration, TSH-R-Ab positivity was present in 65 (63%), 67 (65%), and 87 (84%) for the Cobas and Immulite binding assays and stimulatory TSH-R-Ab [thyroid-stimulating immunoglobin (TSI)] bioassay, respectively (TSI vs Immulite P < .0025, TSI vs Cobas P < .0009). Fifteen newly diagnosed GD patients were all positive in the TSI bioassay, but only 11 (73%) were positive in the Cobas and Immulite binding assays. Nine GD patients with biochemical subclinical hyperthyroidism were TSI-positive but Immulite- and Cobas-negative. Two GD patients were blocking TSH-R-Ab [thyroid-blocking immunoglobin (TBI)]-positive and TSI-negative, and the Immulite and Cobas were positive in both. Additional serum samples from AITD patients that consisted of 30 TBI-positive and 10 TSI-positive samples were blindly tested in the binding assays. Only 6 of the 10 TSI-positive samples were positive in both binding assays, and 30 and 28 of the TBI-positive samples were positive in the Cobas and Immulite assays, respectively. CONCLUSION: Binding TSH-R-Ab assays are less sensitive than TSI bioassays and are not specific for stimulating antibodies. Measuring the function of TSH-R-Ab in a bioassay can provide useful information to clinicians.
PubMed-ID: 39028731
DOI: 10.1210/clinem/dgae448

Anatomical Patterns of Nodal Spread in Unilateral Papillary and Medullary Thyroid Cancer.
Thyroid, 34(7):871-9.
A. Machens, K. Lorenz, F. Weber and H. Dralle. 2024.
Background: Skip metastases, node metastases in the lateral neck sparing the ipsilateral central neck, challenge the current concept of central-to-lateral lymphatic spread. This study sought to delineate patterns of central and lateral neck involvement in unilateral papillary thyroid cancer (PTC) and medullary thyroid cancer (MTC). Methods: This was a retrospective correlative analysis of nodal patterns in surgical specimens from patients with unilateral PTC or MTC who had undergone thyroidectomy with at least ipsilateral central neck dissection between November 1994 and January 2024 at a tertiary referral center. Results: Included were 833 patients with unilateral PTC and 640 patients with unilateral MTC. Simultaneous presence or absence of node metastases was noted in ipsilateral central and lateral neck compartments in 76.6-78.1% of patients with PTC (both node positive in 27.0-54.7% and both node negative in 23.4-49.6%) and 77.3-80.0% of patients with MTC (both node positive in 26.6-33.2% and both node negative in 44.1-53.4%). Only one ipsilateral neck compartment was node positive in 21.9-23.4% of patients with PTC and 20.0-22.7% of patients with MTC. The ipsilateral central, but not the ipsilateral lateral compartment, was node positive in 8.8-16.9% with PTC and 8.6-8.8% of patients with MTC, whereas the ipsilateral lateral, but not the ipsilateral central compartment, was node positive in 6.5-13.1% with PTC and 11.3-14.1% with MTC. Ipsilateral lateral neck involvement sparing the ipsilateral central neck was 1.5-2 times more frequent in patients with node positive MTC than patients with node positive PTC (24.2-25.2% vs. 12.9-17.1%). Greater

numbers of node metastases in the ipsilateral central neck compartment were associated with more frequent involvement of the ipsilateral lateral, contralateral central, and contralateral lateral neck compartments. Thyroid tumor diameter intensified nodal spread without changing nodal spread patterns. Conclusions: These histopathological findings, which need to be interpreted in light of the respective tumor biology, offer an unprecedented glimpse at the metastatic patterns of unilateral PTC and MTC. Customizing neck dissection to the patterns of nodal spread, considering operative status (initial vs. reoperative surgery) and experience with neck dissection, may require more frequent concomitant dissections of ipsilateral central and ipsilateral lateral neck compartments.
PubMed-ID: 38717955
DOI: 10.1089/thy.2024.0076

Use of a dosimetry-based RAI protocol for treatment of benign hyperthyroidism optimises response while minimising exposure to ionising radiation.
Clin Endocrinol (Oxf), 100(6):585-92.
C. Miller, A. Al-Jabri, L. O'Murchada, M. Mustafa, J. Cooke, N. Phelan and M. L. Healy. 2024.
BACKGROUND: The optimal treatment strategy for radioiodine (RAI) treatment protocols for benign hyperthyroidism remains elusive. Although individualised activities are recommended in European Law, many centres continue to provide fixed activities. Our institution implemented a dosimetry protocol in 2016 following years of fixed dosing which facilitates the calculation of individualised activities based on thyroid volume and radioiodine uptake. METHODS: This was a retrospective study comparing success rates using a dosimetry protocol targeting an absorbed dose of 150 Gy for Graves' disease (GD) and 125 Gy for Toxic Multinodular Goiter (TMNG) with fixed dosing (200MBq for GD and 400MBq for TMNG) among 204 patients with hyperthyroidism. Success was defined as a non-hyperthyroid state at 1 year for both disease states. Results were analysed for disease specific or patient specific modulators of response. RESULTS: This study included 204 patients; 74% (n = 151) received fixed activities and 26% (n = 53) of activities administered were calculated using dosimetry. A dosimetry-based protocol was successful in 80.5% of patients with GD and 100% of patients with TMNG. Differences in success rates and median activity administered between the fixed (204Mbq) and dosimetry (246MBq) cohort were not statistically significant (p = .64) however 44% of patients with GD and 70% of patients with TMNG received lower activities following treatment with dosimetry as opposed to fixed activities. Use of dosimetry resulted in successful treatment and reduced RAI exposure for 36% of patients with GD, 70% of patients with TMNG, and 44% of patients overall. CONCLUSION: This retrospective clinical study demonstrated that treatment with a dosimetry-based protocol for TMNG and GD achieved comparable success rates to fixed protocols while reducing RAI exposure for over a third of patients with GD and most patients with TMNG. This study also highlighted that RAI can successfully treat hyperthyroidism for some patients with activities lower than commonplace in clinical practise. No patient or disease specific modulators of treatment response were established in this study; however, the data supports a future prospective trial which further scrutinises the individual patient factors governing treatment response to RAI.
PubMed-ID: 38567706
DOI: 10.1111/cen.15054

Presentation and management of medullary thyroid cancer by sex and race/ethnicity in the United States-A state of disunion.
Am J Surg, 234:17-8.
A. Monreal, A. N. Eze and H. S. Kazaure. 2024.
PubMed-ID: 38644135
DOI: 10.1016/j.amjsurg.2024.04.012

Impact of COVID-19 pandemic on thyroidectomy for malignant diseases in high-volume referral centers.
Updates Surg, 76(3):1073-83.
M. Raffaelli, L. Sessa, C. De Crea, M. P. Cerviere, G. Marincola, F. Zotta, C. E. Ambrosini, B. Gjeloshi, L. De Napoli, L. Rossi, R. Elisei, A. Pontecorvi, F. Basolo, E. D. Rossi, R. Bellantone and G. Materazzi. 2024.
INTRODUCTION: The COVID-19 pandemic has limited the availability of healthcare resources for non-COVID patients and decreased elective surgeries, including thyroidectomy. Despite the prioritization of surgical procedures, it has been reported that thyroidectomy for thyroid cancer (TCa) was adversely impacted. We assessed the impact of the pandemic on the surgical activities of two high-volume referral centers. MATERIALS AND METHODS: Patients operated at two National Referral Centers for Thyroid Surgery between 03/01/2020 and 02/28/2021 (COVID-19 period) were included (P-Group). The cohort was compared with patients operated at the same Centers between 03/01/2019 and 02/29/2020 (pre-COVID-19 pandemic) (C-Group). RESULTS: Overall, 7017 patients were included: 2782 in the P-Group and 4235 in the C-

Group. The absolute number of patients with TCa was not significantly different between the two groups, while the rate of malignant disease was significantly higher in the P-Group (1103/2782 vs 1190/4235) (P < 0.0001). Significantly more patients in the P-Group had central (237/1103 vs 232/1190) and lateral (167/1103 vs 140/1190) neck node metastases (P = 0.001). Overall, the complications rate was significantly lower (11.9% vs 15.1%) and hospital stay was significantly shorter (1.7 +/- 1.5 vs 1.9 +/- 2.2 days) in the P-Group (P < 0.05). CONCLUSION: The COVID-19 pandemic significantly decreased the overall number of thyroidectomies but did not affect the number of operations for TCa. Optimization of management protocols, due to limited resource availability for non-COVID patients, positively impacted the complication rate and hospital stay.
PubMed-ID: 38351271
DOI: 10.1007/s13304-024-01771-0

Increased risk of chronic kidney disease after total thyroidectomy: A nationwide matched cohort study.
J Clin Endocrinol Metab,
R. Reinke, S. Udholm, C. F. Christiansen, M. Almquist, S. Londero, L. Rejnmark, T. B. Rasmussen and L. Rolighed. 2024.
BACKGROUND: Development of hypoparathyroidism (hypoPT) after total thyroidectomy (TT) may increase the risk of kidney-related morbidity. We aimed to examine the risk of hypoPT and chronic kidney disease (CKD) in patients undergoing TT in Denmark over a 20-year period. MATERIALS AND METHODS: Using population-based registries, we identified all Danish individuals with TT between January 1998 and December 2017. We included a matched comparison cohort by randomly selecting 10 citizens for each patient, by sex and birth year. We calculated cumulative incidence and hazard ratio (HR) of CKD by Cox regression in patients with TT compared with the comparison cohort. Further, CKD risks were stratified by indications for TT and comorbidity groups according to Charlson Comorbidity Index. RESULTS: We included 2421 patients with TT and 21.5% had hypoPT. After 10 years, the risk of developing CKD for hypoPT patients was 13.5% (95% CI:9.8-17.7), 11.6% (95% CI: 9.7-13.7) for patients without hypoPT, and 5.8% (95% CI: 5.3-6.2) for the comparison cohort. When compared with the matched comparison cohort, the adjusted HR for CKD in hypoPT patients was 3.23 (95% CI: 2.37-4-41) and 2.27 (1.87-2.75) for patients without hypoPT. For patients without previous comorbidities, the adjusted HR of CKD was higher than in patients with several comorbidities. CONCLUSION: HypoPT was a frequent complication after TT and was associated with an increased risk of CKD. We also found an increased risk of CKD in patients with a normal parathyroid function after TT, which needs to be further evaluated.
PubMed-ID: 39126399
DOI: 10.1210/clinem/dgae534

Malignancy risk of indeterminate lymph node at the central compartment in patients with thyroid cancer and concomitant sonographic thyroiditis.
Head Neck, 46(8):1922-31.
J. H. Rhim, J. Y. Lee, S. W. Park, Y. Lee, S. L. Jung, T. J. Yun, E. J. Ha, J. H. Baek, J. Kim, D. G. Na and J. H. Kim. 2024.
BACKGROUND: To evaluate the malignancy risk of sonographic (US) indeterminate lymph node (LN)s at the central compartment in thyroid cancer patients with US-thyroiditis (ST). METHODS: Among the central compartments of suspicious, indeterminate, and probably benign LN US categories, the malignancy rates were compared between ST and non-US-thyroiditis (non-ST) groups. Those of indeterminate category were compared with suspicious and probably benign categories. RESULTS: At 531 central compartments from 349 patients, the malignancy rate was lower in ST group (34.4% [44/128]) than non-ST group (43.4% [175/403]), although statistically not significant (p = 0.08). The malignancy rate of indeterminate category in ST group (35.7% [5/14]) was lower than non-ST group (71.9% [23/32]) (p = 0.047). Within ST group, the malignancy rate of indeterminate category (35.7% [5/14]) did not differ from probably benign category (29.1% [30/103]) (p = 0.756), but was lower than suspicious category (81.8% [9/11]) (p = 0.042). CONCLUSIONS: The malignancy risk of US indeterminate LNs at the central compartment in thyroid cancer patients with US thyroiditis was lower than that in patients without US thyroiditis.
PubMed-ID: 38305145
DOI: 10.1002/hed.27670

Surgeon-performed transcutaneous laryngeal ultrasound for vocal cord assessment after total thyroidectomy: a prospective study : Original article.
Langenbecks Arch Surg, 409(1):183.
L. Rossi, P. Papini, A. De Palma, L. Fregoli, C. Becucci, C. E. Ambrosini, R. Morganti and G. Materazzi. 2024.
PURPOSE: Assessing vocal cord mobility is crucial for patients undergoing thyroid surgery. We aimed to evaluate the feasibility and efficacy of surgeon-performed transcutaneous laryngeal ultrasound (TLUS) compared to flexible

nasolaryngoscopy. METHOD: From February 2022 to December 2022, we conducted a prospective observational study on patients scheduled for total thyroidectomy at our Institution. All patients underwent TLUS followed by flexible nasolaryngoscopy by a blinded otolaryngologist. Findings were classified as normal or vocal cord movement impairment and then compared. Patients evaluable on TLUS were included in Group A, while those not evaluable were included in Group B, and their features were compared. RESULTS: Group A included 180 patients, while Group B included 21 patients. Male sex ($p < 0.001$), age ($p = 0.034$), BMI ($p < 0.001$), thyroid volume ($p = 0.038$), and neck circumference ($p < 0.001$) were associated with Group B. TLUS showed a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 99.4%, 94.4%, 100%, and 99.4%, respectively. Cohen's K value was 0.984. CONCLUSION: TLUS is a valid, easy-to-perform, non-invasive, and painless alternative for evaluating vocal cords in selected patients. It can be used either as a first level exam and as screening tool for selecting cases for flexible nasolaryngoscopy. TLUS should be integrated into routine thyroid ultrasound examination.
PubMed-ID: 38861184
DOI: 10.1007/s00423-024-03362-4
PMCID: PMC11166737

Evidence for postoperative radiotherapy in medullary thyroid cancer.
Head Neck, 46(7):1846-7.
N. P. Rowell. 2024.
PubMed-ID: 38646954
DOI: 10.1002/hed.27781

From Bench-to-Bedside: How Artificial Intelligence is Changing Thyroid Nodule Diagnostics, a Systematic Review.
J Clin Endocrinol Metab, 109(7):1684-93.
V. R. Sant, A. Radhachandran, V. Ivezic, D. T. Lee, M. J. Livhits, J. X. Wu, R. Masamed, C. W. Arnold, M. W. Yeh and W. Speier. 2024.
CONTEXT: Use of artificial intelligence (AI) to predict clinical outcomes in thyroid nodule diagnostics has grown exponentially over the past decade. The greatest challenge is in understanding the best model to apply to one's own patient population, and how to operationalize such a model in practice. EVIDENCE ACQUISITION: A literature search of PubMed and IEEE Xplore was conducted for English-language publications between January 1, 2015 and January 1, 2023, studying diagnostic tests on suspected thyroid nodules that used AI. We excluded articles without prospective or external validation, nonprimary literature, duplicates, focused on nonnodular thyroid conditions, not using AI, and those incidentally using AI in support of an experimental diagnostic outside standard clinical practice. Quality was graded by Oxford level of evidence. EVIDENCE SYNTHESIS: A total of 61 studies were identified; all performed external validation, 16 studies were prospective, and 33 compared a model to physician prediction of ground truth. Statistical validation was reported in 50 papers. A diagnostic pipeline was abstracted, yielding 5 high-level outcomes: (1) nodule localization, (2) ultrasound (US) risk score, (3) molecular status, (4) malignancy, and (5) long-term prognosis. Seven prospective studies validated a single commercial AI; strengths included automating nodule feature assessment from US and assisting the physician in predicting malignancy risk, while weaknesses included automated margin prediction and interobserver variability. CONCLUSION: Models predominantly used US images to predict malignancy. Of 4 Food and Drug Administration-approved products, only S-Detect was extensively validated. Implementing an AI model locally requires data sanitization and revalidation to ensure appropriate clinical performance.
PubMed-ID: 38679750
DOI: 10.1210/clinem/dgae277
PMCID: PMC11180510

Defining the Genomic Landscape of Diffuse Sclerosing Papillary Thyroid Carcinoma: Prognostic Implications of RET Fusions.
Ann Surg Oncol, 31(9):5525-36.
D. W. Scholfield, C. W. R. Fitzgerald, L. A. Boe, A. Eagan, H. Levyn, B. Xu, R. M. Tuttle, J. A. Fagin, A. R. Shaha, J. P. Shah, R. J. Wong, S. G. Patel, R. Ghossein and I. Ganly. 2024.
BACKGROUND: Diffuse sclerosing papillary thyroid carcinoma (DSPTC) is an aggressive histopathologic subtype of papillary thyroid carcinoma. Correlation between genotype and phenotype has not been comprehensively described. This study aimed to describe the genomic landscape of DSPTC comprehensively using next-generation sequencing (NGS), analyze the prognostic implications of different mutations, and identify potential molecular treatment targets. METHODS: Tumor tissue was available for 41 DSPTC patients treated at Memorial Sloan Kettering Cancer Center between 2004 and 2021.

