EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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Jan - Apr 2019

Data retrival from Pubmed: 8. August 2019

Contents

CTRL-click on category or count number jumps to the according page

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

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

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

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Preliminary

After a short break we are back on track with the ESES Reference List. Most things will be the same as before, for example the fact that we are pretty late again. Sorry for this, but I guess we will not improve by very much on this issue. Each collector - the collegues who select the articles for this Collection - have to go through between 1000 to 2000 articles per 4 month period and pick less than 200 articles in total, thus only about 2% of all published articles in the journals covered will end up in this list. So we should be patient and give our collectors some time to accomplish this great task. In this context it might be interesting to know, that the number of articles to be screened increased by about 25% since we start to make the Collection in 2011. Therefore, a big applause from here for the superb service the collectors provide for the community.

There are also a few changes. The collector Samira Sadowski from Geneva left for the NIH and will no longer act as collector. She will be followed by Marco Demarchi, also from Geneva. Many thanks to Samira for your great efforts, and a warm welcome to Marco in the Collector „familiy“.

In the journal list on the next page, the impact factors were updated to the current version from 2018.

I hope you enjoy the new collection,

yours

Ulrich Beutner

Journals covered

Journal	IF2018	Journal	IF2018
Acta Cytol	1.562†	J Bone Miner Res	5.711
Am J Kidney Dis	6.653	J Clin Endocrinol Metab	5.605
Am J Nephrol	2.961	J Clin Oncol	28.245
Am J Surg	2.201	J Endocrinol	4.381
Am Surgeon	0.610	J Endocrinol Invest	3.439
Ann Surg	9.476	J Nephrol	3.698
Ann Surg Oncol	3.681	J Nucl Med	7.354
ANZ J Surg	1.605	J Surg Oncol	3.114
Br J Surg	5.586	Lancet	59.102
Cancer	6.102	Langenbecks Arch Surg	2.093
Chirurg	0.669	Laryngoscope	2.343
Clin Endocrinol Oxf	2.897	N Engl J Med	70.670
Clin Nucl Med	6.498	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	24.646
Curr Opin Oncol	3.261	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	34.106
Endocr Relat Cancer	4.774	Nephrol Dial Transplant	4.198
Endocr Rev	15.167	Nephron Clin Pract	2.138‡
Eur Arch Otorhinolaryngol	1.750	Neuroendocrinology	6.804
Eur J Endocrinol	5.107	Oncologist	5.252
Eur J Surg Oncol	3.379	Otolaryngol Head Neck Surg	2.310
Gland Surg	1.922	Surg Clin North Am	1.959
Head Neck	2.442	Surg Endosc	3.209
Horm Metab Res	2.423	Surg Laparosc Endosc Percutan Tech	1.345
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	3.502	Surg Oncol	3.000
JAMA Surg (*prev:* Arch Surg)	10.668	Surg Oncol Clin N Am	2.340
Int J Cancer	4.982	Surgery	3.476
J Am Coll Surg	4.450	Thyroid	7.786
J Am Soc Nephrol	8.547	Updates In Surgery	---
J Bone Miner Metab	2.310	World J Surg	2.768

Journal names are links to the journal's homepage!, IF2018: Impact factor 2018, †IF 2013, ‡IF 2016

Thyroid

Meta-Analyses

Cytological Diagnoses Associated with Noninvasive Follicular Thyroid Neoplasms with Papillary-Like Nuclear Features According to the Bethesda System for Reporting Thyroid Cytopathology: A Systematic Review and Meta-Analysis.
Thyroid, 29(2):222-8.
M. Bongiovanni, L. Giovanella, F. Romanelli and P. Trimboli. 2019.
BACKGROUND: The recent introduction of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) in the World Health Organization classification of thyroid tumors has significantly modified the risk of malignancy of cytological diagnoses. In fact, while this tumor was previously classified as a carcinoma (the encapsulated, noninvasive form follicular variant of papillary thyroid carcinoma), it is now considered a neoplasm with low malignant potential. Given that the cytological features of NIFTP are not specific and overlap with other pathologic entities, there is no specific cytological diagnostic category for NIFTP. To obtain more robust information about the cytological findings associated with NIFTP, published articles were systematically reviewed, and a meta-analysis of the data was conducted. METHODS: The review was conducted according to PRISMA guidelines. A comprehensive literature search of the PubMed/MEDLINE and Scopus databases was conducted using a combination of terms "noninvasive," "encapsulated," "follicular variant," "NIFTP," and "thyroid cancer." The search was updated to June 2018, and references of the retrieved articles were also screened. Only original articles reporting the classification of histologically proven NIFTPs with cytological findings according to The Bethesda System for Reporting Thyroid Cytopathology were eligible for inclusion. RESULTS: The literature search revealed 117 articles, of which 15 were included in the study. All studies were retrospective. A total of 915 NIFTP cases were retrieved. The incidence of cases cytologically classified according to the Bethesda system was as follows: non-diagnostic 3%, benign 10%, atypia of undetermined significance or follicular lesion of undetermined significance 30%, follicular neoplasm or suspicious for a follicular neoplasm 21%, suspicious for malignancy 24%, and malignant 8%. Mild heterogeneity between the studies was found. Publication bias was absent. CONCLUSIONS: This meta-analysis shows that the cytological diagnoses associated with NIFTP by fine-needle aspiration cytology includes a wide spectrum of findings. The majority of cases are cytologically indeterminate, and the remainder may be read as non-diagnostic, benign, or malignant. In order to develop an accurate presurgical diagnosis of these cases, further cytological and/or molecular characteristics need to be identified.
PubMed-ID: 30426887
http://dx.doi.org/10.1089/thy.2018.0394

Use of Delphian lymph node metastasis to predict central and lateral involvement in papillary thyroid carcinoma: A systematic review and meta-analysis.
Clin Endocrinol (Oxf), 91(1):170-8.
J. Huang, W. Sun, H. Zhang, P. Zhang, Z. Wang, W. Dong, L. He and T. Zhang. 2019.
OBJECTIVE: Whether Delphian lymph node (DLN) metastasis is a reliable predictor of widespread lymph node metastasis in papillary thyroid carcinoma (PTC) remains controversial. This meta-analysis investigated the value of DLN metastasis for predicting central and lateral involvement in PTC. DESIGN AND METHODS: A literature search using the PubMed, SCIE and the Chinese National Knowledge Infrastructure (CNKI) databases was conducted. Two reviewers independently extracted data and evaluated the studies for inclusion. Fixed-effects and random-effects models were used to analyse the data based on their heterogeneity. A sensitivity analysis was performed, and publication bias was assessed using Begg's funnel plot and Egger's linear regression test. RESULTS: Data from 10 studies were analysed. The risk of central lymph node (CLN) metastasis was significantly higher in the DLN-positive group than in the DLN-negative group (OR = 9.05, 95% CI: 5.13-15.99) with moderate heterogeneity (P = 0.022, I(2) = 53.5%). The risk of lateral lymph node (LLN) metastasis was significantly higher in the DLN-positive group than in the negative group (OR = 10.88, 95% CI: 7.60-15.58), with low heterogeneity (P = 0.603, I(2) = 0.0%). Sensitivity analysis indicated that the results were stable and credible, and no publication bias was found. CONCLUSIONS: Delphian lymph node metastasis is valuable for predicting central and lateral compartment involvement in patients with PTC. The DLN of PTC patients should be dissected intraoperatively and sent for frozen section consultation. If the result is positive, the CLNs should be thoroughly dissected and the LLNs should be further evaluated.
PubMed-ID: 30851206
http://dx.doi.org/10.1111/cen.13965

Thyroidectomy for thyroid cancer in the elderly: A meta-analysis.
Eur J Surg Oncol, 45(3):310-7.
K. R. Joseph, S. Edirimanne and G. D. Eslick. 2019.
Thyroid cancer, the most common endocrine malignancy, has patients who generally have excellent prognosis. It has been shown that elderly patients are more likely to undergo sub-therapeutic management, despite having more aggressive disease, resulting in increased mortality and morbidity. The present study aimed to quantitatively investigate the risks of elderly patients who underwent thyroidectomy for thyroid cancer regarding mortality/survival, recurrence of disease, and complications arising from thyroidectomy. A systematic search and meta-analysis was carried out using the electronic databases PubMed and Medline. We searched for articles containing epidemiological evidence of mortality and recurrence of disease in patients above the age of 60, who are treated for operatively thyroid cancer and data involving complications following total thyroidectomy. The meta-analysis consisted of a total of 16 studies meeting the inclusion and exclusion criteria. The current study confirmed that patients have increased risk of recurrence (HR 4.84; 95% CI=22.2-10.52; I(2)=0.00; P=0.98) including increased risk of lymph node recurrence and distant metastases. Additionally these patients had an increased risk of complications (OR 1.82; 95% CI=0.88-3.77; I(2)=77.01; P=0.005) following thyroidectomy compared to patients in the younger cohort. The current study also qualitatively compared survival data between the different age cohorts, and identified a reduced overall survival and disease free survival for elderly patients. The current study suggests that elderly patients should be classified as higher risk following total thyroidectomy for thyroid cancer and puts an emphasis is early detection and intervention.
PubMed-ID: 30642604
http://dx.doi.org/10.1016/j.ejso.2018.07.055

