EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

Collection: T. Clerici, F. Triponez, M Demarchi, K. Lorenz, M. Elwerr, L. Osmak, G. Franch-Arcas & C. Martinez-Santos

Compilation and design: U. Beutner, ulrich.beutner@kssg.ch

Affiliations see next page

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

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

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Collectors

Thomas Clerici, MD
Department of Surgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Frédéric Triponez, MD
Marco Demarchi, MD
Department of Thoracic and Endocrine Surgery, University Hospitals of Geneva, Geneva, Switzerland

Kerstin Lorenz, MD
Malik Elwerr, MD
Department of General-, Visceral-, and Vascular Surgery, Martin-Luther University of Halle-Wittenberg, Germany

Liliana Osmak, MD
Department of Endocrine Surgery, University Hospital Dijon, Dijon, France

Guzmán Franch-Arcas, MD
Endocrine Surgery, Department of General and Digestive Tract Surgery, University Hospital Salamanca, Salamanca, Spain

Cristina Martinez-Santos, MD
Endocrine Surgery, Hospital Costa del Sol Marbella, Málaga, Spain

Compilation and Coordination

Ulrich Beutner, Ph.D
Department of Surgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
ulrich.beutner@kssg.ch

Journals covered

Journal	IF2021	Journal	IF2021
Acta Cytol	3.000	J Bone Miner Res	6.390
Am J Kidney Dis	11.072	J Clin Endocrinol Metab	6.134
Am J Nephrol	4.605	J Clin Oncol	50.717
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Am Surgeon	1.002	J Endocrinol Invest	5.467
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Horm Metab Res	2.788	Surg Oncol	2.388
JAMA Otolaryngol Head Neck Surg	8.961	Surg Oncol Clin N Am	2.402
JAMA Surg	16.681	Surgery	4.348
Int J Cancer	7.316	Thyroid	6.506
J Am Coll Surg	6.532	Updates In Surgery	2.692
J Am Soc Nephrol	14.978	World J Surg	3.282
J Bone Miner Metab	2.976		

Journal names are links to the journal's homepage!, IF2021: Impact factor 2021

Thyroid

Meta-Analyses

Meta-analysis of the efficacy and safety of thermal ablation for treating large benign thyroid nodules.
Clin Endocrinol (Oxf), 97(5):654-63.
X. Ji, W. Sun, C. Lv, J. Huang and H. Zhang.
OBJECTIVE: Many large benign thyroid nodules have symptoms and cosmetic problems. This study consisted of a meta-analysis to accurately assess the effect of thermal ablation on these nodules.
METHODS: The PubMed, Embase, Web of Science, and Scopus databases were systematically searched for retrospective or prospective studies of thermal ablation since June 1, 2021. The weighted mean differences of the measures were analysed before and after treatment.
RESULTS: A total of 10 eligible studies were included. By comparing the initial nodule volume with the nodular volume after thermal ablation, we found that the volume reduction rate was increased significantly after 1 month (SMD = 0.453, 95% CI: 0.323-0.583, p<.001), 3 months (SMD = 0.655, 95% CI: 0.563-0.747, p<.001), 6 months (SMD = 0.691, 95% CI: 0.607-0.774, p<.001), and 12 months (SMD = 0.694, 95% CI: 0.583-0.803), p<.001). The nodular volume was also found to decrease significantly, after 1 month (SMD = 2.381, 95% CI: 1.278-3.485, p<.001), 3 months (SMD = 5.071, 95% CI: 2.386-7.756, p<.001), 6 months (SMD = 5.363, 95% CI: 2.765-7.962, p<.001), and 12 months (SMD = 8.194, 95% CI: 2.113-14.274), p<.001). Symptom score (SMD = 4.419, 95% CI: 2.573-6.265, p<.001)and cosmetic score (SMD = 4.245, 95% CI: 2.566-5.359, p<.001) were reduced after thermal ablation.
CONCLUSIONS: Thermal ablation could become an alternative to manage large benign thyroid nodules.
PubMed-ID: 35170792
http://dx.doi.org/10.1111/cen.14695

Impact of low iodine diets on ablation success in differentiated thyroid cancer: A mixed-methods systematic review and meta-analysis.
Clin Endocrinol (Oxf), 97(6):702-29.
G. Herbert, C. England, R. Perry, A. Whitmarsh, T. Moore, A. Searle, S. Chotaliya, A. Ness, M. Beasley and C. Atkinson.
BACKGROUND: Debate remains regarding whether to recommend a low iodine diet (LID) before radioactive-iodine treatment and its duration and stringency. This mixed-methods review aimed to determine if iodine status affects treatment success, the most effective diet to reduce iodine status, and how LID impacts wellbeing.
METHODS: Five electronic databases were searched until February 2021. An effectiveness synthesis (quantitative studies) and views synthesis (qualitative, survey, and experience-based evidence) were conducted individually and then integrated. Quality assessment was undertaken.
RESULTS: Fifty-six quantitative and three qualitative studies were identified. There was greater ablation success for those with an iodine status of <50 mcg/L (or mcg/gCr) compared with ≥250 (odds ratio [OR] = 2.63, 95% confidence interval [CI], 1.18-5.86, n = 283, GRADE certainty of evidence very low). One study compared <50 mcg/L (or mcg/gCr) to 100-199 and showed similar rates of ablation success (OR = 1.59, 95% CI, 0.48-6.15, n = 113; moderate risk of bias). People following a stricter LID before ablation had similar rates of success to a less-strict diet (OR = 0.67, 95% CI, 0.26-1.73, n = 256, GRADE certainty of evidence very low). A stricter LID reduced iodine status more than a less strict (SMD = -0.40, 95% CI, -0.56 to -0.24, n = 816), and reduction was seen after 1 and 2 weeks. The main challenges were a negative impact on psychological health, over restriction, confusion, and difficulty for sub-groups.
CONCLUSIONS: Although a LID of 1-2 weeks reduces iodine status, it remains unclear whether iodine status affects treatment success as only a few low-quality studies have examined this. LIDs are challenging for patients. Higher-quality studies are needed to confirm whether a LID is necessary.
PubMed-ID: 35484696
http://dx.doi.org/10.1111/cen.14751

Prevalence of Subclinical Papillary Thyroid Cancer by Age: Meta-analysis of Autopsy Studies.
J Clin Endocrinol Metab, 107(10):2945-52.
N. Arroyo, K. J. L. Bell, V. Hsiao, S. Fernandes-Taylor, O. Alagoz, Y. Zhang, L. Davies and D. O. Francis.
CONTEXT: It is not known how underlying subclinical papillary thyroid cancer (PTC) differs by age. This meta-analysis of autopsy studies investigates how subclinical PTC prevalence changes over the lifetime.

METHODS: We searched PubMed, Embase, and Web of Science databases from inception to May 2021 for studies that reported the prevalence of PTC found at autopsy. Two investigators extracted the number of subclinical PTCs detected in selected age groups and extent of examination. A quality assessment tool was used to assess bias. Logistic regression models with random intercepts were used to pool the age-specific subclinical PTC prevalence estimates.
RESULTS: Of 1773 studies screened, 16 studies with age-specific data met the inclusion criteria (n = 6286 autopsies). The pooled subclinical PTC prevalence was 12.9% (95% CI 7.8-16.8) in whole gland and 4.6% (2.5- 6.6) in partial gland examination. Age-specific prevalence estimates were ≤40 years, 11.5% (6.8-16.1); 41-60 years, 12.1% (7.6-16.5); 61-80 years, 12.7% (8-17.5); and 81+ years, 13.4% (7.9-18.9). Sex did not affect age-specific prevalence and there was no difference in prevalence between men and women in any age group. In the regression model, the OR of prevalence increasing by age group was 1.06 (0.92-1.2, P = .37).
CONCLUSION: This meta-analysis shows the prevalence of subclinical PTC is stable across the lifespan. There is not a higher subclinical PTC prevalence in middle age, in contrast to higher observed incidence rates in this age group. These findings offer unique insights into the prevalence of subclinical PTC and its relationship to age.
PubMed-ID: 35947867
http://dx.doi.org/10.1210/clinem/dgac468

Intra-operative nerve monitoring and recurrent laryngeal nerve injury during thyroid surgery: a network meta-analysis of prospective studies.
Langenbecks Arch Surg, 407(8):3209-19.
E. F. Cleere, M. G. Davey, O. Young, A. J. Lowery and M. J. Kerin.
PURPOSE: Recurrent laryngeal nerve (RLN) injury is a feared complication of thyroid surgery occurring in 1-5% of cases. The present approaches to RLN preservation include RLN visualization with no nerve monitoring (No-NM), intermittent intra-operative nerve monitoring (I-IONM) and continuous intra-operative nerve monitoring (C-IONM). There is ambiguity as to which of these strategies should be the preferred method of RLN preservation.
METHODS: A systematic review of the PubMed, Embase and the Cochrane Collaboration databases was undertaken with network meta-analysis (NMA) performed according to the PRISMA and Cochrane Collaboration guidelines. A Bayesian NMA was conducted using R packages netmeta with outcomes expressed as odds ratios (ORs) with 95% credible intervals (CrI). Only prospective studies were included.
RESULTS: Eighteen studies met inclusion criteria, including 22,080 patients and 40,642 nerves at risk (NAR). Overall, 23,364 NARs (57.5%) underwent I-IONM, 17,176 (42.3%) No-NM and 98 (0.2%) underwent C-IONM. There were no significant differences between groups regarding the incidence of permanent RLN injury following thyroid surgery (I-IONM vs.No-NM, OR 0.84, 95% CrI 0.55-1.19; C-IONM vs. No-NM, OR 0.44, 95% CrI 0.02-5.00). Pooled analysis showed that IONM (I-IONM or C-IONM) demonstrated a protective effect versus No-NM in reducing the incidence of transient RLN injury (OR 0.75, 95% CI 0.59-0.97, p = 0.03).
CONCLUSIONS: IONM strategies did not significantly reduce the incidence of permanent RLN injury following thyroid surgery. However, the small number of C-IONM NARs limits conclusions that may be drawn. Further well-designed prospective studies will be required to definitively assess the utility of C-IONM.
PubMed-ID: 35953619
http://dx.doi.org/10.1007/s00423-022-02651-0

Hypocalcaemia following thyroidectomy among patients who have previously undergone bariatric surgery: systematic review and meta-analysis.
Br J Surg, 109(12):1198-205.
E. F. Cleere, M. G. Davey, T. J. Crotty, O. Young, A. J. Lowery and M. J. Kerin.
BACKGROUND: Hypocalcaemia is a common complication after thyroidectomy. Bariatric surgery is associated with significant changes in calcium metabolism. Some studies have identified bariatric surgery as a risk factor for hypocalcaemia after thyroidectomy. This systematic review and meta-analysis assessed whether a history of bariatric surgery was associated with an increased risk of hypocalcaemia after thyroidectomy.
METHODS: This prospectively registered systematic review (PROSPERO; CRD42021295423) was performed in accordance with PRISMA guidelines. Meta-analysis was undertaken using the Mantel-Haenszel method, with outcomes reported as ORs with 95 per cent confidence intervals.
RESULTS: Twenty studies were included in the qualitative synthesis. Five studies incorporating 19 547 patients met the inclusion criteria for meta-analysis, of whom 196 (1.0 per cent) had a history of bariatric surgery. Patients with a history of bariatric surgery were more likely to develop hypocalcaemia after thyroidectomy (30.6 versus 13.0 per cent; OR 3.90, 95 per cent c.i. 1.50 to 10.12; P = 0.005). Among those with a history of bariatric surgery, patients who underwent a bypass

procedure were more likely to develop hypocalcaemia after thyroidectomy than those who had a restrictive procedure (38 versus 23 per cent; OR 2.12, 1.14 to 3.97; P = 0.020).
CONCLUSION: Patients with a history of bariatric surgery have a significantly greater risk of hypocalcaemia after thyroidectomy, with a heightened risk among those who have had a bypass procedure. Surgeons performing thyroid surgery should be aware of the increased risk of hypocalcaemia after thyroidectomy among these patients.
Low calcium levels are a common complication after surgical removal of the thyroid gland. Patients who have had weight loss surgery (bariatric surgery) have altered calcium metabolism and are prone to low calcium levels. This study assessed whether previous weight loss surgery increased the risk of low calcium levels after thyroid surgery. A search was made of previously published studies assessing the relationship between previous weight loss surgery and low calcium levels after thyroid surgery. Studies have shown that previous weight loss surgery makes patients more than three times more likely to have low calcium levels after thyroid surgery. Management of low calcium in these patients is more challenging than in patients who have not had weight loss surgery. Surgeons performing thyroid surgery need to be aware of whether a patient has previously had weight loss surgery as they have an increased risk of low calcium after thyroid surgery.
PubMed-ID: 36047335
http://dx.doi.org/10.1093/bjs/znac310

Diagnostic Accuracy of Fine-Needle Biopsy in the Detection of Thyroid Malignancy: A Systematic Review and Meta-analysis.
JAMA Surg, 157(12):1105-13.
V. Hsiao, E. Massoud, C. Jensen, Y. Zhang, B. M. Hanlon, M. Hitchcock, N. Arroyo, A. S. Chiu, S. Fernandes-Taylor, O. Alagoz, K. Sundling, V. LiVolsi and D. O. Francis.
IMPORTANCE: Fine-needle biopsy (FNB) became a critical part of thyroid nodule evaluation in the 1970s. It is not clear how diagnostic accuracy of FNB has changed over time.
OBJECTIVE**:** To conduct a systematic review and meta-analysis estimating the accuracy of thyroid FNB for diagnosis of malignancy in adults with a newly diagnosed thyroid nodule and to characterize changes in accuracy over time.
DATA SOURCES: PubMed, SCOPUS, and Cochrane Central Register of Controlled Trials were searched from 1975 to 2020 using search terms related to FNB accuracy in the thyroid. STUDY SELECTION: English-language reports of cohort studies or randomized trials of adult patients undergoing thyroid FNB with sample size of 20 or greater and using a reference standard of surgical histopathology or clinical follow-up were included. Articles that examined only patients with known thyroid disease or focused on accuracy of novel adjuncts, such as molecular tests, were excluded. Two investigators screened each article and resolved conflicts by consensus. A total of 36 of 1023 studies met selection criteria. DATA **EXTRACTION AND SYNTHESIS:** The MOOSE guidelines were used for data abstraction and assessing data quality and validity. Two investigators abstracted data using a standard form. Studies were grouped into epochs by median data collection year (1975 to 1990, 1990 to 2000, 2000 to 2010, and 2010 to 2020). Data were pooled using a bivariate mixed-effects model. MAIN OUTCOMES AND MEASURES: The primary outcome was accuracy of FNB for diagnosis of malignancy. Accuracy was hypothesized to increase in later time periods, a hypothesis formulated prior to data collection.
RESULTS: Of 16,597 included patients, 12,974 (79.2%) were female, and the mean (SD) age was 47.3 (12.9) years. The sensitivity of FNB was 85.6% (95% CI, 79.9-89.5), the specificity was 71.4% (95% CI, 61.1-79.8), the positive likelihood ratio was 3.0 (95% CI, 2.3-4.1), and the negative likelihood ratio was 0.2 (95% CI, 0.2-0.3). The area under the receiver operating characteristic curve was 86.1%. Epoch was not significantly associated with accuracy. None of the available covariates could explain observed heterogeneity.
CONCLUSIONS AND RELEVANCE: Accuracy of thyroid FNB has not significantly changed over time. Important developments in technique, preparation, and interpretation may have occurred too heterogeneously to capture a consistent uptrend over time. FNB remains a reliable test for thyroid cancer diagnosis.
PubMed-ID: 36223097
http://dx.doi.org/10.1001/jamasurg.2022.4989

Randomized controlled trials

The Impact of Post-Thyroidectomy Neck Stretching Exercises on Neck Discomfort, Pressure Symptoms, Voice and Quality of Life: A Randomized Controlled Trial.
World J Surg, 46(9):2212-22.
R. T. Thorsen, H. Døssing, S. J. Bonnema, T. H. Brix, C. Godballe and J. R. Sorensen.

BACKGROUND: Following surgery for benign nodular goiter, patients may experience neck and shoulder pain, neck pressure and tightness, choking sensation, altered voice function, and dysphagia leading to decreased short-term quality of life (QoL). This single-blinded randomized controlled trial investigated the effect of post-thyroidectomy rehabilitative neck stretching and movement exercises on these variables including QoL.
METHODS: Patients undergoing thyroid lobectomy or total thyroidectomy were randomized to perform neck stretching and movement exercises three times daily in four weeks following surgery (intervention group) or conventional follow-up without exercises (control group). Outcome measures were scores in the following questionnaires: Disease-specific Thyroid-Related Patient-Reported Outcome (ThyPRO-39) involving symptoms of "sense of fullness in the neck," "pressure in the throat," and "discomfort swallowing" combined in the multi-item Goiter Symptom Scale, the Voice Handicap-Index-10 (VHI-10), neck and shoulder pain measurement by a numeric rating scale (NRS), and General measure of health (EQ-5D-5L). All scores were assessed prior to surgery and one, two, four weeks, and three months after surgery. Data were analyzed using a linear mixed model.
RESULTS: Eighty-nine patients were included and randomized to the control (n = 45) or the intervention group (n = 44). At three months after surgery, both the control and the intervention group experienced large to moderate improvements in the Goiter symptom and Hyperthyroid symptom scale of the ThyPRO questionnaire ($p < 0.004$). No significant between-group differences were found in any of the other applied scales.
CONCLUSIONS: This study confirms that patients experience profound improvements in QoL after surgery for benign nodular goiter. However, early post-thyroidectomy neck stretching and movement exercises did not result in further QoL improvement, reduction in pain or less impacted subjective voice function for patients primarily undergoing thyroid lobectomy. Trial Registration Number NCT04645056 (https://clinicaltrials.gov).
PubMed-ID: 35637354
http://dx.doi.org/10.1007/s00268-022-06610-0

Near-infrared autofluorescence of the parathyroid glands during thyroidectomy for the prevention of hypoparathyroidism: a prospective randomized clinical trial.
Langenbecks Arch Surg, 407(7):3031-8.
H. W. Wolf, N. Runkel, K. Limberger and C. A. Nebiker.
PURPOSE: Postoperative hypoparathyroidism remains the most often complication in thyroid surgery. Near-infrared autofluorescence (NIR-AF) is a modality to identify parathyroid glands (PG) in vivo with high accuracy, but its use in daily routine surgery is unclear so far. In this randomized controlled trial, we evaluate the ability of NIR-AF to prevent postoperative hypoparathyroidism following total thyroidectomy.
METHODS: Patients undergoing total thyroidectomy were allocated in two groups with the use of NIR-AF in the intervention group or according to standard practice in the control group. The aim was to identify the PGs in an early most stage of the operation to prevent their devascularization or removal. Parathyroid hormone was measured pre- and postoperatively and on postoperative day (POD) 1. Serum calcium was measured on POD 1 and 2. Possible symptoms and calcium/calcitriol supplement were recorded.
RESULTS: A total of 60 patients were randomized, of whom 30 underwent NIR-AF-based PG identification. Hypoparathyroidism at skin closure occurred in 7 out of 30 patients using NIR-AF, respectively, in 14 out of 30 patients in the control group ($p=0.058$). There was no significant difference in serum calcium and parathyroid hormone levels between both groups. Likewise, NIR-AF could not detect PGs at a higher rate.
CONCLUSION: The use of NIR-AF may help surgeons identify and preserve PGs but did not significantly reduce the incidence of postoperative hypoparathyroidism in this trial. Larger case series have to clarify whether there is a benefit in routine thyroidectomy. TRIAL REGISTRATION NUMBER: DRKS00009242 (German Clinical Trial Register). Registration date: 03.09.2015.
PubMed-ID: 35904639
http://dx.doi.org/10.1007/s00423-022-02624-3

Consensus Statements/Guidelines

Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline.
Endocr Relat Cancer, 29(11):G1-G33.
S. R. Howard, S. Freeston, B. Harrison, L. Izatt, S. Natu, K. Newbold, S. Pomplun, H. A. Spoudeas, S. Wilne, T. R. Kurzawinski and M. N. Gaze.
This guideline is written as a reference document for clinicians presented with the challenge of managing paediatric

patients with differentiated thyroid carcinoma up to the age of 19 years. Care of paediatric patients with differentiated thyroid carcinoma differs in key aspects from that of adults, and there have been several recent developments in the care pathways for this condition; this guideline has sought to identify and attend to these areas. It addresses the presentation, clinical assessment, diagnosis, management (both surgical and medical), genetic counselling, follow-up and prognosis of affected patients. The guideline development group formed of a multi-disciplinary panel of sub-speciality experts carried out a systematic primary literature review and Delphi Consensus exercise. The guideline was developed in accordance with The Appraisal of Guidelines Research and Evaluation Instrument II criteria, with input from stakeholders including charities and patient groups. Based on scientific evidence and expert opinion, 58 recommendations have been collected to produce a clear, pragmatic set of management guidelines. It is intended as an evidence base for future optimal management and to improve the quality of clinical care of paediatric patients with differentiated thyroid carcinoma.
PubMed-ID: 35900783
http://dx.doi.org/10.1530/ERC-22-0035

Other Articles

Alemtuzumab-induced autoimmune thyroid events in patients with relapsing-remitting multiple sclerosis: A real-life and monocentric experience at a tertiary-level centre.
Clin Endocrinol (Oxf), 97(3):331-8.
J. Manso, Y. H. Zhu, M. Margoni, F. Rinaldi, S. Censi, S. Carducci, C. Cosma, M. Plebani, P. Gallo and C. Mian.
OBJECTIVE: Alemtuzumab-induced autoimmune thyroid events (AIATEs) are the most common adverse effects observed in relapsing-remitting multiple sclerosis (RRMS) patients. This study aims to explore the clinical and biochemical characteristics of such AIATEs, and to examine the risk factors for their occurrence, particularly for the worst clinical phenotype of fluctuating Graves' disease (GD).
DESIGN, PATIENTS, MEASUREMENTS: We retrospectively analysed a real-life single-centre consecutive series of 57 RRMS patients treated with alemtuzumab whose clinical and biochemical parameters were collected before starting the treatment and then monthly during their follow-up.
RESULTS: AIATEs developed in 39% of patients a mean 17 months ± 11 after the first cycle of alemtuzumab. The most common AIATEs were GD (64%), followed by Hashimoto's thyroiditis with hypothyroidism (23%), TSH-receptor-antibody (TRAb)-positive hypothyroidism (9%), and silent thyroiditis (4%). GD showed a fluctuating course in 57% of cases. Baseline positivity for anti-thyroperoxidase antibodies, and higher absolute titers of anti-thyroglobulin and anti-thyroperoxidase antibodies correlated significantly with the risk of developing AIATEs, but TRAb positivity did not. Higher TRAb titers at the time of GD being diagnosed correlated strongly with a greater risk of the fluctuating GD phenotype. On ROC curve analysis, we found that a cut-off of 7.3 IU/L could be used to predict the risk of developing a fluctuating GD, with a positive predictive value of 100%.
CONCLUSIONS: TRAb levels measured with commercial automatic methods at the time of a patient being diagnosed with alemtuzumab-induced GD emerged as a novel biomarker for predicting a fluctuating disease phenotype, with an influence on subsequent therapeutic decisions and patients' follow-up.
PubMed-ID: 34724236
http://dx.doi.org/10.1111/cen.14616

What Role Does Thyroglobulin Washout Have in Follow-Up Algorithm of Differentiated Thyroid Cancer?
Laryngoscope, 132(11):2087-8.
A. A. Asarkar, J. Pang, J. Mansour and C. O. Nathan.
PubMed-ID: 35040496
http://dx.doi.org/10.1002/lary.30022

Outcomes in Pediatric Thyroidectomy: Results From a Multinational, Multi-institutional Database.
Otolaryngol Head Neck Surg, 167(5):869-76.
M. Maksimoski, A. J. Bauer, K. Kazahaya, S. C. Manning, S. R. Parikh, J. P. Simons, J. D'Souza, J. Maddalozzo, M. R. Purkey, K. Rychlik, B. Ho, M. J. Rutter, W. Jiang, J. D. Prager, G. Diercks, E. J. Propst, R. C. Miyamoto, B. C. Stack, G. W. Randolph and J. C. Rastatter.
OBJECTIVE: Traditionally, data regarding thyroidectomy were extracted from billing databases, but information may be missed. In this study, a multi-institutional pediatric thyroidectomy database was used to evaluate recurrent laryngeal

nerve (RLN) injury and hypoparathyroidism.
STUDY DESIGN: Retrospective multi-institutional cohort study. SETTING: Tertiary care pediatric hospital systems throughout North America.
METHODS: Data were individually collected for thyroidectomies, then entered into a centralized database and analyzed using univariate and multivariable regression models.
RESULTS: In total, 1025 thyroidectomies from 10 institutions were included. Average age was 13.9 years, and 77.8% were female. Average hospital stay was 1.9 nights and 13.5% of patients spent at least 1 night in the pediatric intensive care unit. The most frequent pathology was papillary thyroid carcinoma (42%), followed by Graves' disease (20.1%) and follicular adenoma (18.2%). Overall, 1.1% of patients experienced RLN injury (0.8% permanent), and 7.2% experienced hypoparathyroidism (3.3% permanent). Lower institutional volume (odds ratio [OR], 3.57; 95% CI, 1.72-7.14) and concurrent hypoparathyroidism (OR, 3.51; 95% CI, 1.64-7.53) correlated with RLN injury on multivariable analysis. Graves' disease (OR, 2.27; 95% CI, 1.35-3.80), Hashimoto's thyroiditis (OR, 4.67; 95% CI, 2.39-9.09), central neck dissection (OR, 3.60; 95% CI, 2.36-5.49), and total vs partial thyroidectomy (OR, 7.14; 95% CI, 4.55-11.11) correlated with hypoparathyroidism.
CONCLUSION: These data present thyroidectomy information and complications pertinent to surgeons, along with preoperative risk factor assessment. Multivariable analysis showed institutional volume and hypoparathyroidism associated with RLN injury, while hypoparathyroidism associated with surgical indication, central neck dissection, and extent of surgery. Low complication rates support the safety of thyroidectomy in pediatric tertiary care centers.
PubMed-ID: 35133903
http://dx.doi.org/10.1177/01945998221076065