After DNA extraction, NGS was performed using the Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets platform, which sequences 505 critical cancer genes. Clinicopathologic characteristics were compared using the chi-square test. The Kaplan-Meier method and log-rank statistics were used to compare outcomes. RESULTS: The most common mutation was RET fusion, occurring in 32% (13/41) of the patients. Other oncologic drivers occurred in 68% (28/41) of the patients, including 8 BRAF(V600E) mutations (20%) and 4 USP8 mutations (10%), which have not been described in thyroid malignancy previously. Patients experienced RET fusion-positive tumors at a younger age than other drivers, with more aggressive histopathologic features and more advanced T stage (p = 0.019). Patients who were RET fusion-positive had a significantly poorer 5-year recurrence-free survival probability than those with other drivers (46% vs 84%; p = 0.003; median follow-up period, 45 months). In multivariable analysis, RET fusion was the only independent risk factor for recurrence (hazard ratio [HR], 7.69; p = 0.017). CONCLUSION: Gene-sequencing should be strongly considered for recurrent DSPTC due to significant prognostic and treatment implications of RET fusion identification. The novel finding of USP8 mutation in DSPTC requires further investigation into its potential as a driver mutation.
PubMed-ID: 38847983
DOI: 10.1245/s10434-024-15500-9

A phase I/II trial of sapanisertib in advanced anaplastic and radioiodine refractory differentiated thyroid carcinoma.
J Clin Endocrinol Metab,
K. Sehgal, A. Serritella, M. Liu, O. N. A, C. Nangia, T. Pappa, M. J. Demeure, F. P. Worden, R. Haddad and J. Lorch. 2024.
BACKGROUND: There are limited therapeutic options for patients with recurrent/metastatic anaplastic thyroid carcinoma (ATC), and radioiodine refractory (RAIR) differentiated thyroid carcinoma (DTC) refractory to multi-kinase inhibitors. This multi-center trial evaluated sapanisertib, a next generation oral kinase inhibitor of mTOR complexes 1/2, in ATC and RAIR DTC. METHODS: A safety run-in phase I was followed by non-randomized phase II trial in ATC, with an exploratory cohort in RAIR DTC. Primary endpoint was proportion of patients with ATC who were without disease progression at 4 months. Safety and survival outcomes were key secondary endpoints. RESULTS: Forty-six patients (20 ATC; 26 DTC) were enrolled including 40 (18 ATC; 22 DTC) who received recommended phase II dose of 5 mg daily. Eleven percent (2/18, 95% C.I.: 1.4-34.7%) of patients with ATC were progression-free at 4 months, 22.2% (4/18) had stable disease as best response. Enrollment in the ATC cohort stopped early with 18 patients out of proposed 23 due to overall futility. One confirmed partial response (4.5%, 1/22) occurred in RAIR DTC, with stable disease in 63.6% (14/22) patients. Median progression-free survival was 1.6 (95% C.I.: 0.9-2.8) months and 7.8 (2.0-not reached) months in ATC and DTC, respectively. Grade 3 treatment related adverse events occurred in 30% of patients who received the phase II dose, most common being anorexia, nausea, diarrhea, fatigue, skin rash and hyperglycemia. Genomic alterations in the PI3 K/AKT/mTOR pathway were not associated with response or PFS. CONCLUSIONS: Sapanisertib monotherapy did not meet the primary endpoint of this trial (proportion progression-free at 4 months) in ATC, and did not show clinically meaningfully activity. Clinical trials with alternative therapeutic strategies are needed. CLINICAL TRIAL REGISTRATION: NCT02244463.
PubMed-ID: 38943664
DOI: 10.1210/clinem/dgae443

ASO Author Reflections: Advanced Thyroid Cancers: Individualized Treatments in the Era of the Standard Surgical Approaches.
Ann Surg Oncol, 31(9):5539-40.
L. Sessa, C. De Crea, N. Voloudakis, F. Pennestri and M. Raffaelli. 2024.
PubMed-ID: 38767801
DOI: 10.1245/s10434-024-15462-y

Novel biomarkers reveal mismatch between tissue and serum thyroid hormone status in amiodarone-induced hyperthyroidism.
J Clin Endocrinol Metab,
R. Sinko, M. Katko, G. Toth, G. L. Kovacs, O. Dohan, T. Fulop, P. Costa, B. Doroghazi, D. Kovari, E. V. Nagy, C. Fekete and B. Gereben. 2024.
CONTEXT: Serum TSH and thyroid hormone (TH) levels are routine markers of thyroid function. However, their diagnostic performance is limited under special conditions, e.g. in amiodarone-induced hyperthyroidism (AIH). Such cases would require the assessment of tissue TH action, which is currently unfeasible. OBJECTIVE: Development of an approach that determines how well serum parameters are reflected in tissue TH action of patients. METHODS: TH-responsive marker genes were identified from human hair follicles (HF) with Next Generation Sequencing, validated by qPCR. A classification model was built with these markers to assess tissue TH action and was deployed on amiodarone treated patients. The

impact of amiodarone on tissue TH action was also studied in Thyroid Hormone Action Indicator (THAI) mice. RESULTS: The classification model was validated and shown to predict tissue TH status of subjects with good performance. Serum- and HF-based TH statuses were concordant in hypothyroid and euthyroid amiodarone treated patients. In contrast, amiodarone decreased the coincidence of serum-based and HF-based TH statuses in hyperthyroid patients, indicating that AIH is not unequivocally associated with tissue hyperthyroidism. This was confirmed in the THAI model, where amiodarone prevented tissue hyperthyroidism in THAI mice despite high serum fT4. CONCLUSION: We developed a minimally-invasive approach using HF markers to assess tissue TH economy that could complement routine diagnostics in controversial cases. We observed that a substantial proportion of AIH patients do not develop tissue hyperthyroidism, indicating that amiodarone protects tissues from thyrotoxicosis. Assessing tissue TH action in patients with AIH may be warranted for treatment decisions.
PubMed-ID: 39076009
DOI: 10.1210/clinem/dgae514

Thyroid Dysfunction Risk After Iodinated Contrast Media Administration: A Prospective Longitudinal Cohort Analysis.
J Clin Endocrinol Metab,
S. Y. Sohn, K. Inoue, M. T. Bashir, J. W. Currier, N. V. Neverova, R. Ebrahimi, C. M. Rhee, M. L. Lee and A. M. Leung. 2024.
CONTEXT: Iodinated contrast media (ICM) is a common source of excess iodine in medical settings, given the common use of iodinated radiologic procedures. OBJECTIVE: To determine the long-term risks of thyroid dysfunction following iodinated contrast administration in a prospective study. DESIGN, SETTING, PARTICIPANTS: A longitudinal cohort study was conducted of patients in the U.S. Veterans Affairs medical system who received ICM. MAIN OUTCOME MEASURES: Serum thyroid function, thyroid antibody, and inflammatory markers were measured at baseline. Thyroid function tests were repeated at 1 month, 3 months, and every 6 months thereafter until 36 months. Risk of thyroid dysfunction and longitudinal changes in thyroid hormone levels were assessed using mixed effect models. RESULTS: There were 122 participants (median age, 70.0 [IQR 62.2-74.0] years; 98.4% male). At baseline, six subjects had subclinical thyroid dysfunction prior to ICM receipt. During median follow-up of 18 months, iodine-induced thyroid dysfunction was observed in 11.5% (14/122); six (4.9%) developed hyperthyroidism (including one with overt hyperthyroidism) and eight (6.6%) subclinical hypothyroidism. At last follow-up, ten of 20 subjects with thyroid dysfunction (14 new-onset cases and six with preexisting thyroid dysfunction) had persistent subclinical hyperthyroidism or hypothyroidism. There were also subtle changes in thyroid hormones observed longitudinally within the reference ranges in the overall cohort. CONCLUSIONS: There is a rare long-term risk of an excess iodine load on thyroid dysfunction even among individuals from an overall iodine-sufficient region, supporting the need for targeted monitoring following iodinated contrast administration.
PubMed-ID: 38700099
DOI: 10.1210/clinem/dgae304

Trends in papillary thyroid cancer mortality in Denmark according to stage and education.
Clin Endocrinol (Oxf), 101(6):573-9.
S. M. Sorensen, C. Munk, T. Maltesen, U. Feldt-Rasmussen and S. K. Kjaer. 2024.
OBJECTIVE: Few studies exist on trends in papillary thyroid cancer (PTC) survival and mortality according to stage and level of socioeconomic status. DESIGN: Nationwide cohort study. PATIENTS AND MEASUREMENTS: Patients diagnosed with PTC during 2000-2015 in Denmark were identified from the Danish Cancer Registry and followed until the end of 2020. We evaluated 5-year all-cause mortality and relative survival according to stage and 5-year mortality rates with corresponding average annual percentage changes (AAPCs) according to stage and education. Finally, we assessed the association between several factors and mortality of PTC using Cox regression. RESULTS: For the 2006 cases of PTC diagnosed during 2000-2015, relative survival tended to increase and mortality rates tended to decrease for all stages. For localized PTC, mortality rates tended to decrease among individuals with medium education (AAPC = -7.0, 95% confidence interval [CI]: -14.7 to 1.5), but showed an increasing pattern among individuals with long education (AAPC = 19.8, 95% CI: -4.2 to 50.0). For nonlocalized PTC, mortality rates showed a decreasing tendency among individuals with medium and long education (AAPC = -5.5, 95% CI: -13.2 to 2.9, and AAPC = -10.4, 95% CI: -20.8 to 1.4, respectively). Being diagnosed with PTC in a more recent calendar period and long education were associated with a lower mortality rate in the Cox regression analysis. CONCLUSIONS: A pattern of an increasing relative survival and decreasing mortality rates of PTC across all stages was seen in Denmark during 2000-2015. The decreasing pattern in mortality rates was most evident in individuals with localized stage and medium education, and in individuals with nonlocalized stage and medium or long education.
PubMed-ID: 39113277
DOI: 10.1111/cen.15119

Subgroup analysis of steadily increased trends in medullary thyroid carcinoma incidence and mortality in the USA, 2000-2020: a population-based retrospective cohort study.
Endocr Relat Cancer, 31(5)
Z. Tao, X. Deng, B. Guo, Z. Ding and Y. Fan. 2024.
The incidence rate of medullary thyroid carcinoma (MTC) continues to grow, along with its mortality rate in the USA. However, the subgroup trends in MTC have not yet been established. This population-based retrospective cohort study was based on the Surveillance, Epidemiology, and End Results (SEER) 17/12 registry database. Subgroup analysis was performed through clinicopathological and treatment-related characteristics. Annual average percentage change (AAPC) was calculated using joinpoint regression analysis. A total of 3833 MTC patients and 536 death cases were diagnosed in the SEER database. Between 2000 and 2019, the incidence (AAPC = 1.64) and mortality (AAPC = 3.46) rates of MTC continued to rise. Subgroup analysis showed the proportion of elderly patients (65-84 years) gradually increased in incidence between 2000 and 2020. Patients with early-stage tumors, such as tumors </=20 mm, showed the same trends. Aspects of treatment, the implementation rate of total thyroidectomy (AAPC = 0.38) and lymph node dissection (AAPC = 1.06) also increased persistently in almost all of the age subgroups. The incidence and mortality of MTC consistently increased from 2000 to 2019. Subgroup analysis indicated a significant increase in elderly patients and early-stage patients, and more attention should be paid to the management of these increased subgroups.
PubMed-ID: 38376827
DOI: 10.1530/ERC-23-0319
PMCID: PMC11046345

Tracking dynamic evolution of low- and intermediate-risk differentiated thyroid cancer: Identification of individuals at risk of recurrence.
Clin Endocrinol (Oxf), 101(3):286-94.
F. Volpi, J. Alcalde, J. Larrache, E. Alegre, A. Argueta, M. D. Lozano, C. Colombo and J. C. Galofre. 2024.
OBJECTIVE: The generally good prognosis of low- and intermediate-risk differentiated thyroid cancer (DTC) underscored the need to identify those few patients who relapse. DESIGN: Records of 299 low- or intermediate-risk DTC patients (mean follow-up 8.2 +/- 6.2 years) were retrospectively reviewed. The sample was classified following the American Thyroid Association (ATA) dynamic risk stratification (DRS) system. PATIENTS AND MEASUREMENT: After classifying patients according to DRS at the first visit following initial therapy (FU1), structural recurrence occurred in 2/181 (1.1%), 5/81 (6.2%) and 13/26 (50.0%) with excellent, indeterminate and biochemical incomplete response to treatment, respectively. All relapses but one happened within 5 years from FU1. Univariate analysis comparing excellent, indeterminate and biochemical incomplete with structural incomplete responses at the end of the follow-up, identified tumour size ($p < .001$), T status (<0.001), positive lymph nodes (N) ($p < .01$), multifocality ($p < .004$), need of additional radioactive iodine (RAI) ($p < .0001$) and first DRS status ($p < .0003$) as risk factors of recurrence. In the multivariate analysis, only RAI remained statistically significant ($p < .02$). Comparison between excellent and indeterminate with biochemical and structural incomplete responses, identified tumour size ($p < .0004$), T ($p < .01$), N ($p < .0001$), bilaterality ($p < .03$), first DRS status ($p < .0001$) and RAI ($p < .001$) as recurrence risk factors. T ($p < .01$) and first DRS ($p < .0006$) were confirmed in the multivariate analysis. CONCLUSIONS: Patients with DTC classified as low- or intermediate-risk of recurrence with excellent response to treatment at FU1 rarely develop structural disease and this occurs almost exclusively in the first 5 years. Initial DRS status is an accurate tool for determining the risk of recurrence.
PubMed-ID: 39038163
DOI: 10.1111/cen.15111

Improving the Risk Prediction of the 2015 ATA Recurrence Risk Stratification in Papillary Thyroid Cancer.
J Clin Endocrinol Metab,
H. Wang, Q. Li, T. Tian, B. Liu and R. Tian. 2024.
BACKGROUND: Various prognostic factors are expected to refine the American Thyroid Association (ATA) recurrence risk stratification for patients with papillary thyroid cancer (PTC). However, it remains unclear to what extent integrating these factors improves patient treatment decision-making. METHODS: We developed two predictive models for structural incomplete response (SIR) at the one-year follow-up visit, based on comprehensive clinical data from a retrospective cohort of 2539 patients. Model 1 included the recurrence risk stratification and lymph node features (i.e., number and ratio of metastatic lymph nodes, N stage). Model 2 further incorporated preablation stimulated thyroglobulin (s-Tg). An independent cohort of 746 patients was used for validation analysis. We assessed the models' predictive performance compared to the recurrence risk stratification using the integrated discrimination improvement (IDI) and the continuous net reclassification improvement (NRI). The clinical utility of the models was evaluated using decision curve analysis.

RESULTS: Both Model 1 and Model 2 outperformed the recurrence risk stratification in predicting SIR, with improved correct classification rates (Model 1: IDI=0.02, event NRI=42.31%; Model 2: IDI=0.07, event NRI=53.54%). The decision curves indicated that both models provided greater benefits over the risk stratification system in clinical decision-making. In the validation set, Model 2 maintained similar performance while Model 1 did not significantly improve correct reclassification. CONCLUSION: The inclusion of lymph node features and s-Tg showed potential to enhance the predictive accuracy and clinical utility of the existing risk stratification system for PTC patients.
PubMed-ID: 38980946
DOI: 10.1210/clinem/dgae465

Subcutaneous implantation of nodular goiter after transoral endoscopic thyroidectomy vestibular approach: A case study and review of literature.
Head Neck, 46(6):E61-E6.
Y. J. Weng, K. J. S. Kwan, D. B. Chen, B. L. Hu, J. Jiang, L. Min, Q. Ai, W. C. Chen and Z. H. Huang. 2024.
BACKGROUND: Extrathyroid implantation or dissemination of thyroid tissue secondary to a thyroid procedure is rare. Most of these belonged to thyroid carcinoma with metastatic potential and uncommon for benign pathologies. METHODS: We report the case of a 31-year-old female who was identified to have multiple subcutaneous implantation of thyroid tissue 5 years after transoral endoscopic thyroidectomy vestibular approach. A comprehensive literature search on implantation of thyroid tissue secondary to thyroid procedures was performed. RESULTS: Accidental tearing of the capsule during previous surgery may lead to the subcutaneous implantation. Through literature review, a total 29 articles with 47 patients were identified. 33.3% were benign lesions, and implantation was mostly secondary to fine needle aspiration biopsy (46.5%). CONCLUSIONS: Subcutaneous or port site implantation after endoscopic thyroid surgery may occur in benign thyroid pathologies and therefore, oncologic principles must be strictly followed during surgery regardless of its histopathological nature.
PubMed-ID: 38469981
DOI: 10.1002/hed.27732

Seven years of Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): Rate of Acceptance and Variation of Diagnostic Approaches Across Different Continents.
J Clin Endocrinol Metab,
M. D. Williams, Z. Liu, E. D. Rossi, S. Agarwal, A. Ryska, A. A. Ghuzlan, A. Bychkov, Z. Baloch, R. Chernock, S. L. Chiosea, N. A. Cipriani, S. Erkilic, M. Fridman, J. F. Hang, A. S. Harahap, C. K. Jung, K. Kakudo, M. Khalil, E. Khanafshar, P. Kumarasinghe, R. Lloyd, T. P. Nguyen, I. T. Ocal, M. L. Prasad, M. Pusztaszeri, C. Rana, P. Sadow, D. P. Sajed, R. Seethala, G. Tallini, H. G. Vuong, G. Yegen, V. A. LiVolsi and Y. E. Nikiforov. 2024.
CONTEXT: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced as a new entity replacing the diagnosis of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (PTC). Significant variability in the incidence of NIFTP diagnosed in different world regions has been reported. OBJECTIVE: To investigate the rate of adoption of NIFTP, change in practice patterns, and uniformity in applying diagnostic criteria among pathologists practicing in different regions. METHODS: Two surveys distributed to pathologists of the International Endocrine Pathology Discussion Group with multiple-choice questions on NIFTP adoption into pathology practice and whole slide images of 5 tumors to collect information on nuclear score and diagnosis. Forty-eight endocrine pathologists, including 24 from North America, 8 from Europe, and 16 from Asia/Oceania completed the first survey and 38 the second survey. RESULTS: A 94% adoption rate of NIFTP by the pathologists was found. Yet, the frequency of rendering NIFTP diagnosis was significantly higher in North America than in other regions ($P = .009$). While the highest concordance was found in diagnosing lesions with mildly or well-developed PTC-like nuclei, there was significant variability in nuclear scoring and diagnosing NIFTP for tumors with moderate nuclear changes (nuclear score 2) (case 2, $P < .05$). Pathologists practicing in North America and Europe showed a tendency for lower thresholds for PTC-like nuclei and NIFTP than those practicing in Asia/Oceania. CONCLUSION: Despite a high adoption rate of NIFTP across geographic regions, NIFTP is diagnosed more often by pathologists in North America. Significant differences remain in diagnosing intermediate PTC-like nuclei and respectively NIFTP, with more conservative nuclear scoring in Asia/Oceania, which may explain the geographic differences in NIFTP incidence.
PubMed-ID: 38874075
DOI: 10.1210/clinem/dgae354

Synergy of Nodal Factors in Predicting Recurrence After Treatment of N1b Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 109(12):3137-45.
K. Xian, S. Xu, H. Huang, C. Xing, X. Wang, S. Liu and J. Liu. 2024.
BACKGROUND: Nodal factors are important predictors of prognosis for papillary thyroid carcinoma (PTC), but their synergistic effect is not well understood. We aimed to explore their synergy in predicting recurrence of clinical N1b (cN1b) PTC. METHODS: Patients who underwent surgery for cN1b PTC from 2013 to 2017 were enrolled. The association between nodal factors and recurrence was assessed using Cox proportional hazards regression models. Interaction and stratified analyses were conducted according to significant nodal factors. RESULTS: Of 1067 cN1b PTC patients included, all nodal factors (bilateral metastasis, largest dimension > 3 cm, micro and gross extranodal extension (mENE, gENE), number of metastatic lymph nodes [MLN], lymph node yield [LNY], and ratio LNR]) were significantly associated with all site and nodal recurrence in the univariate analysis (all P < .05). Multivariate analyses revealed largest dimension > 3 cm, gENE and LNR > 0.21 were associated with elevated both all site (hazard ratio [HR] [95% CI], 2.58 [1.67-4.00], 1.87 [1.26-3.01], 1.68 [1.11-2.42], all P < .01) and nodal recurrences (HR [95% CI], 2.63 [1.67-4.13], 1.90 [1.15-3.12], 1.76 [1.17-2.66], all P < .01). LNR and gENE had interactive effect (all site recurrence: P for interaction = .009; nodal recurrence: P for interaction = .02). LNR was significantly associated with recurrence in patients without gENE (HR [95% CI], all site recurrence: 2.41 [1.50-3.87]; nodal recurrence: 2.51 [1.52-4.14], all P < .001), while when gENE appeared, LNR was no longer associated with recurrence (HR [95% CI], all site recurrence: 0.81 [0.43-1.54], P = .53; nodal recurrence: 0.85 [0.43-1.67], P = .64). CONCLUSION: Nodal factors have synergistic effect in predicting recurrence in cN1b PTC patients. Increasing lymph nodes harvest may only decrease recurrence in patients without gENE, while not in gENE patients.
PubMed-ID: 38748619
DOI: 10.1210/clinem/dgae329