Transoral Vestibular Thyroidectomy: Current State of Affairs and Considerations for the Future.
J Clin Endocrinol Metab,
J. O. Russell, C. R. Razavi, M. Shaear, L. W. Chen, A. H. Lee, R. Ranganath and R. P. Tufano. 2019.
CONTEXT: The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a recently described procedure for surgical management of select thyroid pathology without the need for a cutaneous scar. TOETVA is far from the first described remote-access approach to the thyroid. In fact, numerous such techniques have been described over the past 20 years, although none have gained wide-spread implementation in North America or Europe. TOETVA, with its rapid growth worldwide and excellent outcomes to date, however, may succeed where these prior described techniques have failed. EVIDENCE ACQUISITION: The English literature was reviewed using the following keywords: transoral thyroidectomy, remote-access thyroidectomy, minimally-invasive thyroidectomy, and TOETVA. As three recent systematic reviews have been performed in regards to the technique, this manuscript does not seek to provide a fourth such text. Rather, here we summarize salient findings from these reviews and focus on candidates for the procedure, technique-specific characteristics which have led to TOETVA's early success, and prospects for the future. EVIDENCE SYNTHESIS: TOETVA is the only thyroidectomy approach obviating the need for a cutaneous incision, and offers several advantages over prior described remote-access thyroidectomy techniques. These include a favorable anatomic surgical perspective, a comparatively short learning curve, no requirement for expensive instrumentation, and a broad inclusion criterion. These characteristics have facilitated the excellent surgical outcomes to date. CONCLUSIONS: TOETVA is a suitable surgical option for a carefully selected patient population with proven safety and feasibility. The potential value of the procedure outside enhanced cosmesis continues to be defined.
PubMed-ID: 30860578
http://dx.doi.org/10.1210/jc.2019-00116

Microscopically positive surgical margins and local recurrence in thyroid cancer. A meta-analysis.
Eur J Surg Oncol, 45(8):1310-6.
A. Sanabria, A. Rojas, J. Arevalo, L. P. Kowalski and I. Nixon. 2019.
BACKGROUND: Microscopically positive surgical margins are a prognostic factor of recurrence in advanced thyroid carcinoma. However, information on early and completely resected thyroid tumors is scarce. Some studies do not identify any association between positive margin and local recurrence. The objective of this study was to perform a meta-analysis to measure the association of microscopically positive surgical margins and local recurrence in patients who underwent total thyroidectomy. METHODS: Clinical trials assessing the association between microscopically positive surgical margin and local recurrence in patients with early-stage, well-differentiated thyroid carcinoma who underwent total thyroidectomy were evaluated. The outcome measured was local recurrence in the thyroid bed. A systematic review and meta-analysis was done using a random-effects model. RESULTS: Six studies with 7696 patients were identified. Methodological quality was good, and we did not identify statistical heterogeneity or publication bias. The risk difference for microscopically positive

surgical margin and local recurrence was 0% (95% CI 0 to 1). CONCLUSION: Meta-analysis did not find a statistically significant association between microscopically positive surgical margin and local recurrence in this population. A finding of microscopically positive surgical margin in the absence of other adverse factors is not an indication for adjuvant treatment.
PubMed-ID: 30795955
http://dx.doi.org/10.1016/j.ejso.2019.02.007

Effects of Preoperative Iodine Administration on Thyroidectomy for Hyperthyroidism: A Systematic Review and Meta-analysis.
Otolaryngol Head Neck Surg, 160(6):993-1002.
C. H. Tsai, P. S. Yang, J. J. Lee, T. P. Liu, C. Y. Kuo and S. P. Cheng. 2019.
OBJECTIVE: The current guidelines recommend that potassium iodide be given in the immediate preoperative period for patients with Graves' disease who are undergoing thyroidectomy. Nonetheless, the evidence behind this recommendation is tenuous. The purpose of this study is to clarify the benefits of preoperative iodine administration from published comparative studies. DATA SOURCES: We searched PubMed, Embase, Cochrane, and CINAHL from 1980 to June 2018. REVIEW METHODS: Studies were included that compared preoperative iodine administration and no premedication before thyroidectomy. For the meta-analysis, studies were pooled with the random-effects model. RESULTS: A total of 510 patients were divided into the iodine (n = 223) and control (n = 287) groups from 9 selected studies. Preoperative iodine administration was significantly associated with decreased thyroid vascularity and intraoperative blood loss. Significant heterogeneity was present among studies. We found no significant difference in thyroid volume or operative time. Furthermore, the meta-analysis showed no difference in the risk of postoperative complications, including vocal cord palsy, hypoparathyroidism/hypocalcemia, and hemorrhage or hematoma after thyroidectomy. CONCLUSION: Preoperative iodine administration decreases thyroid vascularity and intraoperative blood loss. Nonetheless, it does not translate to more clinically meaningful differences in terms of operative time and postoperative complications.
PubMed-ID: 30721111
http://dx.doi.org/10.1177/0194599819829052

Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-up.
J Clin Endocrinol Metab,
R. M. Tuttle and A. S. Alzahrani. 2019.
CONTEXT: Modern management of differentiated thyroid cancer requires individualized care plans which tailor the intensity of therapy and follow-up to the estimated risks of recurrence and disease-specific mortality. EVIDENCE ACQUISITION: This summary is based on the authors' knowledge and extensive clinical experience supplemented by review of published review articles, thyroid cancer management guidelines, published staging systems, and original articles identified through a PubMed search which included terms such as risk stratification, staging, clinical outcomes, and differentiated thyroid cancer. EVIDENCE SYNTHESIS: In the past, risk stratification in differentiated thyroid cancer usually referred to a static estimate of disease-specific mortality that was based on a small set of clinicopathological features available within a few weeks of completing initial therapy (thyroidectomy with or without radioactive iodine). Today, risk stratification is a dynamic, active process used to predict the appropriateness for minimalistic initial therapy, disease-specific mortality, risk of recurrence, and the most likely response to initial therapy. Rather than being a static prediction available only after initial therapy, modern risk stratification is a dynamic, iterative process that begins as soon as a suspicious nodule is detected and continues through final follow-up. CONCLUSIONS: Dynamic risk assessment should be used to guide all aspects of thyroid cancer management, beginning before a definitive diagnosis is made and continuing through the final follow-up visit.
PubMed-ID: 30874735
http://dx.doi.org/10.1210/jc.2019-00177

Randomized controlled trials

Randomized Controlled Trial Comparing White Light with Near-Infrared Autofluorescence for Parathyroid Gland Identification During Total Thyroidectomy.
J Am Coll Surg, 228(5):744-51.
F. Dip, J. Falco, S. Verna, M. Prunello, M. Loccisano, P. Quadri, K. White and R. Rosenthal. 2019.
BACKGROUND: Parathyroid glands are difficult to identify during total thyroidectomies, and accidental resection

can lead to problematic postoperative hypocalcemia. Our main goals were to evaluate the effectiveness of using near-infrared light (NIRL) autofluorescence intraoperatively for parathyroid gland identification and to measure its impact on postoperative hypocalcemia incidence. STUDY DESIGN: Total thyroidectomies were performed on 170 patients with different thyroid pathologies, block-randomized (1:1) into 2 equal groups. Among controls, traditional overhead white light (WL) was used throughout. In the experimental group, NIRL was used to enhance parathyroid gland recognition before thyroid dissection. The number of parathyroid glands identified was compared after thyroid dissection in controls using WL vs pre-dissection in the experimental using NIRL and with WL vs NIRL before thyroid dissection in the experimental group. Postoperative serum calcium levels and hypocalcemia rates were compared. RESULTS: The mean number of parathyroid glands identified pre-dissection with NIRL was the same identified post-dissection with WL (3.5 vs 3.6). In the experimental group, converting from WL to NIRL increased the number of glands detected from 2.6 to 3.5 ($p < 0.001$), and revealed at least 1 previously missed gland in 67.1% of patients. Calcium levels </=7.5 mg/dL were one-tenth as common in the NIRL group ($p = 0.005$). The adjusted odds of hypocalcemia developing increased by 15% for every 5-g increase in thyroid gland weight (odds ratio 1.15; 95% CI 1.06 to 1.25). All hypocalcemia resolved within 6 months. CONCLUSIONS: Using NIRL during thyroidectomy increases intraoperative identification of parathyroid glands, enhances their detection before thyroid dissection, and decreases the incidence of postoperative hypocalcemia.
PubMed-ID: 30710614
http://dx.doi.org/10.1016/j.jamcollsurg.2018.12.044