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

How Many Nodes to Take? Lymph Node Ratio Below 1/3 Reduces Papillary Thyroid Cancer Nodal Recurrence.
Laryngoscope, 132(9):1883-7.
R. E. Weitzman, N. S. Justicz, D. Kamani, N. Kyriazidis, M. H. Chen and G. W. Randolph.
INTRODUCTION: Papillary thyroid carcinoma (PTC) accounts for the majority of thyroid malignancies; risk of PTC recurrence over a 30-year period is approximately 30%, of which 70% occur as nodal metastases. Patients with nodal disease who are treated with therapeutic dissection are at higher risk for recurrence, but optimal nodal yield has not been defined. We aim to determine variables predictive of nodal recurrence of PTC within the first 5 years of surgery, with a focus on lymph node ratio (LNR), to inform clinical decision-making.
METHODS: Retrospective chart review identified 41 patients with nodal recurrence of PTC and 284 without nodal recurrence following thyroid surgery from 2000 to 2015. Cohorts were compared with regards to clinical history, surgical

findings, and tumor characteristics.
RESULTS: The fraction of the patients who underwent therapeutic central or lateral lymph node dissection was significantly higher in the nodal recurrence cohort. Maximum tumor size, presence of extrathyroidal extension, largest lymph node focus, LNR, postoperative thyroglobulin level, and administration of postoperative radioactive iodine were significantly increased in the PTC nodal recurrence group. LNR greater than 0.3 held the highest level of significance as a binary cutoff and captured the larger proportion of patients in the nodal recurrence cohort (68.3%).
CONCLUSION: This study demonstrates characteristics to help assess risk of nodal recurrence of PTC and suggests LNR of lower than 0.3 is optimal to reduce risk of recurrence. The next steps include cohort studies to validate findings and weight variable analysis to optimize the extent of surgical therapeutic dissection. LEVEL OF EVIDENCE: 4 Laryngoscope, 132:1883-1887, 2022.
PubMed-ID: 35229306
http://dx.doi.org/10.1002/lary.30084

Distant metastasis in medullary thyroid carcinoma: Clinical outcomes and implications of T stage.
Clin Endocrinol (Oxf), 97(5):676-84.
Y. Shao, G. Li, T. Wei, R. Gong, Z. Li, J. Zhu and J. Lei.
BACKGROUND: The eighth edition of the American Joint Committee on Cancer tumour, node, and metastasis staging system did not take T stage into consideration when evaluating Stage IV C medullary thyroid carcinoma (MTC) patients. The aim of this study is to investigate the clinical outcomes and implications of T stage in this population.
METHODS: Eligible patients from the Surveillance, Epidemiology, and End Results database and the Department of Thyroid Surgery in West China Hospital of Sichuan University and who were diagnosed with Stage IV C MTC were included in this study. The overall survival (OS), the cancer-specific survival (CSS), and the precise cause of MTC-induced death were analysed. The potential risk factors, including the T stage, in the OS and CSS were evaluated by univariate and multivariate Cox regression models.
RESULTS: This retrospective study enroled 204 Stage IV C MTC patients. The 5- and 10-year OS rates were 31.8% and 17.1%, respectively, and the 5- and 10-year CSS rates were 40.4% and 22.5%, respectively. More importantly, the rates of MTC-induced death between primary or distant metastatic lesions in Stage IV C MTC patients were comparable in our institution. Additionally, the univariate and multivariate analyses demonstrated that the presence of an advanced T stage was an independent prognostic factor for both the OS (T4 vs. T1-T3, hazard ratio [HR]: 1.714, 95% confidence interval [CI]: 1.175-2.500, p = .005) and the CSS (T4 vs. T1-T3, HR: 1.848, 95% CI: 1.229-2.780, p = .003).
CONCLUSION: To achieve a better risk stratification, further classification of Stage IV C MTC patients by the T stage may be preferable.
PubMed-ID: 35261045
http://dx.doi.org/10.1111/cen.14717

Postradioiodine Graves' management: The PRAGMA study.
Clin Endocrinol (Oxf), 97(5):664-75.
P. Perros, A. Basu, K. Boelaert, C. Dayan, B. Vaidya, G. R. Williams, J. H. Lazarus, J. Hickey, W. M. Drake, A. Crown, S. M. Orme, A. Johnson, D. W. Ray, G. P. Leese, T. H. Jones, P. Abraham, A. Grossman, A. Rees, S. Razvi, F. W. Gibb, C. Moran, A. Madathil, M. P. Žarkovi, Z. Plummer, S. Jarvis, A. Falinska, A. Velusamy, V. Sanderson, N. Pariani, S. L. Atkin, A. A. Syed, T. Sathyapalan, S. Nag, J. Gilbert, H. Gleeson, M. J. Levy, C. Johnston, N. Sturrock, S. Bennett, B. Mishra, I. Malik and N. Karavitaki.
OBJECTIVE: Thyroid status in the months following radioiodine (RI) treatment for Graves' disease can be unstable. Our objective was to quantify frequency of abnormal thyroid function post-RI and compare effectiveness of common management strategies.
DESIGN: Retrospective, multicentre and observational study.
PATIENTS: Adult patients with Graves' disease treated with RI with 12 months' follow-up.
MEASUREMENTS: Euthyroidism was defined as both serum thyrotropin (thyroid-stimulating hormone [TSH]) and free thyroxine (FT4) within their reference ranges or, when only one was available, it was within its reference range; hypothyroidism as TSH ≥ 10 mU/L, or subnormal FT4 regardless of TSH; hyperthyroidism as TSH below and FT4 above their reference ranges; dysthyroidism as the sum of hypo- and hyperthyroidism; subclinical hypothyroidism as normal FT4 and TSH between the upper limit of normal and <10 mU/L; and subclinical hyperthyroidism as low TSH and normal FT4.
RESULTS: Of 812 patients studied post-RI, hypothyroidism occurred in 80.7% and hyperthyroidism in 48.6% of patients. Three principal post-RI management strategies were employed: (a) antithyroid drugs alone, (b) levothyroxine alone, and (c) combination of the two. Differences among these were small. Adherence to national guidelines regarding monitoring

thyroid function in the first 6 months was low (21.4%-28.7%). No negative outcomes (new-onset/exacerbation of Graves' orbitopathy, weight gain, and cardiovascular events) were associated with dysthyroidism. There were significant differences in demographics, clinical practice, and thyroid status postradioiodine between centres.
CONCLUSIONS: Dysthyroidism in the 12 months post-RI was common. Differences between post-RI strategies were small, suggesting these interventions alone are unlikely to address the high frequency of dysthyroidism.
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http://dx.doi.org/10.1111/cen.14719

Recurrent Laryngeal Nerve Invasion by Thyroid Cancer: Laryngeal Function and Survival Outcomes.
Laryngoscope, 132(11):2285-92.
J. A. Brooks, A. H. Abdelhamid Ahmed, Z. Al-Qurayshi, D. Kamani, N. Kyriazidis, R. J. Hammon, H. Ma, N. Sritharan, I. Wasserman, L. N. Trinh, A. J. Iwata, Y. Saito, S. Soylu and G. W. Randolph.
BACKGROUND: Recurrent laryngeal nerve (RLN) invasion by thyroid carcinoma represents an advanced disease status with potentially significant co-morbidity.
METHODS: In a retrospective single-center study, we included patients with invaded RLNs operated on while using nerve monitoring techniques. We studied pre-, intra-, and postoperative parameters associated with postoperative vocal cord paralysis (VCP); 5-year recurrence-free survival (RFS); and 5-year overall survival (OS) in addition to two subgroup analyses of postoperative VCP in patients without preoperative VCP and based on source of RLN invasion.
RESULTS: Of 65 patients with 66 nerves-at-risk, 39.3% reported preoperative voice complaints. Preoperative VCP was documented in 43.5%. The RLN was invaded by primary tumor in 59.3% and nodal metastasis in 30.5%. Papillary thyroid carcinoma was the most common pathologic subtype (80%). After 6 months, 81.8% had VCP. Complete tumor resection of the RLN was not associated with 5-year RFS ($p = 0.24$) or 5-year OS ($p = 0.9$). Resecting the RLN did not offer statistically significant benefit on 5-year RFS ($p = 0.5$) or 5-year OS ($p = 0.38$). Radioactive Iodine (RAI) administration was associated with improvement in 5-year RFS ($p = 0.006$) and 5-year OS ($p = 0.004$). Patients without preoperative VCP had higher IONM amplitude compared with patients with VCP. After a mean follow-up of 65.8 months, 35.9% of patients had distant metastases, whereas 36.4% had recurrence.
CONCLUSION: Preoperative VCP accompanies less than half of patients with RLN invasion. Invaded RLNs may have existent electrophysiologic stimulability. Complete tumor resection and RLN resection were not associated with better 5-year RFS or OS, but postoperative RAI was. LEVEL OF EVIDENCE: 4 Laryngoscope, 132:2285-2292, 2022.
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http://dx.doi.org/10.1002/lary.30115

Using Intra-Operative Laryngeal Ultrasonography as a Real-Time Tool in Assessing Vocal Cord Function During Radiofrequency Ablation of the Thyroid Gland.
World J Surg, 46(9):2206-11.
M. M. H. Fung and B. H. H. Lang.
BACKGROUND: Inadvertent injury of the recurrent laryngeal nerve can occur during radiofrequency ablation (RFA) of thyroid nodules. Methods to avoid permanent injury have not been described. Laryngeal ultrasonography (LUSG) can assess the function of vocal cords (VCs) in real time. The present study aimed to evaluate the feasibility and accuracy of LUSG in assessing real-time VC function during RFA of benign thyroid nodules.
METHODS: Consecutive patients undergoing RFA for benign thyroid nodules under local anesthesia were included. Spontaneous VC movements were checked with intra-operative LUSG (iLUSG) following each transverse ablation plane. In case of reduced VC movement, the ablation was stopped immediately. Post-ablation VC function was rechecked by LUSG on day-0 and flexible laryngoscopy (FL) on day-7. A concordance with day-0 LUSG or day-7 FL was a "true positive" or "true negative" depending on the presence or absence of VC palsy (VCP). Accuracy was calculated as the sum of all true positives and negatives divided by total nerves-at-risk.
RESULTS: Of 65 eligible patients, 56 (86.2%) were females. Twelve (18.5%) patients had bilateral lobe RFA, while 53 (81.5%) had unilateral RFA. The total number of nerves-at-risk was 77. Three unilateral VCPs (3.9%) were initially detected on iLUSG and confirmed by day-0 LUSG. All recovered fully within one week. The overall accuracy of iLUSG was 100%.
CONCLUSION: iLUSG is a highly accurate method that permits real-time feedback on the function of the VCs during RFA procedure. Real-time detection of VCP may prevent permanent injury. Methodological routine use of iLUSG is recommended during thyroid RFA.
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http://dx.doi.org/10.1007/s00268-022-06596-9

Assesment of attainment of recommended TSH levels and levothyroxine compliance in differentiated thyroid cancer patients.
Clin Endocrinol (Oxf), 97(6):833-40.
D. G. Yavuz, C. D. Yazan, Z. Hekimsoy, K. Aydin, N. Gokkaya, C. Ersoy, A. Akalın, O. Topaloglu, B. I. Aydogan, E. N. A. Dilekci, Z. Alphan Uc, G. B. Cansu, L. Ozsari, O. T. Iyidir, M. E. Olgun, L. Keskin, M. Mert, B. Can, K. Gungor, T. Galip, Z. Cantürk, G. Elbuken, Z. Pekkolay, N. O. Kutbay, G. Yorulmaz, A. T. Kalkan, Y. A. Unsal, A. Yay, B. Karagun and E. Bozkur.
OBJECTIVE: Thyroid-stimulating hormone (TSH) suppression treatment can induce signs and symptoms of hyperthyroidism and hypothyroidism due to inappropriate treatment or poor compliance to the treatment. The current study aimed to investigate TSH levels, frequency of being on target TSH, adherence to levothyroxine (LT4) suppression treatment in differentiated thyroid cancer (DTC) patients after surgery in a multicentric setting.
DESIGN AND PATIENTS: This multicentric cross-sectional study was conducted at 21 medical centres from 12 cities in Turkey. DTC patients followed at least one year in the same center included in the study. Clinical data, serum TSH, free thyroxine (FT4), thyroglobulin (Tg) and anti-Tg levels were recorded during the most recent visit. Body mass index, systolic and diastolic blood pressures, pulse rate were measured. LT4 doses were recorded and doses per kilogram of bodyweight were calculated. Pill ingestion habits recorded and adherence to the therapy were evaluated using the Morisky Medication Adherence Scale and categorized as good, moderate or poor compliant based on their scores. Risk stratification forpredicting the disease persistance and/or reccurence was assessed using the American Joint Committee on Cancer-7th edition thyroid cancer staging calculator. TSH serum concentrations were classified as severe suppression (TSH < 0.01 mU/L), moderate suppression (TSH: 0.01-0.1 mU/L), mild suppression (TSHL 0.1-0.5 mU/L), euthyroid (TSH: 0.5-4 mU/L) and hypothyroid (TSH>4 mU/L). TSH levels can also be classified as on being on target, under the target, or beyond over the target, according to the American Thyroid Association recommendations.
RESULTS: A group of 1125 patients (F/M: 941/184, 50.7 ±11.7 years) were included in the study. The mean LT4 daily dosage was 132.4 ± 39.6 mcg/day. TSH levels showed severe suppression in 99 (%8.8) patients, moderate suppression in 277 (%24.6) patients and mild suppression in 315 (%28) patients and euthyroid range in 332 (%29.5) patients and hypothyroid range in 97 (8.6%). TSH levels were in target in 29.2% of the patients 20.4% of the patients were undertreated, 50.4% overtreated. The daily LT4 dose and LT4 dose/kg were significantly higher in the severe suppression group (p<.001, p<.001). According to the Morisky scale, 564 patients (50.1%) were good compliant, 368 patients (32.7%) were moderate compliant, and 193 patients (17.1%) were noncompliant. Patients with poor compliance need a higher dose of LT4 compared to the good compliance group (p<.001). TSH levels of patients with good compliance were 0.67 ± 1.96 mU/L and TSH with poor compliance was 2.74 ± 7.47 mU/L (p<.001). TSH levels were similar in patients on fixed and alternating dosages.
CONCLUSION: In 29.2% of the DTC patients, serum TSH levels were at target levels. Remaining of the study group have TSH levels under or over treatment range, exposing the patient to medication side effects. Majorty of the study group 82.8% have good or moderate adherence to LT4 therapy. Reaching TSH targets requires simplified and applicable guidelines and following the guideline recommendations.
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http://dx.doi.org/10.1111/cen.14787

Quality of life following lobectomy versus total thyroidectomy is significantly related to hypothyroidism.
J Surg Oncol, 126(4):640-8.
D. Yaniv, I. Vainer, I. Amir, E. Robenshtok, D. Hirsch, T. Watt, O. Hilly, Y. Shkedy, T. Shpitzer, G. Bachar, R. Feinmesser and A. Mizrachi.
OBJECTIVE: The aim of the present study was to investigate the differences in quality of life (QOL) following complete or partial thyroidectomy and with regard to thyroid hormone replacement (LT4) therapy.
STUDY DESIGN: Patients who underwent thyroidectomy were asked to complete the validated thyroid-specific ThyPRO QOL questionnaire at least 6 months following surgery. SETTING: Tertiary medical center.
METHODS: Thyroid specific QOL questionnaire analysis.
RESULTS: A total of 190 patients completed the ThyPRO questionnaire. Of them 89 patients had complete thyroidectomy and 101 patients had unilateral thyroid lobectomy. The total thyroidectomy group had significantly worse overall QOL self-assessment score than the lobectomy patients (p < 0.0001). Patients receiving LT4 therapy regardless of the extent of surgery, reported worse QOL compared to patients not receiving LT4.
CONCLUSIONS: Quality of life following thyroid surgery is significantly related to hypothyroidism and the requirement for LT4 therapy, rather to the extent of surgery. The best QOL was reported in patients treated with lobectomy who did not require LT4 therapy.

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http://dx.doi.org/10.1002/jso.26983

Surgical selection and prognostic analysis in patients with unilateral sporadic medullary thyroid carcinoma.
Langenbecks Arch Surg, 407(7):3013-23.
J. Zhang, P. Gu, D. Huang, J. Zhao, X. Zheng and M. Gao.
PURPOSE: The extent of thyroid surgery and cervical lymph node dissection of unilateral sporadic medullary thyroid carcinoma (sMTC) is still controversial, and the aim of this study was to investigate whether hemithyroidectomy was adequate as a locally curative surgery for patients with unilateral sMTC.
METHODS: This study is a retrospective case series of patients with sMTC who underwent curative total thyroidectomy or hemithyroidectomy in our institution from January 2011 to December 2019.
RESULTS: In total, 129 patients who met the inclusion criteria were enrolled including 49 (38.0%) patients who underwent total thyroidectomy and 80 (62.0%) patients who underwent hemithyroidectomy. About 80 (62.0%) patients achieved a biochemical cure (BC), whereas there was no significant difference between two groups in biochemical cure rate (61.2% versus 62.5%, P = 0.885). A logistic regression analysis showed a strong negative correlation between the factors of preoperative calcitonin level and pTNM stage and biochemical cure. In the log-rank test, no significant difference in OS (P = 0.314) and DFS (P = 0.409) was found between the two surgical groups. Lateral cervical lymph node metastasis and pTNM stage were significant prognostic factors affecting DFS in univariate analysis; moreover, absence of biochemical cure, tumor size ≥ 4 cm and lateral cervical lymph node metastasis were independent risk factors of unilateral sMTC patients in our analysis.
CONCLUSION: For patients with unilateral sMTC, hemithyroidectomy was adequate as a locally curative surgery, because the patients underwent total thyroidectomy did not benefit more from it in the aspects of BC/OS/RFS, while the postoperative increasing incidence rate of postoperative hypocalcemia could not improve patients' quality of life.
PubMed-ID: 35748956
http://dx.doi.org/10.1007/s00423-022-02591-9

Fumarate Hydratase is a Novel Gene for Familial Non-Medullary Thyroid Cancer.
J Clin Endocrinol Metab, 107(9):2539-44.
A. S. Alzahrani, M. Alswailem, B. Alghamdi and H. Al-Hindi.
CONTEXT: The majority of cases of epithelial cell-derived thyroid cancer are sporadic. Familial non-medullary thyroid cancer (FNMTC) occurs in about 5% to 9% of cases, either as a part of known syndromes such as Cowden syndrome or in the form of familial clustering of 2 or more affected family members. Hereditary leiomyoma and renal cell cancer (HLRCC) syndrome is a rare familial cancer syndrome. The underlying etiology is heterozygous germline mutations of the fumarate hydratase (FH) gene. In addition to extensive uterine and skin leiomyomas and RCC, other tumors may arise in this syndrome. However, thyroid cancer has never been described as part of HLRCC. Here, we describe a woman who presented with an aggressive poorly differentiated thyroid cancer (PDTC) and was found to have HLRCC syndrome because of a novel heterozygous germline FH mutation.
RESULTS: A 43-year-old woman presented with a large lower neck mass that was found to be PDTC. During her evaluation, she was found to have extensive uterine leiomyomatosis and bilateral adrenal nodules. Whole exome and subsequent Sanger sequencing of leucocyte DNA revealed a novel monoallelic nonsense FH mutation (c.760C>T, p.Q254*). Sequencing of the thyroid tumor tissue showed a biallelic loss at the same mutation site (loss of heterozygosity) and immunohistochemistry of the PDTC showed loss of FH staining in the tumor tissue, indicating the pathogenic role of this mutation in the development of PDTC in this patient.
CONCLUSION: Thyroid cancer is a novel feature of the FH-related HLRCC syndrome. This syndrome can be added to the rare genetic causes of syndromic FNMTC.
PubMed-ID: 35751867
http://dx.doi.org/10.1210/clinem/dgac386

UK national chronic hypoparathyroidism audit.
Clin Endocrinol (Oxf), 97(5):562-7.
J. S. Kiam, V. Sharma, L. Glenister, W. D. Fraser and J. J. O. Turner.
OBJECTIVES: Individuals with chronic hypoparathyroidism may experience suboptimal medical care with high frequency of unplanned hospitalisation and iatrogenic harm. In 2015 the European Society for Endocrinology published consensus guidelines on the management of chronic hypoparathyroidism. We set out to audit compliance with these guidelines.
METHODS: Using these recommendations as audit standards we worked with the Society for Endocrinology and

Parathyroid UK to conduct a national audit of management of chronic hypoparathyroidism in the United Kingdom. Endocrine leads in 117 endocrine departments were invited to participate in the survey by completing a data collection tool on up to 5 sequential cases of chronic hypoparathyroidism seen in their outpatient clinics in the preceding 12 months. Data were collected on 4 treatment standards and 9 monitoring standards. Data on hospitalisations and Quality of Life monitoring were also collected.
RESULTS: Responses were received from 22 departments giving a response rate of 19%, concerning 80 individual cases. The mean age of subjects was 48.4 years. The main findings were that the commonest cause of hypoparathyroidism was post surgical (66.3%). Treatments taken by the group included activated vitamin D analogues (96.3%), oral calcium salts (66.3%), vitamin D supplements (17.5%), thiazide diuretics (5%) and rhPTH(1-34) (1.3%). Compliance with the audit standards varied between 98.8% and 60% for the treatment standards and between 91.3% and 20% for the monitoring standards. Some of the areas of weakness revealed include low rates of 24 h urinary calcium excretion monitoring, serum magnesium monitoring and low rates of renal imaging where indicated. In addition and importantly, 16.3% of subjects had experienced at least one hospital admission in the preceding 12 months.
CONCLUSION: We conclude that further improvements in the UK national standard of management of chronic hypoparathyroidism should be made and that this will benefit both quality of life, morbidity and potentially mortality in this group of patients.
PubMed-ID: 35792134
http://dx.doi.org/10.1111/cen.14798

Case Control Study of Risk Factors for Occurrence of Postoperative Hematoma After Thyroid Surgery: Ten Year Analysis of 6938 Operations in a Tertiary Center in Serbia.
World J Surg, 46(10):2416-22.
K. Tausanovic, V. Zivaljevic, S. S. Grujicic, K. Jovanovic, V. Jovanovic and I. Paunovic.
BACKGROUND: Post-thyroidectomy bleeding is rare, but potentially life-threatening complication. Early recognition with immediate intervention is crucial for the management of this complication. Therefore, it is very important to identify possible risk factors of postoperative hemorrhage as well as timing of postoperative hematoma occurrence.
METHODS: Retrospective review of 6938 patients undergoing thyroidectomy in a tertiary center in a ten year period (2009-2019) revealed 72 patients with postoperative hemorrhage requiring reoperation. Each patient who developed postoperative hematoma was matched with four control patients that did not develop postoperative hematoma after thyroidectomy. The patients and controls were matched by the date of operation and surgeon performing thyroidectomy.
RESULTS: The incidence of postoperative bleeding was 1.04%. On univariate analysis older age, male sex, higher BMI, higher ASA score, preoperative use of anticoagulant therapy, thyroidectomy for retrosternal goiter, larger thyroid specimens, larger dominant nodules, longer operative time, higher postoperative blood pressure and the use of postoperative subcutaneous heparin were identified as risk factors for postoperative bleeding. Sixty-nine patients (95.8%) bled within first 24 h after surgery.
CONCLUSION: The rate of postoperative bleeding in our study is consistent with recent literature. Male sex, the use of preoperative anticoagulant therapy, thyroidectomy for retrosternal goiter and the use of postoperative subcutaneous heparin remained statistically significant on multivariate analysis ($p < 0.001$). When identified, these risk factors may be an obstacle to the outpatient thyroidectomy in our settings.
PubMed-ID: 35798991
http://dx.doi.org/10.1007/s00268-022-06634-6