Role of the Degree of Vascular Invasion in Predicting Prognosis of Follicular Thyroid Carcinoma.
J Clin Endocrinol Metab, 109(5):1291-300.
H. Yamazaki, K. Sugino, R. Katoh, K. Matsuzu, W. Kitagawa, M. Nagahama, Y. Rino, A. Saito and K. Ito. 2024.
OBJECTIVE: The present study investigated the prognostic factors for follicular thyroid carcinoma (FTC) with the incorporation of the histologic subtype and degree of vascular invasion (VI). PATIENTS: The records of 474 patients with FTC confirmed by surgical specimens at Ito Hospital from January 2005 to December 2014 were reviewed in this retrospective cohort study. The Cox proportional hazard model was used to determine factors associated with disease-free survival (DFS) and distant metastasis-free survival. RESULTS: Of the 474 patients, 140 (30%) had minimally invasive FTC, 260 (55%) had encapsulated angio-invasive FTC, and 74 (16%) had widely invasive FTC. Among the 428 patients with M0 FTC, the 10-year DFS rates of patients with minimally invasive FTC (n = 133), encapsulated angio-invasive FTC (n = 247), and widely invasive FTC (n = 48) were 97.3%, 84.2%, and 69.9% (P < .001), respectively. A multivariate analysis identified aged >/=55 years (hazard ratio [HR], 2.204; 95% CI, 1.223-3.969; P = .009), histologic subtype (HR, 2.068; 95% CI, 1.064-4.021; P = .032), VI of >/=2 (HR, 6.814; 95% CI, 3.157-14.710; P < .001), and tumor size >40 mm (HR, 2.014; 95% CI, 1.089-3.727; P = .026) as independent negative prognostic factors for DFS. CONCLUSION: Our study results may enable us to stratify the prognosis of FTC more accurately by combining the histologic subtype with the degree of VI >/=2, aged >/=55 years, and tumor size >40 mm.
PubMed-ID: 38006314
DOI: 10.1210/clinem/dgad689

Complications related to thyroidectomy among patients with hyperthyroidism: Exploring the potential for ambulatory surgery.
Head Neck, 46(5):1094-102.
F. G. Zhang, T. J. Ow, J. Lin, R. V. Smith, B. A. Schiff, C. A. DeBiase, J. C. McAuliffe, N. Bloomgarden and V. Mehta. 2024.
BACKGROUND: Total thyroidectomy for hyperthyroidism is typically followed by overnight admission to monitor for complications including thyrotoxicosis. Outpatient thyroid surgery is increasingly common, but its safety in patients with hyperthyroidism has not been well studied. METHODS: This retrospective study reviewed 183 patients with hyperthyroidism who underwent total thyroidectomy from 2015 to 2022 at one urban, academic center. The main outcomes were rates of thyroid storm, surgical complications, and 30-day ED visits and readmissions. RESULTS: Among 183 patients with hyperthyroidism (mean age, 45 +/- 14.5 years; 82.5% female), there were no cases of thyroid storm and complications included recurrent laryngeal nerve (RLN) palsy (7.0%), symptomatic hypocalcemia (4.4%), and hematoma (1.6%). ED visits were present in 1.1% and no patients were readmitted. CONCLUSION: Total thyroidectomy was not associated with thyroid storm and <6% of patients required inpatient management. Ambulatory total thyroidectomy for hyperthyroidism warrants further consideration through identification of predictive factors for postoperative

complications.
PubMed-ID: 38270487
DOI: 10.1002/hed.27658

Coexisting RET/PTC and TERT Promoter Mutation Predict Poor Prognosis but Effective RET and MEK Targeting in Thyroid Cancer.
J Clin Endocrinol Metab, 109(12):3166-75.
W. Zhang, S. Lin, Z. Wang, W. Zhang and M. Xing. 2024.
CONTEXT: The role of RET/PTC rearrangement in the clinical outcomes of papillary thyroid cancer (PTC) is controversial and remains to be clearly undefined. OBJECTIVE: This work aimed to investigate the role of coexisting RET/PTC rearrangement and TERT promoter mutation in the prognosis and therapeutic targeting in PTC. METHODS: A total of 669 PTC patients with complete clinical follow-up and genetic data were pooled from thyroid cancer data sets TCGA-THCA, MSK-MetTropism, and MSK-IMPACT, from whom 163 patients (112 women and 47 men, 4 unknown) with wild-type (WT) BRAF/RAS were identified, with a median age (interquartile range [IQR]) of 46.00 (33.00-61.00) years and a median follow-up time (IQR) of 16.13 (8.09-27.91) months for comparative genotype cohort analysis of mortality. RESULTS: There was a significant concurrence index between RET/PTC and TERT promoter mutations, being 2.040 (95% CI, 1.110-3.747; P = .023). Mortality occurred in 5 of 100 (5%) patients harboring neither mutation, 2 of 18 (11.1%) patients harboring a TERT promoter mutation alone, 0 of 31 (0%) patients harboring a RET/PTC alone, and 7 of 14 (50%) patients harboring both genetic alterations, corresponding to hazard ratios (95% CI) of 1 (reference), 2.469 (0.405-14.022), 3.296e-09 (0-inf), and 9.019 (2.635-30.870), respectively, which remained essentially unchanged after adjustment for patient race, sex, and age. Similar results were observed with BRAF/RAS and TERT promoter mutations. Mechanistically, RET/PTC used the MAP kinase pathway to upregulate the mutated TERT, but not the WT TERT, and, correspondingly, targeting RET and MEK could suppress mutated TERT but not the WT TERT. CONCLUSION: Coexisting RET/PTC and TERT promoter mutation identify PTC as a unique clinical entity with high mortality, providing new implications for genetic-based prognostication and potential therapeutic targeting of RET and MEK guided by RET/PTC and TERT status.
PubMed-ID: 38735658
DOI: 10.1210/clinem/dgae327
PMCID: PMC11570377

A novel minimally invasive endoscopic approach of thyroid surgery-endoscopic thyroidectomy via sternocleidomastoid muscle posteroinferior approach.
Gland Surg, 13(6):942-51.
J. Zhou, Y. Jing, X. Qi, J. Wu, J. Huang, X. Chen, Y. Ding and X. Chen. 2024.
BACKGROUND: Since the endoscopic thyroidectomy was firstly reported by Huscher in 1997, there has been an ongoing debate regarding whether mainstream endoscopic thyroidectomy can be classified as minimally invasive surgery. In this study, we innovatively proposed the endoscopic thyroidectomy via sternocleidomastoid muscle posteroinferior approach (ETSPIA), a novel minimally invasive surgical technique, and compared its efficacy with the well-established transoral endoscopic thyroidectomy vestibular approach (TOETVA). METHODS: We retrospectively analyzed 50 patients who underwent ETSPIA and 50 patients who underwent TOETVA at Beijing Tongren Hospital, comparing their clinical characteristics, operative duration, blood loss, postoperative alterations in parathyroid hormone (PTH) and serum calcium, recovery post-surgery, complications, and follow-up data. RESULTS: The ETSPIA group had a shorter operation time compared to the TOETVA group (243.40+/-58.67 vs. 278.08+/-78.50 min; P=0.01). The ETSPIA group also had less intraoperative blood loss than the TOETVA group (20.60+/-10.58 vs. 33.00+/-11.11 mL; P<0.001). More central lymph nodes were dissected in the ETSPIA group compared to the TOETVA group (5.90+/-4.72 vs. 3.36+/-2.80; P=0.002). However, the difference in the number of positive central lymph nodes dissected was not statistically significant (1.38+/-2.33 for ETSPIA vs. 0.94+/-1.39 for TOETVA; P=0.26). The ETSPIA group had a shorter length of stay (LOS) compared to the TOETVA group (6.82+/-2.02 vs. 8.26+/-2.72 days; P=0.003). The alteration in PTH levels 1 day after surgery was less pronounced in the ETSPIA group compared to the TOETVA group (-26.38%+/-18.43% vs. -35.75%+/-22.95%; P=0.04). At the 1-month postoperative mark, the ETSPIA group showed a marginal increase in PTH levels, whereas the TOETVA group exhibited a slight decrease (10.12%+/-35.43% vs. -11.53%+/-29.51%; P=0.03). Regarding the average percentage change in serum calcium level 1 day after surgery, the ETSPIA group showed a smaller change, though this difference was not statistically significant (-4.79%+/-5.47% vs. -5.66%+/-3.90%; P=0.40). Furthermore, the incidence of hoarseness attributable to transient recurrent laryngeal nerve (RLN) injury in postoperative patients was lower in the ETSPIA group compared to the TOETVA group, but this difference did not reach statistical significance (0% vs. 4%; P=0.15). CONCLUSIONS: Overall, compared to TOETVA, the ETSPIA is characterized by a shorter operative route, enhanced

protection of the parathyroid glands, reduced trauma, and expedited postoperative recovery.
PubMed-ID: 39015696
DOI: 10.21037/gs-24-48
PMCID: PMC11247576

Parathyroids

Meta-Analyses

Skeletal Effect of Parathyroidectomy on Patients With Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis.
J Clin Endocrinol Metab, 109(10):e1922-e35.
N. Kongsaree, T. Thanyajaroen, B. Dechates, P. Therawit, W. Mahikul and K. Ngaosuwan. 2024.
CONTEXT: Parathyroidectomy (PTX) is recommended for curing primary hyperparathyroidism (PHPT), although uncertainty remains regarding the extent of fracture risk reduction following surgery. OBJECTIVE: This work aimed to compare fracture risk and bone mineral density (BMD) changes in patients with PHPT undergoing PTX vs observation (OBS). METHODS: We systematically searched PubMed, Embase, and the Cochrane Library until September 2022, including randomized controlled trials (RCTs) and cohort studies, and reviewed citations from previous reviews. Among 1260 initial records, 48 eligible articles from 35 studies (5 RCTs; 30 cohorts) included PHPT patients receiving PTX or OBS interventions with reported fracture events at any site, including the hip, spine, or forearm, and/or BMD changes at each location. Data extraction followed Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines by 2 independent reviewers. RESULTS: In 238 188 PHPT patients (PTX: 73 778 vs OBS: 164 410), PTX significantly reduced fractures at any site (relative risk [RR], 0.80; 95% CI, 0.74-0.86) compared to OBS. In 237 217 patients (PTX: 73 458 vs OBS: 163 759), the risk of hip fractures decreased (RR, 0.63; 95% CI, 0.52-0.76). No reduction in forearm and vertebral fractures was observed in 3574 and 3795 patients, respectively. The annual percentage BMD changes from baseline were higher in the PTX group: femoral neck, 1.91% (95% CI, 1.14-2.68); hip, 1.75% (95% CI, 0.58-2.92); radius, 1.75% (95% CI, 0.31-3.18); spine, 2.13% (95% CI, 1.16-3.10). CONCLUSION: PTX significantly reduced overall and hip fracture risks in PHPT patients. Despite minimal BMD increase, the substantial decrease in fracture risk suggests additional benefits of PTX beyond mineral content enhancement.
PubMed-ID: 38739762
DOI: 10.1210/clinem/dgae326

4DCT in Discordant Parathyroid Adenoma Scans: Case Series and Meta-Analysis.
Laryngoscope, 134(5):2198-205.
A. Warshavsky, R. Rubin, N. N. Carmel-Neidermann, A. Brenner, G. Shendler, L. Kampel, E. Izkhakov, N. Muhanna and G. Horowitz. 2024.
OBJECTIVE: To evaluate the accuracy of four-dimensional computerized-tomography (4DCT) for localizing parathyroid adenomas (PTAs) in cases with discordant or non-localizing ultrasonography (US) and Technetium-99 sestamibi (MIBI) scans. DATA SOURCES: Retrospective case series and systematic review. REVIEW METHODS: A case series and meta-analysis of patients diagnosed with primary hyperparathyroidism and discordant US and MIBI scans who underwent 4DCT prior to surgery. A comprehensive search for all relevant publications in the English literature between December 2006 and March 2022 was conducted for the meta-analysis. Patients undergoing parathyroidectomy between January 2015 and December 2021 were identified from the institutional electronic database for the case series. All studies were analyzed for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 4DCT adenoma localization capabilities. RESULTS: Thirteen retrospective studies that included 379 patients and one case series that included 37 patients were identified and analyzed. A per-patient analysis revealed sensitivity for lateralization to the correct side (n = 181) ranging from 80% to 100% with a fixed effects model of 89% (95%confidence interval [CI]: 82%-93%) and a PPV for lateralization ranging from 63%-95% with a random effects model of 87% (95% CI: 77%-95%). Sensitivity of localization to the correct quadrant (n = 172) ranged from 53% to 100% with a random effects model of 90.4% (95% CI: 76%-99%), and the PPV for localization ranged from 52% to 100% with a random effects model of 82% (95% CI: 73%-89%). CONCLUSION: 4DCT enhances imaging capabilities of localizing PTAs in cases of discordant or non-localizing US and MIBI scans. LEVEL OF EVIDENCE: NA Laryngoscope, 134:2198-2205, 2024.
PubMed-ID: 37929814
DOI: 10.1002/lary.31142

Randomized controlled trials

- None -

Consensus Statements/Guidelines

Consensus statement of the European Society of Endocrine Surgeons (ESES) on advanced parathyroid cancer: definitions and management.
Br J Surg, 111(5):undefined-undefined.
O. Makay, O. Agcaoglu, C. Nomine-Criqui, K. Van Den Heede, J. I. Staubitz-Vernazza, F. Pennestri, L. Brunaud, M. Raffaelli, M. Iacobone, S. Van Slycke, T. J. Musholt and J. Villar-Del-Moral. 2024.
PubMed-ID: 38713608
DOI: 10.1093/bjs/znae108

Other Articles

Correlation Between Near-Infrared Autofluorescence Properties and Sestamibi Uptakes of Parathyroid Glands in Primary Hyperparathyroidism.
Otolaryngol Head Neck Surg, 171(5):1341-8.
E. Akgun, A. Ibrahimli, M. Rahman, C. Griffith and E. Berber. 2024.
OBJECTIVE: Near-infrared autofluorescence (NIRAF) characteristics of parathyroid glands in primary hyperparathyroidism (pHPT) vary, with unclarity regarding the underlying mechanism. Similarly, (99m)Tc-sestamibi uptake in diseased parathyroid glands is variable. There is a suggestion that oxyphilic cell content may influence both imaging modalities. This study aims to analyze the relationship between NIRAF imaging characteristics, (99m)Tc-sestamibi uptake, and cellular composition in pHPT. STUDY DESIGN: Retrospective analysis of an Institutional Review Board-monitored prospective database. SETTING: Single tertiary referral center. METHODS: NIRAF characteristics of parathyroid glands of patients with pHPT between 2019 and 2024 were compared with (99m)Tc-sestamibi scan findings from a prospective database. Using third-party software, brightness intensity and heterogeneity index (HI) of the glands were calculated. A subgroup of parathyroid glands obtained from consecutive patients with pHPT in 2020 to 2021 underwent histological analysis. RESULTS: A total of 428 patients with 638 diseased parathyroid glands were analyzed. Forty-seven percent of the glands showed an uptake on (99m)Tc-sestamibi scans. The brightness intensity of the NIRAF signals from parathyroid glands that were seen versus not seen on sestamibi was 2.1 versus 2.3 (P = .002) and HI 0.18 versus 0.17 (P = .35), respectively. On multivariate analysis, low autofluorescence intensity, high gland volume, and single adenoma were associated with detectability on (99m)Tc-sestamibi scan (P < .0001). Intraglandular adipose tissue content was lower in diseased glands that were detected on (99m)Tc-sestamibi scans (0% vs 5%, P < .0001). CONCLUSION: Our findings indicate an inverse relationship between autofluorescence intensity and detectability on (99m)Tc-sestamibi scans and a lack of correlation between different cell types and autofluorescence properties.
PubMed-ID: 39154258
DOI: 10.1002/ohn.948

Changes in cardiac functions in patients treated with parathyroidectomy for secondary hyperparathyroidism.
Updates Surg, 76(4):1443-52.
S. Benli, E. Yesil, D. Tazeoglu, C. Ozcan, I. T. Ozcan and A. Dag. 2024.
Our study aims to investigate the changes in cardiac functions, especially myocardial performance index (MPI), in patients who underwent parathyroidectomy for secondary hyperparathyroidism. Patients who underwent parathyroidectomy for secondary hyperparathyroidism between June 2010 and September 2021 were analyzed retrospectively. The patients were divided into two groups: those who underwent total parathyroidectomy (group 1) and those who underwent subtotal parathyroidectomy (group 2). The groups were compared according to the echocardiogram findings performed in the preoperative period and the postoperative sixth month. In addition, cardiac structure, and systolic and diastolic functions, especially myocardial performance index, were evaluated by echocardiography and Doppler imaging. Thirty-seven patients were examined; 16 (43.2%) underwent total parathyroidectomy, and 21 (56.8%) had subtotal

parathyroidectomy performed. Group 1's mean left ventricular end-systolic diameter (LVES) decreased from 2.53 +/- 0.57 to 2.35 +/- 0.37 cm after parathyroidectomy. In Group 1, the postoperative value of LVES and end-systolic volume decreased significantly compared to the preoperative period (p = 0.042, p = 0.008, respectively). EF increased from 59.25 +/- 0.05 to 67.81 +/- 4.04. In Group 1, EF and EV postoperatively increased significantly compared to the preoperative period (p = 0.023, p = 0.021, respectively). The mean MPI decreased from 0.45 +/- 0.07 to 0.39 +/- 0.04 after parathyroidectomy in group 1. In group 2, it decreased from 0.46 +/- 0.06 to 0.40 +/- 0.04 (p < 0.001). The present study provides an improvement in myocardial functions after parathyroidectomy. While LVES, EF, ejection volume, end-systolic volume, and MPI improved in both groups, the MPI improvement was more evident in the total parathyroidectomy group.
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DOI: 10.1007/s13304-024-01812-8
PMCID: PMC11341577

Syndromic MEN1 parathyroid adenomas consist of both subclonal nodules and clonally independent tumors.
Virchows Arch, 484(5):789-98.
K. Brautigam, C. Nesti, P. Riss, C. Scheuba, B. Niederle, T. Grob, A. Di Domenico, M. Neuenschwander, P. Mazal, N. Kohn, R. Trepp, A. Perren and R. M. Kaderli. 2024.
Primary hyperparathyroidism with parathyroid tumors is a typical manifestation of Multiple Endocrine Neoplasia Type 1 (MEN1) and is historically termed "primary hyperplasia". Whether these tumors represent a multi-glandular clonal disease or hyperplasia has not been robustly proven so far. Loss of Menin protein expression is associated with inactivation of both alleles and a good surrogate for a MEN1 gene mutation. The cyclin-dependent kinase inhibitor 1B (CDKN1B) gene is mutated in MEN4 and encodes for protein p27 whose expression is poorly studied in the syndromic MEN1 setting.Here, we analyzed histomorphology and protein expression of Menin and p27 in parathyroid adenomas of 25 patients of two independent, well-characterized MEN1 cohorts. The pattern of loss of heterozygosity (LOH) was assessed by fluorescence in situ hybridization (FISH) in one MEN1-associated parathyroid adenoma. Further, next-generation sequencing (NGS) was performed on eleven nodules of four MEN1 patients.Morphologically, the majority of MEN1 adenomas consisted of multiple distinct nodules, in which Menin expression was mostly lost and p27 protein expression reduced. FISH analysis revealed that most nodules exhibited MEN1 loss, with or without the loss of centromere 11. NGS demonstrated both subclonal evolution and the existence of clonally unrelated tumors.Syndromic MEN1 parathyroid adenomas therefore consist of multiple clones with subclones, which supports the current concept of the novel WHO classification of parathyroid tumors (2022). p27 expression was lost in a large fraction of MEN1 parathyroids and must therefore be used with caution in suggesting MEN4.
PubMed-ID: 38244045
DOI: 10.1007/s00428-023-03730-3
PMCID: PMC11106174