High-dose preoperative cholecalciferol to prevent post-thyroidectomy hypocalcaemia: A randomized, double-blinded placebo-controlled trial.
Clin Endocrinol (Oxf), 90(2):343-50.
C. W. Rowe, S. Arthurs, C. J. O'Neill, J. Hawthorne, R. Carroll, K. Wynne and C. Bendinelli. 2019.
OBJECTIVE: Post-thyroidectomy hypocalcaemia is a significant cause of morbidity and prolonged hospitalization, usually due to transient parathyroid gland damage, treated with calcium and vitamin D supplementation. We present a randomized, double-blinded placebo-controlled trial of preoperative loading with high-dose cholecalciferol (300 000 IU) to reduce post-thyroidectomy hypocalcaemia. PATIENTS AND MEASUREMENTS: Patients (n = 160) presenting for thyroidectomy at tertiary hospitals were randomized 1:1 to cholecalciferol (300 000 IU) or placebo 7 days prior to thyroidectomy. Ten patients withdrew prior to surgery. The primary outcome was post-operative hypocalcaemia (corrected calcium <2.1 mmol/L in first 180 days). RESULTS: The study included 150 patients undergoing thyroidectomy for Graves' disease (31%), malignancy (20%) and goitre (49%). Mean pre-enrolment vitamin D was 72 +/- 26 nmol/L. Postoperative hypocalcaemia occurred in 21/72 (29%) assigned to cholecalciferol and 30/78 (38%) participants assigned to placebo ($P = 0.23$). There were no differences in secondary end-points between groups. In pre-specified stratification, baseline vitamin D status did not predict hypocalcaemia, although most individuals were vitamin D replete at baseline. Post-hoc stratification by day 1 parathyroid hormone (PTH) (<10 pg/mL, low vs >/=10 pg/mL, normal) was explored due to highly divergent rates of hypocalcaemia in these groups. Using a Cox regression model, the hazard ratio for hypocalcaemia in the cholecalciferol group was 0.56 (95%CI 0.32-0.98, $P = 0.04$) after stratification for Day 1 PTH. Further clinical benefits were observed in these subgroups. CONCLUSIONS: Pre-thyroidectomy treatment with high-dose cholecalciferol did not reduce the overall rate of hypocalcaemia following thyroidectomy. In subgroups stratified by day 1 PTH status, improved clinical outcomes were noted.
PubMed-ID: 30387163
http://dx.doi.org/10.1111/cen.13897

Consensus Statements/Guidelines

American Head and Neck Society Endocrine Section clinical consensus statement: North American quality statements and evidence-based multidisciplinary workflow algorithms for the evaluation and management of thyroid nodules.
Head Neck, 41(4):843-56.
C. J. Meltzer, J. Irish, P. Angelos, N. L. Busaidy, L. Davies, S. Dwojak, R. L. Ferris, B. R. Haugen, R. M. Harrell, M. R. Haymart, B. McIver, J. I. Mechanick, E. Monteiro, J. C. Morris, 3rd, L. G. T. Morris, M. Odell, J. Scharpf, A. Shaha, J. J. Shin, D. C. Shonka, Jr., G. B. Thompson, R. M. Tuttle, M. L. Urken, S. M. Wiseman, R. J. Wong and G. Randolph. 2019.
BACKGROUND: Care for patients with thyroid nodules is complex and multidisciplinary, and research demonstrates variation in care. The objective was to develop clinical guidelines and quality metrics to reduce

unwarranted variation and improve quality. METHODS: Multidisciplinary expert consensus and modified Delphi approach. Source documents were workflow algorithms from Kaiser Permanente Northern California and Cancer Care of Ontario based on the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. RESULTS: A consensus-based, unified preoperative, perioperative, and postoperative workflow was developed for North American use. Twenty-one panelists achieved consensus on 16 statements about workflow-embedded process and outcomes metrics addressing safety, access, appropriateness, efficiency, effectiveness, and patient centeredness of care. CONCLUSION: A panel of Canadian and United States experts achieved consensus on workflows and quality metric statements to help reduce unwarranted variation in care, improving overall quality of care for patients diagnosed with thyroid nodules.
PubMed-ID: 30561068
http://dx.doi.org/10.1002/hed.25526

Controversies, Consensus, and Collaboration in the Use of (131)I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association.
Thyroid, 29(4):461-70.
R. M. Tuttle, S. Ahuja, A. M. Avram, V. J. Bernet, P. Bourguet, G. H. Daniels, G. Dillehay, C. Draganescu, G. Flux, D. Fuhrer, L. Giovanella, B. Greenspan, M. Luster, K. Muylle, J. W. A. Smit, D. Van Nostrand, F. A. Verburg and L. Hegedus. 2019.
BACKGROUND: Publication of the 2015 American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer was met with disagreement by the extended nuclear medicine community with regard to some of the recommendations related to the diagnostic and therapeutic use of radioiodine ((131)I). Because of these concerns, the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging declined to endorse the ATA guidelines. As a result of these differences in opinion, patients and clinicians risk receiving conflicting advice with regard to several key thyroid cancer management issues. SUMMARY: To address some of the differences in opinion and controversies associated with the therapeutic uses of (131)I in differentiated thyroid cancer constructively, the ATA, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association each sent senior leadership and subject-matter experts to a two-day interactive meeting. The goals of this first meeting were to (i) formalize the dialogue and activities between the four societies; (ii) discuss indications for (131)I adjuvant treatment; (iii) define the optimal prescribed activity of (131)I for adjuvant treatment; and (iv) clarify the definition and classification of (131)I-refractory thyroid cancer. CONCLUSION: By fostering an open, productive, and evidence-based discussion, the Martinique meeting restored trust, confidence, and a sense of collegiality between individuals and organizations that are committed to optimal thyroid disease management. The result of this first meeting is a set of nine principles (The Martinique Principles) that (i) describe a commitment to proactive, purposeful, and inclusive interdisciplinary cooperation; (ii) define the goals of (131)I therapy as remnant ablation, adjuvant treatment, or treatment of known disease; (iii) describe the importance of evaluating postoperative disease status and multiple other factors beyond clinicopathologic staging in (131)I therapy decision making; (iv) recognize that the optimal administered activity of (131)I adjuvant treatment cannot be definitely determined from the published literature; and (v) acknowledge that current definitions of (131)I-refractory disease are suboptimal and do not represent definitive criteria to mandate whether (131)I therapy should be recommended.
PubMed-ID: 30900516
http://dx.doi.org/10.1089/thy.2018.0597

Other Articles

Advanced age does not increase morbidity after total thyroidectomy. Result of a prospective study.
Am J Surg, 217(4):767-71.
N. Christou, C. Blanchard, F. Pattou, C. Volteau, L. Brunaud, A. Hamy, M. Dahan, J. M. Prades, G. Landecy, H. P. Dernis, J. C. Lifante, F. Sebag, F. Jegoux, E. Babin, A. Bizon, C. Caillard, M. Mathonnet and E. Mirallie. 2019.
BACKGROUND: It is well known that total thyroidectomy is feasible on elderly patients but is linked to complications because of their underlying comorbidities. In this study we analyzed the specific risks linked to surgery, hypoparathyroidism and recurrent nerve palsy. METHODS: materials-methods:Prospective, multicentre

trial conducted at 13 hospital sites. The primary endpoint was the percentage of patients with postoperative hypocalcaemia (albumin-corrected serum calcium level <2mmol/L at day 2). Secondary endpoints included recurrent nerve palsy rate at day 2, the percentage of patients with hypocalcaemia (serum calcium level <2mmol/L) and recurrent nerve palsy at month 6, operating durations and postoperative pain. Patients were separated in two groups: <70 years and >/=70 years old. RESULTS: In total, 1329 patients who underwent total thyroidectomy were included (median age 51.17 years [18.10; 80.90], 80% women, and hyperthyroidism in 20%, 101>/=70 years old). Rates of hypocalcaemia at day 2 and month 6 were 20.02% and 1.98% respectively. Nasofibroscopy showed postoperative abnormal vocal cord motility in 9.92% cases (hypo-motility 5.76% - immobility 4.16%) and 0.95% at month 6 (hypo-motility 0.48%, immobility 0.48%). Patients >/=70 years had a lower (but non-significant) postoperative and definitive hypocalcaemia rate than patients<70 years: 14.85% vs 20.44% at day 2 (p=0.1773) and 0% vs 2.15% at month 6 respectively (p=0.2557). Abnormal vocal cord motility rate was 12.00% in patients >/=70 years vs 9.75% in patients <70yearsat day 2 (p=0.4702), and 2.06% in patients >/=70 years vs 0.86% at month 6 (p=0.2340). CONCLUSIONS: Total thyroidectomy in patients >/=70 years is feasible and safe. Age does not increase the morbidity. The study is registered with ClinicalTrials.gov number NCT01551914.
PubMed-ID: 30055804
http://dx.doi.org/10.1016/j.amjsurg.2018.07.029