Effect of skip metastasis to lateral neck lymph nodes on outcome of patients with papillary thyroid carcinoma.
Langenbecks Arch Surg, 407(7):3025-30.
J. B. Bertin, C. Buffet, L. Leenhardt, F. Menegaux and N. Chereau.
CONTEXT: Lymph node metastasis (N1) is a prognostic factor for disease recurrence in papillary thyroid carcinoma (PTC) patients. Skip metastasis is defined as only lateral N1 with negative central lymph nodes (LNs).
OBJECTIVE: The aim of this study was to explore the outcome of PTC patients with skip N1.
PATIENTS AND DESIGN: All patients who underwent a total thyroidectomy with ipsilateral central and lateral LN dissection for PTC from 1999 to 2019 in a high-volume endocrine surgery centre were included in this study. MAIN OUTCOME MEASURE: Demographic and outcomes-recurrence and disease-specific survival (DSS)-were compared between three groups: N1a (central N1 only), N1b-CL (central and lateral N1), and N1b-Skip (lateral N1 without central LN involvement).
RESULTS: During the study period, 3046 patients had surgery for PTC, including 1138 with N1 (37%, 860 women, mean age: 44.8 years) comprising 474 N1a (42%), 513 N1b-CL (45%), and 151 N1b-Skip (13%). The median follow-up was 74 months (range 12-216 months). The recurrence rate in the N1b-Skip group was 13% (20/151) and 10% (47/474) in the N1a

group. This was significantly lower than that in the N1b-CL group (27%, 140/513) (p < 0.0001). DSS at 10 years was 99% for group N1a, 98% for the N1b-CL, and 99% in the N1b-Skip group.
CONCLUSION: The recurrence rate of N1b-Skip patients was lower than that of N1b-CL patients and similar to that of N1a patients. This result could be used as an indication for the modality of radioiodine therapy, and for the pattern of follow-up procedures.
PubMed-ID: 35819485
http://dx.doi.org/10.1007/s00423-022-02604-7

Prognostic value of LODDS in medullary thyroid carcinoma based on competing risk model and propensity score matching analysis.
Updates Surg, 74(5):1551-62.
Z. X. Cao, X. Weng, J. S. Huang and X. Long.
Log odds of positive lymph nodes (LODDS) is an independent prognostic factor for patients with medullary thyroid carcinoma (MTC). However, the optimal cutoff value for LODDS needs to be further confirmed, and previous studies have ignored the prevalent competing events of non-cancer deaths among patients with MTC, thus possibly overestimating the risk of death from cancer. The information of patients with MTC who underwent total thyroidectomy was collected from SEER database. Restricted cubic splines (RCS) were used to determine the optimal cutoff for LODDS. Moreover, patients' overall survival (OS) and disease-specific survival (DSS) were determined using Kaplan-Meier and Cox proportional-hazards model. The competing risk models (CRM) were used to reduce the effect of competing events, and propensity score matching was performed to balance the confounding factors between groups. The cutoff value of LODDS determined by RCS was - 1.004, and a total of 2314 patients with MTC were recruited. In the CRM after PSM, factors such as age over 55 years at diagnosis, being male, treatment with chemotherapy or radiotherapy, unknown tumor size, and LODDS > - 1.004 were significantly associated with poor prognosis of patients both in univariate and multivariate analyses, while the presence of multifocal tumor indicated better prognosis. Patients with MTC who were over 55 years old at diagnosis, were male, received chemotherapy or radiation, had an unclear initial tumor size, and had LODDS > - 1.004 had a worse prognosis than patients with multifocal tumor.
PubMed-ID: 35821560
http://dx.doi.org/10.1007/s13304-022-01320-7

Feasibility and Safety of Ambulatory Transoral Endoscopic Thyroidectomy via Vestibular Approach (TOETVA).
World J Surg, 46(11):2678-86.
K. Van Den Heede, N. Brusselaers, S. Gaujoux, F. Menegaux and N. Chereau.
BACKGROUND: In search of an ideal cosmesis, transoral endoscopic thyroidectomy via vestibular approach (TOETVA) has recently been introduced to avoid a visible scar. Although ambulatory thyroid surgery is considered safe in carefully selected patients, this remains unclear for TOETVA.
METHODS: All consecutive adult patients who underwent ambulatory TOETVA or open thyroid surgery at a French university hospital were prospectively enrolled from 12/2020 until 11/2021. The primary outcome was postoperative morbidity (recurrent laryngeal nerve (RLN) palsy, re-intervention for bleeding, wound morbidity, or hospital readmission). The secondary outcome was quality of life (QoL), measured by a survey including a validated questionnaire (SF-12) and a modified thyroid surgery questionnaire six weeks after surgery.
RESULTS: Throughout the study period, 374 patients underwent a unilateral lobectomy or isthmectomy in ambulatory setting, of which 34 (9%) as TOETVA (including 21 (62%) for a possible malignancy). In the TOETVA group, younger age (median 40 (IQR 35-50) vs. 51 (40-60) years, P < 0.001) and lower BMI (median 23.1 (20.9-25.4) vs. 24.9 (22.1-28.9) kg/m(2), P = 0.001) were noted. No cases were converted to open cervicotomy. TOETVA was at least as good as open cervicotomy with nil versus four (1%) re-interventions for bleeding, one temporary (5%) versus 13 (4%) (temporary) RLN palsies, and one (<1%) wound infection (open cervicotomy group). No hospital readmissions occurred in all ambulatory surgery patients. No differences were found in physical (P = 0.280) and mental (P = 0.569) QoL between TOETVA and open surgery.
CONCLUSIONS: In carefully selected patients, the feasibility and safety of ambulatory TOETVA are comparable to open surgery.
PubMed-ID: 35854011
http://dx.doi.org/10.1007/s00268-022-06666-y

Kidney Complications and Hospitalization in Patients With Chronic Hypoparathyroidism: A Cohort Study in Sweden.
J Clin Endocrinol Metab, 107(10):e4098-e105.

O. Swartling, M. Evans, T. Spelman, W. Kamal, O. Kämpe, M. Mannstadt, Y. Trolle Lagerros and S. Björnsdottir.
CONTEXT: Kidney complications may be considerably higher in patients with chronic hypoparathyroidism (hypoPT) treated with activated vitamin D and calcium supplementation.
OBJECTIVE**:** We aimed to investigate the risk of chronic kidney disease (CKD), urolithiasis, and hospitalization in patients with chronic hypoPT.
METHODS: In this population-based cohort study in Sweden, national registries (Swedish National Patient Register, Swedish Prescribed Drug Register, and Total Population Register, 1997-2018) were used to identify patients with chronic hypoPT and controls matched by sex, age, and county of residence. We determined time to CKD and urolithiasis diagnosis, and incidence rates of hospitalization.
RESULTS: A total of 1562 patients with chronic hypoPT without preexisting CKD and 15,620 controls were included. The risk of developing CKD was higher in patients with chronic hypoPT compared with controls (hazard ratio [HR] 4.45; 95% CI, 3.66-5.41). In people without prior urolithiasis (n = 1810 chronic hypoPT and n = 18,100 controls), the risk of developing urolithiasis was higher in patients with chronic hypoPT (HR 3.55; 95% CI, 2.84-4.44) compared with controls. Patients with chronic hypoPT had higher incidence rates for all-cause hospitalization (49.59; 95% CI, 48.50-50.70, per 100 person-years vs 28.43; 95% CI, 28.15-28.71, respectively) and for CKD (3.46; 95% CI, 3.18-3.76, per 100 person-years vs 0.72; 95% CI, 0.68-0.77, respectively), compared with controls. Men with hypoPT appear to have a higher risk of CKD than women.
CONCLUSION: Patients with chronic hypoPT had an increased risk of CKD, urolithiasis, and hospitalization compared with controls.
PubMed-ID: 35907259
http://dx.doi.org/10.1210/clinem/dgac456

Radioactive Iodine Therapy Does not Improve Cancer-specific Survival in Hürthle Cell Carcinoma of the Thyroid.
J Clin Endocrinol Metab, 107(11):3144-51.
X. Wang, X. Zheng, J. Zhu, Z. Li and T. Wei.
CONTEXT: It is unclear whether radioactive iodine (RAI) therapy could improve cancer-specific survival (CSS) in patients with Hürthle cell carcinoma (HCC) of the thyroid.
OBJECTIVE: To investigate the effect of RAI on CSS in HCC patients.
METHODS: HCC patients who underwent total thyroidectomy (TT) were identified from the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2018. The Kaplan-Meier method and the Cox proportional hazards regression model were used to evaluate CSS. Propensity score-matched (PSM) analyses were performed to control the influence of potential confounders.
RESULTS: A total of 2279 patients were identified. RAI treatment was not significantly associated with improved CSS in overall or PSM cohort. Subgroup analyses indicated similar results, even in patients with aggressive features such as age 55 years or older, tumor size greater than 40 mm, distant disease in SEER staging, extrathyroidal extension, and lymph node metastases (all P > .05).
CONCLUSION: RAI has no statistically significant influence on the CSS in HCC patients. This information may aid in decision-making for RAI therapy in these patients.
PubMed-ID: 35908290
http://dx.doi.org/10.1210/clinem/dgac448

Prevalence of Postoperatively Detected High-risk Features in 2- to 4-cm Papillary Thyroid Cancers.
J Clin Endocrinol Metab, 107(10):e4124-e31.
J. H. Choi, J. K. Lee, W. Kim, H. W. Yu, S. J. Kim, Y. J. Chai, J. Y. Choi and K. E. Lee.
CONTEXT: The 2015 American Thyroid Association guidelines proposed thyroid lobectomy as an acceptable option for 1- to 4-cm papillary thyroid cancers (PTC) without extrathyroidal extension (ETE) or lymph node (LN) metastasis. However, high-risk features are often detected postoperatively, even in tumors that are considered low risk on preoperative workup. A continued evaluation is necessary to determine the optimal treatment strategies.
OBJECTIVE: We examined the frequency of preoperatively and postoperatively detected high-risk features in 2- to 4-cm PTCs to assess the appropriate surgical extent.
METHODS: All patients who underwent a thyroid surgery between 2015 and 2020 with a final diagnosis of 2- to 4-cm PTC were selected. Demographics, preoperative findings, perioperative course, and surgical pathology were retrospectively analyzed.
RESULTS: Of the entire study cohort (N = 424), 244 (57.5%) patients had at least 1 of the following high-risk features: gross ETE (18.6%), distant metastasis (1.2%), >3 LN involvement with extranodal extension (24.8%), any LN > 3 cm (0.5%), positive margin (13.2%), TERT mutation (2.6%), vascular invasion (10.8%), cN1 disease (28.5%), and > 5 LN involvement

(30.4%). Two hundred patients had neither ETE nor LN metastasis on preoperative imaging, but 62/200 (31.0%) were found to have at least 1 of the aforementioned high-risk features on final pathology. Preoperative imaging had sensitivities of 75.9% and 44.4% for detecting gross ETE and LN metastasis, respectively.
CONCLUSION: A significant portion of patients with 2- to 4-cm PTCs, including those who preoperatively met the criteria for lobectomy, were found to have high-risk features on final pathology. Careful patient selection and appropriate counseling are necessary when considering lobectomy for tumors greater than 2 cm.
PubMed-ID: 35914522
http://dx.doi.org/10.1210/clinem/dgac457

Variation in the Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features.
J Clin Endocrinol Metab, 107(10):e4072-e7.
D. W. Chen, F. I. Rob, R. Mukherjee, T. J. Giordano, M. R. Haymart and M. Banerjee.
CONTEXT: Noninvasive encapsulated follicular variant of papillary thyroid cancer was reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in January 2017. The impact of this nomenclature change at a population level remains unknown.
OBJECTIVE**:** Examine use of NIFTP across different US regions and populations.
DESIGN: Descriptive epidemiology study using SEER-22 data (2000-2019). PARTICIPANTS: Individuals diagnosed with papillary or follicular thyroid cancer (2000-2019) or NIFTP (2017-2019). MAIN OUTCOME MEASURES: Annual incidence rates of thyroid cancer by subtype and NIFTP. Using 2018-2019 data, (1) rates of NIFTP at the 17 SEER-22 sites and (2) comparison of demographics for patients diagnosed with NIFTP vs papillary and follicular thyroid cancer.
RESULTS: NIFTP comprised 2.2% and 2.6% of cases in 2018 and 2019, respectively. Between 2018 and 2019, large heterogeneity was observed in the regional use of NIFTP diagnosis, with site-specific incidence rates between 0.0% and 6.2% (median 2.8%, interquartile range 1.3-3.6%). A diagnosis of NIFTP (vs papillary and follicular thyroid cancer) in 2018 and 2019 was significantly associated with older age (P = 0.012 and P = 0.009, respectively), Black race (both Ps < 0.001), and non-Hispanic ethnicity (both Ps < 0.001).
CONCLUSIONS: Marked variation exists in the use of the NIFTP diagnosis. The recent 2021 coding change that resulted in NIFTP, a tumor with uncertain malignant potential and for which there is no long-term outcome data available, no longer being a reportable diagnosis to SEER will disproportionately affect vulnerable patient groups such as older patients and Black patients, in addition to patients who reside in regions with higher rates of NIFTP diagnoses.
PubMed-ID: 35918064
http://dx.doi.org/10.1210/clinem/dgac466

ASO Visual Abstract: Novel Strategies for Managing Retropharyngeal Lymph Node Metastases in Head and Neck and Thyroid Cancer with TransOral Robotic Surgery (TORS).
Ann Surg Oncol, 29(12):7893-4.
G. Garas, N. J. Roland, J. Lancaster, M. Zammit, V. A. Manon, K. Davies, T. M. Jones, M. De, F. C. Holsinger, R. J. D. Prestwich and J. C. Fleming.
PubMed-ID: 35941346
http://dx.doi.org/10.1245/s10434-022-12371-w

Horner syndrome after thyroid-related surgery: a review.
Langenbecks Arch Surg, 407(8):3201-8.
M. Tang, S. Yin, Z. Yang, Y. Sun, H. Chen and F. Zhang.
BACKGROUND: Horner syndrome (HS) is caused by damage to the cervical sympathetic nerve. HS is a rare complication after thyroidectomy. The main manifestations of HS include miosis and ptosis of the eyelids, which seriously affect esthetics and quality of life. At present, there is a lack of research on HS after thyroidectomy, and its etiology is not completely clear. This review aimed to evaluate how to reduce the incidence of HS and promote the recovery from HS as well as to provide a reference for the protection of cervical sympathetic nerves during surgery.
RESULTS: HS caused by thyroid surgery is not particularly common, but it is still worthy of our attention. After searching with "Horner Syndrome," "Thyroid" as keywords, a total of 22 related cases were screened in PubMed. The results showed that open surgery, endoscopy, microwave ablation, and other surgical methods may have HS after operation. In addition, the statistics of 1213 thyroid surgeries in our hospital showed that the incidence of HS after endoscopic surgery (0.39%) was slightly higher than that after open surgery (0.29%). Further, this review analyzed potential causes of HS after thyroidectomy, so as to provide a theoretical basis for reducing its incidence.
CONCLUSION: Preventing HS during thyroidectomy is a difficult problem. The close and highly variable anatomical

relationship between the thyroid and cervical sympathetic nerves increases the risk of sympathetic nerve damage during thyroidectomy. Surgery and the use of energy equipment are also closely related to the occurrence of HS.
PubMed-ID: 35947219
http://dx.doi.org/10.1007/s00423-022-02636-z

Propensity Score Matched Outcome Analysis of Lobar Ablation Versus Completion Thyroidectomy in Low-Risk Differentiated Thyroid Cancer Patients: Median Follow-Up of 11 Years.
Thyroid, 32(10):1220-8.
C. Bal, S. Satapathy, A. Tupalli and S. Ballal.
BACKGROUND: Radioactive iodine lobar ablation (RAILA) of the contralateral thyroid lobe has been suggested as an alternative to completion thyroidectomy in patients of differentiated thyroid cancer (DTC) who underwent initial hemithyroidectomy. However, data on long-term outcomes are scarce. In this study, we intended to describe the long-term outcomes of RAILA versus completion thyroidectomy in a cohort of low-risk DTC patients.
METHODS: Data of patients with low-risk DTC who underwent initial hemithyroidectomy, and were subsequently treated with either completion thyroidectomy or RAILA between 1996 and 2015, were collected and analyzed. The treatment outcomes included ablation rate, recurrence rate, recurrence-free survival (RFS), and adverse events, and were validated by propensity score matching analysis.
RESULTS: Of the 1243 patients (median age: 34 years, range: 5-78) with low-risk DTC, 514 patients underwent upfront RAILA while 729 patients underwent completion thyroidectomy followed by remnant ablation. The ablation rate following the first radioactive iodine ((131)I) cycle was 75.3% [95% confidence interval (CI) 71.3-78.9] in the RAILA group versus 84.1% [CI 81.2-86.6] in the completion thyroidectomy group ($p < 0.001$). Over median follow-up of 11.4 years (interquartile range: 8.3-15.8), the recurrence rates between the two groups were not significantly different (1.6% [CI 0.7-3.2] vs. 1.0% [CI 0.4-2.1], respectively, $p = 0.343$). The product limit estimate of RFS at 10 years was 98.6% [CI 97.6-99.6%] in the RAILA group versus 99.1% [CI 98.3-99.9%] in the completion thyroidectomy group ($p = 0.391$). The outcomes in 497 matched pairs generated through propensity score analysis were similar. None of the patients in the RAILA group experienced permanent hypocalcemia or recurrent laryngeal nerve palsy, while the corresponding rates in the completion thyroidectomy group were 10/729 (1.4%) ($p = 0.006$) and 5/729 (0.7%) ($p = 0.080$), respectively. Radiation thyroiditis was seen in 25/514 (4.9%) patients in the RAILA group versus 3/729 (0.4%) in the completion thyroidectomy group ($p < 0.001$).
CONCLUSIONS: Upfront RAILA is seen to be a noninvasive, safe, and effective alternative to surgical completion thyroidectomy in low-risk DTC patients in the absence of macroscopic malignancy in the remaining thyroid lobe.
PubMed-ID: 35983596
http://dx.doi.org/10.1089/thy.2022.0234

Care Fragmentation in Patients with Differentiated Thyroid Cancer.
World J Surg, 46(12):3007-16.
J. A. Greenberg, J. W. Thiesmeyer, C. E. Egan, Y. J. Lee, M. Sivarajah, R. Zarnegar, T. J. Fahey, 3rd, T. Beninato and B. M. Finnerty.
BACKGROUND: Among surgical patients, care fragmentation (CF) is associated with worse outcomes. However, oncologic literature documents an association between high surgical volume and improved outcomes, favoring centralized cancer-surgery centers and thus predisposing to CF in patients with surgically treated tumors. We aimed to identify features associated with CF and ascertain differences in overall survival (OS) among patients with differentiated thyroid cancer (DTC).
METHODS: The National Cancer Database was queried for DTC patients diagnosed from 2009 to 2017. Patients experienced CF if part of their treatment was performed outside of the reporting facility or an associated office. A multivariable logistic regression analysis identified independent features associated with CF. A Cox multivariable regression analysis assessed the impact of CF on OS. A Kaplan-Meier analysis compared survival differences between patients experiencing CF or unified care (UC).
RESULTS: A total of 131,620 patients were included. Among them, 70,204 (53.3%) experienced CF and 61,416 (46.7%) experienced UC. Age < 55, residing in high-income areas, and stage 3 and 4 tumors were features independently associated with CF, whereas uninsured patients were less likely to experience CF than the privately insured. The features most strongly associated with CF were treatment at highest thyroid cancer-surgery volume institutions and traveling in the top distance quartile. While patients with CF experienced minor delays in time from diagnosis to surgery, 5-year OS was improved among patients with CF compared to UC for those with Stage 1-3 disease.
CONCLUSIONS: Among patients with DTC, CF is associated with treatment at a highest thyroid cancer surgery volume facility and improved OS in a setting of minor treatment delays.

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http://dx.doi.org/10.1007/s00268-022-06712-9

Analysis of Delayed Surgery and Clinical Outcomes in Intermediate- and High-risk Papillary Thyroid Cancer.
J Clin Endocrinol Metab, 107(12):3389-97.
H. Zhou, J. Wu, L. Shi, Y. Wang and B. Liu.
CONTEXT: The optimal timing to performing thyroid surgery following a diagnosis of papillary thyroid cancer (PTC) has yet to be fully defined.
OBJECTIVE: We aimed to examine if a delayed surgery may worsen the clinical outcome of PTC patients with intermediate- to high-risk of recurrence.
METHODS: All consecutive PTC patients with intermediate- to high-risk of recurrence who underwent total thyroidectomy and radioactive iodine (RAI) ablation at 3 tertiary hospitals in southwest China were retrospectively included. Excellent response at 1-year follow-up after initial therapy was defined as no clinical, imaging, or biochemical evidence of PTC. Association of the timing of surgery and excellent response rates.
RESULTS: The study included 871 patients. The median time interval between PTC diagnosis and surgery was 2 months (range, 1-87 months). Patients were divided according to the timing of surgery, < 6 months (group A, 624/871 [71.6%]), ≥ 6 to 11 months (group B, 123/871 [14.1%]), or ≥ 12 months (group C, 124/871 [14.2%]). One year after initial therapy, 64.7%, 71.5%, and 66.1% of patients in groups A, B, and C, respectively, achieved excellent response (P = 0.27). The lack of impact of surgery timing was observed across intermediate- to high-risk classifications and all T stage categories. These findings did not change when we separately analyzed the groups according to RAI dose (intermediate-dose group: ≤ 3.7 GBq [n = 654], and high-activity group: 5.5 GBq [n = 217]) further subdivided according to the timing of surgery.
CONCLUSION: Timing of surgery does not seem to affect short-term disease outcomes in intermediate- to high-risk PTC patients. Further research is necessary to assess the impact of delayed surgery on long-term prognosis.
PubMed-ID: 36056633
http://dx.doi.org/10.1210/clinem/dgac502

ASO Visual Abstract: Prognosis of Patients with 1-4-cm Papillary Thyroid Cancer Who Underwent Lobectomy-Focus on Gross Extrathyroidal Extension Invading Only Strap Muscles.
Ann Surg Oncol, 29(12):7843-4.
A. Jang, M. Jin, W. W. Kim, M. J. Jeon, T. Y. Sung, D. E. Song, T. Y. Kim, K. W. Chung, W. B. Kim, Y. K. Shong, Y. M. Lee and W. G. Kim.
PubMed-ID: 36071337
http://dx.doi.org/10.1245/s10434-022-12335-0

Impact of Local Control on Clinical Course in Stage IVC Anaplastic Thyroid Carcinoma.
World J Surg, 46(12):3034-42.
H. Yamazaki, K. Sugino, R. Katoh, K. Masudo, K. Matsuzu, W. Kitagawa, M. Nagahama, Y. Rino and K. Ito.
BACKGROUND: The present study investigated the association between local resection and cause of death in anaplastic thyroid carcinoma (ATC) patients with stage IVC disease.
METHODS: A total of 54 ATC patients with stage IVC disease were included in the study. Information including patient characteristics, laboratory data including complete blood count, treatment, and death were collected for analysis.
RESULTS: The median overall survival (OS) for patients with or without resection was 8.4 [95% confidence interval (CI) 5.9-14.4)] and 4.2 (95% CI 2.5-6.2) months, respectively (p < 0.001). No patients survived without resection at 1 year. Univariate analysis revealed that resection (p < 0.001) and radiotherapy (p = 0.018) were significantly associated with OS. Multivariate analysis revealed that resection (hazard ratio 0.257; 95% CI 0.115-0.575; p < 0.001) was the only independent prognostic factor of OS. In ATC patients with known resection status, the median OS for the patients with a resection status of R0/1 (n = 28) and R2 (n = 7) were 13.0 (95% CI 7.5-18.7) and 1.7 (95% CI 0.1-6.2) months, respectively (p < 0.001). The most common specific cause of death was respiratory insufficiency (35%), followed by airway obstruction (25%) and cerebral cardiovascular-related death (5%). The frequency of airway obstruction was significantly lower in patients with resection (p = 0.018).
CONCLUSIONS: Resection probably impacts on clinical course in ATC patients despite the presence of distant metastasis. However, R2 resection is likely to be harmful and surgeons should carefully consider the resectability of thyroid tumors.
PubMed-ID: 36127501
http://dx.doi.org/10.1007/s00268-022-06739-y

Occult metastasis to the superficial level VI lymph nodes in papillary thyroid carcinoma.
Head Neck, 44(12):2796-802.
H. N. Lee, C. M. Song, Y. B. Ji, J. K. Myung, Y. J. Lee and K. Tae.
BACKGROUND: This study aimed to evaluate the incidence and risk factors of occult metastasis to superficial level VI, defined as the space anterior to the strap muscles, including the lymph nodes between the sternocleidomastoid and sternohyoid muscles and suprasternal space lymph nodes.
METHODS: We studied 129 patients with papillary thyroid carcinoma who underwent thyroidectomy and neck dissection, including superficial level VI dissection.
RESULTS: Of the 129 patients, 62 (48%) had lymph nodes in the harvested specimens of superficial level VI, and the mean number of lymph nodes retrieved was 1.9 ± 1.2. Occult metastasis to superficial level VI occurred in four patients (3.1%). No significant risk factors of superficial level VI occult metastasis were noted in multivariate analysis.
CONCLUSIONS: Occult metastasis to superficial level VI was rare in patients with papillary thyroid carcinoma. Therefore, prophylactic dissection of superficial level VI may not be necessary for primary papillary thyroid carcinoma.
PubMed-ID: 36129318
http://dx.doi.org/10.1002/hed.27191