Parathyroidectomy Improves Bone Density in Women With Primary Hyperparathyroidism and Preoperative Osteopenia.
J Clin Endocrinol Metab, 109(6):1494-504.
S. Frey, M. Gerard, P. Guillot, M. Wargny, K. Bach-Ngohou, E. Bigot-Corbel, N. Renaud Moreau, C. Caillard, E. Mirallie, B. Cariou and C. Blanchard. 2024.
CONTEXT: Osteoporosis and/or bone fractures are indications of parathyroidectomy in primary hyperparathyroidism (PHPT), especially in women. However, the benefit of surgery in patients with osteopenia remains unclear. OBJECTIVE: To evaluate bone mineral density (BMD) and bone remodeling biomarkers changes 1 year after parathyroidectomy in women with PHPT. DESIGN: In the prospective, monocentric, observational prospective cohort with primary hyperparathyroidism patients (CoHPT) cohort, women operated for sporadic PHPT since 2016 with >/=1 year follow-up were included. BMD (dual-X ray absorptiometry) and bone remodeling biomarkers [cross-linked C-telopeptide (CTX), procollagen type 1 N-terminal propeptide (P1NP), and bone-specific alkaline phosphatases] were assessed before and 1 year after parathyroidectomy. SETTING: Referral center. PATIENTS: A total of 177 women with PHPT (62.5 +/- 13.3 years, 83.1% menopausal, 43.9% osteopenic, and 45.1% osteoporotic) were included. INTERVENTION: Parathyroidectomy. MAIN OUTCOME MEASURE: BMD change between before and 1 year after parathyroidectomy. RESULTS: Parathyroidectomy resulted in significant increase in BMD and decrease in serum bone remodeling biomarker concentrations. In the 72 patients with baseline osteopenia, mean BMD significantly increased at the lumbar spine [+0.05 g/cm2 (95% confidence interval [CI], 0.03-0.07)], the femoral neck [+0.02 g/cm2 (95% CI 0.00-0.04)], the total hip [+0.02 g/cm2 (95% CI 0.01-0.02)], and the forearm [+0.01 (95% CI 0.00-0.02)], comparable to osteoporotic patients. Among osteopenic patients, those with individual BMD gain (>0.03 g/cm2) at >/=1 site had higher preoperative serum CTX, P1NP, and urine calcium

concentrations than those without improvement. CONCLUSION: Parathyroidectomy significantly improved BMD and remodeling biomarkers in women with osteopenia, thereby supporting the benefit of parathyroidectomy in these patients. Preoperative serum CTX and P1NP concentrations could be useful to predict expected BMD gain.
PubMed-ID: 38152848
DOI: 10.1210/clinem/dgad718

Ultrafast intraoperative parathyroid hormone monitoring system: prospective, multicentre, clinical validity study.
Br J Surg, 111(5):undefined-undefined.
T. R. Kurzawinski, A. Zielke, M. Busch, J. Wagner, C. Soromani, A. Abdelsalam, T. Abdel-Aziz, V. R. Garcia, M. Matias, S. Morley, J. Barth and C. A. Smaxwil. 2024.
BACKGROUND: Intraoperative parathyroid hormone (PTH) monitoring is a proven and reliable adjunct to parathyroid surgery, able to improve the outcomes and efficiency of the diagnostic and therapeutic pathway for patients with primary hyperparathyroidism. This study evaluated the innovative, compact, fully automated NBCL CONNECT Analyzer, which can measure whole-blood PTH in 5 min. METHODS: A prospective multicentre study was conducted in stages: results reviews, recommendations, and implementation of improvements to the mechanical design, components of cartridges, calibration, and sampling protocols. Patients undergoing parathyroidectomy had PTH levels measured on the Analyzer and main laboratory platforms, either Roche or Abbott. The Miami criterion of a 50% drop in PTH concentration was used to define biochemical cure during surgery, and normal postoperative calcium level as cure of primary hyperparathyroidism. Measurements on the Analyzer were done by laboratory staff in London and nurses in Stuttgart. The Pearson coefficient (R) and Wilcoxon test were used for statistical analysis. RESULTS: Some 234 patients (55 male, 179 female) with a median age of 58.5 (age full range 15-88) years underwent parathyroidectomy (195 minimally invasive, 38 bilateral neck exploration, 1 thoracoscopic; 12 conversions) for primary hyperparathyroidism between November 2021 and July 2022. Primary hyperparathyroidism was cured in 225 patients (96.2%). The sensitivity, specificity, and overall accuracy of the Analyzer assay in predicting biochemical cure were 83.9, 100, and 84.8% in phase 1; 91.2, 100, and 91.3% in phase 2; and 98.6, 100, and 98.6% in phase 3. There were no false-positive results (positive predictive value 100%). Correlations between Analyzer measurements and those obtained using the Roche device were very strong ($R = 0.98$, $P < 0.001$ in phase 1; $R = 0.92$, $P < 0.001$ in phase 2; $R = 0.94$, $P < 0.001$ in phase 3), and correlations for Analyzer readings versus those from the Abbott platform were strong ($R = 0.82$, $P < 0.001$; $R = 0.89$, $P < 0.001$; $R = 0.91$, $P < 0.001$). The Analyzer showed continued good mechanical performance, with stable and repeatable operations (calibrations, quality controls). Introducing a stricter sampling protocol and improvements in the clot-detecting system led to a decrease in the number of clotted samples and false-negative results. Outcomes were not affected by measurements performed either by nurses or laboratory staff. CONCLUSION: Intraoperative PTH monitoring during parathyroid surgery can be done accurately, simply, and quickly in whole blood using the Analyzer.
PubMed-ID: 38713606
DOI: 10.1093/bjs/znae101

Intraoperative Parathyroid Hormone Monitoring In Normohormonal Primary Hyperparathyroidism: How Low Do You Go?
Laryngoscope, 134(5):2480-4.
R. H. Law, K. A. Larrabee, A. J. Stefan, D. L. Quan, E. L. Peterson and M. C. Singer. 2024.
OBJECTIVE: The primary goal of this study was to determine in patients with normohormonal primary hyperparathyroidism (NHHPT) what percent reduction in post-excision intraoperative parathyroid hormone (IOPTH) from baseline would yield a rate of cure comparable to that in patients with classical primary hyperparathyroidism (PHPT). METHODS: This is a retrospective cohort study of patients who underwent parathyroidectomy between July 2013 and February 2020. Demographic data, preoperative, intraoperative, and postoperative metrics were collected. Patients with NHHPT were compared to those with classical PHPT. Subgroup analyses were performed. RESULTS: Of the 496 patients included in the study, 66 (13.3%) were of the normohormonal variant based on preoperative intact parathyroid hormone (PTH) levels and 28 (5.6%) based on baseline IOPTH levels. The cure rates in the two normohormonal groups were not significantly different from their classical counterparts (98.4% and 100.0% vs. 97.1%, $p = 1.000$). The median percent decline in post-excision IOPTH from baseline that achieved cure in the normohormonal groups were 82.6% and 80.4% compared to their respective controls at 87.3%, $p = 0.011$ and $p = 0.001$. Although the rate of multiglandular disease was higher in one of the normohormonal variant groups, this difference was due to a higher rate of double adenomas, not four-gland hyperplasia. CONCLUSION: Patients with NHHPT undergoing parathyroidectomy can expect cure rates similar to that in patients with classical PHPT. The results of this study indicate that achieving an 80% drop or more in IOPTH levels predicts a high likelihood of cure. This is true irrespective of whether the patient is deemed normohormonal based on

preoperative or intraoperative testing. LEVEL OF EVIDENCE: 3 Laryngoscope, 134:2480-2484, 2024.
PubMed-ID: 37772923
DOI: 10.1002/lary.31076

A Comparative Genomic Analysis of Parathyroid Adenomas and Carcinomas Harboring Heterozygous Germline CDC73 Mutations.
J Clin Endocrinol Metab,
Y. Li, W. F. Simonds and H. Chen. 2024.
CONTEXT: Parathyroid cancer has been linked to germline mutations of the CDC73 gene. However, carriers harboring cancer-associated germline CDC73 mutations may develop only parathyroid adenoma or no parathyroid disease. This incomplete penetrance indicates that additional genomic events are required for parathyroid tumorigenesis. OBJECTIVE: (1) Determine the status of the second CDC73 allele in parathyroid tumors harboring germline CDC73 mutations, and (2) compare the genomic landscapes between parathyroid carcinomas and adenomas. DESIGN: Whole-exome and RNA sequencing of 12 parathyroid tumors harboring germline CDC73 mutations (6 adenomas and 6 carcinomas) and their matched normal tissues. RESULTS: All 12 parathyroid tumors had gained one somatic event predicted to cause a complete inactivation of the second CDC73 allele. Several distinctive genomic features were identified in parathyroid carcinomas compared to adenomas, including more single nucleotide variants bearing the C>G transversion and APOBEC deamination signatures, frequent mutations of the genes involved in the PI-3K/mTOR signaling, a greater number of copy number variations, and substantially more genes with altered expression. Parathyroid carcinomas also share some genomic features with adenomas. For instance, both have recurrent somatic mutations and copy number loss that impact the genes involved in T-cell receptor signaling and tumor antigen presentation, suggesting a shared strategy to evade immune surveillance. CONCLUSIONS: Biallelic inactivation of CDC73 is essential for parathyroid tumorigenesis in carriers harboring germline mutations of this gene. Despite sharing some genomic features with adenomas, parathyroid carcinomas have more distinctive alterations in the genome, some of which may be critical for cancer formation.
PubMed-ID: 39044678
DOI: 10.1210/clinem/dgae506

Surgery for nonlocalizing hyperparathyroidism in high volume center.
Head Neck, 46(7):1788-94.
A. B. Miller, E. Frank, A. A. Simental, Jr. and M. Feng. 2024.
BACKGROUND: Patients with nonlocalizing hyperparathyroidism pose a significant challenge to surgeons when undergoing neck exploration for parathyroidectomy. METHODS: We evaluated 536 patients that had parathyroidectomy for primary hyperparathyroidism (PHPT) from 2005 to 2018 at a single tertiary academic center, and 155 (29%) had standard nonlocalizing preoperative imaging (negative ultrasound and sestamibi scans). RESULTS: There were a total of 102 (66%) non-ectopic single adenomas in the nonlocalizing group and 325 (85%) single adenomas in the localizing group. There was no significant difference ($p = 0.09$) in adenoma quadrant between localizing and nonlocalizing single adenomas, but the most common location in both groups was right inferior. Patients with nonlocalizing scans were more likely to have double adenomas (21% vs. 9%, $p < 0.001$), ectopic glands (10% vs. 5%, $p = 0.052$), and multi-gland disease (13% vs. 8%, $p = 0.002$). CONCLUSION: Nonlocalizing PHPT patients experienced similar cure and complication rates as localizing PHPT, but required more bilateral explorations and increased operative time.
PubMed-ID: 38362817
DOI: 10.1002/hed.27686

Whole-exome sequencing of atypical parathyroid tumors detects novel and common genes linked to parathyroid tumorigenesis.
J Clin Endocrinol Metab,
E. Pardi, A. M. Poma, L. Torregrossa, L. Pierotti, S. Borsari, S. D. Valentina, C. Marcocci and F. Cetani. 2024.
CONTEXT: Atypical parathyroid tumor (APT) represents a neoplasm characterized by histological features typical of parathyroid carcinoma (PC) but lacking local infiltration and/or distant metastasis, leading to uncertainty regarding its malignant potential. OBJECTIVE: To characterize the molecular landscape and deregulated pathways in APT. METHODS: Whole exome sequencing (WES) was conducted on 16 APTs. DNA from tumors and matched peripheral blood underwent WES using Illumina HiSeq3000. RESULTS: A total of 192 nonsynonymous variants were identified. The median number of protein-altering mutations was 9. The most frequently mutated genes included BCOR, CLMN, EZH1, JAM2, KRTAP13-3, MUC16, MUC19, and OR1S1. Seventeen mutated genes belong to the Cancer Gene Census list. The most consistent hub genes identified through STRING network analysis were ATM, COL4A5, EZH2, MED12, MEN1, MTOR, PI3, PIK3CA, PIK3CB,

and UBR5. Deregulated pathways included the PI3 K/AKT/mTOR pathway, Wnt signaling, and extracellular matrix organization. Variants in genes such as MEN1, CDC73, EZH2, PIK3CA, and MTOR, previously reported as established or putative/candidate driver genes in benign adenoma (PA) and/or PC, were also identified in APT. CONCLUSIONS: APT does not appear to have a specific molecular signature but shares genomic alterations with both PA and PC. The incidence of CDC73 mutations is low, and it remains unclear whether these mutations are associated with a higher risk of recurrence. Our study confirms that PI3 K/AKT/mTOR and Wnt signaling represents the pivotal pathways in parathyroid tumorigenesis and also revealed mutations in key epigenetic modifier genes (BCOR, KDM2A, MBD4, and EZH2) involved in chromatin remodeling, DNA, and histone methylation.
PubMed-ID: 38940486
DOI: 10.1210/clinem/dgae441

Effect of Delayed Parathyroidectomy on Risk of Future Cardiovascular and Nephrolithiasis Interventions in Adults with Primary Hyperparathyroidism [Original Study].
Ann Surg,
K. M. Ramonell, R. Liou, X. Zheng, Z. Song, J. A. Lee, A. Sedrakyan and H. Chen. 2024.
OBJECTIVE: To determine whether the timing of parathyroid surgery impacts the risk of renal stone retreatment and cardiovascular interventions. SUMMARY BACKGROUND DATA: Long-term, untreated primary hyperparathyroidism is associated with significant morbidity including nephrolithiasis and cardiovascular disease. METHODS: We conducted a Population-based Cohort study of New York and California state-wide data from 2000-2020. Adult patients who underwent renal stone treatment and subsequently diagnosed with primary hyperparathyroidism (pHPT) and underwent parathyroidectomy (PTX) were included. Patients were excluded if PTX was prior to index stone procedure, they underwent second stone treatment within 6 months, with stage V CKD, with secondary or tertiary hyperparathyroidism, with prior kidney transplant or hemodialysis, or with prior cancer diagnosis. Rate of renal stone retreatment and cardiovascular interventions after PTX in pHPT patients with nephrolithiasis who underwent parathyroid surgery at </= 2 years and >2 years after index stone procedure was measured. RESULTS: We identified 2,093 patients who underwent first-time stone treatment and subsequent PTX. The median time to PTX was 560 days (IQR 187-1477) and follow-up was 7.4 years (IQR 4.5-13.1). Delaying PTX for more than 2 years increased the risk of renal stone retreatment by 59% (HR 1.59; P<0.001), increased the risk of experiencing coronary disease or associated interventions by 118% (HR=2.18; P=0.01), and increased the risk of experiencing an overall cardiovascular event by 52% (HR 1.52; P<0.01). CONCLUSIONS AND RELEVANCE: In symptomatic pHPT, delaying PTX significantly increases the risk of requiring future stone retreatment and cardiac/vascular surgical interventions. This highlights the importance of early surgical referral and multidisciplinary approaches to optimize outcomes and resource utilization in pHPT.
PubMed-ID: 39176567
DOI: 10.1097/SLA.0000000000006508

Fertility and pregnancy outcomes in primary hyperparathyroidism: Observations from a large insured population.
J Clin Endocrinol Metab,
V. R. Sant, H. Zhou, M. M. Zhou, A. L. Adams, D. S. Ryan, S. K. Case, Y. J. Seo, P. I. Haigh, C. Janzen and M. W. Yeh. 2024.
CONTEXT: Primary hyperparathyroidism (PHPT) has initially been implicated in adverse maternal and neonatal outcomes, while subsequent population studies have failed to show an association. OBJECTIVE: To compare maternal, pregnancy, and neonatal outcomes in patients with and without PHPT. DESIGN: Retrospective matched-cohort study (2005-2020). SETTING: An integrated healthcare delivery system in Southern California. PATIENTS: Women aged 18-44 years were included. Patients with biochemical diagnosis of PHPT were matched 1:3 with eucalcemic controls (non-PHPT). MAIN OUTCOME MEASURES: Achievement of pregnancy, pregnancy outcomes (including rates of abortion, maternal complications), and neonatal outcomes (including hypocalcemia, need for intensive care). RESULTS: The cohort comprised 386 women with PHPT and 1158 age-matched controls. Pregnancy rates between PHPT and control groups were similar (10.6% vs 12.8%). The adjusted rate ratio of pregnancy was 0.89 (95% CI: 0.64-1.24) (PHPT vs non-PHPT). Twenty-nine pregnancies occurred in women with co-existing PHPT and 191 pregnancies occurred in controls, resulting in 23 (79.3%) and 168 (88.0%) live births, respectively (p=0.023). Neonatal outcomes were similar. Live birth rates were similar (86.4%, 80%, 79.2%) for those undergoing parathyroidectomy prior (n=22), during (n=5), or after pregnancy/never (n=24). Among patients who underwent parathyroidectomy during pregnancy, no spontaneous abortions occurred in women entering pregnancy with peak calcium <11.5 mg/dL [2.9 mmol/L]. CONCLUSIONS: We observed no difference in pregnancy rates between women with or without PHPT. Performing parathyroidectomy before pregnancy or during the second trimester appears to be a safe and successful strategy, and adherence to this strategy may be most critical for patients with higher calcium levels (>/=11.5 mg/dL [2.9 mmol/L]).