Risk Stratification of Thyroid Nodules Using the Thyroid Imaging Reporting and Data System (TIRADS): The Omission of Thyroid Scintigraphy Increases the Rate of Falsely Suspected Lesions.
J Nucl Med, 60(3):342-7.
S. Schenke, P. Seifert, M. Zimny, T. Winkens, I. Binse and R. Gorges. 2019.
Thyroid nodules are a common finding, especially in iodine-deficient regions. Ultrasonographic scoring systems such as the Thyroid Imaging Reporting and Data System (TIRADS) are helpful in differentiating between benign and malignant thyroid nodules by offering a risk stratification model. Depending on the constellation or number of suspicious ultrasound features, a fine-needle biopsy is recommended. However, none of the previous TIRADS publications considered the functional status of the nodules. Hyperfunctioning thyroid nodules (HTNs) were presumed to exclude malignancy with a very high negative predictive value. Particularly in regions where the iodine supply is low, most HTNs are seen in patients with normal thyroid-stimulating hormone levels. Therefore, thyroid scintigraphy is essential for the detection of HTNs. We investigated whether TIRADS identifies HTNs as nonsuspicious. Methods: We evaluated 615 HTNs (23.2 +/- 10.0 mm in maximum diameter in 582 patients ([442 women, 57.7 +/- 13.2 y old, and 140 men, 60.1 +/- 12.7 y old) detected by (99m)Tc-pertechnetate or (123)I scintigraphy. Before evaluating the scintigraphic appearance, all nodules were analyzed prospectively with sonography, using the TIRADS model referenced in Kwak et al., wherein fine-needle biopsy is recommended for TIRADS 4A or higher. We also investigated 2 subgroups, 42 nodules with available histology and 117 patients with subclinical or overt hyperthyroidism. Results: Whereas 15.9% of the nodules were classified as TIRADS 3 or lower and less than 0.1% as TIRADS 5, most of the nodules were classified as TIRADS 4A (29.3%), 4B (29.3%), or 4C (24.9%). Altogether, more than 80% of the autonomous thyroid nodules were classified as TIRADS 4A or higher, a grade that would result in a recommendation of fine-needle biopsy. Focusing on those 117 HTNs that were already associated with hyperthyroid laboratory values, the rates were similar: 81.2% were categorized as TIRADS 4A or higher (4A, 33.3%; 4B, 29.9%; 4C,17.1%; 5, 0.9%). In the subgroup of patients who underwent thyroid surgery, all nodules were benign, confirming the known negative predictive value of HTNs with regard to malignancy exclusion. Conclusion: Integration of thyroid scintigraphy into the TIRADS model is essential to prevent unnecessary fine-needle biopsy and thyroid surgery.
PubMed-ID: 30097501
http://dx.doi.org/10.2967/jnumed.118.211912

Time to Separate Persistent From Recurrent Differentiated Thyroid Cancer: Different Conditions With Different Outcomes.
J Clin Endocrinol Metab, 104(2):258-65.
G. Sapuppo, M. Tavarelli, A. Belfiore, R. Vigneri and G. Pellegriti. 2019.
Context: Differentiated thyroid cancer (DTC) has an excellent prognosis, but up to 20% of patients with DTC have disease events after initial treatment, indistinctly defined as persistent/recurrent disease. Objective: To evaluate the prevalence and outcome of "recurrent" disease (relapse after being 12 months disease-free) compared with "persistent" disease (present ab initio since diagnosis). Design: Retrospective analysis of persistent/recurrent disease in patients with DTC (1990 to 2016) with 6.5 years of mean follow-up. Setting: Tertiary referral center for thyroid cancer. Patients: In total, 4292 patients all underwent surgery +/- 131I treatment of DTC. Main Outcome Measures: DTC cure of disease persistence or recurrence. Results: A total of 639 of 4292 (14.9%) patients had disease events after initial treatment, most (498/639, 78%) with persistent

disease and 141 (22%) with recurrent disease. Relative to patients with recurrent disease, patients with persistent disease were significantly older (mean age 46.9 vs 45.7 years) and with a lower female to male ratio (1.9/1 vs 4.8/1). Moreover, in this group, structured disease was more frequent (65.7% vs 41.1%), and more important, distant metastases were significantly more frequent (38.4% vs 17.0%). At multivariate analysis, male sex (OR = 1.7), age (OR = 1.02), follicular histotype (OR = 1.5), T status (T3; OR = 3), and N status (N1b; OR = 7.7) were independently associated with persistent disease. Only the N status was associated with recurrent disease (N1b; OR = 2.5). Conclusions: In patients with DTC not cured after initial treatment, persistent disease is more common and has a worse outcome than recurrent disease. Postoperative status evaluated during first-year follow-up may have important clinical implications for planning tailored treatment strategies and long-term follow-up procedures.
PubMed-ID: 30165559
http://dx.doi.org/10.1210/jc.2018-01383

Current Treatment Strategies in Metastasized Differentiated Thyroid Cancer.
J Nucl Med, 60(1):9-15.
M. C. Kreissl, M. J. R. Janssen and J. Nagarajah. 2019.
On successful completion of this activity one should be able to judge the prognosis of patients harboring metastasized differentiated thyroid cancer (DTC); identify suitable treatment regimens, taking into account the characteristics of the tumor and the patient's general condition; and know the basics of radioiodine treatment, tyrosine kinase treatment, and redifferentiation treatment for metastasized DTC.
PubMed-ID: 30190306
http://dx.doi.org/10.2967/jnumed.117.190819

Association Between Age and Patient-Reported Changes in Voice and Swallowing After Thyroidectomy.
Laryngoscope, 129(2):519-24.
Z. Sahli, J. K. Canner, O. Najjar, E. B. Schneider, J. D. Prescott, J. O. Russell, R. P. Tufano, M. A. Zeiger and A. Mathur. 2019.
OBJECTIVES: Despite intact recurrent laryngeal nerves, patient-reported voice and swallowing changes are common after thyroidectomy. The association between patient age or frailty status and these changes is unknown. The aim of this study was to evaluate the impact of age and frailty on the incidence of voice and swallowing alterations after thyroidectomy. METHODS: We performed an institutional review board (IRB)-approved retrospective review of consecutive patients who underwent total thyroidectomy with intraoperative recurrent laryngeal nerve (RLN) monitoring at a single institution between January 2014 and September 2016. Patients with RLN injury were excluded. After data extraction, a modified frailty index (mFI) was calculated for each patient. The association among risk factors, including age, mFI, prior history of neck surgery, frequent voice use, presence of malignancy or gastroesophageal reflux disease, and smoking status and reported voice and/or swallowing changes was examined. RESULTS: Of 924 patients undergoing thyroidectomy, 148 (16.0%) reported only changes in voice; 52 (5.6%) reported only difficulty in swallowing; and 26 (2.8%) reported changes with both voice and swallowing. On multivariate analysis, we found a significant increase in voice or swallowing alterations up to the age of 50 years (5% increased odds per year), after which these changes plateaued. We found that mFI was not associated with voice or swallowing changes. CONCLUSION: Age >/= 50 years is independently associated with the development of voice or swallowing changes after thyroidectomy, despite intact RLN. Additional prospective studies are needed to validate these findings, further define this association, and identify risk factors for developing these changes. LEVEL OF EVIDENCE: 2b Laryngoscope, 129:519-524, 2019.
PubMed-ID: 30194684
http://dx.doi.org/10.1002/lary.27297

Enhanced interdisciplinary communication: development of an interactive thyroid nodule/cancer disease map.
Laryngoscope, 129(1):269-74.
S. P. Moubayed, R. Machado, R. M. Tuttle, L. A. Orloff, G. Randolph, J. C. Hernandez-Prera, M. J. Griffin and M. L. Urken. 2019.
OBJECTIVES: Deficits related to inadequate clinical communication can result in incorrect diagnoses, inappropriate surgery, incorrect disease stratification, pathologic reporting, and/or interpretation. There are currently no validated or defined solutions to disease-specific communication with regard to thyroid care. METHODS: We propose a solution that could ameliorate problems arising from inadequate disease-specific communications between physicians through the development of a thyroid disease-specific database, the Thyroid Care Collaborative. RESULTS: To improve the quality of thyroid nodule and cancer care, we have

developed an imaging module for enhanced reporting of ultrasound, cytologic, surgical, and pathologic details that are obtained during the workup and treatment of a patient. CONCLUSION: The main advantages of this disease-specific, dynamic, three-dimensional, anatomic disease map are: 1) portability across institutions and disciplines, 2) disease specificity to thyroid nodule and cancer care, and 3) ability to trigger more detailed evaluation or reconciliation of any change in a patient's status regarding the nature or the extent of a patient's disease. The first and second advantages above have been identified as areas representing opportunities for quality improvement in health informatics research. Laryngoscope, 129:269-274, 2019.
PubMed-ID: 30194697
http://dx.doi.org/10.1002/lary.27244

Prediction of Postoperative Vocal Fold Function After Intraoperative Recovery of Loss of Signal.
Laryngoscope, 129(2):525-31.
R. Schneider, G. Randolph, G. Dionigi, M. Barczynski, F. Y. Chiang, C. W. Wu, T. Musholt, M. Uludag, O. Makay, A. Sezer, S. Teksoz, T. Weber, C. Sekulla, K. Lorenz, M. Ozdemir, A. Machens and H. Dralle. 2019.
OBJECTIVES/HYPOTHESIS: This multicenter study aimed to 1) evaluate early postoperative vocal fold function in relation to intraoperative amplitude recovery, and 2) determine optimal absolute and relative thresholds of intraoperative amplitude recovery heralding normal early postoperative vocal fold function, both after segmental type 1 and after global type 2 loss of signal (LOS). STUDY DESIGN: Prospective outcome study. METHODS: This study, encompassing nine surgical centers from four countries, correlated intraoperative amplitude recovery with early postoperative vocal fold function using receiver operating characteristic analysis. RESULTS: Included in this study were 68 patients, 48 women and 20 men, who sustained transient recurrent laryngeal nerve injury during thyroid surgery under continuous intraoperative nerve monitoring. Early transient vocal fold palsy was seen in 18 (64%) of 28 patients with ipsilateral segmental LOS type 1, and in 10 (25%) of 40 patients with ipsilateral global LOS type 2. On receiver operating characteristic analysis, relative amplitude thresholds were superior to absolute amplitude thresholds in predicting vocal fold function after LOS type 2 (area under the curve [AUC]: 0.83 vs. 0.65; P = .01 vs. P = .15; Youden index 44% and 253 microV) and LOS type 1 (AUC: 0.96 vs. 0.97; P < .001 each; Youden index 49% and 455 microV). Amplitude recovery >/=50% of baseline after LOS always indicated intact vocal fold function. CONCLUSIONS: When the nerve amplitude recovers >/=50% of baseline after segmental LOS type 1 or global LOS type 2, it is appropriate to extend completion thyroidectomy to the other side during the same session. LEVEL OF EVIDENCE: 2b Laryngoscope, 129:525-531, 2019.
PubMed-ID: 30247760
http://dx.doi.org/10.1002/lary.27327