Correction: Encapsulated Angioinvasive Follicular Thyroid Carcinoma: Prognostic Impact of the Extent of Vascular Invasion.
Ann Surg Oncol, 29(13):8213.
H. Yamazaki, R. Katoh, K. Sugino, K. Matsuzu, C. Masaki, J. Akaishi, K. Y. Hames, C. Tomoda, A. Suzuki, K. Ohkuwa, W. Kitagawa, M. Nagahama, Y. Rino and K. Ito.
PubMed-ID: 36138288
http://dx.doi.org/10.1245/s10434-022-12593-y

How Effective is the Use of Molecular Testing in Preoperative Decision Making for Management of Indeterminate Thyroid Nodules?
World J Surg, 46(12):3043-50.
D. Steinmetz, M. Kim, J. H. Choi, T. Yeager, K. Samuel, N. Khajoueinejad, A. Buseck, S. Imtiaz, G. Fernandez-Ranvier, D. Lee, R. Owen and A. Taye.
INTRODUCTION: We performed Thyroseq v2 molecular testing on indeterminate thyroid nodules and evaluated whether they underwent a management change from the standard of thyroid lobectomy.
METHODS: We conducted a retrospective analysis of all indeterminate thyroid nodules that underwent Thyroseq v2 molecular testing from 2014 to 2019 at a large academic center. Pathology was reviewed by thyroid cytopathologists. Thyroseq results were reported benign (malignancy probability less than 10%) or suspicious (malignancy probability greater than 30%). The primary endpoint was a management change from a diagnostic lobectomy.
RESULTS: A total of 142 nodules were included: 113 (80%) Bethesda III and 29 (20%) Bethesda IV. Seventy-three nodules underwent surgical management and 69 did not. We noted a change in management in 64% (91/142) of nodules. Patients who underwent a change in management to no surgery had a significantly higher rate of benign Thyroseq result than those without a change (75.8% vs. 49.0%, p = 0.001). On logistic regression analysis, a benign Thyroseq result was a positive independent predictor of a change to no surgery (OR 3.87, 95% CI 1.69-8.89). Nodule size, multiple nodules, compressive symptoms, and history of hypothyroidism were not significant. Of the 91 patients who underwent a management change, 71% (65/91) did not undergo surgery. On follow-up (average 985 ± 615 days), 12% (8/65) of those nodules were growing or developed suspicious features requiring surgery.
CONCLUSIONS: Molecular testing helped avoid surgery in almost half our population with indeterminate thyroid nodules, and benign results may help avoid surgery in asymptomatic patients with indeterminate thyroid nodules.
PubMed-ID: 36167834
http://dx.doi.org/10.1007/s00268-022-06744-1

Quality of Life in Post-Surgical Hypoparathyroidism (PoSH) in Thyroid and Parathyroid Surgery.
World J Surg, 46(12):3025-33.
S. L. Hillary, J. E. Chooi, J. Wadsley, J. D. Newell-Price, N. J. Brown and S. P. Balasubramanian.
BACKGROUND: Post-surgical hypoparathyroidism (PoSH) is often long term, with significant associated morbidity and ongoing treatment. A recent systematic review found impaired quality of life (QoL) in patients with PoSH, despite stable treatment. Most studies did not include an appropriate control arm and further studies were recommended, taking into account underlying disease and comorbidities. This study aims to compare QoL in patients with PoSH with appropriate

control groups.
METHODS: This was a cross-sectional observational study using the general quality of life SF-36 tool and a hypocalcaemia symptom score (HcSS) to assess QoL in patients with PoSH and controls (who had similar surgery but without PoSH). Participants were identified from two patient groups (the Butterfly Thyroid Cancer Trust and the Association for Multiple Endocrine Neoplasia Disorders) and a single tertiary centre in the UK.
RESULTS: Four hundred and thirty-nine responses (female n = 379, PoSH n = 89) were included with a median (range) age of 52 (19-92) years. Reported dates of surgery ranged from 1973 to 2019. HcSS scores showed significantly more associated symptoms in patients with PoSH than those without ($p < 0.001$). Although there was no overall difference in QoL between groups, patients with PoSH consistently had lower scores ($p = 0.008$) in the energy/fatigue subdomain of the SF-36.
CONCLUSION: Patients with PoSH reported significantly more fatigue and loss of energy compared to appropriately matched controls, but overall QoL was not significantly different. Standardised QoL measures may not be sensitive enough to highlight the impact on QoL in these patients. A disease-specific tool may be required.
PubMed-ID: 36184675
http://dx.doi.org/10.1007/s00268-022-06730-7

Progression of Low-Risk Papillary Thyroid Microcarcinoma During Active Surveillance: Interim Analysis of a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma in Korea.
Thyroid, 32(11):1328-36.
E. K. Lee, J. H. Moon, Y. Hwangbo, C. H. Ryu, S. W. Cho, J. Y. Choi, E. J. Chung, W. J. Jeong, Y. S. Jung, J. Ryu, S. J. Kim, M. J. Kim, Y. K. Kim, C. Y. Lee, J. Y. Lee, H. W. Yu, J. H. Hah, K. E. Lee, Y. J. Lee, S. K. Park, D. J. Park, J. H. Kim and Y. J. Park.
BACKGROUND: Active surveillance (AS) is an alternative to thyroidectomy for the management of low-risk papillary thyroid microcarcinoma (PTMC). However, prospective AS data collected from diverse populations are needed.
METHODS: This multicenter prospective cohort study enrolled patients from three referral hospitals in Korea. The participants were self-assigned into two groups, AS or immediate surgery. All patients underwent neck ultrasound every 6-12 months to monitor for disease progression. Progression under AS was evaluated by a criterion of tumor size increment by 3 mm in one dimension (3 mm), 2 mm in two dimensions (2 × 2 mm), new extrathyroidal extension (ETE), or new lymph node metastasis (LNM), and a composite outcome was defined using all four criteria.
RESULTS: A total of 1177 eligible patients with PTMC (919 female, 78.1%) with a median age of 48 years (range 19-87) were enrolled; 755 (64.1%) patients chose AS and 422 (35.9%) underwent surgery. Among 755 patients under AS, 706 (female 537, 76.1%) underwent at least two ultrasound examinations and were analyzed. Over a follow-up period of 41.4 months (standard deviation, 16.0), 163 AS patients (23.1%) underwent surgery. Progression defined by the composite outcome was observed in 9.6% (68/706) of patients, and the 2- and 5-year progression estimates were 5.3% and 14.2%, respectively. The observed progression rates were 5.8% (41/706) and 5.4% (38/706) as defined by tumor size enlargement by 3 mm and 2 × 2 mm, respectively, and 1.3% (9/706) and 0.4% (3/706) for new LNM and ETE, respectively. No distant metastases developed during AS. In multivariate logistic regression analysis examining variables associated with progression under AS, age at diagnosis <30 years (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.10 - 7.45), male sex (OR, 2.48; 95% CI, 1.47 - 4.20), and tumor size 6 mm (OR, 1.89; 95% CI, 1.09 - 3.27) were independently significant.
CONCLUSIONS: The progression of low-risk PTMC during AS in the Korean population was low, but slightly higher than previously reported in other populations. Risk factors for disease progression under AS include younger age, male sex, and larger tumor size. Clinical trial registration: Clinicaltrials.gov NCT02938702.
PubMed-ID: 36205563
http://dx.doi.org/10.1089/thy.2021.0614

Accuracy of Fine-Needle Aspiration for Cytologic Categorization of Thyroid Nodules-Incremental Progress vs Quantum Improvement.
JAMA Surg, 157(12):1113-4.
A. G. Antunez and G. M. Doherty.
PubMed-ID: 36223131
http://dx.doi.org/10.1001/jamasurg.2022.4997

Biological behavior of familial papillary thyroid microcarcinoma: Spanish multicenter study.
Langenbecks Arch Surg, 407(8):3631-42.
A. Ríos, M. A. Rodríguez, J. A. Puñal, P. Moreno, E. Mercader, E. Ferrero, J. Ruiz-Pardo, M. A. Morlán, J. Martín, M. Durán-Poveda, J. M. Bravo, D. Casanova, M. P. S. Egea, N. M. Torregrosa, A. Exposito-Rodríguez, G. Martínez-Fernández, A. M.

Carrión, O. Vidal, F. Herrera, G. Ruiz-Merino and J. M. Rodríguez.
PURPOSE: Familial papillary thyroid microcarcinoma (FPTMC) can present a more aggressive behavior than the sporadic microcarcinoma. However, few studies have analyzed this situation. The objective is to analyze the recurrence rate of FPTMC and the prognostic factors which determine that recurrence in Spain.
METHODS: Spanish multicenter longitudinal analytical observational study was conducted. Patients with FPTMC received treatment with curative intent and presented cure criteria 6 months after treatment. Recurrence rate and disease-free survival (DFS) were analyzed. Two groups were analyzed: group A (no tumor recurrence) vs. group B (tumor recurrence).
RESULTS: Ninety-four patients were analyzed. During a mean follow-up of 73.3 ± 59.3 months, 13 recurrences of FPTMC (13.83%) were detected and mean DFS was 207.9 ± 11.5 months. There were multifocality in 56%, bilateral thyroid involvement in 30%, and vascular invasion in 7.5%; that is to say, they are tumors with histological factors of poor prognosis in a high percentage of cases. The main risk factors for recurrence obtained in the multivariate analysis were the tumor size (OR: 2.574, 95% CI 1.210-5.473; p = 0.014) and the assessment of the risk of recurrence of the American Thyroid Association (ATA), both intermediate risk versus low risk (OR: 125, 95% CI 10.638-1000; p < 0.001) and high risk versus low risk (OR: 45.454, 95% CI 5.405-333.333; p < 0.001).
CONCLUSION: FPTMC has a recurrence rate higher than sporadic cases. Poor prognosis is mainly associated with the tumor size and the risk of recurrence of the ATA.
PubMed-ID: 36251077
http://dx.doi.org/10.1007/s00423-022-02704-4

Surgical resources in advanced thyroid cancer treatment with aerodigestive tract invasion.
Surg Oncol, 46:101863.
E. Mercader-Cidoncha, L. Zaraín-Obrador, J. M. Lasso and C. Simón-Adiego.
BACKGROUND: Despite papillary thyroid cancer (PTC) excellent prognosis, 10-15% of patients may present aggressive local behaviour. We present two cases with different aerodigestive tract invasion partners in which two reconstructions were used, out of all the surgical resources we have planned preoperatively [1-4].
METHODS: Case 1: 57-year-old woman with asymmetric goitre and a 60mm nodule (Bethesda-VI). CT showed suspected involvement of aero-digestive tract. Endobronchial ultrasound (EBUS) showed no tracheal invasion. Per oral endoscopic-US confirmed transmural oesophageal involvement. Surgery included total thyroidectomy(left recurrent laryngeal nerve was sacrificed), bilateral central and left lateral lymph node dissection, oesophageal partial resection and reconstruction with free radial flap. Case 2: 75-year-old male with cervical mass and haemoptysis. US showed a 62 mm nodule (Bethesda-VI). PET-CT showed tracheal invasion(bronchoscopy confirmatory). Per oral endoscopic-US showed no transmural oesophageal involvement. Surgery included total thyroidectomy (right recurrent laryngeal nerve was sacrificed), bilateral central lymph node dissection, tracheal resection and extra-mucosal oesophageal resection.
RESULTS: First patient required tracheostomy. She presented a self-limiting salivary fistula. She was discharged after 6 weeks with good oral intake and tracheostomy closed. Pathology report showed multifocal papillary thyroid cancer(tall cells, 70mm),micro-metastatic lymph node involvement. Afterwards, radioiodine ablation was performed. Six months after surgery there was no evidence of structural disease and analysis showed Tg 1 g/L. Second patient developed nosocomial pneumonia and was discharged after 3 weeks. Pathology report showed papillary thyroid cancer (insular growth, 52 mm), bilateral neck central lymph nodes involvement, transmural tracheal infiltration, free margins. Radioiodine ablation is pending.
CONCLUSIONS: Surgical treatment of advanced/invasive PTC offers good results in terms of survival and quality of life. Adequate pre-surgical planning, which includes multiple surgical resources, and a multidisciplinary team approach are required.
PubMed-ID: 36542909
http://dx.doi.org/10.1016/j.suronc.2022.101863

Parathyroids

Meta-Analyses

Less Than Subtotal Parathyroidectomy for Multiple Endocrine Neoplasia Type 1 Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis.
World J Surg, 46(11):2666-75.
D. Bouriez, C. Gronnier, M. Haissaguerre, A. Tabarin and H. Najah.
BACKGROUND: Multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) is classically associated with an asymmetric and asynchronous parathyroid involvement. Subtotal parathyroidectomy (STP), which is currently the recommended surgical treatment, carries a high risk of permanent hypoparathyroidism. The results of less than subtotal parathyroidectomy (LSTP) are conflicting, and its place in this setting is still a matter of debate. The aim of this study was to identify the place of LSTP in the surgical management of patients with MEN-associated pHPT.
METHODS: A systematic literature review was conducted in accordance with PRISMA and MOOSE guidelines, for studies comparing STP and LSTP for MEN1-associated pHPT. The results of the two techniques, regarding permanent hypoparathyroidism, persistent hyperparathyroidism and recurrent hyperparathyroidism were computed using pairwise random-effect meta-analysis.
RESULTS: Twenty-five studies comparing STP and LSTP qualified for inclusion in the quantitative synthesis. In total, 947 patients with MEN1-associated pHPT were allocated to STP (n = 569) or LSTP (n = 378). LSTP reduces the risk of permanent hypoparathyroidism [odds ratio (OR) 0.29, confidence interval (CI) 95% 0.17-0.49)], but exposes to higher rates of persistent hyperparathyroidism [OR 4.60, 95% CI 2.66-7.97]. Rates of recurrent hyperparathyroidism were not significantly different between the two groups [OR 1.26, CI 95% 0.83-1.91].
CONCLUSIONS: LSTP should not be abandoned and should be considered as a suitable surgical option for selected patients with MEN1-associated pHPT. The increased risk of persistent hyperparathyroidism could improve with the emergence of more efficient preoperative localization imaging techniques and a more adequate patients selection.
PubMed-ID: 35767091
http://dx.doi.org/10.1007/s00268-022-06633-7

Randomized controlled trials

- None -

Consensus Statements/Guidelines

The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Secondary and Tertiary Renal Hyperparathyroidism.
Ann Surg, 276(3):e141-e76.
S. Dream, L. E. Kuo, J. H. Kuo, S. M. Sprague, F. E. Nwariaku, M. Wolf, J. A. Olson, Jr., S. M. Moe, B. Lindeman and H. Chen.
OBJECTIVE: To develop evidence-based recommendations for safe, effective, and appropriate treatment of secondary (SHPT) and tertiary (THPT) renal hyperparathyroidism.
BACKGROUND: Hyperparathyroidism is common among patients with chronic kidney disease, end-stage kidney disease, and kidney transplant. The surgical management of SHPT and THPT is nuanced and requires a multidisciplinary approach. There are currently no clinical practice guidelines that address the surgical treatment of SHPT and THPT.
METHODS: Medical literature was reviewed from January 1, 1985 to present January 1, 2021 by a panel of 10 experts in SHPT and THPT. Recommendations using the best available evidence was constructed. The American College of Physicians grading system was used to determine levels of evidence. Recommendations were discussed to consensus. The American Association of Endocrine Surgeons membership reviewed and commented on preliminary drafts of the content.
RESULTS: These clinical guidelines present the epidemiology and pathophysiology of SHPT and THPT and provide recommendations for work-up and management of SHPT and THPT for all involved clinicians. It outlines the preoperative, intraoperative, and postoperative management of SHPT and THPT, as well as related definitions, operative techniques,

morbidity, and outcomes. Specific topics include Pathogenesis and Epidemiology, Initial Evaluation, Imaging, Preoperative and Perioperative Care, Surgical Planning and Parathyroidectomy, Adjuncts and Approaches, Outcomes, and Reoperation.
CONCLUSIONS: Evidence-based guidelines were created to assist clinicians in the optimal management of secondary and tertiary renal hyperparathyroidism.
PubMed-ID: 35848728
http://dx.doi.org/10.1097/SLA.0000000000005522

Other Articles

Preoperative imaging in primary hyperparathyroidism: Are (11) C-Choline PET/CT and (99m) Tc-MIBI/(123) Iodide subtraction SPECT/CT interchangeable or do they supplement each other?
Clin Endocrinol (Oxf), 97(3):258-67.
J. W. Christensen, A. Ismail, S. B. Søndergaard, F. N. Bennedbaek, B. Nygaard, L. T. Jensen, W. Trolle, C. Holst-Hahn, B. Zerahn, B. Kristensen and M. Krakauer.
OBJECTIVE: Preoperative location of hyperfunctioning parathyroid glands (HPGs) is vital when planning minimally invasive surgery in patients with primary hyperparathyroidism (PHPT). Dual-isotope subtraction scintigraphy with (99m) Tc-MIBI/(123) Iodide using SPECT/CT and planar pinhole imaging (Di-SPECT) has shown high sensitivity, but is challenged by high radiation dose, time consumption and cost. (11) C-Choline PET/CT (faster with a lower radiation dose) is non-inferior to Di-SPECT. We aim to clarify to what extent the two are interchangeable and how often there are discrepancies.
DESIGN: This is a prospective, GCP-controlled cohort study.
PATIENTS AND MEASUREMENTS: One hundred patients diagnosed with PHPT were included and underwent both imaging modalities before parathyroidectomy. Clinical implications of differences between imaging findings and negative imaging results were assessed. Surgical findings confirmed by biochemistry and pathology served as reference standard.
RESULTS: Among the 90 patients cured by parathyroidectomy, sensitivity was 82% (95% confidence interval [CI]: 74%-88%) and 87% (95% CI: 79%-92%) for Choline PET and Di-SPECT, respectively, p = .88. In seven cases at least one imaging modality found no HPG. Of these, neither modality found any true HPGs and only two were cured by surgery. When a positive finding in one modality was incorrect, the alternative modality was correct in approximately half of the cases.
CONCLUSION: Choline PET and Di-SPECT performed equally well and are both appropriate as first-line imaging modalities for preoperative imaging of PHPT. When the first-line modality fails to locate an HPG, additional preoperative imaging with the alternate modality offers no benefit. However, if parathyroidectomy is unsuccessful, additional imaging with the alternate modality has merit before repeat surgery.
PubMed-ID: 35150160
http://dx.doi.org/10.1111/cen.14688

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

living. Symptom management is crucial for improving QOL in hypoPT patients but socioeconomic factors like work-ability need to be considered when treating hypoPT patients.
PubMed-ID: 35192212
http://dx.doi.org/10.1111/cen.14701

Reduced fracture incidence in patients having surgery for primary hyperparathyroidism.
Clin Endocrinol (Oxf), 97(3):276-83.
M. Nilsson, E. Ståhl, K. E. Åkesson, M. Thier, E. Nordenström, M. Almquist and A. Bergenfelz.
OBJECTIVE: The indication of surgery in primary hyperparathyroidism has been controversial, as many patients experience mild disease. The primary aim was to evaluate fracture incidence in a contemporary population-based cohort of patients having surgery for primary hyperparathyroidism. The secondary aim was to investigate whether preoperative serum calcium, adenoma weight or multiglandular disease influence fracture incidence.
DESIGN: A retrospective cohort study with population controls. Primary outcomes, defined by discharge diagnoses and prescriptions, were any fracture and fragility fracture, secondary outcomes were multiple fractures anytime and osteoporosis. Subjects were followed 10 years pre- and up to 10 years postoperatively (or 31 December 2015). Multiple events per subject were allowed. Fracture incidence rate ratios (IRRs) for patients pre- and postoperatively were tabulated and evaluated with mixed-effects Poisson regression. Secondary outcomes were evaluated using conditional logistic regression.
PATIENTS: A Swedish nationwide cohort of patients having surgery for primary hyperparathyroidism (n = 5009) from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery between 2003 and 2013 was matched with population controls (n = 14,983). Data were cross-linked with Statistics Sweden and the National Board of Health and Welfare.
MEASUREMENTS: Preoperative serum calcium and adenoma weight at pathological examination.
RESULTS: Patients had an increased incidence rate of any fracture preoperatively, IRR 1.27 (95% confidence interval: 1.11-1.46), highest in the last year before surgery. Fracture incidence was not increased postoperatively. Serum calcium, adenoma weight and multiglandular disease were not associated with fracture incidence.
CONCLUSIONS: Fracture incidence is higher in patients with primary hyperparathyroidism but is normalized after surgery.
PubMed-ID: 35192220
http://dx.doi.org/10.1111/cen.14703

Long-term Cure of Primary Hyperparathyroidism After Scan-Directed Parathyroidectomy: Outcomes From A UK Endocrine Surgery Unit.
World J Surg, 46(9):2189-94.
N. Patel and R. Mihai.
BACKGROUND: Two-decades ago, the advent of sestamibi scintigraphy led to an enthusiastic acceptance of minimally invasive parathyroidectomy (MIP) in most surgical centres. More recently, concerns have been raised about the efficacy of limited neck exploration and some surgeons proposed bilateral neck exploration to be (once again) the gold standard operation for primary hyperparathyroidism in 2020s.
METHODS: A departmental database was used to identify patients who had MIP after concordant dual localisation with sestamibi scintigraphy and ultrasound scans. Long-term follow-up data were obtained from electronic patient records to ascertain any further treatment for recurrent disease and confirm most recent biochemical status. Patients with negative localisation scans and those with familial disease were excluded from analysis.
RESULTS: Between June 2001 and August 2014 a total of 404 patients (108 M:296F, median age 63 years, range 17-90 years) underwent MIP and had normalisation of calcium in first 6 weeks after the operation. Information on electronic patient records were missing in 14 patients; therefore, data on 390 patients were analysed. During median follow-up of 78 months (IQR: 21.25-111.75 months), 375 patients had normocalcaemia (2.36 mmol/L, IQR: 2.29-2.44 mmol/L) at a median 75 months, (IQR: 20-118 months) after their operation. Overall, 15 (3.85%) patients had biochemical evidence of recurrent disease (2.70 mmol/L IQR: 2.63-2.75 mmol/L) at 92 months (Range: 6-196) after initial operation. Of these, 5 (1.28%) patients underwent a second parathyroid procedure.
CONCLUSION: Recurrence after scan-directed unilateral neck exploration occurred in 4% of patients after a long disease-free interval. Only one patient had recurrent disease within 1-year of primary surgery. The data suggest that bilateral neck exploration at the time of initial operation, in this selected cohort, is unlikely to have uncovered multi-gland disease and prevent disease recurrence. Focused parathyroidectomy in patients with convincing localisation studies should continue.
PubMed-ID: 35412058
http://dx.doi.org/10.1007/s00268-022-06556-3

Impact of parathyroidectomy on kidney graft function in post-transplant tertiary hyperparathyroidism: a comparative study.
Langenbecks Arch Surg, 407(6):2489-98.
S. Frey, T. Goronflot, C. Blanchard, C. Kerleau, P. A. Gourraud, M. Wargny, C. Caillard, M. Hourmant, L. Figueres and É. Mirallié.
PURPOSE: Parathyroidectomy to treat tertiary hyperparathyroidism (THPT) is now on a par with calcimimetic treatment. The effects of cinacalcet and parathyroidectomy on kidney transplant function remain controversial. The aim of this study was to evaluate kidney transplant function in THPT patients treated either by parathyroidectomy, cinacalcet, or not treated.
METHODS: Between 2009 and 2019, 231 patients with functional grafts presenting THPT, defined either by calcaemia superior to 2.5 mmol/L with elevated PTH level or hypercalcaemia with non-adapted PTH level 1 year after kidney transplantation, were included. Hyperparathyroid patients treated by cinacalcet and parathyroidectomy were matched for age, sex, graft rank, and baseline eGFR with cinacalcet-only and untreated patients. Conditional logistic regression models were used to compare eGFR variations 1 year after parathyroidectomy between operated patients and matched controls. Five-year survivals were compared with the Mantel-Cox test.
RESULTS: Eleven patients treated with parathyroidectomy and cinacalcet were matched with 16 patients treated by cinacalcet-only and 29 untreated patients. Demographic characteristics were comparable between groups. Estimated odds ratios for eGFR evolution in operated patients compared with cinacalcet-only and untreated patients were 0.92 [95%CI 0.83-1.02] and 0.99 [0.89-1.10] respectively, indicating no significant impairment of eGFR 1 year after surgery. Five-year allograft survival was not significantly impaired in operated patients.
CONCLUSIONS: Parathyroidectomy did not appear to substantially alter or improve graft function 1 year after surgery or 5-year allograft survival. It could be hypothesized that in addition to its known benefits, parathyroidectomy can be safely performed vis-à-vis graft function in tertiary hyperparathyroidism.
PubMed-ID: 35596781
http://dx.doi.org/10.1007/s00423-022-02555-z

Long-Term Cure of Primary Hyperparathyroidism After Scan-Directed Parathyroidectomy: Outcomes from a UK Endocrine Surgery Unit.
World J Surg, 46(9):2195-6.
S. Sidhu.
PubMed-ID: 35672587
http://dx.doi.org/10.1007/s00268-022-06543-8

Accuracy of Parathyroid Adenoma Localization by Preoperative Ultrasound and Sestamibi in 1089 Patients with Primary Hyperparathyroidism.
World J Surg, 46(9):2197-205.
K. A. Iwen, J. Kußmann, V. Fendrich, K. Lindner and A. Zahn.
BACKGROUND: Primary hyperparathyroidism (pHPT) is well treatable surgically. Sonography (US) and sestamibi scintigraphy (MIBI) are used routinely, but it is unclear how valuable they are in determining Parathyroid glands' different locations. This study aimed to evaluate the prognostic value of US and MIBI in relation to the different localization of parathyroid adenomas in one of the largest study populations analyzed to date.
METHODS: 1089 patients with pHPT who had treatment in one tertiary referral center between 2007 and 2016 were analyzed. Preoperative US and MIBI reports were compared with the parathyroid adenoma's intraoperative localization. All parathyroid glands were confirmed by histological diagnosis.
RESULTS: No gland was detectable in 22.5% and 27.7% of all patients, by US or by MIBI, respectively. In relation to the different adenoma locations, the sensitivity of US ranged from 21.3% (upper right) to 68.9% (lower left) and of MIBI ranged from 23.5% (upper right) to 72% (lower left). The specificity for US ranged from 85% (lower right) to 99.2% (upper right) and for MIBI ranged from 86.1% (lower right) to 99.1% (upper right. Positive predictive values for all gland sites were 54% and 59% for MIBI and US, respectively. The value increased for side-only prediction to 73% and 78%, respectively. Neither the parathyroid hormone level nor the calcium value level influenced the sensitivity or specificity of the two test methods.
CONCLUSIONS: The validity of preoperative US and MIBI depends crucially on the specific localization of adenomas. This should be considered when planning the extent of parathyroid surgery.