PubMed-ID: 38867506
DOI: 10.1210/clinem/dgae409

Clinical utility of untimed spot urine sampling in measuring calcium creatinine clearance in the diagnostic work-up of PTH-dependent hypercalcaemia.
Clin Endocrinol (Oxf), 101(3):203-5.
E. Sharma, C. Boot, J. Ramsingh, P. Truran, R. Bliss, A. James and Y. Mamoojee. 2024.
PubMed-ID: 39004955
DOI: 10.1111/cen.15116

Some thoughts on surgery for primary hyperparathyroidism.
Am J Surg, 234:179-80.
A. Sitges-Serra. 2024.
PubMed-ID: 38365558
DOI: 10.1016/j.amjsurg.2024.02.006

Opportunities to improve the diagnosis and treatment of primary hyperparathyroidism: retrospective cohort study.
Gland Surg, 13(7):1201-13.
M. P. Vivero, Y. J. Chen, A. G. Antunez, N. L. Cho, M. A. Nehs, G. M. Doherty, D. W. Bates and J. B. Liu. 2024.
BACKGROUND: Although primary hyperparathyroidism (PHPT) is readily diagnosed biochemically and can be cured with low-risk surgery, it is often underrecognized and undertreated. Our objectives were to characterize, within our health system, how often patients with hypercalcemia were evaluated for PHPT and how often patients with PHPT underwent definitive treatment with parathyroidectomy. METHODS: Ambulatory patients aged 18 years or older seen at our health system between January 2018 and June 2023 with chronic hypercalcemia were identified from the medical record. After excluding causes of secondary hyperparathyroidism, the proportion of patients with parathyroid hormone (PTH) tests was calculated. Among patients with biochemical evidence of PHPT, the proportion of patients who underwent parathyroidectomy was calculated. Multivariable logistic regression was used to identify factors associated with an evaluation for PHPT and, separately, with parathyroidectomy. RESULTS: Of 7,675 patients with chronic hypercalcemia, 3,323 (43.3%) had a PTH test obtained within 6 months. An age between 40-49 vs. <30 years [(odds ratio (OR) =3.2; 95% confidence interval (CI): 1.8-5.6; P<0.001], a serum calcium level between 11.6-12.0 vs. <11.0 mg/dL (OR =3.9; 95% CI: 3.2-4.7; P<0.001), and osteoporosis (OR =3.1; 95% CI: 2.7-3.5; P<0.001) were associated with an evaluation for PHPT. Among those with PTH levels, 1,327 (39.9%) had PHPT but only 916 (69.0%) were recognized. Three hundred and forty-five (26.0%) patients with PHPT underwent parathyroidectomy. An increasing number of surgical indications was associated with parathyroidectomy (P<0.001), though overall rates remained less than 40%. Among indications for surgery, including age and serum total calcium level, only osteoporosis was associated with parathyroidectomy (OR =2.0; 95% CI: 1.4-2.8; P<0.001). CONCLUSIONS: In this study, more than half of patients with chronic hypercalcemia were not evaluated for PHPT. Among patients with biochemical evidence of PHPT, one-third were unrecognized and only one-in-four received curative treatment. Opportunities to improve the management of PHPT exist within our large integrated health system.
PubMed-ID: 39175695
DOI: 10.21037/gs-24-128
PMCID: PMC11336797

Very elevated parathyroid hormone levels in patients with primary hyperparathyroidism: Is it cancer?
Am J Surg, 231:140-1.
C. Wu, M. Holland, Z. Song, R. Wang, A. Gillis, P. Zmijewski, B. Lindeman, J. Fazendin and H. Chen. 2024.
PubMed-ID: 38155074
DOI: 10.1016/j.amjsurg.2023.12.026
PMCID: PMC11180976

Screening for asymptomatic nephrolithiasis in primary hyperparathyroidism patients is warranted.
Am J Surg, 231:91-5.
T. Zabolotniuk, M. Guo, M. Kwon, A. Watanabe, J. M. H. Teichman and S. M. Wiseman. 2024.
BACKGROUND: We aimed to investigate the prevalence, characteristics, and management of nephrolithiasis in primary hyperparathyroidism (PHPT) patients. METHODS: Medical records of patients who underwent parathyroidectomy at a tertiary care hospital in British Columbia from January 2016 to April 2023 were retrospectively reviewed. Demographic

data, laboratory results, imaging reports, and urologic consultations were examined. Descriptive statistics and relevant statistical tests, including logistic regressions, were utilized for data analysis. RESULT: Of the 413 PHPT patients included in the study population, 41.9% harbored renal stones, and nearly half (48.6%) required urological interventions. Male sex, elevated preoperative serum ionized calcium (iCa) and 24-h urinary calcium (24 h urine Ca) levels were independent risk factors for stone formation. Additionally, male sex, younger age, and lower preoperative serum 25-hydroxyvitamin D (25(OH)D) level were associated with higher odds of requiring urological intervention for stones. CONCLUSIONS: This study identified significant prevalence of asymptomatic renal calcifications in PHPT patients, with a substantial proportion necessitating urological intervention. These findings emphasize the importance of incorporating screening and treatment of renal stones into the management of PHPT patients.
PubMed-ID: 38480062
DOI: 10.1016/j.amjsurg.2024.03.007

Higher risk of incident diabetes among patients with primary hyperparathyroidism.
Clin Endocrinol (Oxf), 101(6):605-13.
Y. Zhang, H. Wu, A. Yang, Y. H. N. N, X. Zhang, E. S. H. Lau, E. W. K. Chow, A. P. S. Kong, E. Y. K. Chow, J. C. N. Chan, A. O. Y. Luk and R. C. W. Ma. 2024.
OBJECTIVES: There is relatively scarce data regarding the association between primary hyperparathyroidism (PHPT) and incident diabetes in large population-based longitudinal studies. We aimed to evaluate the risk of incident diabetes in individuals with and without PHPT and investigate the association between serum calcium concentrations and the risk of incident diabetes in patients with PHPT. METHODS: We included 2749 PHPT patients and 13,745 age, sex and index year matched non-PHPT individuals during 2000-2019. We used Cox regression models to compare the risk of incident diabetes in individuals with and without PHPT, and the risk of incident diabetes in PHPT patients with serum calcium concentration above and below the median value. The association between serum calcium concentrations and the risk of incident diabetes was examined by restricted cubic spline analyses in patients with PHPT. RESULTS: During a median follow-up time of 5.17 years (IQR 2.17, 9.58), 433 patients (15.75%) with PHPT and 2110 individuals (15.35%) without PHPT developed diabetes, respectively. Patients with PHPT had a higher incidence rate of diabetes compared to non-PHPT individuals (27.60 [95% CI 25.00, 30.30] vs. 23.90 [95% CI 22.80, 24.90] per 1000 person-years, log-rank test p = .007]. Crude Cox regression model showed PHPT was associated with a 15% higher risk of incident diabetes (HR 1.15, 95%CI 1.04, 1.28). In patients with PHPT, a 44% higher risk of incident diabetes was found in patients with serum calcium concentrations above the median value (2.63 mmol/L), compared to those below the median value (HR 1.44, 95%CI 1.08, 1.90). Restricted cubic spline analyses confirmed a positive linear association between serum calcium concentrations and the risk of incident diabetes in those with PHPT (p-value for nonlinear = .751) CONCLUSIONS: Patients with PHPT had a higher risk of incident diabetes compared to non-PHPT individuals. A positive linear association was found between serum calcium concentrations and the risk of incident diabetes in patients with PHPT.
PubMed-ID: 39038182
DOI: 10.1111/cen.15118

ASO Author Reflections: Distant Metastatic Parathyroid Carcinoma: Risk Factors, Patterns, and Outcomes.
Ann Surg Oncol, 31(10):6893-4.
T. Zhao, W. Yang, R. Shen, Q. Chen, M. Jin, H. Gu, H. Shen, Q. Wang, J. Wang, X. Liu, D. Feng, L. Zhao, G. An and B. Wei. 2024.
PubMed-ID: 38922544
DOI: 10.1245/s10434-024-15680-4

Risk Factors of Distant Metastatic Parathyroid Carcinoma and Insights into Therapeutic Perspectives.
Ann Surg Oncol, 31(10):6865-74.
T. Zhao, W. Yang, R. Shen, Q. Chen, M. Jin, H. Gu, H. Shen, Q. Wang, J. Wang, X. Liu, D. Feng, L. Zhao, G. An and B. Wei. 2024.
BACKGROUND: Distant metastatic parathyroid carcinoma (DM-PC) is a rare but often lethal entity with limited data about prognostic indicators. We sought to investigate the risk factors, patterns, and outcomes of DM-PC. METHODS: In this observational cohort study, 126 patients who underwent surgery for PC at a tertiary referral center from 2010 to 2023 were enrolled, among whom 38 had DMs. Univariate and multivariate Cox regression analyses were used to assess the effects of prognostic factors on DM. RESULTS: The cumulative incidence of DM was 14.1%, 33.8%, and 66.9% at 5, 10, and 20 years in the duration of disease course, respectively. DM-PC patients suffered a worse 5-year overall survival of 37.1% compared with 89.8% in the non-DM patients ($p < 0.001$). DM-PC patients also suffered more previous operations ($p <$

0.001), higher preoperative serum calcium (p<0.001) and parathyroid hormone (PTH) levels (p < 0.001), lower frequencies of R0 resection (p < 0.001), higher rates of pathological vascular invasion (p = 0.020), thyroid infiltration (p = 0.027), extraglandular extension (p = 0.001), upper aerodigestive tract (UAT) invasion (p < 0.001), and lymph node metastasis (p < 0.001). Multivariate Cox regression revealed that non-R0 resection (HR 6.144, 95% CI 2.881-13.106, p < 0.001), UAT invasion (HR 3.718, 95% CI 1.782-7.756, p < 0.001), and higher preoperative PTH levels (HR 1.001, 95% CI 1.000-1.001, p = 0.012) were independent risk factors of DM. CONCLUSIONS: Upper aerodigestive tract invasion and higher preoperative PTH levels might be risk factors for possible metastatic involvement of PC. R0 resection and closer surveillance should be considered in such cases to minimize the risk of DM and to optimize patient care.
PubMed-ID: 38879674
DOI: 10.1245/s10434-024-15611-3

Adrenals

Meta-Analyses

Outcomes of SDHB Pathogenic Variant Carriers.
J Clin Endocrinol Metab, 109(9):2400-10.
D. F. Davidoff, R. De Abreu Lourenco, V. H. M. Tsang, D. E. Benn and R. J. Clifton-Bligh. 2024.
CONTEXT: Carriers of germline pathogenic variants (PVs) in succinate dehydrogenase type B (SDHB) are at increased risk of developing pheochromocytomas and paragangliomas (PPGLs). Understanding their outcomes can guide recommendations for risk assessment and early detection. OBJECTIVE: We performed a systematic review and meta-analysis of the following outcomes in SDHB PV carriers: age-specific risk of developing tumors, metastatic progression, second primary tumor development, and mortality. METHODS: PubMed, MEDLINE, and EMBASE were searched. Sixteen studies met the inclusion criteria and were sorted into 4 outcome categories: age-specific penetrance, metastatic disease, risk of second tumor, and mortality. We assessed heterogeneity and performed a meta-analysis across studies using a random-effects model with the DerSimonian and Laird method. RESULTS: Penetrance of PPGLs for nonproband/nonindex SDHB PV carriers by age 20 was 4% (95% CI, 3%-6%), 11% (95% CI, 8%-15%) by age 40, 24% (95% CI, 19%-31%) by age 60%, and 35% (95% CI, 25%-47%) by age 80. The overall risk of metastatic disease for nonproband/nonindex carriers with PPGLs was 9% (95%, CI 5%-16%) per lifetime. In all affected cases (combining both proband/index and nonproband/nonindex carriers with tumors), the risk of a second tumor was 24% (95% CI, 18%-31%) and all-cause 5-year mortality was 18% (95% CI, 6%-40%). CONCLUSION: Penetrance for PPGLs in SDHB PV carriers increases linearly with age. Affected carriers are at risk of developing and dying of metastatic disease, or of developing second tumors. Lifelong surveillance is appropriate.
PubMed-ID: 38605204
DOI: 10.1210/clinem/dgae233
PMCID: PMC11318991

Efficacy and safety of adrenal arterial embolization for primary aldosteronism: a systematic review and meta-analysis.
Gland Surg, 13(6):825-32.
S. Fu, W. Xu, T. Wang, J. Liu and H. Li. 2024.
BACKGROUND: Primary aldosteronism (PA) is related with resistant hypertension and cardiovascular events. Adrenal artery embolization (AAE) is a choice for patients who refused surgery and medical therapy. However, whether AAE can effectively and safely treat PA is unclear. We performed this meta-analysis to determine the efficacy and safety of AAE for patients with PA. METHODS: Databases including Cochrane Library, Embase, PubMed and Web of Science were used to obtain relevant articles published before July 30, 2023. The primary outcome was blood pressure before and after AAE. The second outcomes included changes in plasma aldosterone level, serum potassium level, and plasma cortisol level. RESULTS: Finally, 7 prospective studies with 222 patients were included. The results showed that systolic and diastolic blood pressure was reduced by 21.68 mmHg (P<0.001) and 10.54 mmHg (P=0.007) respectively after AAE. The change in plasma aldosterone and serum potassium level was -11.52 ng/dL and 0.61 mmol/L respectively (P<0.001), whereas the reduction in cortisol level was not apparent. Moreover, AAE is a relatively safe procedure which only causes some minor complications such as back pain and fever. CONCLUSIONS: This meta-analysis indicated that AAE could effectively and safely treat PA. It is a good choice for patients that are not suitable for adrenalectomy or drug therapy.
PubMed-ID: 39015722
DOI: 10.21037/gs-23-523
PMCID: PMC11247589

The Prevalence of Obstructive Sleep Apnea in Patients With Primary Aldosteronism.
J Clin Endocrinol Metab, 109(10):2681-91.
J. Y. Sheu, L. Y. Chang, J. Y. Chen, M. H. Chuang, V. C. Wu and J. S. Chueh. 2024.
CONTEXT: Investigating the co-occurrence of obstructive sleep apnea (OSA) and primary aldosteronism (PA) is crucial for understanding their interrelation. OBJECTIVE: This work aimed to evaluate the prevalence of OSA in individuals diagnosed with PA and to assess the prevalence of PA within the OSA population, with a specific focus on hypertensive individuals. METHODS: An exhaustive search was performed across PubMed, Embase, CINAHL, Scopus, and Web of Science up to September 2023, without restrictions on language or publication date. Studies were selected based on their focus on the prevalence of OSA in PA patients and vice versa, specifically in hypertensive individuals. Data were extracted using

standard guidelines, focusing on patient characteristics, prevalence rates, and other relevant clinical parameters. RESULTS: Proportional meta-analysis using a random-effects model revealed a 59.8% prevalence of OSA in hypertensive PA patients, with 45.4% exhibiting moderate-to-severe OSA. Meta-regression showed no significant effect of age, sex, body mass index, antihypertensive medication, systolic blood pressure, diastolic blood pressure, or serum potassium on OSA prevalence. However, a significant positive association was found with the glomerular filtration rate (GFR) (P < .001). Subgroup analysis also revealed that a hyperfiltration rate (GFR >/= 100 mL/min per 1.73 m2) may be associated with a higher prevalence of OSA (71%, P value for interaction < .01). Among hypertensive OSA patients, 11.2% had PA. CONCLUSION: A substantial prevalence of OSA in individuals with PA was identified, demonstrating a complex interplay between these conditions in hypertensive patients. Notably, the prevalence of OSA was significantly associated with kidney hyperfiltration.
PubMed-ID: 38941133
DOI: 10.1210/clinem/dgae415

Randomized controlled trials

Adrenalectomy Improves Body Weight, Glucose, and Blood Pressure Control in Patients With Mild Autonomous Cortisol Secretion: Results of an Randomized Controlled Trial by the Co-work of Adrenal Research (COAR) Study.
Ann Surg, 279(6):945-52.
J. M. Koh, K. Song, M. K. Kwak, S. Suh, B. J. Kim, T. Y. Sung, J. H. Hong, B. C. Jeong, J. H. Kim and S. H. Lee. 2024.
OBJECTIVE: To assess the metabolic effects of adrenalectomy in patients with mild autonomous cortisol secretion (MACS). BACKGROUND: Despite retrospective studies showing the association of adrenalectomy for MACS with beneficial metabolic effects, there have been only 2 randomized prospective studies with some limitations to date. METHODS: A prospective, multicenter study randomized 132 patients with adrenal incidentaloma without any features of Cushing syndrome but with serum cortisol >50 nmol/L after a 1 mg overnight dexamethasone suppression test into an adrenalectomy group (n = 66) or control group (n = 66). The primary outcomes were changes in body weight, glucose, and blood pressure (BP). RESULTS: Among the 118 participants who completed the study with a median follow-up duration of 48 months (range: 3-66), the adrenalectomy group (n = 46) exhibited a significantly higher frequency of improved weight control, glucose control, and BP control (32.6%, 45.7%, and 45.7%, respectively) compared with the control group (n = 46; 6.5%, P = 0.002; 15.2%, P = 0.002; and 23.9%, P = 0.029, respectively) after matching for age and sex. Adrenalectomy [odds ratio (OR) = 10.38, 95% CI = 2.09-51.52, P = 0.004], body mass index (OR = 1.39, 95% CI = 1.08-1.79, P = 0.010), and cortisol after a 1 mg overnight dexamethasone suppression test levels (OR = 92.21, 95% CI = 5.30-1604.07, P = 0.002) were identified as independent factors associated with improved weight control. Adrenalectomy (OR = 5.30, 95% CI = 1.63-17.25, P = 0.006) and diabetes (OR = 8.05, 95% CI = 2.34-27.65, P = 0.001) were independently associated with improved glucose control. Adrenalectomy (OR = 2.27, 95% CI = 0.87-5.94, P = 0.095) and hypertension (OR = 10.77, 95% CI = 3.65-31.81, P < 0.001) demonstrated associations with improved BP control. CONCLUSIONS: adrenalectomy improved weight, glucose, and BP control in patients with MACS.
PubMed-ID: 38126763
DOI: 10.1097/SLA.0000000000006183

Consensus Statements/Guidelines

- None -

Other Articles

Correlation of Histopathologic Subtypes of Primary Aldosteronism with Clinical Phenotypes and Postsurgical Outcomes.
J Clin Endocrinol Metab, 109(8):e1582-e92.
C. H. Ahn, Y. B. Lee, J. H. Kim, Y. L. Oh, J. H. Kim and K. C. Jung. 2024.
CONTEXT: Clinical implications of unilateral primary aldosteronism (PA) histopathology remain to be determined in various

ethnic populations. OBJECTIVE: We examined the histopathology of unilateral PA using CYP11B2 immunostaining in relation to clinical phenotypes and postsurgical outcomes. METHODS: Patients consecutively operated for unilateral PA from 2010 to 2020 at 3 tertiary hospitals in South Korea were retrospectively enrolled. Adrenals with solitary aldosterone-producing adenomas and/or dominant aldosterone-producing nodules were classified as the classical and the others as the nonclassical groups. The classical group was subdivided into mixed or solitary group according to whether other aldosterone-producing lesions coexist or not. RESULTS: Of the 240 cases, 124 were solitary, 86 mixed, and 30 nonclassical. Baseline serum potassium concentration was lower in the solitary group than the mixed or nonclassical group. Plasma aldosterone concentration after saline loading was the highest in the solitary group (median 31.65 ng/dL), followed by the mixed group (median 25.40 ng/dL), and the lowest in the nonclassical group (median 14.20 ng/dL). Solitary and mixed groups showed higher lateralization indices and lower contralateral indices than the nonclassical group. The contralateral index was lower in the solitary group than the mixed group. At 6 to 12 months after adrenalectomy, fewer antihypertensive medications were required for the solitary and mixed groups than the nonclassical group. CONCLUSION: The solitary group, followed by the mixed group, was associated with more severe hyperaldosteronism and more suppressed aldosterone production from the contralateral side than the nonclassical group. Histopathologic phenotypes were related to the clinical manifestations and may suggest postoperative prognosis.
PubMed-ID: 38127970
DOI: 10.1210/clinem/dgad747