Clinical and Molecular Characteristics May Alter Treatment Strategies of Thyroid Malignancies in DICER1 Syndrome.
J Clin Endocrinol Metab, 104(2):277-84.
K. van der Tuin, L. de Kock, E. J. Kamping, S. E. Hannema, M. M. Pouwels, M. Niedziela, T. van Wezel, F. J. Hes, M. C. Jongmans, W. D. Foulkes and H. Morreau. 2019.
Context: DICER1 syndrome is a rare autosomal-dominantly inherited disorder that predisposes to a variety of cancerous and noncancerous tumors of mostly pediatric and adolescent onset, including differentiated thyroid carcinoma (DTC). DTC has been hypothesized to arise secondarily to the increased prevalence of thyroid hyperplastic nodules in syndromic patients. Objective: To determine somatic alterations in DICER1-associated DTC and to study patient outcomes. Design: Retrospective series. Setting: Tertiary referral centers. Patients: Ten patients with germline pathogenic DICER1 variants and early-onset DTC. Methods: Somatic DICER1 mutation analysis, extensive somatic DNA variant and gene fusion analyses were performed on all tumors. Results: Median age at DTC diagnosis was 13.5 years and there was no recurrent or metastatic disease (median follow-up, 8 years). All thyroid specimens showed diffuse nodular hyperplasia with at least one focus suspicious of DTC but without infiltrative growth, extrathyroidal extension, vascular invasion, or lymph node metastasis. Most of the individual nodules (benign and malignant) sampled from the 10 tumors harbored distinct DICER1 RNase IIIb hotspot mutations, indicating a polyclonal composition of each tumor. Furthermore, nine of 10 DICER1-related DTCs lacked well-known oncogenic driver DNA variants and gene rearrangements. Conclusion: On the basis of our clinical, histological, and molecular data, we consider that most DICER1-related DTCs form a low-risk subgroup. These tumors may arise within one of multiple benign monoclonal nodules; thus, hemi-thyroidectomy or, more likely, total thyroidectomy may often be required. However, radioiodine treatment may be unnecessary given the patients' ages and the tumors' low propensity for metastases.
PubMed-ID: 30260442
http://dx.doi.org/10.1210/jc.2018-00774

Central Lymph Node Dissection by Endoscopic Bilateral Areola Versus Open Thyroidectomy.
Surg Laparosc Endosc Percutan Tech, 29(1):e1-e6.
D. Zhang, T. Wang, G. Dionigi, J. Zhang, G. Xue and H. Sun. 2019.
BACKGROUND: Endoscopic thyroidectomy by bilateral areola approach (ETBAA) potentially expose a technical limitation for anatomize the central compartment lymph nodes located in its most caudal portion because of visual obstruction and instrument interference of clavicles and sternum. We provide a comparative analysis of ETBAA versus open thyroidectomy approach (OTA) for central compartment dissection (CND). METHODS: From October 2013 to August 2017, 400 patients with papillary thyroid cancer (PTC) underwent CND; 200 patients were enrolled in each group. For the endoscopic group, a 10-mm curved incision is made along the margin of the right areola at 2 to 4'oclock for the 30 degrees endoscope. Bilaterally 5-mm incisions are on the edges of the areola at 11 to 12'oclock as accessory operating ports. Supplementary video (Supplemental Digital Content 1, http://links.lww.com/SLE/A180) depicts steps of ETBAA with CND. RESULTS: In ETBAA group, a total of 1049 lymph nodes were removed, nodes excision ranged from 1 to 19 (mean, 5.25), the ratio positive/metastatic rate was 18.6%. In OTA group, 916 lymph nodes were excised, nodes removal amplitude was 1 to 20 (average, 4.58), 12.1% were metastatic. Compared with the open group, significantly more lymph nodes were extracted during ETBAA ($P<0.05$). There was no significant difference between the 2 groups per resected side or surgical morbidity ($P>0.05$). Periodic monitoring of PTC patients revealed no clinical or US recurrence, undetectable serum Tg in both groups. CONCLUSIONS: Our results show the feasibility of CND in ETBAA.
PubMed-ID: 30260916
http://dx.doi.org/10.1097/SLE.0000000000000579

Lung Metastasis in Pediatric Thyroid Cancer: Radiological Pattern, Molecular Genetics, Response to Therapy, and Outcome.
J Clin Endocrinol Metab, 104(1):103-10.
A. S. Alzahrani, M. Alswailem, Y. Moria, R. Almutairi, M. Alotaibi, A. K. Murugan, E. Qasem, B. Alghamdi and H. Al-Handi. 2019.
Context: Lung metastases are common in pediatric thyroid cancer (TC). We present an analysis of a series of lung metastases in pediatric TC. Patients and Methods: Data from 20 patients (16 females, 4 males; median age, 14.5 years; range 10 to 18 years) were analyzed. The tumors included differentiated TC in 19 patients and poorly differentiated TC in 1 patient. Results: Lung metastasis presented with three distinct radiological patterns: lung uptake on diagnostic radioactive iodine whole body scan (DxWBS) only in 3 patients (15%); lung uptake on DxWBS and CT scan as micrometastases (</=1 cm) in 16 patients (80%); and lung uptake on DxWBS and CT scan as macrometastases (>1 cm) in 1 patient (5%). Iodine-131 therapies were administered to all patients (median, three; range one to eight) with a median cumulative administered activity of 317.5 mCi (range, 109 to 682 mCi). None of the patients achieved a complete response but the biochemical response was substantial. During a median follow-up period of 8.2 years (range, 0.75 to 16.3 years), 1 patient (5%) died, 1 patient (5%) had a biochemically incomplete response, 2 patients (10%) had an indeterminate response, 1 patient (5%) had progressive structural disease, and 14 patients (70%) had stable structural disease. Mutational testing of 10 of 20 tumors revealed only two PIK3CA mutations in a single tumor. Conclusions: Lung metastases are common in pediatric TC and present most frequently with bilateral radioiodine-avid micrometastases. Known single point mutations in adult TC are rare in pediatric TC. The biochemical response to iodine-131 can be substantial but resolution of structural abnormalities is rare.
PubMed-ID: 30272236
http://dx.doi.org/10.1210/jc.2018-01690

Depressive Disorder in Thyroid Cancer Patients after Thyroidectomy: A Longitudinal Follow-up Study Using a National Cohort.
Otolaryngol Head Neck Surg, 160(2):239-45.
H. G. Choi, B. Park, Y. B. Ji, K. Tae and C. M. Song. 2019.
OBJECTIVE: The present study compared the frequency of depressive disorder in patients with thyroid cancer who had undergone thyroidectomy with the frequency in control individuals. STUDY DESIGN: Retrospective population-based cohort study. SETTING: This study used data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort. SUBJECT AND METHODS: A total of 3609 participants with thyroid cancer who had undergone thyroidectomy between 2003 and 2011 were enrolled in this study and matched 1:4 with 14,436 control participants by age, sex, income, and region of residence. The cumulative incidence of postoperative depressive disorder was evaluated over a period of 10 years after the thyroidectomies and compared with the incidence in controls. Depressive disorder was diagnosed by a psychiatrist. RESULTS: The incidence of depressive disorder was significantly higher in the thyroid cancer with

thyroidectomy group than in the controls up to postoperative year 1. A subgroup analysis showed the same higher incidence of depressive disorder in the thyroid cancer group than controls for up to 1 year after operations in young adult (</=44 years old), female, urban, and low-income groups. However, the incidence was elevated only in the year of the thyroidectomies themselves in middle-aged and older, rural, and high-income groups. CONCLUSION: Patients with thyroid cancer who undergo thyroidectomy have depressive disorder more frequently than normal controls. However, the frequency of depressive disorder after thyroidectomy recovers in a shorter period in middle-aged or older, high-income, and rural-dwelling patients, compared to younger, low-income, and urban-dwelling patients.
PubMed-ID: 30274554
http://dx.doi.org/10.1177/0194599818802190