PubMed-ID: 35705875
http://dx.doi.org/10.1007/s00268-022-06593-y

Serum calcium levels are associated with cognitive function in hypoparathyroidism: a neuropsychological and biochemical study in an Italian cohort of patients with chronic post-surgical hypoparathyroidism.
J Endocrinol Invest, 45(10):1909-18.
F. Saponaro, G. Alfi, F. Cetani, A. Matrone, L. Mazoni, M. Apicella, E. Pardi, S. Borsari, M. Laurino, E. Lai, A. Gemignani and C. Marcocci.
PURPOSE: Hypoparathyroidism (HypoPT) is a rare endocrine disease and conventional therapy is based on calcium and vitamin D analogues. Conventional therapy does not restore calcium homeostasis and patients complain with neuropsychological symptoms, which have been evaluated with nonspecific self-administered questionnaires. This study aims to evaluate cognitive functions of patients with chronic post-surgical (PS)-HypoPT compared to a control population, using a standardized neuropsychological approach and evaluating the relationship with serum calcium (Alb-Ca).
METHODS: Observational, monocentric study on 33 patients with PS-HypoPT and 24 controls, in whom biochemical testing and a standardized neuropsychological assessment by a trained psychologist were performed.
RESULTS: In patients with PS-HypoPT, low Alb-Ca correlated with a worse performance on semantic memory abilities and executive function, as suggested by a significant inverse correlation between Alb-Ca and Trail Making Test A (TMT-A) scores ($r = -0.423$; $p = 0.014$) and by a positive correlation with Semantic Fluency Test scores (SF)($r = 0.510$; $p = 0.002$). PS-HypoPT patients with Alb-Ca ≤ 8.9 mg/dl had a significantly lower test performance compared with PS-HypoPT patients with Alb-Ca > 8.9 mg/dl, both at the TMT-A test (mean score: 34.53-18.55; $p < 0.0001$) and at SF test (mean score: 41.94-48.68; $p = 0.01$) and also a significantly lower test performance compared with control patients' group at TMT-A (mean score: 34.53-25.5; $p = 0.0057$).
CONCLUSIONS: Patients with chronic PS-HypoPT in conventional therapy do not show a severe cognitive impairment; however, cognitive functions namely visuo-spatial attention, executive function and semantic memory appear to be modulated by Alb-Ca and impaired by its low levels.
PubMed-ID: 35751804
http://dx.doi.org/10.1007/s40618-022-01822-6

Questionable value of [(99m)Tc]-sestamibi scintigraphy in patients with pHPT and negative ultrasound.
Langenbecks Arch Surg, 407(8):3661-9.
C. Lenschow, A. Wennmann, A. Hendricks, C. T. Germer, M. Fassnacht, A. Buck, R. A. Werner, L. Plassmeier and N. Schlegel.
PURPOSE: A successful focused surgical approach in primary hyperparathyroidism (pHPT) relies on accurate preoperative localization of the parathyroid adenoma (PA). Most often, ultrasound is followed by [(99m)Tc]-sestamibi scintigraphy, but the value of this approach is disputed. Here, we evaluated the diagnostic approach in patients with surgically treated pHPT in our center with the aim to further refine preoperative diagnostic procedures.
METHODS: A single-center retrospective analysis of patients with pHPT from 01/2005 to 08/2021 was carried out followed by evaluation of the preoperative imaging modalities to localize PA. The localization of the PA had to be confirmed intraoperatively by the fresh frozen section and significant dropping of the intraoperative parathyroid hormone (PTH) levels.
RESULTS: From 658 patients diagnosed with pHPT, 30 patients were excluded from the analysis because of surgery for recurrent or persistent disease. Median age of patients was 58.0 (13-93) years and 71% were female. Neck ultrasound was carried out in 91.7% and localized a PA in 76.6%. In 23.4% (135/576) of the patients, preoperative neck ultrasound did not detect a PA. In this group, [(99m)Tc]-sestamibi correctly identified PA in only 25.4% of patients. In contrast, in the same cohort, the use of [(11)C]-methionine or [(11)C]-choline PET resulted in the correct identification of PA in 79.4% of patients (OR 13.23; 95% CI 5.24-33.56).
CONCLUSION: [(11)C]-Methionine or [(11)C]-choline PET/CT are superior second-line imaging methods to select patients for a focused surgical approach when previous ultrasound failed to identify PA.
PubMed-ID: 35945299
http://dx.doi.org/10.1007/s00423-022-02648-9

Invited Commentary: Less than Subtotal Parathyroidectomy for Multiple Endocrine Neoplasia Type 1 Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis.
World J Surg, 46(11):2676-7.
F. F. Palazzo.
PubMed-ID: 36042033
http://dx.doi.org/10.1007/s00268-022-06707-6

Long-term outcome of surgical techniques for sporadic primary hyperparathyroidism in a tertiary referral center in Belgium.
Langenbecks Arch Surg, 407(7):3045-55.
K. Van Den Heede, A. Bonheure, N. Brusselaers and S. Van Slycke.
PURPOSE: Surgery remains the only permanent treatment option for primary hyperparathyroidism (pHPT). To date, the number of long-term outcome studies of parathyroidectomy is limited. This study aims to compare different surgical approaches and evaluate the importance of preoperative localization imaging in the treatment of pHPT.
METHODS: All 200 consecutive patients with a parathyroidectomy for sporadic pHPT without planned concomitant surgery between 09/2009 and 04/2021 in a Belgian tertiary referral hospital were enrolled. All patients underwent at least two preoperative localization imaging studies (neck ultrasound, CT, SPECT, and/or Sestamibi scintigraphy) of the parathyroid glands. The main outcomes were the (long-term) cured proportion and postoperative morbidity (hypocalcemia, recurrent laryngeal nerve palsy, return to theater for bleeding, and wound morbidity).
RESULTS: Most patients were referred with concordant positive imaging (82%, n = 164). Only nine patients (4.5%) had double negative imaging, not revealing a possible adenoma. The remaining 27 (13.5%) were referred with discordant imaging. Parathyroidectomy was performed via traditional cervicotomy (30%), mini-open approach (39.5%), or endoscopic approach (30.5%). Morbidity was low with no persistent hypocalcemia, one return to theater for bleeding, and no 30-day mortality. In the concordant imaging population, 13 patients (8%) had multiglandular disease. Overall, 97.5% was considered cured. Long-term recurrence was 12% with a minimal follow-up of 5 years.
CONCLUSION: This consecutive, single-surgeon, single-center cohort with extensive data collection and long-term follow-up confirms the safety and excellent cured proportions of minimally invasive parathyroidectomy. Disease recurrence becomes more important long after surgery.
PubMed-ID: 36048245
http://dx.doi.org/10.1007/s00423-022-02660-z

A reappraisal of risk factors for early hypocalcemia after parathyroidectomy in dialysis patients.
Updates Surg, 74(6):1961-70.
L. Cao, X. Sun, T. Zhang, Y. Niu, H. Suo, Z. Zhao, C. Wang and J. Bai.
We aimed to identify risk factors for early hypocalcemia after parathyroidectomy in patients with secondary hyperparathyroidism. We retrospectively enrolled 106 of 120 consecutive patients with secondary hyperparathyroidism who underwent parathyroidectomy between January 2019 and July 2021. Perioperative laboratory parameters, preoperative computerized tomography (CT) images, and postoperative histology were evaluated. Parathyroid calcification was defined as hyperdense regions with a density of > 130 Hounsfield Units on CT images of the parathyroid. Subtotal parathyroidectomy, total parathyroidectomy without auto-transplantation, or total parathyroidectomy with auto-transplantation were performed in the present study. Postoperative hypocalcemia was defined as a serum calcium concentration < 2.1 mmol/L within 4 days of surgery. The participants were categorized according to the presence (n = 33) or absence (n = 73) of postoperative hypocalcemia. The demographics, comorbidities, and surgical details were similar in the two groups. Multivariate analysis showed that the preoperative alkaline phosphatase activity, serum intact parathyroid hormone and calcium concentrations, and parathyroid calcification were independent risk factors for postoperative hypocalcemia (all $P < 0.05$). Receiver operating characteristic analysis generated areas under the curves for preoperative alkaline phosphatase, intact parathyroid hormone, and parathyroid calcification of 0.82, 0.80, and 0.70, respectively (all $P < 0.05$). Cut-off values for preoperative alkaline phosphatase (> 242.9 IU/L) and intact parathyroid hormone (> 2,104 pg/mL) were found to be predictive of postoperative hypocalcemia. High preoperative alkaline phosphatase activity and serum intact parathyroid hormone concentration and low serum calcium are associated with higher risks of postoperative hypocalcemia. Calcification of the parathyroid may represent a novel radiologic means of predicting postoperative hypocalcemia.
PubMed-ID: 36194380
http://dx.doi.org/10.1007/s13304-022-01395-2

Persistence of primary hyperparathyroidism: a single-center experience.
Langenbecks Arch Surg, 407(8):3651-9.
D. M. Buzanakov, I. V. Sleptsov, A. A. Semenov, R. A. Chernikov, K. Y. Novokshonov, Y. V. Karelina, N. I. Timofeeva, A. A. Uspenskaya, V. A. Makarin, I. K. Chinchuk, E. A. Fedorov, N. A. Gorskaya, I. V. Sablin, Y. N. Malugov, S. A. Alekseeva, K. A. Gerasimova, A. A. Pushkaruk, M. V. Lyubimov, D. V. Rebrova, S. S. Shikhmagomedov, T. A. Dzhumatov, A. V. Zolotoukho and A. N. Bubnov.
BACKGROUND: Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism (PHPT). Precise localization of abnormal glands is a key to a successful surgery. Most patients are expected to be successfully treated with focused parathyroidectomy. However, this approach is associated with a risk of existing multiglandular disease which may lead to the postoperative persistence of PHPT.
METHODS: Eight hundred ten patients who underwent an initial surgery for PHPT at SPBU Hospital in 2017-2018 were included in the study. Preoperative imaging results were evaluated. Multivariate logistic regressions were calculated to estimate predictive values of preoperative data for the risk of postoperative persistence and risk of MGD.
RESULTS: Multiglandular disease was found to be a leading cause of persistent hyperparathyroidism. An anamnesis of thyroid surgery was found to be a significant risk factor for the persistence of hyperparathyroidism. The rate of persistence did not differ significantly between groups with bilateral neck exploration and focused parathyroidectomy. Age, sex, body mass index as well as negative results of preoperative US, MIBI, and 4D CT were not independently associated with a higher risk of MGD. All preoperative imaging modalities showed from low to moderate sensitivity for the detection of MGD. The frequency of cases of a missed second adenoma did not differ significantly between patients with concordant and discordant preoperative data. There were 7 cases with previously unsuspected second adenomas found solely due to bilateral neck exploration.
CONCLUSIONS: None of the combination of preoperative visualization modalities was able to rule out the MGD and reliably identify patients for focused parathyroidectomy. Additional preoperative visualization failed to improve overall results. Bilateral neck exploration appeared to have a slight benefit for the patients with concordant preoperative imaging results.
PubMed-ID: 36251078
http://dx.doi.org/10.1007/s00423-022-02711-5

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

American Association of Endocrine Surgeons Guidelines for Adrenalectomy: Executive Summary.
JAMA Surg, 157(10):870-7.
L. Yip, Q. Y. Duh, H. Wachtel, C. Jimenez, C. Sturgeon, C. Lee, D. Velázquez-Fernández, E. Berber, G. D. Hammer, I. Bancos, J. A. Lee, J. Marko, L. F. Morris-Wiseman, M. S. Hughes, M. J. Livhits, M. A. Han, P. W. Smith, S. Wilhelm, S. L. Asa, T. J. Fahey, 3rd, T. J. McKenzie, V. E. Strong and N. D. Perrier.
IMPORTANCE: Adrenalectomy is the definitive treatment for multiple adrenal abnormalities. Advances in technology and genomics and an improved understanding of adrenal pathophysiology have altered operative techniques and indications.
OBJECTIVE: To develop evidence-based recommendations to enhance the appropriate, safe, and effective approaches to adrenalectomy.
EVIDENCE REVIEW: A multidisciplinary panel identified and investigated 7 categories of relevant clinical concern to practicing surgeons. Questions were structured in the framework Population, Intervention/Exposure, Comparison, and Outcome, and a guided review of medical literature from PubMed and/or Embase from 1980 to 2021 was performed. Recommendations were developed using Grading of Recommendations, Assessment, Development and Evaluation methodology and were discussed until consensus, and patient advocacy representation was included.
FINDINGS: Patients with an adrenal incidentaloma 1 cm or larger should undergo biochemical testing and further imaging characterization. Adrenal protocol computed tomography (CT) should be used to stratify malignancy risk and concern for pheochromocytoma. Routine scheduled follow-up of a nonfunctional adrenal nodule with benign imaging characteristics and unenhanced CT with Hounsfield units less than 10 is not suggested. When unilateral disease is present, laparoscopic adrenalectomy is recommended for patients with primary aldosteronism or autonomous cortisol secretion. Patients with clinical and radiographic findings consistent with adrenocortical carcinoma should be treated at high-volume multidisciplinary centers to optimize outcomes, including, when possible, a complete R0 resection without tumor disruption, which may require en bloc radical resection. Selective or nonselective α blockade can be used to safely prepare patients for surgical resection of paraganglioma/pheochromocytoma. Empirical perioperative glucocorticoid replacement therapy is indicated for patients with overt Cushing syndrome, but for patients with mild autonomous cortisol secretion, postoperative day 1 morning cortisol or cosyntropin stimulation testing can be used to determine the need for glucocorticoid replacement therapy. When patient and tumor variables are appropriate, we recommend minimally invasive adrenalectomy over open adrenalectomy because of improved perioperative morbidity. Minimally invasive adrenalectomy can be achieved either via a retroperitoneal or transperitoneal approach depending on surgeon expertise, as well as tumor and patient characteristics.
CONCLUSIONS AND RELEVANCE: Twenty-six clinically relevant and evidence-based recommendations are provided to assist surgeons with perioperative adrenal care.
PubMed-ID: 35976622
http://dx.doi.org/10.1001/jamasurg.2022.3544

Other Articles

The role of molecular profiling in adrenocortical carcinoma.
Clin Endocrinol (Oxf), 97(4):460-72.
J. Lippert, M. Fassnacht and C. L. Ronchi.
Adrenocortical carcinoma (ACC) is a rare, aggressive cancer with still partially unknown pathogenesis, heterogenous clinical behaviour and no effective treatment for advanced stages. Therefore, there is an urgent clinical unmet need for better prognostication strategies, innovative therapies and significant improvement of the management of the individual patients. In this review, we summarize available studies on molecular prognostic markers and markers predictive of response to standard therapies as well as newly proposed drug targets in sporadic ACC. We include in vitro studies and available clinical trials, focusing on alterations at the DNA, RNA and epigenetic levels. We also discuss the potential of biomarkers to be implemented in a clinical routine workflow for improved ACC patient care.
PubMed-ID: 34750847
http://dx.doi.org/10.1111/cen.14629

Investigating the role of somatic sequencing platforms for phaeochromocytoma and paraganglioma in a large UK cohort.
Clin Endocrinol (Oxf), 97(4):448-59.
B. Winzeler, N. Tufton, S. L. E, B. G. Challis, S. M. Park, L. Izatt, P. V. Carroll, A. Velusamy, T. Hulse, B. C. Whitelaw, E. Martin, F. Rodger, M. Maranian, G. R. Clark, A. A. S, E. R. Maher and R. T. Casey.
OBJECTIVES: Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumours with malignant potential and a hereditary basis in almost 40% of patients. Germline genetic testing has transformed the management of PPGL enabling stratification of surveillance approaches, earlier diagnosis and predictive testing of at-risk family members. Recent studies have identified somatic mutations in a further subset of patients, indicating that molecular drivers at either a germline or tumour level can be identified in up to 80% of PPGL cases. The aim of this study was to investigate the clinical utility of somatic sequencing in a large cohort of patients with PPGL in the United Kingdom.
DESIGN AND PATIENTS: Prospectively collected matched germline and tumour samples (development cohort) and retrospectively collected tumour samples (validation cohort) of patients with PPGL were investigated.
MEASUREMENTS: Clinical characteristics of patients were assessed and tumour and germline DNA was analysed using a next-generation sequencing strategy. A screen for variants within 'mutation hotspots' in 68 human cancer genes was performed.
RESULTS: Of 141 included patients, 45 (32%) had a germline mutation. In 37 (26%) patients one or more driver somatic variants were identified including 26 likely pathogenic or pathogenic variants and 19 variants of uncertain significance. Pathogenic somatic variants, observed in 25 (18%) patients, were most commonly identified in the VHL, NF1, HRAS and RET genes. Pathogenic somatic variants were almost exclusively identified in patients without a germline mutation (all but one), suggesting that somatic sequencing is likely to be most informative for those patients with negative germline genetic test results.
CONCLUSIONS: Somatic sequencing may further stratify surveillance approaches for patients without a germline genetic driver and may also inform targeted therapeutic strategies for patients with metastatic disease.
PubMed-ID: 34870338
http://dx.doi.org/10.1111/cen.14639

Adrenal androgens versus cortisol for primary aldosteronism subtype determination in adrenal venous sampling.
Clin Endocrinol (Oxf), 97(3):241-9.
M. Viukari, E. Kokko, I. Pörsti, H. Leijon, T. Vesterinen, T. Hinkka, M. Soinio, C. Schalin-Jäntti, N. Matikainen and P. I. Nevalainen.
OBJECTIVE: We examined if measurement of adrenal androgens adds to subtype diagnostics of primary aldosteronism (PA) under cosyntropin-stimulated adrenal venous sampling (AVS).
DESIGN: A prospective pre-specified secondary endpoint analysis of 49 patients with confirmed PA, of whom 29 underwent unilateral adrenalectomy with long-term follow-up.
METHODS: Concentrations of androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) were measured during AVS in addition to aldosterone and cortisol. Subjects with lateralisation index (LI) of ≥4 were treated with unilateral adrenalectomy, and the immunohistochemical subtype was determined with CYP11B2 and CYP11B1 stains. The performance of adrenal androgens was evaluated by receiver operating characteristics (ROC) curve analyses in adrenalectomy and medical therapy groups.

RESULTS: During AVS, the correlations between cortisol and androstenedione, DHEA and DHEAS for LI and selectivity index (SI) were highly significant. The right and left side SIs for androstenedione and DHEA were higher ($p < .001$) than for cortisol. In ROC analysis, the optimal LI cut-off values for androstenedione, DHEA and DHEAS were 4.2, 4.5 and 4.6, respectively. The performance of these LIs for adrenal androgens did not differ from that of cortisol.
CONCLUSIONS: Under cosyntropin-stimulated AVS, the measurement of androstenedione and DHEA did not improve the cannulation selectivity. The performance of cortisol and adrenal androgens are confirmatory but not superior to cortisol-based results in lateralisation diagnostics of PA.
PubMed-ID: 35167715
http://dx.doi.org/10.1111/cen.14691

Operative approach and case volume are associated with negative resection margins for adrenocortical carcinoma.
Surg Endosc, 36(12):9288-96.
J. Tseng, T. Diperi, N. Gonsalves, Y. Chen, A. Ben-Shlomo, D. Shouhed, E. Phillips, M. Burch and M. Jain.
BACKGROUND: Surgical resection with negative margins is the treatment of choice for adrenocortical carcinoma (ACC). This study was undertaken to determine factors associated with negative resection margins.
METHODS: National Cancer Database was queried from 2010 to 2016 to identify patients with AJCC/ENSAT Stage I-III ACC who underwent adrenalectomy. Patient, tumor, facility, and operative characteristics were compared by margin status (positive-PM or negative-NM) and operative approach (open-OA, laparoscopic-LA, or robotic-RA). Multivariable logistic regression was used to identify factors associated with PM.
RESULTS: Eight hundred and eighty-one patients were identified, of which 18.4% had PM and 81.6% had NM. Patients with advanced pathologic T stage and pathologic N1 stage were more likely to have PM (vs. NM) (T3, 49.7% vs. 24.8%, $p < 0.01$; T4, 26.2% vs. 10.0%, $p < 0.01$; N1, 6.7% vs. 3.5%, $p < 0.01$). Patients undergoing OA (vs. LA and RA) were more likely to have advanced clinical T stage (T4, 16.6% vs. 5.7% vs. 7.8%, $p < 0.01$) and larger tumors (> 6 cm, 84.6% vs. 64.1% vs. 62.3%, $p < 0.01$). High-volume centers (≥ 5 cases) were more likely to utilize OA. Patients undergoing LA (vs. RA) were more likely to require conversion to open (20.3% vs. 7.8%, $p = 0.011$). On multivariable analysis, factors associated with higher odds of PM included T3 disease (OR 7.02, 95% CI 2.66-18.55), T4 disease (OR 10.22, 95% CI 3.66-28.53), and LA (OR 1.99, 95% CI 1.28-3.09). High-volume centers were associated with lower odds of PM (OR 0.67, 95% CI 0.45-0.98). There was no significant difference in margin status between OA and RA (OR 1.44, 95% CI 0.71-2.90).
CONCLUSION: Centers with higher ACC case volumes have lower odds of PM and utilize OA more often. LA is associated with higher odds of PM, whereas RA is not. These factors should be considered when planning the operative approach for ACC.
PubMed-ID: 35246741
http://dx.doi.org/10.1007/s00464-022-09167-0

Clonidine suppression test for a reliable diagnosis of pheochromocytoma: When to use.
Clin Endocrinol (Oxf), 97(5):541-50.
S. Tsiomidou, C. Pamporaki, A. Geroula, L. Van Baal, F. Weber, H. Dralle, K. W. Schmid, D. Führer and N. Unger.
OBJECTIVE: In clinical practice, false-positive results in biochemical testing for suspected pheochromocytoma/paraganglioma (PPGL) are not infrequent and may lead to unnecessary examinations. We aimed to evaluate the role of the clonidine suppression test (CST) in the era of analyses of plasma-free metanephrines for the diagnosis or exclusion of PPGL in patients with adrenal tumours and/or arterial hypertension.
DESIGN AND METHODS: This single-centre, prospective trial investigated the use of CST in 60 patients with suspected PPGL associated with out-patient elevations of plasma normetanephrine (NMN) and/or metanephrine (MN), in most cases accompanied with hypertension or an adrenal mass. Measurements of plasma catecholamines and free metanephrines were performed by liquid chromatography with electrochemical detection and tandem mass spectrometry, respectively.
RESULTS: Forty-six patients entered final analysis (n = 20 with PPGL and n = 26 with a nonfunctional adrenal mass and/or hypertension). CST reliably excluded false-positive baseline NMN results with a specificity of 100%. The sensitivity of CST improved from 85% to 94% when tumours with isolated MN increase (n = 3) were not considered. In patients with elevated baseline NMN (n = 24), CST correctly identified all patients without PPGL. Patients with falsely elevated baseline NMN results (n = 7, 26.9%) exhibited increases of baseline NMN up to 1.7-fold above the upper reference limit.
CONCLUSION: CST qualifies as a useful diagnostic tool for differential diagnosis of borderline elevated plasma-free NMN in patients with suspected PPGL. In this **CONTEXT**, CST helps to correctly identify all false-positive NMN screening results.
PubMed-ID: 35274752
http://dx.doi.org/10.1111/cen.14724