Genetic testing for primary aldosteronism in SPAIN: Results from the SPAIN-ALDO Registry and review of the literature.
J Clin Endocrinol Metab,
M. Araujo-Castro, J. G. Ruiz-Sanchez, C. Gonzalvo, C. Lamas, P. Parra Ramirez, P. Martin Marcos-Rojas, M. Paja, C. Robles Lazaro, T. Michalapou, M. Tous, M. Gonzalez, J. M. Recio Cordova, A. Casteras, P. Fernandez-Alvarez, V. Barca Tierno and P. Mulatero. 2024.
PURPOSE: To determine the rate of genetic testing for familial hyperaldosteronism (FH) in the SPAIN-ALDO Registry and to describe the clinical characteristics of patients with FH. In addition, a literature review of reports of FH cases was performed. METHODS: A retrospective multicenter study of primary aldosteronism (PA) in patients followed in 35 Spanish tertiary hospitals (SPAIN-ALDO Registry). RESULTS: Twenty-five of the 855 patients (3%) with PA included in the registry underwent genetic testing for FH, with complete results available in only 24 patients. However, we found that there were 57 patients who met the criteria for performing a genetic study of PA. Only 8 out of these 57 patients were genetically tested (14.0%), while the reasons to perform a genetic study in the remaining 9 genetically studied cases were quite heterogeneous. A positive result for FH was found only in one case for FH type III (KCNJ5 pathogenic variant). A systematic review of the literature was performed and identified a total of 25 articles reporting 246 patients with FH type I; 12 articles reporting 72 patients with FH type II; 14 articles reporting 29 cases of FH type III and 3 articles reporting 12 patients with FH type IV. CONCLUSION: The genetic study of familial hyperaldosteronism is often scarce in real-world clinical practice, as 86% of patients with criteria to undergo genetic study were not evaluated in our cohort. Nevertheless, FH is an uncommon cause of PA, representing only 0.2% of cases in the SPAIN-ALDO Registry, although its prevalence may be as high as 4% among suspected cases might be studied.
PubMed-ID: 39058909
DOI: 10.1210/clinem/dgae523

The effect of adrenalectomy on overall survival in metastatic adrenocortical carcinoma.
J Clin Endocrinol Metab,
A. Assad, R. B. Incesu, S. Morra, L. Scheipner, A. Baudo, C. Siech, M. De Angelis, Z. Tian, S. Ahyai, N. Longo, F. K. H. Chun, S. F. Shariat, D. Tilki, A. Briganti, F. Saad and P. I. Karakiewicz. 2024.
CONTEXT: Although complete surgical resection provides the only means of cure in adrenocortical carcinoma (ACC), the magnitude of the survival benefit of adrenalectomy in metastatic ACC (mACC) is unknown. OBJECTIVE: To assess the effect of adrenalectomy on survival outcomes in patients with mACC in a real-world setting. DESIGN AND SETTING: Patients with mACC were identified within the Surveillance, Epidemiology, and End Results database (SEER 2004-2020) and we tested for differences according to adrenalectomy status. PATIENTS: Patients aged >/=18 years with metastatic ACC at initial presentation who were treated between 2004-2020. INTERVENTION: Primary tumor resection status (Adrenalectomy vs no-adrenalectomy). MAIN OUTCOME AND MEASURES: Kaplan-Meier plots, multivariable Cox regression models and landmark analyses were used. Sensitivity analyses focused on use of systemic therapy, contemporary (2012-2020) vs. historical (2004-2011), single vs. multiple metastatic sites and assessable specific solitary metastatic sites (lung only and liver only). RESULTS: Of 543 patients with mACC, 194 (36%) underwent adrenalectomy. In multivariable analyses, adrenalectomy was associated with lower overall mortality without (hazard ratio [HR]: 0.39; p<0.001), as well as with

three months' landmark analyses (HR: 0.57, p=0.002). The same association effect with three months' landmark analyses was recorded in patients exposed to systemic therapy (HR: 0.49, p<0.001), contemporary patients (HR: 0.57, p=0.004), historical patients (HR: 0.42 , p<0.001), and in those with lung only solitary metastasis (HR: 0.50, p=0.02). In contrast, no significant association was recorded in patients naive to systemic therapy (HR: 0.68, p=0.3), those with multiple metastatic sites (HR: 0.55, p=0.07) and those with liver only solitary metastasis (HR: 0.98, p=0.9). CONCLUSIONS: The current results indicate a potential protective effect of adrenalectomy in mACC, particularly in patients exposed to systemic therapy and those with lung-only metastases.
PubMed-ID: 39162017
DOI: 10.1210/clinem/dgae571

Double CYP11B1/CYP11B2 Immunohistochemistry and Detection of KCNJ5 Mutations in Primary Aldosteronism.
J Clin Endocrinol Metab, 109(10):2433-43.
B. Caroccia, L. Lenzini, G. Ceolotto, F. Gioco, A. Benetti, A. Giannella, H. Ajjour, F. Galuppini, G. Pennelli, T. M. Seccia, C. Gomez-Sanchez and G. P. Rossi. 2024.
CONTEXT: The search for somatic mutations in adrenals resected from patients with primary aldosteronism (PA) is performed by Sanger sequencing, often implemented with immunohistochemistry (IHC)-guidance focused on aldosterone-producing (CYP11B2-positive) areas. OBJECTIVE: To investigate the impact of double IHC for CYP11B1 and CYP11B2 on Sanger and next-generation sequencing (NGS). METHODS: We investigated 127 consecutive adrenal aldosterone-producing adenomas from consenting surgically cured PA patients using double IHC for CYP11B1 and CYP11B2, by Sanger sequencing and NGS. RESULTS: Double IHC for CYP11B2 and CYP11B1 revealed 3 distinct patterns: CYP11B2-positive adenoma (pattern 1), mixed CYP11B1/CYP11B2-positive adenoma (pattern 2), and adrenals with multiple small CYP11B2-positive nodules (pattern 3). Sanger sequencing allowed detection of KCNJ5 mutations in 44% of the adrenals; NGS revealed such mutations in 10% of those negative at Sanger and additional mutations in 61% of the cases. Importantly the rate of KCNJ5 mutations differed across patterns: 17.8% in pattern 1, 71.4% in pattern 2, and 10.7% in pattern 3 (chi2 = 22.492, P < .001). CONCLUSION: NGS allowed detection of mutations in many adrenals that tested negative at Sanger sequencing. Moreover, the different distribution of KCNJ5 mutations across IHC patterns indicates that IHC-guided sequencing protocols selecting CYP11B2-positive areas could furnish results that might not be representative of the entire mutational status of the excised adrenal, which is important at a time when KCNJ5 mutations are suggested to drive management of patients with aldosterone-producing adenomas.
PubMed-ID: 38888173
DOI: 10.1210/clinem/dgae411

Clinical and biochemical data for the diagnosis of endogenous hypercortisolism: the "Cushingomic" approach.
J Clin Endocrinol Metab,
F. Ceccato, A. Bavaresco, E. Ragazzi, M. Barbot, M. Boscaro, D. Basso, C. Scaroni and G. Antonelli. 2024.
CONTEXT: The clinical presentation of Cushing's syndrome (CS) overlaps with common conditions. Recommended screening tests are serum cortisol after 1-mg overnight dexamethasone suppression test (DST), urinary free cortisol (UFC), and late-night salivary cortisol (LNSC). METHODS: We analyzed the diagnostic accuracy of screening tests in 615 patients without CS (263 suspected CS, 319 adrenal and 33 pituitary incidentaloma) and 40 with CS. Principal component analysis, K-means clustering, and neural network were used to compute an integrated analysis among tests, comorbidities, and signs/symptoms of hypercortisolism. RESULTS: The diagnostic accuracy of screening tests for CS was high, DST and UFC were slightly superior to LNSC. The threshold of DST should be adapted to the population considered, especially in adrenal incidentaloma with mild autonomous cortisol secretion: the cutoff to differentiate CS should be increased to 196 nmol/L. Diabetes, hypertension, and obesity were more common in patients without CS: the direction of their vectors was not aligned and their correlation with screening tests was poor. Clustering allowed us to differentiate those patients without CS in cluster one (aged osteoporotic patients with impaired screening tests), cluster two (hypertensive and metabolic phenotype), and cluster three (young subjects with a low likelihood of overt CS). A neural network model that combined screening tests and clinical presentation was able to predict the CS diagnosis in the validation cohort with 99% precision and 86% accuracy. CONCLUSIONS: Despite the high diagnostic accuracy of screening tests to detect CS, cortisol-related comorbidities or adrenal incidentaloma should be considered when interpreting a positive test.
PubMed-ID: 39056252
DOI: 10.1210/clinem/dgae517

Letter to the Editor From A.H. Jan Danser and Ingrid M. Garrelds: The Clinical Impact of Sample Storage at -20 degrees C on Renin Reference Intervals and Aldosterone-Renin Ratio Calculations.
J Clin Endocrinol Metab, 109(9):e1806-e7.
A. H. J. Danser and I. M. Garrelds. 2024.
PubMed-ID: 38629832
DOI: 10.1210/clinem/dgae243

Adrenocortical carcinoma: what you at least should know.
Br J Surg, 111(8):undefined-undefined.
C. de Ponthaud, M. Roy and S. Gaujoux. 2024.
PubMed-ID: 39107063
DOI: 10.1093/bjs/znae177

ASO Author Reflections: Continued Refinement of Perioperative Protocols to Predict Secondary Adrenal Insufficiency After Unilateral Adrenalectomy.
Ann Surg Oncol, 31(12):8146-7.
S. Johnson, S. Dream and T. S. Wang. 2024.
PubMed-ID: 39068314
DOI: 10.1245/s10434-024-15900-x

Assessing Lateralization Index of Adrenal Venous Sampling for Surgical Indication in Primary Aldosteronism.
J Clin Endocrinol Metab,
H. Kobayashi, Y. Nakamura, M. Abe, O. Ragnarsson, E. Gkaniatsa, M. A. Grytaas, K. Lovas, N. Wada, T. Ichijo, D. A. Heinrich, W. Drake, S. O'Toole, T. Kocjan, D. Kastelan, I. Kraljevic, K. Yamamoto, M. Tsuiki, S. Kloock, U. Dischinger, M. Parasiliti-Caprino, G. Sven, A. Spyroglou, R. M. Furnica, F. Fallo, G. Maiolino, M. Kometani, V. C. Wu, F. Beuschlein, M. Reincke and M. Naruse. 2024.
BACKGROUND: Clinical practice guidelines recommend the Lateralization Index (LI) as the standard for determining surgical eligibility in primary aldosteronism (PA). Our goal was to identify the optimal LI cut-offs in adrenal venous sampling (AVS) for diagnosing PA that is amenable to surgical cure. METHODS: We conducted a retrospective international cohort study across 16 institutions in 11 countries, including 1,550 patients with PA who underwent AVS, with and/or without ACTH stimulation. The establishment of optimal cut-offs was informed by a survey of 82 PA patients in Japan, aimed at determining the LI cut-off aligned with patient expectations for a surgical cure rate. RESULTS: The survey revealed that a median cure rate expectation of 80% would motivate PA patients towards undergoing adrenalectomy. The optimal LI cut-offs achieving an adjusted positive predictive value (PPV) of 80% were identified as 3.8 for unstimulated AVS and 3.4 for ACTH-stimulated AVS. Furthermore, a contralateral ratio of less than 0.4 and the detection of an adrenal nodule on CT imaging were identified as independent predictors of surgically curable PA. Incorporating these factors with the optimal LI cut-offs, the adjusted PPV increased to 96.6% for unstimulated AVS and 89.6% for ACTH-stimulated AVS. No clear differences in predictive ability between unstimulated and ACTH-stimulated LI were found. CONCLUSIONS AND RELEVANCE: The present study clarified the optimal LI cut-offs for without and with ACTH stimulation. The presence of contralateral suppression and adrenal nodule on CT imaging seems to provide additional available information besides LI for surgical indication.
PubMed-ID: 38747468
DOI: 10.1210/clinem/dgae336

Immune checkpoint molecules in adrenocortical carcinoma: hope for immunotherapy.
J Clin Endocrinol Metab,
E. Lalli. 2024.
PubMed-ID: 38739542
DOI: 10.1210/clinem/dgae311

Clinical outcomes from surgical management of primary aldosteronism based on inconclusive adrenal vein sampling.
Clin Endocrinol (Oxf), 101(1):10-2.
R. Norman, C. Carr-Knox, C. Boot, R. Jackson, M. Ramzan, P. Truran, J. Ramsingh, R. Bliss, A. James, Y. Mamoojee and R. V. I. E. Group. 2024.

PubMed-ID: 38764308
DOI: 10.1111/cen.15076

Reply to: Letter to the Editor From A.H. Jan Danser and Ingrid M. Garrelds: The Clinical Impact of Sample Storage at -20 degrees C on Renin Reference Intervals and Aldosterone-renin Ratio Calculations.
J Clin Endocrinol Metab, 109(9):e1810-e1.
O. Ozcan, J. J. Hillebrand, W. P. J. den Elzen and A. C. Heijboer. 2024.
PubMed-ID: 38629857
DOI: 10.1210/clinem/dgae245

Biochemical Control in Cushing's syndrome: Outcomes of the treatment in a large single center cohort.
J Clin Endocrinol Metab,
K. Ritzel, J. Fazel, L. August, V. Fedtke, E. Nowak, F. Vogel, L. Braun, S. Zopp, C. Then, H. Kunzel, N. Reisch, P. Zimmermann, J. Thorsteinsdottir, J. Schopohl, M. Bidlingmaier, F. Beuschlein, M. Reincke and G. Rubinstein. 2024.
BACKGROUND: Normalization of hypercortisolism is essential to reduce morbidity and mortality in patients with Cushing's syndrome (CS). The aim of this analysis was to assess biochemical control rates in patients with Cushing's disease (CD), ectopic Cushing's syndrome (ECS) and adrenal Cushing's syndrome (ACS). METHODS: Patients with confirmed CS (n= 296) treated in a single tertiary care center were retrospectively analysed (185 CD, 27 ECS, 84 uni- and bilateral ACS). RESULTS: Firstline treatment led to biochemical control in 82% of the patients. Time to biochemical control (median, IQR) was longer in CD (11.0 weeks, 5.6-29.8; p< 0.05) than in ACS (7.7 weeks, 4.1-17.1) and ECS (5.6 weeks, 4.1-23.3). Disease persistence or recurrence after first-line therapy was observed more often in CD (24% and 18%; p< 0.05) than in ECS (15% and 15%) and ACS (6% and 4%). Total time in hypercortisolism since diagnosis was significantly shorter in patients with CD diagnosed since 2013, after specialized patient care was implemented, compared to patients diagnosed before 2013 (13.5 weeks, vs. 26.1 weeks; p< 0.0070). Control of hypercortisolism at last follow up (76 months, 38-163) was achieved in 94% of patients with ACS, 100% of patients with ECS and 92% of patients with CD. CONCLUSIONS: Biochemical control can be achieved in most patients with different subtypes of CS within a reasonable time frame. Control of hypercortisolism has improved over time.
PubMed-ID: 38767080
DOI: 10.1210/clinem/dgae337

Adrenal cysts less than 10 cm can be safely observed.
World J Surg, 48(8):1934-40.
E. Rodriguez, T. Fedorova, M. Daskam, E. Baraban, D. C. Foote, R. Salvatori, N. Singla, E. K. Fishman, S. M. Chen Cardenas, D. W. Ball, A. H. Hamrahian, A. Mathur and L. F. Morris-Wiseman. 2024.
BACKGROUND: Adrenal cysts are rare and appropriate management is unclear due to a lack of data on their natural history. Understanding adrenal cyst growth patterns would assist in clinical management. METHODS: This single-institution study included all adult patients diagnosed with simple adrenal cysts between 2004 and 2021. Baseline characteristics and outcomes of those who underwent resection (ADX) or observation (OBS) were compared using the chi-squared test, student's t-test, and Wilcoxon rank-sum test. Growth curves and sensitivity analysis were plotted for all patients who had follow-up imaging. RESULTS: We identified 77 patients with imaging-confirmed adrenal cysts. The majority were female (75.3%) and more than half were white (55.8%). One-third of patients underwent ADX, and the remaining were observed. ADX patients were younger (median age [IQR]: 55.5 y [45.0-68.2 y] vs. 44.2 y [38.7-55.0 y], p = 0.01) and more likely to be Hispanic (12% vs. 0%, p = 0.05). ADX patients presented with larger cysts (5.6 vs. 2.6 cm, p = 0.002). The median time from diagnosis to last follow-up was 1.1 y for ADX and 4.1 y for OBS. Average growth for OBS was 0.3 cm/y, while average growth for ADX was 3.9 cm/y. In ADX patients, cysts >10 cm grew significantly faster than cysts <10 cm (median growth rate 13.2 cm/y vs. 0.3 cm/y, p < 0.05). There was no adrenal malignancy diagnosis, hyperfunctionality, or observation-related complications (e.g., rupture). CONCLUSION: While size >4-6 cm has guided surgical referral for solid adrenal masses, this study demonstrates a size threshold of 10 cm, below which asymptomatic, simple adrenal cysts can safely be observed.
PubMed-ID: 38972990
DOI: 10.1002/wjs.12275

The Immune Landscape of Pheochromocytoma and Paraganglioma: Current Advances and Perspectives.
Endocr Rev, 45(4):521-52.
O. Uher, K. Hadrava Vanova, D. Taieb, B. Calsina, M. Robledo, R. Clifton-Bligh and K. Pacak. 2024.
Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors derived from neural crest cells from adrenal medullary chromaffin tissues and extra-adrenal paraganglia, respectively. Although the current treatment for PPGLs is surgery, optimal treatment options for advanced and metastatic cases have been limited. Hence, understanding the role of the immune system in PPGL tumorigenesis can provide essential knowledge for the development of better therapeutic and tumor management strategies, especially for those with advanced and metastatic PPGLs. The first part of this review outlines the fundamental principles of the immune system and tumor microenvironment, and their role in cancer immunoediting, particularly emphasizing PPGLs. We focus on how the unique pathophysiology of PPGLs, such as their high molecular, biochemical, and imaging heterogeneity and production of several oncometabolites, creates a tumor-specific microenvironment and immunologically "cold" tumors. Thereafter, we discuss recently published studies related to the reclustering of PPGLs based on their immune signature. The second part of this review discusses future perspectives in PPGL management, including immunodiagnostic and promising immunotherapeutic approaches for converting "cold" tumors into immunologically active or "hot" tumors known for their better immunotherapy response and patient outcomes. Special emphasis is placed on potent immune-related imaging strategies and immune signatures that could be used for the reclassification, prognostication, and management of these tumors to improve patient care and prognosis. Furthermore, we introduce currently available immunotherapies and their possible combinations with other available therapies as an emerging treatment for PPGLs that targets hostile tumor environments.
PubMed-ID: 38377172
DOI: 10.1210/endrev/bnae005
PMCID: PMC11244254