Risk factors for thyroid surgery-related unilateral vocal fold paralysis.
Laryngoscope, 129(1):275-83.
H. C. Chen, Y. C. Pei and T. J. Fang. 2019.
OBJECTIVES/HYPOTHESIS: We aimed to identify the risk factors for iatrogenic unilateral vocal fold paralysis (UVFP) caused by thyroid surgery, to allow the identification of patients requiring nerve-protection procedures and monitoring technologies. STUDY DESIGN: Retrospective case study in a medical center. METHODS: Patients who underwent thyroid surgery from April 2011 to February 2016 and who were diagnosed with UVFP by laryngoscopy and laryngeal electromyography were included. Patient demographics, types of surgery, and characteristics of the thyroid lesions were analyzed. RESULTS: Sixty (2.1%) of 2,815 patients who received thyroid surgery developed UVFP. The risk of UVFP was higher in patients over 60 years old (odds ratio, 1.89; 95% confidence interval, 1.01-3.26; P = .01). Involvement of the external branch of superior laryngeal nerve (EBSLN) occurred in 19 (31.7%) of the 60 UVFP patients, and was more likely to occurr in patients with diabetes mellitus (odds ratio, 14.19; 95% confidence interval, 3.80-52.94; P < .001). The incidence of UVFP and involvement of the EBSLN differed among surgery types, and was the highest among patients undergoing total thyroidectomy with neck dissection (TTND) (10/158, 6.3% and 5/158, 3.2%, respectively). CONCLUSIONS: The risk of thyroid surgery-related UVFP is higher in older patients. EBSLN involvement is more likely in patients with diabetes mellitus. TTND is associated with higher risks of UVFP and EBSLN injury than other types of surgery, implying the need of intraoperative nerve monitoring in these high-risk characteristics. LEVEL OF EVIDENCE: 4 Laryngoscope, 129:275-283, 2019.
PubMed-ID: 30284255
http://dx.doi.org/10.1002/lary.27336

Predicting outcomes and complications following radioiodine therapy in Graves' thyrotoxicosis.
Clin Endocrinol (Oxf), 90(1):192-9.
E. T. Aung, N. N. Zammitt, A. R. Dover, M. W. J. Strachan, J. R. Seckl and F. W. Gibb. 2019.
OBJECTIVE: Radioiodine (RAI) is an effective treatment for Graves' thyrotoxicosis but is associated with a failure rate of 15% and may be a risk factor for thyroid eye disease (TED) and weight gain. We sought to examine predictors of RAI failure, weight gain, TED and patient satisfaction. DESIGN: Retrospective cohort study. PATIENTS: A total of 655 episodes of RAI in Graves' thyrotoxicosis patients (2006-2015). MEASUREMENTS: Biochemical assessment, including TFTs and thyrotropin receptor antibodies (TRAb), clinical features (eg, TED, weight and thionamide use) and patient questionnaire. RESULTS: The treatment failure rate was 17%. Failure was greater with higher fT4 (P = 0.002) and higher TRAb (P = 0.004). Failure rate was 42.2% when TRAb >40 U/L. Median weight gain was 3.2 kg in those with normal fT4 prior to RAI and 5.8 kg when fT4 was elevated (P < 0.001). New TED developed in 7.6% but was not associated with post-RAI dysthyroidism. Treatment satisfaction was generally high (median response 8/10). CONCLUSIONS: Treatment failure after RAI occurs in predictable groups and this should be reflected in the information provided to patients. Weight gain is common and may not entirely be explained by a return to pre-thyrotoxic baseline. We were unable to detect any significant impact of post-RAI dysthyroidism on weight gain, TED or thyroid symptoms in this large cohort.
PubMed-ID: 30291728
http://dx.doi.org/10.1111/cen.13873

Medullary Thyroid Carcinoma: Do Ultrasonography and F-DOPA-PET-CT Influence the Initial Surgical Strategy?
Ann Surg Oncol, 25(13):3919-27.
L. Brammen, M. B. Niederle, P. Riss, C. Scheuba, A. Selberherr, G. Karanikas, G. Bodner, O. Koperek and B. Niederle. 2018.
BACKGROUND: At the time of diagnosis, one-third of medullary thyroid carcinoma (MTC) patients show lymph

node (LN) or distant metastasis. A metastasized MTC requires different surgical strategies. OBJECTIVE: This study aimed to determine the value of ultrasound and [18F]fluoro-dihydroxyphenylalanine positron emission tomography with computed tomography (F-DOPA-PET-CT) in localizing MTC, as well as LN and distant metastasis. METHODS: The study included 50 patients (24 males/26 females) with preoperative ultrasound, F-DOPA-PET-CT, and histologically proven MTC. Imaging results were correlated with both preoperative basal calcitonin (bCt) levels and final histology. RESULTS: Tumors were classified as pT1a:17 (diameter, mean +/- standard deviation: 5.8 +/- 3.0 mm), pT1b:15 (15.0 +/- 3.2 mm), pT2:9 (27.3 +/- 7.0 mm), and pT3:9 (38.3 +/- 24.2 mm). The median bCt level was 202 pg/mL (lower/upper quartile: 82/1074 pg/mL). Ultrasound was positive for tumor in 45/50 (92%) patients (20.0 +/- 16.0 mm) and negative in 5 patients (3.2 +/- 2.2 mm). Overall, 43/50 (86%) patients had positive F-DOPA local scans (20.0 +/- 16.4 mm), while 7 (14%) patients were negative (7.7 +/- 8.1 mm). Lastly, 21/50 (42%) patients had LN metastasis; 8/21 (38%) patients had positive LNs suspected with ultrasound, and 12/21 (57%) patients had positive LNs suspected with F-DOPA. Tumor and LN sensitivity of ultrasound was 92% and 43%, respectively, and 86% and 57% of F-DOPA-PET-CT, respectively. In 3/50 (6%) patients and 3/50 (6%) patients, mediastinal LN metastasis and distant metastasis, respectively, were diagnosed only by F-DOPA-PET-CT. CONCLUSION: Ultrasound and F-DOPA-PET-CT are sensitive for the localization of MTC but not for the presence and location of LN metastasis (limitations: size/number). Only F-DOPA ensures the diagnosis of distant metastasis and influences the extent of LN surgery. Surgical strategy cannot be predicted based on neither ultrasound nor F-DOPA-PET-CT.
PubMed-ID: 30306375
http://dx.doi.org/10.1245/s10434-018-6829-3

Utility of Intraoperative Frozen Section in Large Thyroid Nodules.
Otolaryngol Head Neck Surg, 160(1):49-56.
C. A. Bollig, J. B. Jorgensen, R. P. Zitsch, 3rd and L. M. Dooley. 2019.
OBJECTIVE: To determine if the routine use of intraoperative frozen section (iFS) results in cost savings among patients with nodules >4 cm with nonmalignant cytology undergoing a thyroid lobectomy. STUDY DESIGN: Case series with chart review; cost minimization analysis. SETTING: Single academic center. SUBJECTS AND METHODS: Records were reviewed on a consecutive sample of 48 patients with thyroid nodules >4 cm and nonmalignant cytology who were undergoing thyroid lobectomy in which iFS was performed between 2010 and 2015. A decision tree model of thyroid lobectomy with iFS was created. Comparative parameters were obtained from the literature. A cost minimization analysis was performed comparing lobectomy with and without iFS and the need for completion thyroidectomy with costs estimated according to 2014 data from Medicare, the Bureau of Labor Statistics, and the Nationwide Inpatient Sample. RESULTS: The overall malignancy rate was 25%, and 33% of these malignancies were identified intraoperatively. When the malignancy rates obtained from our cohort were applied, performing routine iFS was the less costly scenario, resulting in a savings of $486 per case. When the rate of malignancy identified on iFS was adjusted, obtaining iFS remained the less costly scenario as long as the rate of malignancies identified on iFS exceeded 12%. If patients with follicular lesions on cytology were excluded, 50% of malignancies were identified intraoperatively, resulting in a savings of $768 per case. CONCLUSIONS: For patients with nodules >4 cm who are undergoing a diagnostic lobectomy, the routine use of iFS may result in decreased health care utilization. Additional cost savings could be obtained if iFS is avoided among patients with follicular lesions.
PubMed-ID: 30322356
http://dx.doi.org/10.1177/0194599818802183

Thyroid Ultrasound and the Increase in Diagnosis of Low-Risk Thyroid Cancer.
J Clin Endocrinol Metab, 104(3):785-92.
M. R. Haymart, M. Banerjee, D. Reyes-Gastelum, E. Caoili and E. C. Norton. 2019.
Context: Thyroid cancer incidence increased with the greatest change in adults aged >/=65 years. Objective: To determine the relationship between area-level use of imaging and thyroid cancer incidence over time. Design, Setting and Participants: Longitudinal imaging patterns in Medicare patients aged >/=65 years residing in Surveillance, Epidemiology, and End Results (SEER) regions were assessed in relationship to differentiated thyroid cancer diagnosis in patients aged >/=65 years included in SEER-Medicare. Linear mixed-effects modeling was used to determine factors associated with thyroid cancer incidence over time. Multivariable logistic regression was used to determine patient characteristics associated with receipt of thyroid ultrasound as initial imaging. Main Outcome Measure: Thyroid cancer incidence. Results: Between 2002 and 2013, thyroid ultrasound use as initial imaging increased ($P < 0.001$). Controlling for time and demographics, use of thyroid ultrasound was associated with thyroid cancer incidence ($P < 0.001$). Findings persisted when cohort was restricted to papillary thyroid cancer ($P < 0.001$), localized papillary thyroid cancer ($P = 0.004$), and localized papillary thyroid cancer with tumor size </=1 cm ($P = 0.01$). Based on our model, from 2003 to 2013, at least