Differences in Clinicopathologic Behavior of Oncocytic Adrenocortical Neoplasms and Conventional Adrenocortical Carcinomas.
Ann Surg Oncol, 29(9):5555-63.
A. S. Shirali, J. Zagzag, Y. J. Chiang, H. Huang, M. Zhang, M. A. Habra, E. G. Grubbs, S. B. Fisher, N. D. Perrier, J. E. Lee and P. H. Graham.
BACKGROUND: Oncocytic adrenocortical neoplasms (OANs) are rare endocrine tumors that present as a spectrum from benign to malignant. The outcomes after surgical resection of the oncocytic variant of adrenocortical carcinoma remain poorly understood. We sought to characterize the clinicopathologic features of OAN and compare oncocytic adrenocortical carcinoma (OAC) with conventional adrenocortical carcinoma (ACC).
PATIENTS AND METHODS: Adult patients who underwent adrenalectomy for OAN or ACC between January 1990 and September 2020 were identified. Demographics, clinicopathologic factors, American Joint Committee on Cancer stage, and cancer-related outcomes were reviewed. A matched cohort analysis of disease-free survival (DFS) and overall survival (OS) was performed between patients with OACs and those with ACCs.
RESULTS: Forty-one patients with OAN and 214 patients with ACC were included. The OAN cohort median age was 45.2 years [interquartile ratio (IQR) 38.5-54.0 years], and 61.0% were female. OANs were benign (n = 11), of uncertain malignant potential (UMP, n = 9), or OAC (n = 21). Disease recurrence occurred in 12 (57.1%) patients with OAC compared with 1 (11.1%) and 0 patients with UMP or benign OAN, respectively ($p < 0.001$). Seven (33.3%) patients with OAC died during follow-up compared with 0 patients with UMP or benign OAN ($p = 0.020$). Kaplan-Meier survival analysis found no difference in DFS between ACC and OAC groups before ($p = 0.218$) and after 2:1 matching ($p = 0.417$). Overall survival was shorter for patients who had ACC compared with those who had OAC ($p = 0.031$), but the difference was not evident with matched analysis ($p = 0.200$).
CONCLUSIONS: OAN presents as a spectrum from benign indolent tumors to aggressive carcinomas. OACs demonstrate similar clinicopathologic behavior and recurrence-free and overall survival when matched to conventional ACCs.
PubMed-ID: 35499784
http://dx.doi.org/10.1245/s10434-022-11626-w

ASO Author Reflections: The Impact of Oncocytic Histology on Survival in Adrenocortical Carcinoma.
Ann Surg Oncol, 29(9):5564-5.
A. S. Shirali and P. H. Graham.
PubMed-ID: 35536522
http://dx.doi.org/10.1245/s10434-022-11635-9

Cost-effectiveness of adrenal vein sampling- vs computed tomography-guided adrenalectomy for unilateral adrenaloma in primary aldosteronism.
J Endocrinol Invest, 45(10):1899-908.
S. Arjani, T. J. Bostonian, V. Prasath, P. L. Quinn and R. J. Chokshi.
PURPOSE: Adrenalectomies performed for the treatment of primary aldosteronism due to unilateral adenoma are traditionally confirmed with, and guided by, results from adrenal vein sampling (AVS). However, the usefulness of AVS at the expense of cost and complications is debated, and many institutions have independent protocols that use AVS to varying degrees.
METHODS: Cost-effectiveness of AVS- vs computed tomography (CT)-based adrenalectomy was calculated using decision tree models. The tree was populated with values describing biochemical post-operative outcomes from the published literature; patients were placed into AVS- or CT-dependent treatment arms. Biochemical outcomes were defined based on patients' potassium levels and aldosterone-renin ratios. Patients underwent adrenalectomies and received medical management dosed based on surgical outcomes. Costs were represented by Medicare (FY2021) reimbursement rates (US$) and quality-adjusted life-years (QALYs) were calculated using published morbidity and survival data. A willingness-to-pay of $100,000 per QALY gained was set to determine the most cost-effective strategy. The primary outcome was the incremental cost-effectiveness ratio (ICER) associated with biochemical outcomes.
RESULTS: The base case analyses favored the use of AVS-guided care, which cost $307.65 more but yielded 0.78 more QALYs, resulting in an ICER of $392.57. These results were upheld by all one-way and two-way sensitivity analyses. In 100,000 random-sampling simulations, AVS-guided care was favored 100% of the time.
CONCLUSIONS: For patients with primary aldosteronism receiving adrenalectomies with curative intent, the more cost-effective method based on biochemical outcomes is AVS-based care. Recent literature suggests biochemical resolution should be favored over clinical resolution, due to long-term detriments of increased aldosterone independent of clinical symptoms.

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http://dx.doi.org/10.1007/s40618-022-01821-7

Differences in morbidity and mortality between unilateral adrenalectomy for adrenal Cushing's syndrome and bilateral adrenalectomy for therapy refractory extra-adrenal Cushing's syndrome.
Langenbecks Arch Surg, 407(6):2481-8.
J. Reibetanz, M. Kelm, K. L. Uttinger, M. Reuter, N. Schlegel, M. Hankir, V. Wiegering, C. T. Germer, M. Fassnacht, J. F. Lock and A. Wiegering.
PURPOSE: In selected cases of severe Cushing's syndrome due to uncontrolled ACTH secretion, bilateral adrenalectomy appears unavoidable. Compared with unilateral adrenalectomy (for adrenal Cushing's syndrome), bilateral adrenalectomy has a perceived higher perioperative morbidity. The aim of the current study was to compare both interventions in endogenous Cushing's syndrome regarding postoperative outcomes.
METHODS: We report a single-center, retrospective cohort study comparing patients with hypercortisolism undergoing bilateral vs. unilateral adrenalectomy during 2008-2021. Patients with adrenal Cushing's syndrome due to adenoma were compared with patients with ACTH-dependent Cushing's syndrome (Cushing's disease and ectopic ACTH production) focusing on postoperative morbidity and mortality as well as long-term survival.
RESULTS: Of 83 patients with adrenalectomy for hypercortisolism (65.1% female, median age 53 years), the indication for adrenalectomy was due to adrenal Cushing's syndrome in 60 patients (72.2%; 59 unilateral and one bilateral), and due to hypercortisolism caused by Cushing's disease (n = 16) or non-pituitary uncontrolled ACTH secretion of unknown origin (n = 7) (27.7% of all adrenalectomies). Compared with unilateral adrenalectomy (n = 59), patients with bilateral adrenalectomy (n = 24) had a higher rate of severe complications (0% vs. 33%; p < 0.001) and delayed recovery (median: 10.2% vs. 79.2%; p < 0.001). Using the MTL30 marker, patients with bilateral adrenalectomy fared worse than patients after unilateral surgery (MTL30 positive: 7.2% vs. 25.0% p < 0.001). Postoperative mortality was increased in patients with bilateral adrenalectomy (0% vs. 8.3%; p = 0.081).
CONCLUSION: While unilateral adrenalectomy for adrenal Cushing's syndrome represents a safe and definitive therapeutic option, bilateral adrenalectomy to control ACTH-dependent extra-adrenal Cushing's syndrome or Cushing's disease is a more complicated intervention with a mortality of nearly 10%.
PubMed-ID: 35633419
http://dx.doi.org/10.1007/s00423-022-02568-8

One Adrenal Is Worth Two-Reply.
JAMA Surg, 157(9):859.
M. Fiore, L. Conti and E. Seregni.
PubMed-ID: 35675048
http://dx.doi.org/10.1001/jamasurg.2022.2078

One Adrenal Is Worth Two.
JAMA Surg, 157(9):858-9.
P. Loli.
PubMed-ID: 35675069
http://dx.doi.org/10.1001/jamasurg.2022.2075

Ambulatory fludrocortisone suppression test in the diagnosis of primary aldosteronism: Safety, accuracy and cost-effectiveness.
Clin Endocrinol (Oxf), 97(6):730-9.
A. Carasel, J. Calissendorff, K. Avander, I. Shabo, C. Volpe and H. Falhammar.
OBJECTIVE: The aims of this study were to explore if the ambulatory fludrocortisone suppression test (FST) was safe, accurate and cost-effective.
CONTEXT: The diagnosis of primary aldosteronism (PA) remains time-consuming and complex. The FST is used to confirm PA, but it is an in-patient test due to potentially serious complications such as hypokalemia. In Stockholm, FST has been performed since 2005 as an ambulatory procedure.
DESIGN: This is a retrospective study including all patients investigated with FST in four hospitals in Stockholm, Sweden, during 2005-2019.
PATIENTS/MEASUREMENTS: In total, 156 cases of ambulatory FST (FSTamb) and 15 cases of in-patient FST (FSTin) were included. FSTamb and FSTin were compared regarding health costs, clinical characteristics and laboratory results.

RESULTS: No difference was found in the outcomes of FSTamb and FSTin. No severe complications were reported in FSTamb patients. No difference was found in the median value for plasma potassium on Day 5 between the two groups. Only three patients (1.9%) in the FSTamb had to repeat the test due to incomplete intake of medications. FSTamb and FSTin were equally accurate. The cost of performing FSTamb was at least 50% lower compared with FSTin ($2400 vs. $5200 per patient). The time needed for FSTamb was 60 min of physician's time and 150 min of nurse's time which were lower than the 5 days in FSTin.
CONCLUSIONS: Ambulatory FST is safe and accurate and can be performed with significantly less healthcare costs compared to FSTin.
PubMed-ID: 35762021
http://dx.doi.org/10.1111/cen.14793

Preanalytical Considerations and Outpatient Versus Inpatient Tests of Plasma Metanephrines to Diagnose Pheochromocytoma.
J Clin Endocrinol Metab, 107(9):e3689-e98.
G. Pommer, C. Pamporaki, M. Peitzsch, H. Remde, T. Deutschbein, S. Nölting, L. M. Müller, L. Braun, S. Gruber, A. Pecori, S. Hampson, E. Davies, A. Stell, G. P. Rossi, L. Lenzini, F. Ceccato, H. Timmers, J. Deinum, L. Amar, A. Blanchard, S. Baron, M. Fassnacht, P. Dobrowolski, A. Januszewicz, M. C. Zennaro, A. Prejbisz and G. Eisenhofer.
CONTEXT: Sampling of blood in the supine position for diagnosis of pheochromocytoma and paraganglioma (PPGL) results in lower rates of false positives for plasma normetanephrine than seated sampling. It is unclear how inpatient vs outpatient testing and other preanalytical factors impact false positives.
OBJECTIVE**:** We aimed to identify preanalytical precautions to minimize false-positive results for plasma metanephrines.
METHODS: Impacts of different blood sampling conditions on plasma metanephrines were evaluated, including outpatient vs inpatient testing, sampling of blood in semi- vs fully recumbent positions, use of cannulae vs direct venipuncture, and differences in outside temperature. A total of 3147 patients at 10 tertiary referral centers were tested for PPGL, including 278 with and 2869 without tumors. Rates of false-positive results were analyzed.
RESULTS: Outpatient rather than inpatient sampling resulted in 44% higher plasma concentrations and a 3.4-fold increase in false-positive results for normetanephrine. Low temperature, a semi-recumbent position, and direct venipuncture also resulted in significantly higher plasma concentrations and rates of false-positive results for plasma normetanephrine than alternative sampling conditions, although with less impact than outpatient sampling. Higher concentrations and rates of false-positive results for plasma normetanephrine with low compared with warm temperatures were only apparent for outpatient sampling. Preanalytical factors were without impact on plasma metanephrines in patients with PPGL.
CONCLUSION: Although inpatient blood sampling is largely impractical for screening patients with suspected PPGL, other preanalytical precautions (eg, cannulae, warm testing conditions) may be useful. Inpatient sampling may be reserved for follow-up of patients with difficult to distinguish true- from false-positive results.
PubMed-ID: 35767279
http://dx.doi.org/10.1210/clinem/dgac390

Histopathology and Genetic Causes of Primary Aldosteronism in Young Adults.
J Clin Endocrinol Metab, 107(9):2473-82.
K. Nanba, J. E. Baker, A. R. Blinder, N. R. Bick, C. J. Liu, J. S. Lim, H. Wachtel, D. L. Cohen, T. A. Williams, M. Reincke, M. L. Lyden, I. Bancos, W. F. Young, T. Else, T. J. Giordano, A. M. Udager and W. E. Rainey.
CONTEXT: Due to its rare incidence, molecular features of primary aldosteronism (PA) in young adults are largely unknown. Recently developed targeted mutational analysis identified aldosterone-driver somatic mutations in aldosterone-producing lesions, including aldosterone-producing adenomas (APAs), aldosterone-producing nodules (APNs), and aldosterone-producing micronodules, formerly known as aldosterone-producing cell clusters.
OBJECTIVE**:** To investigate histologic and genetic characteristics of lateralized PA in young adults.
METHODS: Formalin-fixed, paraffin-embedded adrenal tissue sections from 74 young patients with lateralized PA (<35 years old) were used for this study. Immunohistochemistry (IHC) for aldosterone synthase (CYP11B2) was performed to define the histopathologic diagnosis. Somatic mutations in aldosterone-producing lesions were further determined by CYP11B2 IHC-guided DNA sequencing.
RESULTS: Based on the CYP11B2 IHC results, histopathologic classification was made as follows: 48 APAs, 20 APNs, 2 multiple aldosterone-producing nodules (MAPN), 1 double APN, 1 APA with MAPN, and 2 nonfunctioning adenomas (NFAs). Of 45 APAs with successful sequencing, 43 (96%) had somatic mutations, with KCNJ5 mutations being the most common genetic cause of young-onset APA (35/45, 78%). Of 18 APNs with successful sequencing, all of them harbored somatic mutations, with CACNA1D mutations being the most frequent genetic alteration in young-onset APN (8/18, 44%).

Multiple CYP11B2-expressing lesions in patients with MAPN showed several aldosterone-driver mutations. No somatic mutations were identified in NFAs.
CONCLUSION: APA is the most common histologic feature of lateralized PA in young adults. Somatic KCNJ5 mutations are common in APAs, whereas CACNA1D mutations are often seen in APNs in this young PA population.
PubMed-ID: 35779252
http://dx.doi.org/10.1210/clinem/dgac408

Subtyping primary aldosteronism by inconclusive adrenal vein sampling: A derivation and validation study in a tertiary centre.
Clin Endocrinol (Oxf), 97(6):849-59.
K. Zibar Tomsic, T. Dusek, A. Alduk, N. Knezevic, V. Molnar, I. Kraljevic, T. Skoric Polovina, A. Balasko, M. Solak, N. Matas, H. Popovac, S. Kralik-Oguic and D. Kastelan.
OBJECTIVE: Indices based on aldosterone/cortisol (A/C) concentration in the successfully cannulated adrenal vein (AV) and in the inferior vena cava (IVC) (AV/IVC) appear to be possible markers to verify the subtype of primary aldosteronism (PA) in the case of inconclusive results of adrenal vein sampling (AVS). The variability of results in previous studies encouraged us to calculate AV/IVC and adrenal A/C cutoff values that could predict the aetiology of PA.
METHODS: This retrospective study included 96 patients who underwent AVS due to PA between 2015 and 2020. The derivation cohort ultimately consisted of 60 patients with bilaterally successful AVS and a clear diagnosis of unilateral or bilateral disease. Receiver operating characteristic analysis was used to find the optimal A/C and AV/IVC cutoff values predicting the subtype of PA. The validation cohort consisted of 11 patients with either unsuccessful cannulation or a borderline lateralization index (LI), those patients underwent adrenalectomy because their indices were suggestive of unilateral disease based on the derivation cohort data.
RESULTS: The cutoff values of A/C ≤ 0.63 or AV/IVC ≤ 0.37 identified unaffected glands with a sensitivity of 91.2% and 97.1%, respectively, and a specificity of 90.7% and 88.4%, respectively. Unilateral ipsilateral gland involvement was characterized by A/C ≥ 3.5 or AV/IVC ≥ 3.4 with a corresponding specificity of 100%. All patients in the validation cohort achieved biochemical remission postoperatively.
CONCLUSIONS: A/C and AV/IVC cutoff values could be a useful tool to determine the subtype of PA in patients with unilateral successful AVS as well as in patients with a borderline LI.
PubMed-ID: 35781892
http://dx.doi.org/10.1111/cen.14794

Presentation, Management, and Outcomes of Urinary Bladder Paraganglioma: Results From a Multicenter Study.
J Clin Endocrinol Metab, 107(10):2811-21.
K. Yu, A. L. Ebbehøj, H. Obeid, A. Vaidya, T. Else, H. Wachtel, A. M. Main, E. Søndergaard, L. Lehmann Christensen, C. Juhlin, J. Calissendorff, D. L. Cohen, B. Bennett, M. S. Andersen, C. Larsson, M. Q. Almeida, L. Fishbein, S. A. Boorjian, W. F. Young and I. Bancos.
CONTEXT: Urinary bladder paraganglioma (UBPGL) is rare.
OBJECTIVE: We aimed to characterize the presentation and outcomes of patients diagnosed with UBPGL.
METHODS: We conducted a multicenter study of consecutive patients with pathologically confirmed UBPGL evaluated between 1971 and 2021. Outcomes included repeat bladder surgery, metastases, and disease-specific mortality.
RESULTS: Patients (n=110 total; n=56 [51%] women) were diagnosed with UBPGL at a median age of 50 years (interquartile range [IQR], 36-61 years). Median tumor size was 2 cm (IQR, 1-4 cm). UBPGL was diagnosed prior to biopsy in only 37 (34%), and only 69 (63%) patients had evaluation for catecholamine excess. In addition to the initial bladder surgery, 26 (25%) required multiple therapies, including repeat surgery in 10 (9%). Synchronous metastases were present in 9 (8%) patients, and 24 (22%) other patients with UBPGL developed metachronous metastases at a median of 4 years (IQR, 2-10 years) after the initial diagnosis. Development of metachronous metastases was associated with younger age (hazard ratio [HR] 0.97; 95% CI, 0.94-0.99), UBPGL size (HR 1.69; 95% CI, 1.31-2.17), and a higher degree of catecholamine excess (HR 5.48; 95% CI, 1.40-21.39). Disease-specific mortality was higher in patients with synchronous metastases (HR 20.80; 95% CI, 1.30-332.91). Choice of initial surgery, genetic association, sex, or presence of muscular involvement on pathology were not associated with development of metastases or mortality.
CONCLUSIONS: Only a minority of patients were diagnosed before biopsy/surgery, reflecting need for better diagnostic strategies. All patients with UBPGL should have lifelong monitoring for development of recurrence and metastases.
PubMed-ID: 35882219
http://dx.doi.org/10.1210/clinem/dgac427

The Adhesive Perinephric Fat Score is Correlated with Outcomes of Retroperitoneal Laparoscopic Adrenalectomy for Benign Diseases.
World J Surg, 46(11):2687-94.
W. Chen, Q. Fang, S. Ding, X. Wu, P. Zhang, J. Cao and D. Wu.
BACKGROUND: Retroperitoneal laparoscopic adrenalectomy (RLA) possessing unique superiority with minimal abdominal interference is complicated by the status of periadrenal fat, including its quantity and texture. We hypothesized that an adherent perinephric fat predictor, the Mayo Adhesive Probability score (Mayo score), is associated with the perioperative outcomes of RLA.
METHODS: This retrospective study included consecutive patients who underwent RLA for the diagnosis of benign adrenal tumors at our institution between 2017 and 2020. Medical records were reviewed to evaluate the association between Mayo scores obtained from preoperative computed tomography imaging and surgical outcomes as well as complications. Factors independently related to perioperative results were analyzed using multivariable regression models.
RESULTS: In total, 186 RLA were included. According to their Mayo scores, the patients were divided as follows: 0 (n = 51, 27.4%), 1 (n = 34, 18.3%), 2 (n = 45, 24.2%), 3 (n = 29, 15.6%), 4 (n = 16, 8.6%) and 5 (n = 11, 5.9%). Longer operative time (92.0 ± 25.0 vs. 114.7 ± 30.6 vs. 137.4 ± 27.1 min, P<0.001), higher estimated blood loss (42.2 ± 28.1 vs. 70.5 ± 44.9 vs. 132.6 ± 63.4 mL, P<0.001) and greater decline of hemoglobin (0.7 ± 0.4 vs. 1.0 ± 0.4 vs. 1.3 ± 0.6 g/dL, P<0.001) were significantly associated with elevated Mayo score risks. No difference in complication rates was found. The score was identified as a unique, independent risk factor for perioperative outcomes on multivariable analysis.
CONCLUSIONS: The Mayo score is a vital outcome predictor of RLA. It may be utilized in the preoperative planning for patients undergoing RLA.
PubMed-ID: 35913599
http://dx.doi.org/10.1007/s00268-022-06671-1

Succinate: A Serum Biomarker of SDHB-Mutated Paragangliomas and Pheochromocytomas.
J Clin Endocrinol Metab, 107(10):2801-10.
C. Lamy, H. Tissot, M. Faron, E. Baudin, L. Lamartina, C. Pradon, A. Al Ghuzlan, S. Leboulleux, J. L. Perfettini, A. Paci, J. Hadoux and S. Broutin.
CONTEXT: Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors that are frequently associated with succinate dehydrogenase (SDH) germline mutations. When mutated, SDH losses its function, thus leading to succinate accumulation.
OBJECTIVE: In this study, we evaluated serum succinate levels as a new metabolic biomarker in SDHx-related carriers.
METHODS: Retrospective monocentric study of 88 PPGL patients (43 sporadic, 35 SDHB, 10 SDHA/C/D), 17 tumor-free familial asymptomatic carriers (13 SDHB, 4 SDHC/D), and 60 healthy controls. Clinical, biological, and imaging data were reviewed. Serum succinate levels (n = 280) were quantified by an ultra-performance liquid chromatography coupled to a tandem mass spectrometry method and correlated to SDHx mutational status, disease extension, and other biological biomarkers.
RESULTS: Serum succinate levels > 7 µM allowed identification of tumor-free asymptomatic SDHB-mutated cases compared to a healthy control group (100% specificity; 85% sensitivity). At PPGL diagnosis, SDHB-mutated patients had a significantly increased median succinate level (14 µM) compared to sporadic patients (8 µM) (P < 0.01). Metastatic disease extension was correlated to serum succinate levels (r = 0.81). In the SDHB group, patients displaying highest tumor burdens showed significant increased succinate levels compared to the sporadic group (P < 0.0001).
CONCLUSIONS: In this pilot study, we showed that serum succinate level is an oncometabolic biomarker that should be useful to identify SDHB-related carriers. Succinate levels are also a marker of metabolic tumor burden in patients with a metastatic PPGL and a potential marker of treatment response and follow-up.
PubMed-ID: 35948272
http://dx.doi.org/10.1210/clinem/dgac474

Targeted Therapies in Pheochromocytoma and Paraganglioma.
J Clin Endocrinol Metab, 107(11):2963-72.
K. Wang, J. Crona, F. Beuschlein, A. B. Grossman, K. Pacak and S. Nölting.
Molecular targeted therapy plays an increasingly important role in the treatment of metastatic pheochromocytomas and paragangliomas (PPGLs), which are rare tumors but remain difficult to treat. This mini-review provides an overview of established molecular targeted therapies in present use, and perspectives on those currently under development and evaluation in clinical trials. Recently published research articles, guidelines, and expert views on molecular targeted therapies in PPGLs are systematically reviewed and summarized. Some tyrosine kinase inhibitors (sunitinib, cabozantinib)

are already in clinical use with some promising results, but without formal approval for the treatment of PPGLs. Sunitinib is the only therapeutic option which has been investigated in a randomized placebo-controlled clinical trial. It is clinically used as a first-, second-, or third-line therapeutic option for the treatment of progressive metastatic PPGLs. Some other promising molecular targeted therapies (hypoxia-inducible factor 2 alpha [HIF2α] inhibitors, tumor vaccination together with checkpoint inhibitors, antiangiogenic therapies, kinase signaling inhibitors) are under evaluation in clinical trials. The HIF2α inhibitor belzutifan may prove to be particularly interesting for cluster 1B-/VHL/EPAS1-related PPGLs, whereas antiangiogenic therapies seem to be primarily effective in cluster 1A-/SDHx-related PPGLs. Some combination therapies currently being evaluated in clinical trials, such as temozolomide/olaparib, temozolomide/talazoparib, or cabozantinib/atezolizumab, will provide data for novel therapy for metastatic PPGLs. It is likely that advances in such molecular targeted therapies will play an essential role in the future treatment of these tumors, with more personalized therapy options paving the way towards improved therapeutic outcomes.
PubMed-ID: 35973976
http://dx.doi.org/10.1210/clinem/dgac471