Approach to the Patient With Bilateral Adrenal Masses.
J Clin Endocrinol Metab, 109(8):2136-48.
D. A. Vassiliadi, D. A. Delivanis, O. Papalou and S. Tsagarakis. 2024.
Bilateral adrenal masses, increasingly encountered in clinical practice, manifest across diverse contexts, including incidental discovery, malignancy staging, and targeted imaging after hormonal diagnosis of adrenal disorders. The spectrum encompasses various pathologies, such as cortical adenomas, macronodular adrenal disease, pheochromocytomas, myelolipomas, infiltrative disorders, and primary and secondary malignancies. Notably, not all masses in both adrenal glands necessarily share the same etiology, often exhibiting diverse causes. Recently, the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors updated guidelines, introduced a 4-option schema based on imaging, aiding in targeted hormonal testing and management. This "Approach to the Patient" review delves into the latest advancements in imaging, biochemical, and genetic approaches for the diagnostic and management nuances of bilateral adrenal masses. It provides insights and a contemporary framework for navigating the complexities associated with this clinical entity.
PubMed-ID: 38478374
DOI: 10.1210/clinem/dgae164

A visual diagnosis of phaeochromocytoma crisis characterised by cyclic fluctuations of blood pressure: be on the look-out for rapid changes.
Lancet, 404(10450):375-6.
M. Wernhart, C. Wiesinger, M. Windpessl, L. Madl-Liebenberger, E. Lassnig, R. K. Binder and T. Weber. 2024.
PubMed-ID: 39067904
DOI: 10.1016/S0140-6736(24)00849-3

Cushing's Syndrome is Associated with a Higher Risk of Cancer - A Nationwide Cohort Study.
J Clin Endocrinol Metab,
W. C. Wu, J. L. Wu, T. S. Huang, C. Y. Li and H. Y. Li. 2024.
CONTEXT: Patients with Cushing's syndrome (CS) have higher risk of obesity and diabetes, which are important risk factors of cancers. However, if patients with CS have a higher incidence of cancer remains unknown. OBJECTIVE: To investigate if endogenous CS is associated with increased cancer incidence. DESIGN: A nationwide cohort study. SETTING: Analysis of the data retrieved from Taiwan's National Health Insurance program in 2006-2017. PARTICIPANTS: Between 2006-2017, 1278 patients with newly diagnosed endogenous CS were identified. Among them, 1246 patients without a history of malignancy were enrolled in this study. EXPOSURES: Endogenous CS. MAIN OUTCOMES MEASURES: The age- and sex-

standardized incidence rate of all-cause cancer and age-sex-calendar year standardized incidence ratio (SIR) of cancer in association with endogenous CS. RESULTS: The age- and sex-standardized incidences of CS decreased from 4.84 to 3.77 per million person-years between 2006-2017. The age at diagnosis of CS was 45.3 +/- 14.8 years, and 80.0% of the patients were female. Cushing's disease and adrenal CS accounted for 35.4% and 64.6% of patients with CS, respectively. The incidence rate of cancer in patients with CS was 7.77 (95% Confidence Interval [CI] = 5.84-10.14) per 1000 person-years, with an SIR of 2.08 (95% CI = 1.54-2.75). The three most common cancer types were liver (27.7%), kidney (16.7%), and lung (13.0%). CONCLUSIONS: Patients with endogenous CS have a higher incidence of cancer.
PubMed-ID: 38867482
DOI: 10.1210/clinem/dgae405

NET

Meta-Analyses

Impact of Regional Metastasis on Survival for Patients with Nonfunctional Pancreatic Neuroendocrine Tumors: A Systematic Review.
Ann Surg Oncol, 31(8):4976-85.
C. N. Clarke, E. Ward, V. Henry, K. Nimmer, A. Phan and D. B. Evans. 2024.
BACKGROUND: Controversy exists regarding the benefit of lymphadenectomy for nonfunctional pancreatic neuroendocrine tumors (NF-PNET). PATIENTS AND METHODS: MEDLINE/PubMed, EMBASE, and the Cochrane Library were searched for studies of pancreatic neuroendocrine tumors (PNET) published between 1990 and 2021. Studies of functional PNET were excluded. Reported incidence of lymph node metastasis (LNM) and survival analysis of either disease-free survival (DFS) or overall survival (OS) were required for inclusion. RESULTS: Overall, 52 studies analyzing 24,608 PNET met the inclusion criteria. The reported LNM rate for NF-PNET ranged from 7 to 64 % (median 24.5%). Reported LNM rates ranged from 7 to 51% (median 11%) for NF-PNET< 2 cm in 14 studies and 29-47% (median 38%) in NF-PNET > 2 cm. In total, 19 studies (66%) reported LNM to have a negative impact on DFS. Additionally, 21 studies (60%) reported LNM to have a negative impact on OS. Two studies investigating the impact of lymphadenectomy (LND) found LND had the greatest impact for large, high-grade tumors. The overall quality of available evidence was low as assessed by the Grading of Recommendations, Assessment, Development, and Evaluation System. CONCLUSIONS: Published literature evaluating the impact of regional LNM and LND in PNET is confounded by heterogeneity in practice patterns and the retrospective nature of these cohort studies. Most studies suggest high rates of LNM in NF-PNET that negatively impact DFS and OS. Given the high rate of LNM in NF-PNET and its potential detrimental effect on DFS and OS, we recommend lymphadenectomy be completed for NF-PNET > 2 cm and strongly considered for NF-PNET < 2 cm.
PubMed-ID: 38652199
DOI: 10.1245/s10434-024-15249-1

Randomized controlled trials

[(177)Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study.
Lancet, 403(10446):2807-17.
S. Singh, D. Halperin, S. Myrehaug, K. Herrmann, M. Pavel, P. L. Kunz, B. Chasen, S. Tafuto, S. Lastoria, J. Capdevila, A. Garcia-Burillo, D. Y. Oh, C. Yoo, T. R. Halfdanarson, S. Falk, I. Folitar, Y. Zhang, P. Aimone, W. W. de Herder, D. Ferone and N.-T. I. all the. 2024.
BACKGROUND: There are currently no standard first-line treatment options for patients with higher grade 2-3, well-differentiated, advanced, gastroenteropancreatic neuroendocrine tumours. We aimed to investigate the efficacy and safety of first-line [(177)Lu]Lu-DOTA-TATE ((177)Lu-Dotatate) treatment. METHODS: NETTER-2 was an open-label, randomised, parallel-group, superiority, phase 3 trial. We enrolled patients (aged >/=15 years) with newly diagnosed higher grade 2 (Ki67 >/=10% and </=20%) and grade 3 (Ki67 >20% and </=55%), somatostatin receptor-positive (in all target lesions), advanced gastroenteropancreatic neuroendocrine tumours from 45 centres across nine countries in North America, Europe, and Asia. We used interactive response technologies to randomly assign (2:1) patients to receive four cycles (cycle interval was 8 weeks +/- 1 week) of intravenous (177)Lu-Dotatate plus intramuscular octreotide 30 mg long-acting repeatable (LAR) then octreotide 30 mg LAR every 4 weeks ((177)Lu-Dotatate group) or high-dose octreotide 60 mg LAR every 4 weeks (control group), stratified by neuroendocrine tumour grade (2 vs 3) and origin (pancreas vs other). Tumour assessments were done at baseline, week 16, and week 24, and then every 12 weeks until disease progression or death. The primary endpoint was progression-free survival by blinded, independent, central radiology assessment. We did the primary analysis at 101 progression-free survival events as the final progression-free survival analysis. NETTER-2 is registered with ClinicalTrials.gov, NCT03972488, and is active and not recruiting. FINDINGS: Between Jan 22, 2020, and Oct 13, 2022, we screened 261 patients, 35 (13%) of whom were excluded. We randomly assigned 226 (87%) patients (121 [54%] male and 105 [46%] female) to the (177)Lu-Dotatate group (n=151 [67%]) and control group (n=75 [33%]). Median

progression-free survival was 8.5 months (95% CI 7.7-13.8) in the control group and 22.8 months (19.4-not estimated) in the (177)Lu-Dotatate group (stratified hazard ratio 0.276 [0.182-0.418]; p<0.0001). During the treatment period, adverse events (of any grade) occurred in 136 (93%) of 147 treated patients in the (177)Lu-Dotatate group and 69 (95%) of 73 treated patients in the control group. There were no study drug-related deaths during the treatment period. INTERPRETATION: First-line (177)Lu-Dotatate plus octreotide LAR significantly extended median progression-free survival (by 14 months) in patients with grade 2 or 3 advanced gastroenteropancreatic neuroendocrine tumours. (177)Lu-Dotatate should be considered a new standard of care in first-line therapy in this population. FUNDING: Advanced Accelerator Applications, a Novartis Company.
PubMed-ID: 38851203
DOI: 10.1016/S0140-6736(24)00701-3

Consensus Statements/Guidelines

Surgery for advanced neuroendocrine tumours of the small bowel: recommendations based on a consensus meeting of the European Society of Endocrine Surgeons (ESES).
Br J Surg, 111(4):undefined-undefined.
K. Van Den Heede, D. J. van Beek, S. Van Slycke, I. Borel Rinkes, O. Norlen, P. Stalberg and E. Nordenstrom. 2024.
BACKGROUND: Small bowel neuroendocrine tumours often present with locally advanced or metastatic disease. The aim of this paper is to provide evidence-based recommendations regarding (controversial) topics in the surgical management of advanced small bowel neuroendocrine tumours. METHODS: A working group of experts was formed by the European Society of Endocrine Surgeons. The group addressed 11 clinically relevant questions regarding surgery for advanced disease, including the benefit of primary tumour resection, the role of cytoreduction, the extent of lymph node clearance, and the management of an unknown primary tumour. A systematic literature search was performed in MEDLINE to identify papers addressing the research questions. Final recommendations were presented and voted upon by European Society of Endocrine Surgeons members at the European Society of Endocrine Surgeons Conference in Mainz in 2023. RESULTS: The literature review yielded 1223 papers, of which 84 were included. There were no randomized controlled trials to address any of the research questions and therefore conclusions were based on the available case series, cohort studies, and systematic reviews/meta-analyses of the available non-randomized studies. The proposed recommendations were scored by 38-51 members and rated 'strongly agree' or 'agree' by 64-96% of participants. CONCLUSION: This paper provides recommendations based on the best available evidence and expert opinion on the surgical management of locally advanced and metastatic small bowel neuroendocrine tumours.
PubMed-ID: 38626261
DOI: 10.1093/bjs/znae082

Other Articles

Minimally invasive versus open distal pancreatectomy for resectable pancreatic neuroendocrine tumors: A propensity score matched multicentric comparative French study.
Surgery, 176(2):433-9.
P. Addeo, P. de Mathelin, A. Doussot, T. Durin, G. Canali, U. Marchese, A. Sauvanet, S. Dokmak, Z. Cherkaoui, D. Fuks, C. Laurent, M. Andre, A. Ayav, C. Magallon, O. Turrini, L. Sulpice, F. Robin, P. Bachellier, F. R. Souche, T. Bardol, J. Perinel, M. Adham, S. Tzedakis, D. J. Birnbaum, O. Facy, J. Gagniere, S. Gaujoux, E. Tribillon, E. Roussel, L. Schwarz, L. Barbier, N. Regenet, A. Iannelli, J. M. Regimbeau, G. Piessen, S. Truant and M. El Amrani. 2024.
BACKGROUND: Minimally invasive surgery has gained momentum for left pancreatic resections. However, debate remains about whether it has any advantage over open surgery for distal pancreatectomy for pancreatic neuroendocrine tumors. METHODS: This retrospective review examined pancreatectomies performed for resectable pancreatic neuroendocrine tumors at 21 centers in France between January 2014 and December 2018. Short and long-term outcomes were compared before and after propensity score matching based on tumor size, sex, age, body mass index, center, and method of pancreatic transection. RESULTS: During the period study, 274 patients underwent left pancreatic resection for pancreatic neuroendocrine tumors [109 underwent distal splenopancreatectomy, and 165 underwent spleen-preserving distal pancreatectomy [(splenic vessel preservation (n = 97; 58.7%)/splenic vessel resection (n = 68; 41.3%)]. Before propensity

score matching, minimally invasive surgery was associated with a lower rate of major morbidity (P = .004), lower rate of postoperative delayed gastric emptying (P = .04), and higher rate of "textbook" outcomes (P = .04). After propensity score matching, there were 2 groups of 54 patients (n = 30 distal splenopancreatectomy; n = 78 spleen-preserving distal pancreatectomy). Minimally invasive surgery was associated with less blood loss (P = .05), decreased rate of major morbidity (6% vs. 24%; P = .02), less delayed gastric emptying (P = .05) despite similar rates of postoperative fistula, hemorrhage, and reoperation (P > .05). The 5-year overall survival (79% vs. 75%; P = .74) and recurrence-free survival (10% vs 17%; P = .39) were similar. CONCLUSION: Minimally invasive surgery for left pancreatic resection can be safely proposed for patients with resectable left pancreatic neuroendocrine tumors. Minimally invasive surgery decreases the rate of major complications while providing comparable long-term oncologic outcomes.
PubMed-ID: 38797604
DOI: 10.1016/j.surg.2024.04.005

Neuroendocrine Tumors of Unknown Primary in the Setting of Cytoreductive Hepatectomy.
Ann Surg Oncol, 31(8):4931-41.
M. Ammann, H. Gudmundsdottir, H. Hackl, S. K. A. Antwi, J. Santol, E. B. Habermann, C. A. Thiels, S. G. Warner, M. J. Truty, M. L. Kendrick, R. L. Smoot, D. M. Nagorney, S. P. Cleary, T. R. Halfdanarson and P. P. Starlinger. 2024.
BACKGROUND: Surgical cytoreduction for neuroendocrine tumor liver metastasis (NETLM) consistently shows positive long-term outcomes. Despite reservations in guidelines for surgery when the primary tumor is unidentified (UP-NET), this study compared the surgical and oncologic long-term outcomes between patients with these rare cases undergoing cytoreductive surgery and patients who had liver resection for known primaries. METHODS: The study identified 32 unknown primary liver metastases (UP-NETLM) in 522 retrospectively evaluated patients who underwent resection of well-differentiated NETLM between January 2000 and December 2020. Tumor and patient characteristics were compared with those in 490 cases of liver metastasis from small intestinal (SI-NETLM) or pancreatic (pNETLM) primaries. Survival analysis was performed to highlight long-term outcome differences. Surgical outcomes were compared between liver resections alone and simultaneous primary resections to assess surgical risk distinctions. RESULTS: The UP-NET patients had fewer NETLMs (p = 0.004), which on the average were larger than SI-NETLMs or pNETLMs (p = 0.002). Expression of Ki-67 was balanced among the groups. Major hepatectomy was performed more often in the UP-NETLM group (p = 0.017). The 10-year survival rate of 53% for UP-NETLM was comparable with that for SI-NETML (58%; p = 0.463) and pNETLMs (47%; p = 0.497). The median hepatic progression-free survival was 26 months for the UP-NETLM patients and 25 months for the SI-NETLM patients compared to 12 months for the pNETLM patients (p < 0.001). Perioperative mortality was lower than 2%, and severe postoperative morbidity occurred in 21%, similarly distributed among all the groups. CONCLUSION: The surgical risk and long-term outcomes for the UP-NETLM patients were comparable with those for other NETLM cases, affirming the validity of equally aggressive surgical cytoreduction as a therapeutic option in carefully selected cases.
PubMed-ID: 38717544
DOI: 10.1245/s10434-024-15374-x

Prognostic significance of nodal micrometastases of non-functioning pancreatic neuroendocrine tumours.
Br J Surg, 111(4):undefined-undefined.
V. Andreasi, S. Partelli, M. Schiavo Lena, F. Muffatti, A. Battistella, D. Tamburrino, N. Pecorelli, S. Crippa, G. Balzano, C. Doglioni and M. Falconi. 2024.
PubMed-ID: 38682424
DOI: 10.1093/bjs/znae076
PMCID: PMC11056795

Radio-Guided Surgery with a New-Generation beta-Probe for Radiolabeled Somatostatin Analog, in Patients with Small Intestinal Neuroendocrine Tumors.
Ann Surg Oncol, 31(7):4189-96.
E. Bertani, F. Mattana, F. Collamati, M. E. Ferrari, V. Bagnardi, S. Frassoni, E. Pisa, R. Mirabelli, S. Morganti, N. Fazio, U. Fumagalli Romario and F. Ceci. 2024.
BACKGROUND: Radio-guided surgery (RGS) holds promise for improving surgical outcomes in neuroendocrine tumors (NETs). Previous studies showed low specificity (SP) using gamma-probes to detect radiation emitted by radio-labeled somatostatin analogs. OBJECTIVE: We aimed to assess the sensitivity (SE) and SP of the intraoperative RGS approach using a beta-probe with a per-lesion analysis, while assessing safety and feasibility as secondary objectives. METHODS: This prospective, single-arm, single-center, phase II trial (NCT05448157) enrolled 20 patients diagnosed with small intestine NETs (SI-NETs) with positive lesions detected at (68)Ga-DOTA-TOC positron emission tomography/computed tomography

(PET/CT). Patients received an intravenous injection of 1.1 MBq/Kg of 68Ga-DOTA-TOC 10 min prior to surgery. In vivo measurements were conducted using a beta-probe. Receiver operating characteristic (ROC) analysis was performed, with the tumor-to-background ratio (TBR) as the independent variable and pathology result (cancer vs. non-cancer) as the dependent variable. The area under the curve (AUC), optimal TBR, and absorbed dose for the surgery staff were reported. RESULTS: The intraoperative RGS approach was feasible in all cases without adverse effects. Of 134 specimens, the AUC was 0.928, with a TBR cut-off of 1.35 yielding 89.3% SE and 86.4% SP. The median absorbed dose for the surgery staff was 30 microSv (range 12-41 microSv). CONCLUSION: This study reports optimal accuracy in detecting lesions of SI-NETs using the intraoperative RGS approach with a novel beta-probe. The method was found to be safe, feasible, and easily reproducible in daily clinical practice, with minimal radiation exposure for the staff. RGS might potentially improve radical resection rates in SI-NETs. CLINICAL TRIALS REGISTRATION: (68)Ga-DOTATOC Radio-Guided Surgery with beta-Probe in GEP-NET (RGS GEP-NET) [NCT0544815; https://classic. CLINICALTRIALS: gov/ct2/show/NCT05448157].
PubMed-ID: 38652200
DOI: 10.1245/s10434-024-15277-x