6594 patients aged >/=65 years were diagnosed with thyroid cancer in the United States due to increased use of thyroid ultrasound. Thyroid ultrasound as initial imaging was associated with female sex and comorbidities. Conclusion: Greater thyroid ultrasound use led to increased diagnosis of low-risk thyroid cancer, emphasizing the need to reduce harms through reduction in inappropriate ultrasound use and adoption of nodule risk stratification tools.
PubMed-ID: 30329071
http://dx.doi.org/10.1210/jc.2018-01933

Effect of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) on Malignancy Rates in Thyroid Nodules: How to Counsel Patients on Extent of Surgery.
Ann Surg Oncol, 26(1):93-7.
B. M. Lindeman, M. A. Nehs, T. E. Angell, E. K. Alexander, A. A. Gawande, F. D. Moore, Jr., G. M. Doherty and N. L. Cho. 2019.
PURPOSE: To investigate the impact of the nomenclature change to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) on reported malignancy rates following thyroidectomy. METHODS: Retrospective cohort study of patients with thyroid nodules sampled preoperatively with fine-needle aspiration (FNA) and subsequently removed at one tertiary-care hospital from 4/2016 to 2/2017. Surgical procedure, anatomic pathology, thyroid cytopathology classification, and demographic characteristics were recorded. RESULTS: Thyroidectomy was performed in 353 patients. Twenty-six patients (7.3%) had NIFTP on anatomic pathology. Preoperative FNA demonstrated atypia of undetermined significance (AUS/Bethesda III) in 13 (50%), suspicious for malignancy (SUS/Bethesda V) in 6 (23%), suspicious for follicular neoplasm (SFN/Bethesda IV) in 4 (15%), benign/Bethesda I in 2 (8%), and malignant/Bethesda VI in 1 (4%). Invasive malignancy rates across cytologic categories changed as follows: benign (n = 74) from 4 to 1%, AUS (n = 85) from 33 to 18% ($p < 0.05$), SFN (n = 58) from 29 to 22%, SUS (n = 33) from 91 to 73% ($p < 0.05$), and malignant (n = 99) from 99 to 98%. Overall decrease in invasive malignancy was 7.3% for the entire population and 13.1% for indeterminate preoperative FNA cytology (Bethesda III-V). Among 26 NIFTP patients, 17 had thyroid lobectomy (TL) and 9 underwent total thyroidectomy (TT). Eight of the nine patients with TT could have been definitively treated with TL, an 89% decrease. CONCLUSIONS: The NIFTP nomenclature change led to an overall decrease in the malignancy rate at our institution, especially for Bethesda III-V categories. Patients may be counseled toward more conservative surgical options if NIFTP is in the differential.
PubMed-ID: 30341576
http://dx.doi.org/10.1245/s10434-018-6932-5

Impact of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) on the Outcomes of Lobectomy.
Ann Surg Oncol, 26(1):306.
P. W. Rosario. 2019.
PubMed-ID: 30374926
http://dx.doi.org/10.1245/s10434-018-6947-y

Lobectomy Is Feasible for 1-4 cm Papillary Thyroid Carcinomas: A 10-Year Propensity Score Matched-Pair Analysis on Recurrence.
Thyroid, 29(1):64-70.
E. Song, M. Han, H. S. Oh, W. W. Kim, M. J. Jeon, Y. M. Lee, T. Y. Kim, K. W. Chung, W. B. Kim, Y. K. Shong, S. J. Hong, T. Y. Sung and W. G. Kim. 2019.
BACKGROUND: Current guidelines allow lobectomy as treatment for 1-4 cm papillary thyroid carcinomas (PTCs), as previous studies reported no clear survival advantages for total thyroidectomy (TT). However, data on recurrence based on surgical extent are limited. METHODS: This study enrolled 2345 patients with 1-4 cm PTC. Those with lateral cervical lymph node metastasis or initial distant metastasis were excluded. Disease-free survival (DFS) was compared after 1:1 propensity score matching by age, sex, tumor size, extrathyroidal extension, multifocality, and cervical lymph node metastasis. RESULTS: Lobectomy was performed in 383 (16.3%) and TT in 1962 (83.7%) patients. In the matched-pair analysis (381 patients in each group), no significant difference in DFS was observed during the median follow-up of 9.8 years (hazard ratio [HR] = 1.35 [confidence interval (CI) 0.40-1.36], $p = 0.33$). When stratified by tumor size, DFS did not differ between the group with 1-2 cm tumors and that with 2-4 cm tumors (HR = 1.57 [CI 0.75-3.25], $p = 0.228$; HR = 0.93 [CI 0.30-2.89], $p = 0.902$, respectively). Multivariate analysis showed that the surgical extent did not play an independent role in structural persistent/recurrent disease development (HR = 1.43 [CI 0.72-2.83], $p = 0.306$). CONCLUSION: Patients with 1-4 cm PTCs who underwent lobectomy exhibited DFS rates similar to those who underwent TT after controlling for major prognostic factors. This supports the feasibility of lobectomy as initial surgical approach

for these patients and emphasizes that tumor size should not be an absolute indication for TT.
PubMed-ID: 30375260
http://dx.doi.org/10.1089/thy.2018.0554

The definition of lymph node micrometastases in pathologic N1a papillary thyroid carcinoma should be revised.
Surgery, 165(3):652-6.
Y. M. Lee, J. H. Park, J. W. Cho, S. J. Hong and J. H. Yoon. 2019.
BACKGROUND: The aim of this study was to identify the risk factors for structural recurrence with a focus on lymph node-related factors and to determine the optimal cutoff size of lymph node micrometastases in patients with pathologic N1a classical papillary thyroid carcinoma. METHODS: We included patients who underwent total thyroidectomy with central compartment lymph node dissection for classic papillary thyroid carcinoma with pathologic N1a classification. RESULTS: A total of 398 patients were followed up for a median of 131 months. Structural recurrence occurred in 17.3% of patients (69/398). The multivariate analysis reported the following independent risk factors for structural recurrence: tumor size >1.95 cm, bilaterality, lymphatic and/or vascular invasion, a maximum diameter of the metastatic lymph node focus >3.5 mm, distribution of metastatic lymph node foci size >3.0 mm, and >/=4 metastatic lymph nodes. CONCLUSION: The newly proposed cutoff of 3.5 mm for a definition of lymph node micrometastasis in pathologic N1a papillary thyroid carcinoma patients can reclassify the risk estimates of structural recurrence, thus modifying postoperative management plans and follow-up strategies.
PubMed-ID: 30385127
http://dx.doi.org/10.1016/j.surg.2018.09.015

Thyroid surgery and obesity: Cohort study of surgical outcomes and local specific complications.
Am J Surg, 217(1):142-5.
M. Farag, K. Ibraheem, M. E. Garstka, H. Shalaby, C. DuCoin, M. Killackey and E. Kandil. 2019.
INTRODUCTION: Obesity is associated with numerous complications after elective general surgeries. The aim is to compare surgical outcomes and local specific complications in obese and non-obese patients after thyroid surgery. METHODS: Retrospective study over a 3-year period at a North American academic institution. Outcome measures were operative time, estimated blood loss, hospital length of stay, and local specific complications (hypocalcemia, recurrent laryngeal nerve injury, wound hematoma, wound seroma, and chyle leakage). RESULTS: A total of 469 patients were included (mean [SD] age, 50.11 [15.01] years; mean [SD] BMI, 30.5 [8.3] kg/m(2); 207 [44.14%] obese). There was no difference in operative time (125.7 vs. 129.6, p=0.52), estimated blood loss (16.88 vs. 14.56, p=0.28), or hospital length of stay (0.95 vs. 0.95, p=0.96). Overall, there was no difference in the rates of local specific complications between the two groups. CONCLUSIONS: Obesity is not associated with adverse outcomes in patients undergoing thyroid surgery.
PubMed-ID: 30389117
http://dx.doi.org/10.1016/j.amjsurg.2018.07.038

A propensity-matched analysis of clinical outcomes between open thyroid lobectomy and high-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules.
Surgery, 165(1):85-91.
B. H. H. Lang, C. K. H. Wong, E. P. M. Ma, Y. C. Woo and K. W. Chiu. 2019.
BACKGROUND: High-intensity focused ultrasound is a promising, nonoperative treatment for benign thyroid nodules. Our study aimed to compare treatment outcomes of single-session high-intensity focused ultrasound ablation with open lobectomy after propensity score matching. METHODS: After propensity matching, we compared treatment-related morbidity, treatment time, duration of hospitalization, improvement in symptom score, cost, and acoustic parameters of consecutive patients who underwent high-intensity focused ultrasound ablation or lobectomy. All eligible patients completed the computerized, multidimensional voice program and Voice Handicap Index questionnaire before, and 3 and 6 months after treatment. RESULTS: The matched cohort comprised 154 patients (77 in each group). Although treatment-related morbidity was comparable between the two groups (P=.368), treatment time (P <.001), duration of hospitalization (P <.001), and medical cost (P <.001) were less in the high-intensity focused ultrasound group. After high-intensity focused ultrasound ablation, the 6-month nodule shrinkage (mean +/- SD) was 64% +/- 26% and the 6-month symptom improvement score was comparable with lobectomy (P=.283). At 6 months, none of the acoustic parameters were changed from the baseline in both groups (P >.05), and the Voice Handicap Index questionnaire did not differ between the two groups (P >.05). CONCLUSION: Despite having similar treatment-related morbidity and voice outcomes, there were possibly some advantages with high-intensity focused ultrasound during open lobectomy, including the avoidance of a neck scar, shorter treatment time and duration of hospitalization, and

lower medical cost.
PubMed-ID: 30392858
http://dx.doi.org/10.1016/j.surg.2018.05.080