Influence of cortisol cosecretion on non-ACTH-stimulated adrenal venous sampling in primary aldosteronism: a retrospective cohort study.
Eur J Endocrinol, 187(5):637-50.
D. A. Heinrich, M. Quinkler, C. Adolf, L. Handgriff, L. Müller, H. Schneider, L. Sturm, H. Künzel, M. Seidensticker, S. Deniz, R. Ladurner, F. Beuschlein and M. Reincke.
OBJECTIVE: Cortisol measurements are essential for the interpretation of adrenal venous samplings (AVS) in primary aldosteronism (PA). Cortisol cosecretion may influence AVS indices. We aimed to investigate whether cortisol cosecretion affects non-adrenocorticotrophic hormone (ACTH)-stimulated AVS results.
DESIGN: Retrospective cohort study at a tertiary referral center.
METHODS: We analyzed 278 PA patients who underwent non-ACTH-stimulated AVS and had undergone at least a 1-mg dexamethasone suppression test (DST). Subsets underwent additional late-night salivary cortisol (LSC) and/or 24-h urinary free cortisol (UFC) measurements. Patients were studied from 2013 to 2020 with follow-up data of 6 months following adrenalectomy or mineralocorticoid antagonist therapy initiation. We analyzed AVS parameters including adrenal vein aldosterone/cortisol ratios, selectivity, lateralization (LI) and contralateral suppression indices and post-operative ACTH-stimulation. We classified outcomes according to the primary aldosteronism surgical outcome (PASO) criteria.
RESULTS: Among the patients, 18.9% had a pathological DST result (1.9-5 µg/dL: n = 44 (15.8%); >5 µg/dL: n = 8 (2.9%)). Comparison of AVS results stratified according to the 1-mg DST (≤1.8 vs >1.8 µg/dL: P = 0.499; ≤1.8 vs 1.8 ≤ 5 vs >5 µg/dL: P = 0.811) showed no difference. Lateralized cases with post DST serum cortisol values > 5 µg/dL had lower LI (≤1.8 µg/dL: 11.11 (5.36; 26.76) vs 1.9-5 µg/dL: 11.76 (4.9; 31.88) vs >5 µg/dL: 2.58 (1.67; 3.3); P = 0.008). PASO outcome was not different according to cortisol cosecretion.
CONCLUSIONS: Marked cortisol cosecretion has the potential to influence non-ACTH-stimulated AVS results. While this could result in falsely classified lateralized cases as bilateral, further analysis of substitutes for cortisol are required to unmask effects on clinical outcome.
PubMed-ID: 36070424
http://dx.doi.org/10.1530/EJE-21-0541

Adrenalectomy for metastases.
Br J Surg, 109(11):1030-1.
A. M. Zaborowski and R. S. Prichard.
PubMed-ID: 36076286
http://dx.doi.org/10.1093/bjs/znac315

Robot-assisted vs laparoscopic lateral transabdominal adrenalectomy: a propensity score matching analysis.
Surg Endosc, 36(11):8619-29.
C. De Crea, F. Pennestrì, N. Voloudakis, L. Sessa, P. F. Procopio, P. Gallucci, R. Bellantone and M. Raffaelli.
BACKGROUND: Laparoscopic adrenalectomy (LA) is the gold standard treatment for adrenal lesions. Robot-assisted adrenalectomy (RAA) is a safe approach, associated with higher costs in absence of clear-cut benefits. Several series reported some advantages of RAA over LA in challenging cases, but definitive conclusions are lacking. We evaluated the cost effectiveness and outcomes of robotic (R-LTA) and laparoscopic (L-LTA) approach for lateral transabdominal adrenalectomy in a high-volume center.
METHODS: Among 356 minimally invasive adrenalectomies (January 2012-August 2021), 286 were performed with a

lateral transabdominal approach: 191 L-LTA and 95 R-LTA. The R-LTA and L-LTA patients were matched for lesion side and size, hormone secretion, and BMI with propensity score matching (PSM) analysis. Postoperative complications, operative time (OT), postoperative stay (POS), and costs were compared.
RESULTS: PSM analysis identified 184 patients, 92 in R-LTA and 92 in L-LTA group. The two groups were well matched. The median lesion size was 4 cm in both groups ($p = 0.533$). Hormonal hypersecretion was detected in 55 and 54 patients of R-LTA and L-LTA group, respectively ($p = 1$). Median OT was significantly longer in R-LTA group (90.0 vs 65.0 min) ($p < 0.001$). No conversion was registered. Median POS was similar (4.0 vs 3.0 days in the R-LTA and L-LTA) ($p = 0.467$). No difference in postoperative complications was found ($p = 1$). The cost margin analysis showed a positive income for both procedures (3137 vs 3968 € for R-LTA and L-LTA). In the multiple logistic regression analysis, independent risk factors for postoperative complications were hypercortisolism (OR = 3.926, $p = 0.049$) and OT > 75 min (OR = 8.177, $p = 0.048$).
CONCLUSIONS: The postoperative outcomes of R-LTA and L-TLA were similar in our experience. Despite the higher cost, RAA appears to be cost effective and economically sustainable in a high-volume center (60 adrenalectomies/year), especially if performed in challenging cases, including patients with large (> 6 cm) and/or functioning tumors.
PubMed-ID: 36190555
http://dx.doi.org/10.1007/s00464-022-09663-3

NET

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Targeted α-Emitter Therapy with (212)Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors: First-in-Humans Dose-Escalation Clinical Trial.
J Nucl Med, 63(9):1326-33.
E. S. Delpassand, I. Tworowska, R. Esfandiari, J. Torgue, J. Hurt, A. Shafie and R. Núñez.
Peptide receptor radiotherapy with somatostatin analogs has been successfully used for years as a treatment for somatostatin-overexpressing tumors. Treatment of neuroendocrine tumors (NETs) with the β-particle emitter (177)Lu-DOTATATE is currently considered the standard of care for subjects with gastroenteropancreatic NETs. Despite the success of (177)Lu-DOTATATE, there remains significant room for improvement in terms of both safety and efficacy. Targeted α -emitter therapy with isotopes such as (212)Pb has the potential to improve both. Here, we present the preliminary results of the phase 1 first-in-humans dose-escalation trial evaluating (212)Pb-DOTAMTATE (a bifunctional metal chelator [DOTAM] and the SSTR-targeting peptide [TATE]) in patients with somatostatin receptor-positive NETs.
METHODS: Twenty subjects with histologically confirmed NETs, prior positive somatostatin analog scans, and no prior history of (177)Lu/(90)Y/(111)In peptide receptor radiotherapy, with different primary sites of the disease, were enrolled. Treatment began with single ascending doses of (212)Pb-DOTAMTATE, with subsequent cohorts receiving an incremental 30% dose increase, which was continued until a tumor response or a dose-limiting toxicity was observed. This was followed by a multiple ascending dose regimen. The recommended phase 2 dose regimen consisted of 4 cycles of 2.50 MBq/kg (67.6 μCi/kg) of (212)Pb-DOTAMTATE administered at 8-wk intervals, intravenously.
RESULTS: Ten subjects received the highest dose, 2.50 MBq/kg/cycle (67.6 μCi/kg/cycle). Treatment was well tolerated, with the most common treatment-emergent adverse events being nausea, fatigue, and alopecia. No serious treatment-emergent adverse events were related to the study drug, and no subjects required treatment delay or a dose reduction. An objective radiologic response of 80% was observed for the first 10 subjects treated at the recommended phase 2 dose.
CONCLUSION: Targeted α -therapy with (212)Pb-DOTAMTATE has been shown to be well tolerated. Preliminary efficacy results are highly promising. If these results are confirmed in a larger, multicenter clinical trial, (212)Pb-DOTAMTATE would provide a substantial benefit over currently Food and Drug Administration-approved therapies for patients with metastatic or inoperable SSTR-expressing NETs regardless of the grade and location of the primary tumor.
PubMed-ID: 34992153
http://dx.doi.org/10.2967/jnumed.121.263230

Predicting resectability of primary tumor and mesenteric lymph-node masses in patients with small-intestine neuroendocrine tumors.
Updates Surg, 74(5):1697-704.
E. Bertani, F. Zugni, D. Radice, F. Spada, G. Bonomo, U. Fumagalli Romario, N. Fazio and L. Funicelli.
BACKGROUND: Vascular infiltration may jeopardize resection of the primary tumor and mesenteric metastatic masses in small-intestine neuroendocrine tumors (SI-NETs). However, other factors may play a role in predicting resectability.

METHODS: After computed tomography (CT) scan, three radiological parameters were considered: (1) degree of superior mesenteric artery involvement (SMA) according to a previous classification (2) degree of superior mesenteric venous involvement (SMV) as either absent, peripheral or proximal (3) presence or not of mesenteric fibrosis retraction (MF). Pre-surgical parameters were matched to surgical outcome.
RESULTS: Forty-nine consecutive patients were submitted to laparotomy. Of them, 37 had complete primary tumor and mesenteric masses resection. SMA ($p = 0.001$), SMV ($p = 0.008$), metastasis site ($p = 0.001$) and MF ($p < 0.001$) were all significantly associated with the likelihood to receive resection at univariate analysis. All the five patients with infiltration of SMV proximal to middle colic vein were unresectable. At multivariable analysis excluding SMA stage, the absence of MF (HR 13.1, I.C. 1.44-119; $p = 0.002$) was the only factor associated with the likelihood to receive primary tumor and mesentery radical surgery.
CONCLUSIONS: SMA stage 3-up and/or signs of MF, as well as infiltration of SMV proximal to middle colic vein at CT scan are predictive of operative failure in patients with SI-NETs. The assessment of such factors should be always considered in the decision-making process of such patients especially in those with asymptomatic disease with synchronous unresectable liver metastases.
PubMed-ID: 35224681
http://dx.doi.org/10.1007/s13304-022-01251-3

Functional Imaging of Neuroendocrine Tumors: Stacking the Odds in a Patient's Favor.
J Clin Endocrinol Metab, 107(9):e3953-e4.
K. Pacak, D. Taieb and A. Jha.
PubMed-ID: 35536703
http://dx.doi.org/10.1210/clinem/dgac298

ASO Author Reflection: Risk of Recurrence After Radical Resection in Entero-Pancreatic Neuroendocrine Tumors.
Ann Surg Oncol, 29(9):5578-9.
E. Merola.
PubMed-ID: 35581515
http://dx.doi.org/10.1245/s10434-022-11882-w

Radical Resection in Entero-Pancreatic Neuroendocrine Tumors: Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence.
Ann Surg Oncol, 29(9):5568-77.
E. Merola, A. Pascher, A. Rinke, D. K. Bartsch, A. Zerbi, G. Nappo, C. Carnaghi, M. Ciola, M. G. McNamara, W. Zandee, E. Bertani, S. Marcucci, R. Modica, R. Grützmann, N. Fazio, W. de Herder, J. W. Valle, T. M. Gress, G. D. Fave, G. de Pretis, A. Perren, B. Wiedenmann and M. E. Pavel.
BACKGROUND: Surgery with radical intent is the only potentially curative option for entero-pancreatic neuroendocrine tumors (EP-NETs) but many patients develop recurrence even after many years. The subset of patients at high risk of disease recurrence has not been clearly defined to date.
OBJECTIVE: The aim of this retrospective study was to define, in a series of completely resected EP-NETs, the recurrence-free survival (RFS) rate and a risk score for disease recurrence.
PATIENTS AND METHODS: This was a multicenter retrospective analysis of sporadic pancreatic NETs (PanNETs) or small intestine NETs (SiNETs) [G1/G2] that underwent R0/R1 surgery (years 2000-2016) with at least a 24-month follow-up. Survival analysis was performed using the Kaplan-Meier method and risk factor analysis was performed using the Cox regression model.
RESULTS: Overall, 441 patients (224 PanNETs and 217 SiNETs) were included, with a median Ki67 of 2% in tumor tissue and 8.2% stage IV disease. Median RFS was 101 months (5-year rate 67.9%). The derived prognostic score defined by multivariable analysis included prognostic parameters, such as TNM stage, lymph node ratio, margin status, and grading. The score distinguished three risk categories with a significantly different RFS ($p < 0.01$).
CONCLUSIONS: Approximately 30% of patients with EP-NETs recurred within 5 years after radical surgery. Risk factors for recurrence were disease stage, lymph node ratio, margin status, and grading. The definition of risk categories may help in selecting patients who might benefit from adjuvant treatments and more intensive follow-up programs.
PubMed-ID: 35583694
http://dx.doi.org/10.1245/s10434-022-11837-1

Prognostic Effect of Lymph Node Metastases and Mesenteric Deposits in Neuroendocrine Tumors of the Small Bowel.
J Clin Endocrinol Metab, 107(12):3209-21.
F. Grillo, M. Albertelli, P. Malandrino, A. Dotto, G. Pizza, G. Cittadini, A. Colao and A. Faggiano.
Well-differentiated, low-grade neuroendocrine tumors (NETs) are the most frequent tumor types of the small bowel. Despite their generally indolent growth patterns and grade, these tumors tend to metastasize; indeed, at presentation, approximately 50% show nodal metastases and 30% of patients have distant metastases, even though they potentially show long survival. Little is available in the literature concerning the optimal nodal yield in small-bowel resections, and the clinical significance of nodal metastases and lymph node ratio (LNR) at this site is still debated. The aim of this review, through a systematic literature search, is to explore and analyze data regarding nodal status, adequacy of lymphadenectomy, and LNR on the prognosis of small bowel NETs using defined end points (progression-free survival, recurrence-free survival, and overall survival). Some surgical series have demonstrated that extended regional mesenteric lymphadenectomy, together with primary tumor resection, is associated with improved patient survival, and LNR is proving a prognostically important parameter. The new feature of mesenteric tumor deposits (MTDs; neoplastic deposits found in the mesenteric perivisceral adipose tissue that are not LN associated) seems to be a better prognostic predictor in small-bowel NETs compared to nodal metastases, and this feature is explored and critiqued in this review. In particular, increasing number of tumor deposits is correlated with increased risk of disease-specific death, and MTDs seem to correlate with peritoneal carcinomatosis.
PubMed-ID: 35639999
http://dx.doi.org/10.1210/clinem/dgac326

Safety and Outcomes of Combined Pancreatic and Hepatic Resections for Metastatic Pancreatic Neuroendocrine Tumors.
Ann Surg Oncol, 29(11):6949-57.
H. Gudmundsdottir, R. Pery, R. P. Graham, C. A. Thiels, S. G. Warner, R. L. Smoot, M. J. Truty, M. L. Kendrick, T. R. Halfdanarson, E. B. Habermann, D. M. Nagorney and S. P. Cleary.
BACKGROUND: Approximately 40-50% of patients with pancreatic neuroendocrine tumors (pNETs) initially present with distant metastases. Little is known about the outcomes of patients undergoing combined pancreatic and hepatic resections for this indication.
METHODS: Patients who underwent hepatectomy for metastatic pNETs at Mayo Clinic Rochester from 2000 to 2020 were retrospectively reviewed. Major pancreatectomy was defined as pancreaticoduodenectomy or total pancreatectomy, and major hepatectomy as right hepatectomy or trisegmentectomy. Characteristics and outcomes of patients who underwent pancreatectomy with simultaneous hepatectomy were compared with those of patients who underwent isolated hepatectomy (with or without prior history of pancreatectomy).
RESULTS: 205 patients who underwent hepatectomy for metastatic pNETs were identified: 131 underwent pancreatectomy with simultaneous hepatectomy and 74 underwent isolated hepatectomy. Among patients undergoing simultaneous hepatectomy, 89 patients underwent minor pancreatectomy with minor hepatectomy, 11 patients underwent major pancreatectomy with minor hepatectomy, 30 patients underwent minor pancreatectomy with major hepatectomy, and 1 patient underwent major pancreatectomy with major hepatectomy. Patients undergoing simultaneous hepatectomy had more numerous liver lesions (10 or more lesions in 54% vs. 34%, p = 0.008), but the groups were otherwise similar. Rates of any major complications (31% versus 24%, p = 0.43), hepatectomy-specific complications such as bile leak, hemorrhage, and liver failure (0.8-7.6% vs. 1.4-12%, p = 0.30-0.99), and 90-day mortality (1.5% vs. 2.7%, p = 0.62) were similar between the two groups. 5-year overall survival was 64% after combined resections and 65% after isolated hepatectomy (p = 0.93).
CONCLUSION: For patients with metastatic pNETs, combined pancreatic and hepatic resections can be performed with acceptable morbidity and mortality in selected patients at high-volume institutions.
PubMed-ID: 35731358
http://dx.doi.org/10.1245/s10434-022-12029-7

Long-term Outcomes of Parenchyma-sparing and Oncologic Resections in Patients With Nonfunctional Pancreatic Neuroendocrine Tumors <3 cm in a Large Multicenter Cohort.
Ann Surg, 276(3):522-31.
L. Bolm, M. Nebbia, A. C. Wei, A. H. Zureikat, C. Fernández-Del Castillo, J. Zheng, A. Pulvirenti, A. A. Javed, Y. Sekigami, N. Petruch, M. Qadan, K. D. Lillemoe, J. He and C. R. Ferrone.
INTRODUCTION: The role of parenchyma-sparing resections (PSR) and lymph node dissection in small (<3 cm) nonfunctional pancreatic neuroendocrine tumors (PNET) is unlikely to be studied in a prospective randomized clinical trial.

By combining data from 4 high-volume pancreatic centers we compared postoperative and long-term outcomes of patients who underwent PSR with patients who underwent oncologic resections.
METHODS: Retrospective review of prospectively collected clinicopathologic data of patients who underwent pancreatectomy between 2000 and 2021 was collected from 4 high-volume institutions. PSR and lymph node-sparing resections (enucleation and central pancreatectomy) were compared to those who underwent oncologic resections with lymphadenectomy (pancreaticoduodenectomy, distal pancreatectomy). Statistical testing was performed using χ 2 test and t test, survival estimates with Kaplan-Meier method and multivariate analysis using Cox proportional hazard model.
RESULTS: Of 810 patients with small sporadic nonfunctional PNETs, 121 (14.9%) had enucleations, 100 (12.3%) had central pancreatectomies, and 589 (72.7%) patients underwent oncologic resections. The median age was 59 years and 48.2% were female with a median tumor size of 2.5 cm. After case-control matching for tumor size, 221 patients were selected in each group. Patients with PSR were more likely to undergo minimally invasive operations (32.6% vs 13.6%, P <0.001), had less intraoperative blood loss (358 vs 511 ml, P <0.001) and had shorter operative times (180 vs 330 minutes, P <0.001) than patients undergoing oncologic resections. While the mean number of lymph nodes harvested was lower for PSR (n=1.4 vs n=9.9, P <0.001), the mean number of positive lymph nodes was equivalent to oncologic resections (n=1.1 vs n=0.9, P =0.808). Although the rate of all postoperative complications was similar for PSR and oncologic resections (38.5% vs 48.2%, P =0.090), it was higher for central pancreatectomies (38.5% vs 56.6%, P =0.003). Long-term median disease-free survival (190.5 vs 195.2 months, P =0.506) and overall survival (197.9 vs 192.6 months, P =0.372) were comparable. Of the 810 patients 136 (16.7%) had no lymph nodes resected. These patients experienced less blood loss, shorter operations (P <0.001), and lower postoperative complication rates as compared to patients who had lymphadenectomies (39.7% vs 56.9%, P =0.008). Median disease-free survival (197.1 vs 191.9 months, P =0.837) and overall survival (200 vs 195.1 months, P =0.827) were similar for patients with no lymph nodes resected and patients with negative lymph nodes (N0) after lymphadenectomy.
CONCLUSION: In small <3 cm nonfunctional PNETs, PSRs and lymph node-sparing resections are associated with lower blood loss, shorter operative times, and lower complication rates when compared to oncologic resections, and have similar long-term oncologic outcomes.
PubMed-ID: 35758433
http://dx.doi.org/10.1097/SLA.0000000000005559

ASO Author Reflections: Combined Pancreatic and Hepatic Resections for Metastatic Pancreatic Neuroendocrine Tumors-A Single Operation is Feasible in Most Patients.
Ann Surg Oncol, 29(11):6958-9.
H. Gudmundsdottir, T. R. Halfdanarson and S. P. Cleary.
PubMed-ID: 35780453
http://dx.doi.org/10.1245/s10434-022-12106-x

ASO Visual Abstract: Radical Resection in Enteropancreatic Neuroendocrine Tumors-Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence.
Ann Surg Oncol, 29(9):5580-1.
E. Merola, A. Pascher, A. Rinke, D. K. Bartsch, A. Zerbi, G. Nappo, C. Carnaghi, M. Ciola, M. G. McNamara, W. Zandee, E. Bertani, S. Marcucci, R. Modica, R. Grützmann, N. Fazio, W. de Herder, J. W. Valle, T. M. Gress, G. Delle Fave, G. de Pretis, A. Perren, B. Wiedenmann and M. E. Pavel.
PubMed-ID: 35789310
http://dx.doi.org/10.1245/s10434-022-12049-3

ASO Author Reflections: Comprehensive Clinical Analysis of Gallbladder Neuroendocrine Neoplasms.
Ann Surg Oncol, 29(12):7631.
Q. Zhang, Y. Wang and T. Liang.
PubMed-ID: 35794367
http://dx.doi.org/10.1245/s10434-022-12121-y

Is There a Role for Surgical Resection of Grade 3 Neuroendocrine Neoplasms?
Ann Surg Oncol, 29(11):6936-46.
L. C. Borbon, C. G. Tran, S. K. Sherman, P. H. Ear, C. Chandrasekharan, A. M. Bellizzi, J. S. Dillon, T. M. O'Dorisio and J. R. Howe.
BACKGROUND: Grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are aggressive tumors with

poor survival outcomes for which medical management is generally recommended. This study sought to evaluate outcomes of surgically treated G3 GEP-NEN patients.
METHODS: A single-institutional prospective NEN database was reviewed. Patients with G3 GEP-NENs based on World Health Organization (WHO) 2019 definitions included well-differentiated neuroendocrine tumors (G3NET) and poorly differentiated neuroendocrine carcinomas (G3NEC). Clinicopathologic factors were compared between groups. Overall survival from G3 diagnosis was assessed by the Kaplan-Meier method.
RESULTS: Surgical resection was performed for 463 patients (211 G1, 208 G2, 44 G3). Most had metastatic disease at presentation (54% G1, 69% G2, 91% G3; $p < 0.001$). The G3 cohort included 39 G3NETs and 5 G3NECs, 22 of pancreatic and 22 of midgut origin. Median overall survival (mOS; in months) was 268.1 for G1NETs, 129.9 for G2NETs, 50.5 for G3NETs, and 28.5 for G3NECs ($p < 0.001$). Over the same period, 31 G3 patients (12 G3NETs, 19 G3NECs) were treated non-surgically, with mOS of 19.0 for G3NETs and 12.4 for G3NECs.
CONCLUSIONS: Surgical resection of G3 GEP-NENs remains controversial due to poor prognosis, and surgical series are rare. This large, single-institutional study found significantly lower mOS in patients with resected G3NENs than those with G1/G2 tumors, reflecting more aggressive tumor biology and a higher proportion with metastatic disease. The mOS for resected G3NETs and G3NECs exceeded historical non-surgical G3NEN series (mOS 11-19 months), suggesting surgery should be considered in carefully selected patients with G3NENs, especially those with well-differentiated tumors.
PubMed-ID: 35802214
http://dx.doi.org/10.1245/s10434-022-12100-3

Sequencing of Therapies in Progressive Neuroendocrine Tumors.
Ann Surg Oncol, 29(11):6501-3.
J. R. Howe.
PubMed-ID: 35816247
http://dx.doi.org/10.1245/s10434-022-12149-0

Primary Tumor Resection is Associated with Improved Disease-Specific Mortality in Patients with Stage IV Small Intestinal Neuroendocrine Tumors (NETs): A Comparison of Upfront Surgical Resection Versus a Watch and Wait Strategy in Two Specialist NET Centers.
Ann Surg Oncol, 29(12):7822-32.
S. Levy, J. D. Arthur, M. Banks, N. F. M. Kok, S. W. Fenwick, R. Diaz-Nieto, M. E. van Leerdam, D. J. Cuthbertson, G. D. Valk, K. F. D. Kuhlmann and M. E. T. Tesselaar.
INTRODUCTION: Small intestinal neuroendocrine tumors (SI-NETs) often present with metastatic disease. An ongoing debate exists on whether to perform primary tumor resection (PTR) in patients with stage IV SI-NETs, without symptoms of the primary tumor and inoperable metastatic disease.
OBJECTIVE: The aim of this study was to compare a treatment strategy of upfront surgical resection versus a surveillance strategy of watch and wait.
METHODS: This was a retrospective cohort study of patients with stage IV SI-NETs at diagnosis, between 2000 and 2018, from two tertiary referral centers (Netherlands Cancer Institute [NKI] and Aintree University Hospital [AUH]) who had adopted contrasting treatment approaches: upfront surgical resection and watch and wait, respectively. Patients without symptoms related to the primary tumor were included. Multivariable intention-to-treat (ITT), per-protocol (PP), and instrumental variable (IV) analyses using 'institute' as an IV were performed to assess the influence of PTR on disease-specific mortality (DSM).
RESULTS: A total of 557 patients were identified, with 145 patients remaining after exclusion of stage I-III disease or symptoms of the primary tumor (93 from the NKI and 52 from AUH). The cohorts differed in performance status (PS; $p = 0.006$) and tumor grade ($p < 0.001$). PTR was independently associated with reduced DSM irrespective of statistical methods employed: ITT hazard ratio [HR] 0.60, $p = 0.005$; PP HR 0.58, $p < 0.001$; and IV HR 0.07, $p = 0.019$. Other factors associated with DSM were age, PS, high chromogranin A, and somatostatin analog treatment.
CONCLUSION: Taking advantage of contrasting institutional treatment strategies, this study identified PTR as an independent predictor of DSM. Future prospective studies should aim to validate these results.
PubMed-ID: 35842528
http://dx.doi.org/10.1245/s10434-022-12030-0