Surgical management of pancreatic neuroendocrine tumors - An EYSAC and E-AHPBA international survey of current practice.
Eur J Surg Oncol, 50(10):108544.
A. Brandl, D. Lundon, A. K. Siriwardena, D. Sochorova, W. Ceelen, M. Besselink, K. Soreide and S. Stattner. 2024.
INTRODUCTION: Pancreatic neuroendocrine tumors (pNET) exhibit a wide spectrum of clinical behavior, which makes their assessment and management quite challenging. The purpose of this study was to comprehensively assess the existing treatment landscape for patients with pNET. MATERIALS AND METHODS: The study was conducted with the support of the ESSO-EYSAC Research Academy in collaboration with the E-AHPBA. An online survey was distributed via email and social media to surgical networks across Europe and beyond (September 1-30, 2023). RESULTS: Overall, 155 complete responses were obtained. A specialized NET tumor board was present at the institutions of 94 (61 %) of the study participants. The most frequently applied guidelines were from ENETS (n = 97; 63 %), NCCN (n = 74; 48 %), and ESMO (n = 53; 34 %). For resectability, similar criteria as in pancreatic ductal adenocarcinoma were used by 111 (72 %) participants, even though 116 (75 %) participants believed that pNET/pNEC should have their own resectability criteria. Most respondents used somatostatin analogues (n = 126; 81 %) and chemotherapy (n = 85; 55 %) as neoadjuvant treatments, followed by molecularly targeted agents (n = 45; 29 %) and PRRT (n = 37; 24 %). Only 17 (11 %) participants agreed/strongly agreed that the management of pNET/pNEC is sufficiently addressed in surgical education programs. CONCLUSION: This international survey highlighted areas for improvement in the care of pNET, namely the lack of pNET-specific resectability criteria and educational programs addressing pNET management.
PubMed-ID: 39059195
DOI: 10.1016/j.ejso.2024.108544

AJCC Cancer Staging System Version 9: Practice-Informing Updates for Gastroenteropancreatic Neuroendocrine Tumors.
Ann Surg Oncol, 31(8):4834-6.
K. Chan, A. Chauhan and C. Shi. 2024.
PubMed-ID: 38869764
DOI: 10.1245/s10434-024-15597-y

Subgrading of G2 Pancreatic Neuroendocrine Tumors as 2A (Ki67 3% to < 10%) Versus 2B (10% to </= 20%) Identifies Behaviorally Distinct Subsets in Keeping with the Evolving Management Protocols.
Ann Surg Oncol, 31(10):7001-11.
O. C. Eren, P. Bagci, S. Balci, N. Ohike, B. Saka, C. Sokmensuer, C. B. Leblebici, Y. Xue, M. D. Reid, A. M. Krasinskas, D. Kooby, S. K. Maithel, J. Sarmiento, J. D. Cheng, O. C. Taskin, Y. Kapran, Z. C. Tarcan, C. Luchini, A. Scarpa, O. Basturk and N. V. Adsay. 2024.
BACKGROUND: Grade 1/2 PanNETs are mostly managed similarly, typically without any adjunct treatment with the belief that their overall metastasis rate is low. In oncology literature, Ki67-index of 10% is increasingly being used as the cutoff in stratifying patients to different protocols, although there are no systematic pathology-based studies supporting this approach. METHODS: Ki67-index was correlated with clinicopathologic parameters in 190 resected PanNETs. A validation cohort (n = 145) was separately analyzed. RESULTS: In initial cohort, maximally selected rank statistics method revealed 12% to be the discriminatory cutoff (close to 10% rule of thumb). G2b cases had liver/distant metastasis rate of almost threefold higher than that of G2a and showed significantly higher frequency of all histopathologic signs of aggressiveness (tumor size, perineural/vascular invasion, infiltrative growth pattern, lymph node metastasis). In validation cohort, these

figures were as striking. When all cases were analyzed together, compared with G1, the G2b category had nine times higher liver/distant metastasis rate (6.1 vs. 58.5%; p < 0.001) and three times higher lymph node metastasis rate (20.5 vs. 65.1%; p < 0.001). CONCLUSIONS: G2b PanNETs act very similar to G3, supporting management protocols that regard them as potential therapy candidates. Concerning local management, metastatic behavior in G2b cases indicate they may not be as amenable for conservative approaches, such as watchful waiting or enucleation. This substaging should be considered into diagnostic guidelines, and clinical trials need to be devised to determine the more appropriate management protocols for G2b (10% to </= 20%) group, which shows liver/distant metastasis in more than half of the cases, which at minimum warrants closer follow-up.
PubMed-ID: 38955993
DOI: 10.1245/s10434-024-15632-y
PMCID: PMC11413052

Value of Surgical Cytoreduction in Patients with Small Intestinal Neuroendocrine Tumors Metastatic to the Liver and Peritoneum.
Ann Surg Oncol, 31(8):5370-6.
H. Gudmundsdottir, A. Fogliati, T. E. Grotz, C. A. Thiels, S. G. Warner, R. L. Smoot, M. J. Truty, M. L. Kendrick, D. M. Nagorney, T. R. Halfdanarson, S. P. Cleary and P. Starlinger. 2024.
BACKGROUND: Cytoreductive hepatectomy can improve survival and symptoms of hormonal excess in patients with small intestinal neuroendocrine tumor (siNET) liver metastases, but whether to proceed when peritoneal metastases are encountered at the time of planned cytoreductive hepatectomy is controversial. METHODS: This was a retrospective review of patients who underwent surgical management of metastatic siNETs at Mayo Clinic between 2000 and 2020. Patients who underwent cytoreductive operation for isolated liver metastases or both liver and peritoneal metastases were compared. RESULTS: Of 261 patients who underwent cytoreductive operation for siNETs, 211 had isolated liver metastases and 50 had liver and peritoneal metastases. Complete cytoreduction was achieved in 78% of patients with isolated liver metastases and 56% of those with liver and peritoneal metastases (p = 0.002). After complete cytoreduction, median overall survival (OS) was 11.5 years for isolated liver metastases and 11.2 years for liver and peritoneal metastases (p = 0.10), and relief of carcinoid syndrome was >/= 97% in both groups. After incomplete cytoreduction with debulking of > 90% of hepatic disease and/or closing Lyon score of 1-2, median OS was 6.4 years for isolated liver metastases and 7.1 years for liver and peritoneal metastases (p = 0.12). CONCLUSIONS: Patients with siNETs metastatic to both the liver and peritoneum have favorable outcomes after aggressive surgical cytoreduction, with the best outcomes observed after complete cytoreduction. Therefore, the presence of peritoneal metastases should not by itself preclude surgical cytoreduction in this population.
PubMed-ID: 38689169
DOI: 10.1245/s10434-024-15316-7

Invited Editorial: Long-Term Survival Outcomes After Minimally Invasive Surgery for Ileal Neuroendocrine Tumors.
Ann Surg Oncol, 31(9):5487-8.
A. Gustafson and S. M. Sadowski. 2024.
PubMed-ID: 38839670
DOI: 10.1245/s10434-024-15563-8

Genetic disorders and insulinoma/glucagonoma.
Endocr Relat Cancer, 31(5)
F. Marini, F. Giusti and M. L. Brandi. 2024.
Insulinoma and glucagonoma are two rare functioning neoplasms of the neuroendocrine cells of the pancreas, respectively, characterized by an uncontrolled over-secretion of insulin or glucagon, responsible for the development of the hypoglycemic syndrome and the glucagonoma syndrome. They prevalently arise as sporadic tumors; only about 10% of cases develop in the context of rare inherited tumor syndromes, such as multiple endocrine neoplasia type 1 (MEN1), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC), being the result of an autosomal-dominant germline heterozygous loss-of-function mutation in a tumor-suppressor gene. Here, we reviewed the main epidemiological and clinical aspects of insulinoma and glucagonoma in the context of genetic syndromes.
PubMed-ID: 38552306
DOI: 10.1530/ERC-23-0245

Pancreatic neuroendocrine tumors in French VHL mutation carriers: a multicentric retrospective study.
J Clin Endocrinol Metab,
M. Muller, P. Hammel, A. Couvelard, A. L. Vedie, J. Cros, N. Burnichon, A. Hercent, A. Sauvanet, S. Richard and L. de Mestier. 2024.
BACKGROUND: Von Hippel-Lindau disease (VHL) is a rare autosomal dominant hereditary cancer-predisposition syndrome caused by germline pathogenic variants (PV) in VHL gene. It is associated with a high penetrance of benign and malignant vascular tumors in multiples organs, including pancreatic neuroendocrine tumors (PanNETs), whose long-term natural history is ill-known. METHODS: Patients with both documented germline PV in VHL gene and PanNETs included in the French PREDIR database between 1995 and 2022 were included. Primary endpoint was the proportion of patients with PanNET-related metastases and secondary endpoint was overall survival (OS). Genotype/phenotype correlations were studied. RESULTS: We included 121 patients with 259 PanNETs. Median age at diagnosis was 38 years. Median follow-up was 89.5 months. PanNET surgical resection was performed in 51 patients. Overall, 29 patients (24%) had metastases (5 synchronous, 10 metachronous), with a higher risk in case of larger PanNET size (p=0.0089; best threshold 28 mm) and grade 2 PanNET (p=0.048), and a pejorative prognostic impact (p=0.043). Patients with PV in VHL exon 1 had larger PanNETs (p=0.018), more often metastatic disease (48% vs 11.5%; p < 0.001) and a trend toward shorter OS (p=0.16). CONCLUSION: The risk of metastases associated to VHL-related PanNETs remains low (24%) but increases with tumor size >28 mm, higher grade and in case of PV located VHL exon 1. These data might help improving the management of these patients, who should be referred to an expert center.
PubMed-ID: 38706378
DOI: 10.1210/clinem/dgae310

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Beyond MEN1, When to Think About MEN4? Retrospective Study on 5600 Patients in the French Population and Literature Review.
J Clin Endocrinol Metab, 109(7):e1482-e93.
B. Chevalier, L. Coppin, P. Romanet, T. Cuny, J. C. Maiza, J. Abeillon, J. Forestier, T. Walter, O. Gilly, M. Le Bras, S. Smati, M. L. Nunes, A. Geslot, S. Grunenwald, C. Mouly, G. Arnault, K. Wagner, E. Koumakis, C. Cortet-Rudelli, E. Merlen, A. Jannin, S. Espiard, I. Morange, E. Baudin, M. Cavaille, I. Tauveron, M. P. Teissier, F. Borson-Chazot, D. Mirebeau-Prunier, F. Savagner, E. Pasmant, S. Giraud, M. C. Vantyghem, P. Goudet, A. Barlier, C. Cardot-Bauters and M. F. Odou. 2024.
CONTEXT: Germline CDKN1B variants predispose patients to multiple endocrine neoplasia type 4 (MEN4), a rare MEN1-like syndrome, with <100 reported cases since its discovery in 2006. Although CDKN1B mutations are frequently suggested to explain cases of genetically negative MEN1, the prevalence and phenotype of MEN4 patients is poorly known, and genetic counseling is unclear. OBJECTIVE: To evaluate the prevalence of MEN4 in MEN1-suspected patients and characterize the phenotype of MEN4 patients. DESIGN: Retrospective observational nationwide study. Narrative review of literature and variant class reassessment. PATIENTS: We included all adult patients with class 3/4/5 CDKN1B variants identified by the laboratories from the French Oncogenetic Network on Neuroendocrine Tumors network between 2015 and 2022 through germline genetic testing for MEN1 suspicion. After class reassessment, we compared the phenotype of symptomatic patients with class 4/5 CDKN1B variants (ie, with genetically confirmed MEN4 diagnosis) in our series and in literature with 66 matched MEN1 patients from the UMD-MEN1 database. RESULTS: From 5600 MEN1-suspected patients analyzed, 4 with class 4/5 CDKN1B variant were found (0.07%). They presented with multiple duodenal NET, primary hyperparathyroidism (PHPT) and adrenal nodule, isolated PHPT, PHPT, and pancreatic neuroendocrine tumor. We listed 29 patients with CDKN1B class 4/5 variants from the literature. Compared with matched MEN1 patients, MEN4 patients presented lower NET incidence and older age at PHPT diagnosis. CONCLUSION: The prevalence of MEN4 is low. PHPT and pituitary adenoma represent the main associated lesions, NETs are rare. Our results suggest a milder and later phenotype than in MEN1. Our observations will help to improve genetic counseling and management of MEN4 families.
PubMed-ID: 38288531
DOI: 10.1210/clinem/dgae055

Clinical management and outcome of head and neck paragangliomas (HNPGLs): A single centre retrospective study.
Clin Endocrinol (Oxf), 101(3):243-8.
M. Darrat, L. Lau, C. Leonard, S. Cooke, M. A. Shahzad, C. McHenry, D. R. McCance, S. J. Hunter, K. Mullan, J. R. Lindsay, U. Graham, N. Bailie, S. Hampton, S. Rajendran, F. Houghton, D. Conkey, P. J. Morrison and P. C. Johnston. 2024.
CONTEXT: Head and neck paragangliomas (HNPGLs) are rare, usually benign, slow-growing tumours arising from neural crest-derived tissue. Definitive management pathways for HNPGLs have yet to be clearly defined. OBJECTIVE: To review our experience of the clinical features and management of these tumours and to analyse outcomes of different treatment modalities. METHODS: Demographic and clinical data were obtained from The Northern Ireland Electronic Care Record

(NIECR) as well from a prospectively maintained HNPGL database between January 2011 through December 2023. RESULTS: There were 87 patients; 50 females: 37 males with a mean age of 52.3 +/- 14.2 years old (range 17-91 years old). 58.6% (n = 51) of patients had carotid body tumours, 25.2% (n = 22) glomus vagal tumours, 6.8% (n = 6) tumours in the middle ear, 2.2% (n = 2) in the parapharyngeal space and 1.1% (n = 1) in the sphenoid sinus. 5.7% (n = 5) of patients had multifocal disease. The mean tumour size at presentation was 3.2 +/- 1.4 cm (range 0.5-6.9 cm). Pathogenic SDHD mutations were identified in 41.3% (n = 36), SDHB in 12.6% (n = 11), SDHC in 2.2% (n = 2) and SDHA in 1.1% (n = 1) of the patients. Overall treatment modalities included surgery alone in 51.7% (n = 45) of patients, radiotherapy in 14.9% (n = 13), observation in 28.7% (n = 25), and somatostatin analogue therapy with octreotide in 4.5% (n = 4) of patients. Factors associated with a significantly higher risk of recurrence included age over 60 years (p = .04), tumour size exceeding 2 cm (p = .03), positive SDHx variants (p = .01), and vagal and jugular tumours (p = .04). CONCLUSION: The majority of our patients underwent initial surgical intervention and achieved disease stability. Our results suggest that carefully selected asymptomatic or medically unfit patients can be safely observed provided lifelong surveillance is maintained. We advocate for the establishment of a UK and Ireland national HNPGL registry, to delineate optimal management strategies for these rare tumours and improve long term outcomes.
PubMed-ID: 38696538
DOI: 10.1111/cen.15070

Comparison of Octreotide and Vasopressors as First-Line Treatment for Intraoperative Carcinoid Crisis.
Ann Surg Oncol, 31(6):3976-7.
M. Ammann, M. A. O. Kinney, H. Gudmundsdottir, J. Santol, C. A. Thiels, S. G. Warner, M. J. Truty, M. L. Kendrick, R. L. Smoot, A. L. Anderson, T. R. Halfdanarson, D. M. Nagorney and P. P. Starlinger. 2024.
PubMed-ID: 38619707
DOI: 10.1245/s10434-024-15264-2

Genotype-specific development of MEN 2 constituent components in 683 RET carriers.
Endocr Relat Cancer, 31(7)
A. Machens, K. Lorenz, F. Weber, T. Brandenburg, D. Fuhrer-Sakel and H. Dralle. 2024.
The age-specific development of the three constituent components of multiple endocrine neoplasia type 2 (MEN 2) is incompletely characterized for many of the >30 causative rearranged during transfection (RET) mutations, which this genetic association study aimed to specify. Included in the study were 683 carriers of heterogeneous RET germline mutations: 53 carriers with 1 highest-risk mutation (codon 918); 240 carriers with 8 different high-risk mutations (codon 634); 176 carriers with 16 different intermediate-risk mutations (codon 609, 611, 618, 620, or 630); and 214 carriers with 6 different low-risk mutations (codon 768, 790, 804, or 891).There was a strong genotype-specific development of MEN 2 constituent components, with distinct age gradients from C cell disease to node negative medullary thyroid cancer (MTC), from node negative to node positive MTC, from node positive MTC to pheochromocytoma, and from pheochromocytoma to primary hyperparathyroidism. Primary hyperparathyroidism was not observed among the 53 MEN 2B patients who carried highest-risk mutations (age range: 0.5-50 years), of whom no more than 12 (23%) and 3 (6%) carriers were older than age 30 years and 35 years, respectively. The age-specific development of MTC differed significantly between the four RET risk categories, whereas the age-specific development of pheochromocytoma differed significantly only between the two strongest RET risk categories. No significant differences were noted in the development of primary hyperparathyroidism. These findings delineate age-specific disease manifestation corridors for the three constituent components of MEN 2 by RET genotype. These corridors are useful for initial risk assessment and organ-specific surveillance of newly identified RET carriers going forward.
PubMed-ID: 38753300
DOI: 10.1530/ERC-24-0038

Paraaortic Extra-Adrenal Paraganglioma: Challenging Robotic Resection.
Ann Surg Oncol, 31(7):4197-8.
A. Nikiforchin, E. Baron, J. A. Wernberg and R. Sharma. 2024.
BACKGROUND: Up to 41% of intra- and extra-adrenal paragangliomas are linked to germline mutations with autosomal dominant transmission, which necessitates genetic testing for patients and their relatives.(1-4) Certain alterations, such as the succinate dehydrogenase (SDH) subunit B gene mutation, are associated with a significant risk of extra-adrenal, malignant, and metastatic disease forms.(4-7) This highlights the need for routine genetic counseling and diligent surveillance, as well as surgeon awareness of hereditary paraganglioma-pheochromocytoma syndrome (HPPS). METHODS: We present a multimedia article featuring a step-by-step video of a complex retroperitoneal resection, enriched with

perioperative management insights. RESULTS: A 17-year-old female presented with episodes of hypertension, tachycardia, and diffuse diaphoresis. CT revealed a paraaortic mass adjacent to the left renal hilum later confirmed by a SPECT/CT with iodine-123 meta-iodobenzylguanidine.(8) Additional imaging with gallium-68 DOTATATE was not performed then due to unknown mutation status. The patient underwent robotic removal of the tumor and adjacent lymph nodes. Pathology confirmed a poorly differentiated paraganglioma with 0/6 lymph node metastases. Genetic tests revealed SDHB gene mutation, indicative of HPPS.(9,10) At 12 months, the patient remained disease-free on CT with normalized metanephrines levels and no detectable circulating tumor DNA. Familial screening detected her mother, maternal uncle, and maternal grandfather to be SDHB mutation carriers, although phenotypically silent. CONCLUSIONS: Robotic-assisted resection can be safe and effective for retroperitoneal malignant paragangliomas. However, management extends beyond surgery and requires cascade genetic testing to address familial risks. Because of the high probability of cancer associated with SDHB mutation, lifelong patient surveillance is imperative.
PubMed-ID: 38615151
DOI: 10.1245/s10434-024-15267-z