ASO Visual Abstract: Is There a Role for Surgical Resection of Grade 3 Neuroendocrine Neoplasms?
Ann Surg Oncol, 29(11):6947-8.
L. C. Borbon, C. G. Tran, S. K. Sherman, P. H. Ear, C. Chandrasekharan, A. M. Bellizzi, J. S. Dillon, T. M. O'Dorisio and J. R. Howe.
PubMed-ID: 35849292
http://dx.doi.org/10.1245/s10434-022-12229-1

ASO Visual Abstract: Comprehensive Clinical Analysis of Gallbladder Neuroendocrine Neoplasms-A Large-Volume Multicenter Study over One Decade.
Ann Surg Oncol, 29(12):7632-3.
Y. Wang, Q. Zhang and T. Liang.
PubMed-ID: 35896918
http://dx.doi.org/10.1245/s10434-022-12289-3

ASO Visual Abstract: Primary Tumour Resection is Associated with Improved Disease-Specific Mortality in Patients with Stage IV Small Intestinal Neuroendocrine Tumours (NET)-A Comparison of Upfront Surgical Resection versus a Watch-and-Wait Strategy in Two Specialist NET Centres.
Ann Surg Oncol, 29(12):7833-4.
S. Levy, J. D. Arthur, M. Banks, N. F. M. Kok, S. W. Fenwick, R. Diaz-Nieto, M. E. van Leerdam, D. J. Cuthbertson, G. D. Valk, K. F. D. Kuhlmann and M. E. T. Tesselaar.
PubMed-ID: 35906323
http://dx.doi.org/10.1245/s10434-022-12080-4

Continuing challenges of primary neuroendocrine tumours of the thymus: A concisereview.
Eur J Surg Oncol, 48(12):2360-8.
J. Lau, T. Ioan Cvasciuc, D. Simpson, C. d. J. M and R. Parameswaran.
Primary neuroendocrine tumours of the thymus (NETTs) are exceedingly rare tumours, usually presenting around mid-life, which have a propensity towards males and smokers. They are seen more often in those with MEN-1, but multiple different genetic mutations have been found to be involved in the tumorigenesis of NETTs. Histologically, NETTs are classified according to number of mitoses, the presence of necrosis, and the presence or absence of small cell features. NETTs display a wide spectrum of behavior, and they can be incidentally found on chest imaging, on screening in MEN-1, or present with symptoms of local compression. Advanced disease and paraneoplastic syndromes are common. CT-, PET/CT-, MRI-scans, and somatostatin receptor scintigraphy are the imaging modalities of choice both for the initial assessment as well as for monitoring after treatment. For patients with localized disease, complete surgical resection with lymphadenectomy provides the best chance of long-term, disease-free survival, and can be achieved through either an open or thoracoscopic approach. While chemotherapy-regimens based on platinum, taxane, and temozolomide are used most often, the optimum chemotherapy regimen in the adjuvant and palliative settings remains unclear, as does the role of radiotherapy. Ongoing research on the most effective use of somatostatin analogues, peptide receptor radionuclide therapy (PPRT), kinase inhibitors and immunotherapy in patients with other types of advanced neuroendocrine tumours may lead to further treatment options for NETTs in the future.
PubMed-ID: 35922282
http://dx.doi.org/10.1016/j.ejso.2022.07.017

Treatment options of metastatic and nonmetastatic VIPoma: a review.
Langenbecks Arch Surg, 407(7):2629-36.
A. Azizian, A. König and M. Ghadimi.
PURPOSE: VIPoma belongs to the group of neuroendocrine neoplasms. These tumours are located mostly in the pancreas and produce high levels of vasoactive intestinal peptide (VIP). In most cases, a metastatic state has already been reached at the initial diagnosis, with high levels of VIP leading to a wide spectrum of presenting symptoms. These symptoms include intense diarrhoea and subsequent hypopotassaemia but also cardiac complications, with life-threatening consequences. Treatment options include symptomatic therapy, systemic chemotherapy and targeted therapy, as well as radiation and surgery. Due to the low incidence of VIPoma, there are no prospective studies or evidence-based therapeutic standards to date.
METHODS: To evaluate the possible impact of different therapy strategies, we performed literature research using PubMed.

RESULTS: All possible treatment modalities for VIPoma have at least one of two therapy goals: antisecretory effects (symptom control) and antitumoural effects (tumour burden reduction). Symptomatic therapy is the most important in the emergency setting to rehydrate, balance electrolytes and stabilise the patient. Symptomatic therapy is also of great importance perioperatively. Somatostatin analogues play a major role in symptom control, although their efficiency is often limited. Chemotherapy may be effective in reaching stable disease for a certain time period, although its impact on symptom control is limited and often delayed. Among targeted therapy options, the usage of sunitinib appears to be the most effective in terms of symptom control and showing antitumoural effects at the same time. Experience with radiation is still limited; however, local ablative procedures seem to be promising options. Peptide receptor radiotherapy (PRRT) with radiolabelled somatostatin analogues (SSAs, 177Lu-DOTATATE) offers a targeted approach, especially in patients with high somatostatin receptor density. Surgery is the first-line therapy for nonmetastatic VIPoma. Additionally, if the resection of all visible tumour lesions is possible, the surgical approach seems preferable to other strategies in highly symptomatic patients. The role of surgery in very advanced stages where only tumour debulking is possible remains debatable. However, a high rate of immediate symptom control can be achieved by tumour debulking followed by somatostatin therapy, although the impact on survival remains unclear.
CONCLUSION: Surgery is the only curative option for nonmetastatic VIPoma. Additionally, surgery should be a first-line therapy option for highly symptomatic patients, especially if the resection of all tumour lesions (primary tumour and metastasis) is achievable. In frail patients, other modalities can be used.
PubMed-ID: 35931878
http://dx.doi.org/10.1007/s00423-022-02620-7

Long-Term Outcomes for Patients with Multiple Endocrine Neoplasia Type 1 and Duodenopancreatic Neuroendocrine Neoplasms.
Ann Surg Oncol, 29(12):7808-17.
J. B. Liu, J. Cai, M. Dhir, A. Paniccia, A. H. Zureikat, K. M. Ramonell, K. L. McCoy, S. E. Carty and L. Yip.
BACKGROUND: Liver metastasis from duodenopancreatic neuroendocrine neoplasms (DP-NENs) is a major cause of mortality in multiple endocrine neoplasia type 1 (MEN1) patients, yet much of their natural history is unknown.
METHODS: This longitudinal, retrospective cohort study analyzed all MEN1 patients with imageable functional (F) and nonfunctional (NF) DP-NENs (1990-2021) for liver metastasis-free survival (LMFS) and overall survival (OS).
RESULTS: Of 138 patients, 85 (61.6%) had imageable DP-NENs (28 F, 57 NF), and the mean largest tumor size was 1.8 ± 1.4 cm. Multifocality was present in 32 patients (37.7%). Surgery was performed for 49 patients (57.7%). During an 11-year median follow-up period (IQR, 6-17 years), 23 (27.1%) of the patients had liver metastasis, and 19 (22.4%) patients died. Death was attributed to liver metastasis in 60% of cases. The patients with F-DP-NENs versus NF-DP-NENs more often had liver metastasis (46.4% vs. 15.8%; p = 0.002) but had similar 10-year LMFS (80.9 vs. 87.0%; p = 0.44) and OS (82.7 vs. 94.3%; p = 0.69). The patients with NF-DP-NENs had surgery when their tumors were larger (p < 0.001). Tumor size was not associated with liver metastasis (p = 0.89). The average growth rate was 0.04 cm/year (SE, 0.02 cm/year; p = 0.01) during active surveillance for NF-DP-NENs (n = 38). Liver metastasis developed in four patients with tumors smaller than 2 cm. The risk of liver metastasis was independent of surgery (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.21-2.93; p = 0.72) and death (HR, 0.51; 95% CI, 0.08-3.06; p = 0.46).
CONCLUSIONS: Although the observed outcomes in this study were better than historical data, small NF-DP-NENs still developed liver metastasis and liver metastasis remains a major cause of death. These results suggest that size as a sole criterion for surgery may be insufficient to predict tumor behavior.
PubMed-ID: 35963905
http://dx.doi.org/10.1245/s10434-022-12350-1

Management of asymptomatic sporadic non-functioning pancreatic neuroendocrine neoplasms no larger than 2 cm: interim analysis of prospective ASPEN trial.
Br J Surg, 109(12):1186-90.
S. Partelli, S. Massironi, A. Zerbi, P. Niccoli, W. Kwon, L. Landoni, F. Panzuto, A. Tomazic, A. Bongiovanni, G. Kaltsas, A. Sauvanet, E. Bertani, V. Mazzaferro, M. Caplin, T. Armstrong, M. O. Weickert, J. Ramage, E. Segelov, G. Butturini, S. Staettner, M. Cives, A. Frilling, C. A. Moulton, J. He, F. Boesch, A. Selberheer, O. Twito, A. Castaldi, C. G. De Angelis, S. Gaujoux, K. Holzer, C. H. Wilson, H. Almeamar, E. Vigia, F. Muffatti, M. Lucà, A. Lania, J. Ewald, H. Kim, R. Salvia, M. Rinzivillo, A. Smid, A. Gardini, M. Tsoli, O. Hentic, S. Colombo, D. Citterio, C. Toumpanakis, E. Ramsey, H. S. Randeva, R. Srirajaskanthan, D. Croagh, P. Regi, S. Gasteiger, P. Invernizzi, C. Ridolfi, M. Giovannini, J. Y. Jang, C. Bassi and M. Falconi.
PubMed-ID: 35986682
http://dx.doi.org/10.1093/bjs/znac267

ASO Visual Abstract: Long-Term Outcomes of Patients with Multiple Endocrine Neoplasia Type 1 and Duodenopancreatic Neuroendocrine Neoplasms.
Ann Surg Oncol, 29(12):7818-9.
J. B. Liu, J. Cai, M. Dhir, A. Paniccia, A. H. Zureikat, K. M. Ramonell, K. L. McCoy, S. E. Carty and L. Yip.
PubMed-ID: 36109415
http://dx.doi.org/10.1245/s10434-022-12423-1

A novel tool to predict nodal metastasis in small pancreatic neuroendocrine tumors: A multicenter study.
Surgery, 172(6):1800-6.
A. A. Javed, A. Pulvirenti, J. Zheng, T. Michelakos, Y. Sekigami, S. Razi, C. A. McIntyre, E. Thompson, D. S. Klimstra, V. Deshpande, A. D. Singhi, M. J. Weiss, C. L. Wolfgang, J. L. Cameron, A. C. Wei, A. H. Zureikat, C. R. Ferrone and J. He.
BACKGROUND: Nonfunctional pancreatic neuroendocrine tumors display a wide range of biological behavior, and nodal disease is associated with metastatic disease and poorer survival. The aim of this study was to develop a tool to predict nodal disease in patients with small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors.
METHODS: A multicenter retrospective study was performed on patients undergoing resection for small nonfunctional pancreatic neuroendocrine tumors. Patients with genetic syndromes, metastatic disease at diagnosis, neoadjuvant therapy, or positive resection margin were excluded. Factors associated with nodal disease were identified to develop a predictive model. Internal validation was performed using bootstrap with 1,000 resamples.
RESULTS: Nodal disease was observed in 39 (11.1%) of the 353 patients included. Presence of nodal disease was significantly associated with lower 5-year disease-free survival (71.6% vs 96.2%, P < .001). Two predictors were strongly associated with nodal disease: G2 grade (odds ratio: 3.51, 95% confidence interval: 1.71-7.22, P = .001) and tumor size (per mm increase, odds ratio: 1.14, 95% confidence interval: 1.03-1.25, P = .009). Adequate discrimination was observed with an area under the curve of 0.71 (95% confidence interval: 0.63-0.80). Based on risk distribution, 3 risk groups of nodal disease were identified; low (<5%), intermediate (≥5% to <20%), and high (≥20%) risk. The observed mean risk of nodal disease was 3.7% in the low-risk patients, 9.6% in the intermediate-risk patients, and 30.4% in the high-risk patients (P < .001). The 10-year disease-free survival in the low, intermediate, and high-risk groups was 100%, 88.8%, and 50.1%, respectively.
CONCLUSION: Our model using tumor grade and size can predict nodal disease in small nonfunctional pancreatic neuroendocrine tumors. Integration of this tool into clinical practice could help guide management of these patients.
PubMed-ID: 36192215
http://dx.doi.org/10.1016/j.surg.2022.08.022

Peptide Receptor Radionuclide Therapy.
J Clin Endocrinol Metab, 107(12):3199-208.
J. Hofland, T. Brabander, F. A. Verburg, R. A. Feelders and W. W. de Herder.
The concept of using a targeting molecule labeled with a diagnostic radionuclide for using positron emission tomography or single photon emission computed tomography imaging with the potential to demonstrate that tumoricidal radiation can be delivered to tumoral sites by administration of the same or a similar targeting molecule labeled with a therapeutic radionuclide termed "theranostics." Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs (SSAs) is a well-established second/third-line theranostic treatment for somatostatin receptor-positive well-differentiated (neuro-)endocrine neoplasms (NENs). PRRT with 177Lu-DOTATATE was approved by the regulatory authorities in 2017 and 2018 for selected patients with low-grade well-differentiated gastroenteropancreatic (GEP) NENs. It improves progression-free survival as well as quality of life of GEP NEN patients. Favorable symptomatic and biochemical responses using PRRT with 177Lu-DOTATATE have also been reported in patients with functioning metastatic GEP NENs like metastatic insulinomas, Verner Morrison syndromes (VIPomas), glucagonomas, and gastrinomas and patients with carcinoid syndrome. This therapy might also become a valuable therapeutic option for inoperable low-grade bronchopulmonary NENs, inoperable or progressive pheochromocytomas and paragangliomas, and medullary thyroid carcinomas. First-line PRRT with 177Lu-DOTATATE and combinations of this therapy with cytotoxic drugs are currently under investigation. New radiolabeled somatostatin receptor ligands include SSAs coupled with alpha radiation emitting radionuclides and somatostatin receptor antagonists coupled with radionuclides.
PubMed-ID: 36198028
http://dx.doi.org/10.1210/clinem/dgac574

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

A practical guide to genetic testing in endocrinology.
Clin Endocrinol (Oxf), 97(4):388-99.
L. Izatt, M. M. Owens, H. Pierce, S. Wilcox and S. M. Park.
Rapid advances in sequencing technology have led to significant improvements in genomic analysis, resulting in increased understanding of the molecular basis of many endocrine conditions. Genomic testing for rare disease is being integrated into everyday clinical practice, as the importance of confirming a genetic diagnosis earlier in a patient's pathway helps direct their clinical care and specialized management. In England, the new nationally commissioned Genomic Medicine Service has started to deliver testing for rare and inherited disease and cancer somatic tissue via seven Genomic Laboratory Hubs. The range of genetic tests, technology employed and eligibility criteria for patient testing are all defined in the National Genomic Test Directory. This review provides practical guidance on how to access genomic testing for endocrine disease, how to interpret and relay results, and details how genetic counselling can help integrate results into ongoing care of the individual and their family. This article discusses general principles as well as specifics related to the process of genomic testing in England. We illustrate mainstream genetic testing with a clinical scenario involving an individual with inherited endocrine neoplasia, followed by a generic description of the different steps involved, including informed consent to proceed to diagnostic testing. Most genetic tests analyse multiple genes simultaneously by next-generation sequencing, and variant interpretation may yield not only pathogenic explanatory results, but also ambiguous outcomes, with variants of unknown significance or incidental findings. Delivery of results and posttest genetic counselling are therefore key components of integrating genetic testing into routine endocrine care.
PubMed-ID: 34528717
http://dx.doi.org/10.1111/cen.14596

Update on the clinical management of multiple endocrine neoplasia type 1.
Clin Endocrinol (Oxf), 97(4):409-23.
C. R. C. Pieterman and G. D. Valk.
This review provides an overview of novel insights in the clinical management of patients with Multiple Endocrine Neoplasia Type 1, focusing on the last decade since the last update of the MEN1 guidelines. With regard to Diagnosis: Mutation-negative patients with 2/3 main manifestations have a different clinical course compared to mutation-positive patients. As for primary hyperparathyroidism: subtotal parathyroidectomy is the initial procedure of choice. Current debate centres around the timing of initial parathyroidectomy as well as the controversial topic of unilateral clearance in young patients. For duodenopancreatic neuroendocrine tumours (NETs), the main challenge is accurate and individualized risk stratification to enable personalized surveillance and treatment. Thymus NETs remain one of the most aggressive MEN1-related tumours. Lung NETs are more frequent than previously thought, generally indolent, but rare aggressive cases do occur. Pituitary adenomas are most often prolactinomas and nonfunctioning microadenomas with an excellent prognosis and good response to therapy. Breast cancer is recognized as part of the MEN1 syndrome in women and

periodical screening is advised. Clinically relevant manifestations are already seen at the paediatric age and initiating screening in the second decade is advisable. MEN1 has a significant impact on quality of life and US data show a significant financial burden. In conclusion, patient outcomes have improved, but much is still to be achieved. For care tailored to the needs of the individual patient and improving outcomes on an individual basis, studies are now needed to define predictors of tumour behaviour and effects of more individualized interventions.
PubMed-ID: 35319130
http://dx.doi.org/10.1111/cen.14727

Unexpected deaths after endocrine surgery: learning from rare events using a national audit of surgical mortality.
Br J Surg, 109(11):1164-71.
J. N. Chui, A. J. Papachristos, R. Mechera, S. B. Sidhu, M. S. Sywak, J. C. Lee, J. Gundara, C. Lai and A. R. Glover.
BACKGROUND: The mortality rate is low in endocrine surgery, making it a difficult outcome to use for quality improvement in individual units. Lessons from population data sets are of value in improving outcomes. Data from the Australian and New Zealand Audit of Surgical Mortality (ANZASM) were used here to understand and elucidate potential systems issues that may contribute to preventable deaths.
METHODS: ANZASM data relating to 30-day mortality after thyroidectomy, parathyroidectomy, and adrenalectomy from 2009 to 2020 were reviewed. Mortality rates were calculated using billing data. Thematic analysis of independent assessor reports was conducted to produce a coding framework.
RESULTS: A total of 67 deaths were reported, with an estimated mortality rate of 0.03-0.07 per cent (38 for thyroidectomy (0.03-0.06 per cent), 16 for parathyroidectomy (0.03-0.06 per cent), 13 for adrenalectomy (0.15-0.33 per cent)). Twenty-seven deaths (40 per cent) were precipitated by clinically significant adverse events, and 18 (27 per cent) were judged to be preventable by independent ANZASM assessors. Recurrent themes included inadequate preoperative assessment, lack of anticipation of intraoperative pitfalls, and failure to recognize and effectively address postoperative complications. Several novel themes were reiterated, such as occult ischaemic heart disease associated with death after parathyroid surgery, unexpected intraoperative difficulties from adrenal metastasis, and complications due to anticoagulation therapy after thyroid surgery.
CONCLUSION: This study represents a large-scale national report of deaths after endocrine surgery and provides insights into these rare events. Although the overall mortality rate is low, 27 per cent of deaths involved systems issues that were preventable following independent peer review.
PubMed-ID: 35927948
http://dx.doi.org/10.1093/bjs/znac276

Endocrine surgeons are performing more thyroid lobectomies for low-risk differentiated thyroid cancer since the 2015 ATA guidelines.
Surgery, 172(5):1392-400.
P. C. Conroy, A. Wilhelm, L. Calthorpe, T. M. Ullmann, S. Davis, C. Y. Huang, W. T. Shen, J. Gosnell, Q. Y. Duh, S. Roman and J. A. Sosa.
BACKGROUND: The 2015 American Thyroid Association guidelines recommended either total thyroidectomy or lobectomy for surgical treatment of low-risk differentiated thyroid cancer and de-escalated recommendations for central neck dissections. The study aim was to investigate how practice patterns among endocrine surgeons have changed over time.
METHODS: All adult patients with low-risk differentiated thyroid cancers (T1-T2, N0/Nx, M0/Mx) in the Collaborative Endocrine Surgery Quality Improvement Program (2014-2021) were identified. The outcomes between patients undergoing lobectomy versus total thyroidectomy were compared using multivariable logistic regression. The annual percent change in the proportion of lobectomies and central neck dissections performed was estimated using joinpoint regression.
RESULTS: In total, 5,567 patients with low-risk differentiated thyroid cancers were identified. Of these, 2,261 (40.6%) were very low-risk tumors ≤ 1 cm, and 2,983 (53.6%) were low-risk tumors >1 and <4 cm. Most patients (67.9%) underwent total thyroidectomy. Compared to total thyroidectomy, lobectomy was associated with outpatient surgery (adjusted odds ratio 5.19, P < .001), a decreased risk of postoperative emergency department visits (adjusted odds ratio 0.63, P = .03), and decreased risk of hypoparathyroidism events (adjusted odds ratio 0.03, P < .001). Compared to before (2014-2015), patients undergoing surgery after publication of the revised guidelines (2016-2021) had higher odds of lobectomy and lower odds of central neck dissection for tumors ≤ 1 cm (lobectomy adjusted odds ratio 2.70, P < .001; central neck dissections adjusted odds ratio 0.64, P = .03) and tumors between 1 and 4 cm (lobectomy adjusted odds ratio 2.27, P < .001; central neck dissection adjusted odds ratio 0.62, P < .001).

CONCLUSION: After publication of the 2015 American Thyroid Association guidelines, there has been an increase in thyroid lobectomies as a proportion of all thyroid operations performed by endocrine surgeons for low-risk differentiated thyroid cancer. This has implications for reduced health care use and costs, with potential population-level benefits.
PubMed-ID: 36002375
http://dx.doi.org/10.1016/j.surg.2022.06.031

Use of fluorescence imaging and indocyanine green during thyroid and parathyroid surgery: Results of an intercontinental, multidisciplinary Delphi survey.
Surgery, 172(6S):S6-S13.
F. Dip, P. F. Alesina, A. Anuwong, E. Arora, E. Berber, J. Bonnin-Pascual, N. D. Bouvy, M. S. Demarchi, J. Falco, K. Hallfeldt, K. D. Lee, M. L. Lyden, C. Maser, E. Moore, T. Papavramidis, J. Phay, J. M. Rodriguez, B. Seeliger, C. C. Solórzano, F. Triponez, A. Vahrmeijer, R. J. Rosenthal, K. P. White and M. Bouvet.
BACKGROUND: In recent years, fluorescence imaging-relying both on parathyroid gland autofluorescence under near-infrared light and angiography using the fluorescent dye indocyanine green-has been used to reduce risk of iatrogenic parathyroid injury during thyroid and parathyroid resections, but no published guidelines exist regarding its use. In this study, orchestrated by the International Society for Fluorescence Guided Surgery, areas of consensus and nonconsensus were examined among international experts to facilitate future drafting of such guidelines.
METHODS: A 2-round, online Delphi survey was conducted of 10 international experts in fluorescence imaging use during endocrine surgery, asking them to vote on 75 statements divided into 5 modules: 1 = patient preparation and contraindications to fluorescence imaging (n = 11 statements); 2 = technical logistics (n = 16); 3 = indications (n = 21); 4 = potential advantages and disadvantages of fluorescence imaging (n = 20); and 5 = training and research (n = 7). Several methodological steps were taken to minimize voter bias.
RESULTS: Overall, parathyroid autofluorescence was considered better than indocyanine green angiography for localizing parathyroid glands, whereas indocyanine green angiography was deemed superior assessing parathyroid perfusion. Additional surgical scenarios where indocyanine green angiography was thought to facilitate surgery are (1) when >1 parathyroid gland requires resection; (2) during redo surgeries, (3) facilitating parathyroid autoimplantation; and (4) for the predissection visualization of abnormal glands. Both parathyroid autofluorescence and indocyanine green angiography can be used during the same procedure and employing the same imaging equipment. However, further research is needed to optimize the dose and timing of indocyanine green administration.
CONCLUSION: Though further research remains necessary, using fluorescence imaging appears to have uses during thyroid and parathyroid surgery.
PubMed-ID: 36427932
http://dx.doi.org/10.1016/j.surg.2022.09.004