Recombinant Thyrotropin vs Levothyroxine Withdrawal in 131I Therapy of N1 Thyroid Cancer: A Large Matched Cohort Study (ThyrNod).
J Clin Endocrinol Metab, 104(4):1020-8.
L. Leenhardt, S. Leboulleux, C. Bournaud, S. Zerdoud, C. Schvartz, R. Ciappuccini, A. Kelly, O. Morel, I. Dygai-Cochet, D. Rusu, C. N. Chougnet, G. Lion, M. C. Eberle-Pouzeratte, B. Catargi, M. Kabir-Ahmadi, E. Le Peillet Feuillet and D. Taieb. 2019.
CONTEXT: Recombinant human thyrotropin (rhTSH) has been shown to be an effective stimulation method for radioactive iodine (RAI) therapy in differentiated thyroid cancer, including in those with nodal metastases (N1 DTC). OBJECTIVES: To demonstrate the noninferiority of rhTSH vs thyroid hormone withdrawal (THW) in preparation to RAI regarding disease status at the first evaluation in the real-life setting in patients with N1 DTC. DESIGN: This was a French multicenter retrospective study. Groups were matched according to age (<45/>/=45 years), number of N1 nodes (</=5/>5 lymph nodes), and stage (pT1-T2/pT3). RESULTS: The cohort consisted of 404 patients pT1-T3/N1/M0 DTC treated with rhTSH (n = 205) or THW (n = 199). Pathological characteristics and initially administrated RAI activities (3.27 +/- 1.00 GBq) were similar between the two groups. At first evaluation (6 to 18 months post-RAI), disease-free status was defined by thyroglobulin levels below threshold and a normal ultrasound. Disease-free rate was not inferior in the rhTSH group (75.1%) compared with the THW group (71.9%). The observed difference between the success rates was 3.3% (-6.6 to 13.0); rhTSH was therefore considered noninferior to THW because the upper limit of this interval was <15%. At the last evaluation (29.7 +/- 20.7 months for rhTSH; 36.7 +/- 23.8 months for THW), 83.5% (rhTSH) and 81.5% (THW) of patients achieved a complete response. This result was not influenced by any of the known prognostic factors. CONCLUSIONS: A preparation for initial RAI treatment with rhTSH was noninferior to that with THW in our series of pT1-T3/N1/M0-DTC on disease-free status outcomes at the first evaluation and after 3 years.
PubMed-ID: 30398518
http://dx.doi.org/10.1210/jc.2018-01589

Comprehensive Lateral Neck Dissection in Papillary Thyroid Carcinoma may Reduce Lateral Neck Recurrence Rates.
Ann Surg Oncol, 26(1):86-92.
V. Strajina, B. M. Dy, T. J. McKenzie, Z. Al-Hilli, M. Ryder, D. R. Farley, G. B. Thompson and M. L. Lyden. 2019.
OBJECTIVE: To Identify predictors of recurrent disease following lateral neck dissection (LND) for papillary thyroid carcinoma (PTC). METHODS: A retrospective review of patients who underwent first-time LND for PTC at our institution (2000-2015) was performed. Medical records were examined for biopsy or pathologically proven lateral neck recurrence. Differences between the groups with and without recurrence were compared. All LNDs were then classified in to two groups: "comprehensive" (CND), involving levels IIa-Vb at minimum, or "selective", labelling less extensive dissection (SND). RESULTS: Four hundred nine patients underwent 467 LNDs. Surveillance data were available for 317 patients who underwent 362 LNDs (mean age 45 +/- 16; range 18-88). The median follow-up was 64 +/- 48 months (range 3-197). Recurrence was detected in 71 lateral necks (20%). The total number of lymph nodes was greater in the group without recurrence compared to those with recurrence (23 vs. 19, p = 0.02). Among patient demographics, radioactive iodine treatment, primary tumor characteristics and characteristics of nodal metastases, only an older patient age (mean 50 vs. 43 years) was associated with lateral neck recurrence (p < .01). CND was performed in 102 lateral necks and SND in 143 necks. There were 12 recurrences recorded in the CND group (12%) vs. 31 in the SND group (22%, p = .04). The majority of recurrences (70%) involved levels included in the original dissection. CONCLUSIONS: Younger patients, more extensive dissection and a higher total number of lymph nodes removed are associated with a lower incidence of lateral neck recurrence after LND for papillary thyroid carcinoma.
PubMed-ID: 30411267
http://dx.doi.org/10.1245/s10434-018-6871-1

Stage migration with the new American Joint Committee on Cancer (AJCC) staging system (8th edition) for differentiated thyroid cancer.
Surgery, 165(1):6-11.
A. R. Shaha, J. C. Migliacci, I. J. Nixon, L. Y. Wang, R. J. Wong, L. G. T. Morris, S. G. Patel, J. P. Shah, R. M. Tuttle and I. Ganly. 2019.
BACKGROUND: Tumor, node, and metastasis staging in thyroid carcinoma is important for assessing prognosis. However, patients with stage III or IV disease have an overall survival rate of 90%. The change to 55

years of age as the cutoff will create stage migration and many patients will be downstaged. METHODS: We reviewed our database of 3,650 patients to analyze the impact of the new American Joint Committee on Cancer staging system. There were 994 men (27%) and 2,656 women (73%). The median age was 46 years. Patients were staged using both 7th and 8th editions, with a cutoff of 55 years of age and new definitions of T3 and T4, and nodal staging. RESULTS: Of 3,650 patients, 1,057 (29%) were downstaged. There were 104 (10%) who went from stage IV to I, 109 (10%) who went from stage IV to stage II, and 68 (6%) who went to stage III. There were 218 (21%) who went from stage III to I, 347 (33%) who went from stage III to stage II, and 211 (20%) who went from stage II to I. The overall disease-specific and relapse-free survival was analyzed and showed better stratification with the new staging system. CONCLUSION: The new staging system reflects more appropriately the biology of thyroid cancer and will have significant impact on the management of thyroid cancer.
PubMed-ID: 30415873
http://dx.doi.org/10.1016/j.surg.2018.04.078

NIFT-P: Are they indolent tumors? Results of a multi-institutional study.
Surgery, 165(1):12-6.
N. Chereau, T. Greilsamer, E. Mirallie, S. M. Sadowski, M. Pusztaszeri, F. Triponez, G. Baud, F. Pattou, N. Christou, M. Mathonnet, L. Brunaud, N. Santucci, P. Goudet, C. Guerin, F. Sebag, G. Donatini, J. L. Kraimps, F. Tissier, C. Lussey-Lepoutre, L. Leenhardt and F. Menegaux. 2019.
BACKGROUND: Encapsulated follicular variant of papillary thyroid carcinoma has recently been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features on the basis of its highly indolent behavior, as proposed by an international group of experienced thyroid pathologists. METHODS: All patients from 9 high-volume endocrine surgery departments who underwent surgery between 2005 and 2015 and whose final surgical pathology revealed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (>10 mm) were included in this study. The primary outcome was to determine the potential for recurrent disease in these patients. RESULTS: Among the 363 patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features, 76% were female with a median age of 50 years (5-86 years); 345 patients (95%) underwent total thyroidectomy. A total of 65 patients had an associated micropapillary thyroid carcinoma. In the group of 133 patients who underwent prophylactic lymph node dissection (37%), 1 patient had a micrometastasis but with an associated micropapillary thyroid carcinoma. Over a median follow-up period of 5 years, 1 patient with an associated micropapillary thyroid carcinoma had recurrent disease at 6 years. All patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features without micropapillary thyroid carcinoma had no lymph node metastasis or recurrent disease. CONCLUSION: We found that noninvasive follicular thyroid neoplasm with papillary-like nuclear features presents with indolent behavior. However, the identification of an associated micropapillary thyroid carcinoma should be carefully evaluated because it could be a factor for lymph node metastasis and/or of recurrence.
PubMed-ID: 30420090
http://dx.doi.org/10.1016/j.surg.2018.04.089

Thyroid Cancer and Benign Nodules After Exposure In Utero to Fallout From Chernobyl.
J Clin Endocrinol Metab, 104(1):41-8.
M. Hatch, A. V. Brenner, E. K. Cahoon, V. Drozdovitch, M. P. Little, T. Bogdanova, V. Shpak, E. Bolshova, G. Zamotayeva, G. Terekhova, E. Shelkovoy, V. Klochkova, K. Mabuchi and M. Tronko. 2019.
Background: Children and adolescents exposed to radioactive iodine-131 (I-131) in fallout from the 1986 Chernobyl nuclear accident appear to be at increased risk of thyroid cancer and benign thyroid nodules. The prenatal period is also considered radiosensitive, and the fetal thyroid can absorb I-131 from the maternal circulation. Objectives: We aimed to estimate the risk of malignant and benign thyroid nodules in individuals exposed prenatally. Methods: We studied a cohort of 2582 subjects in Ukraine with estimates of I-131 prenatal thyroid dose (mean = 72.6 mGy), who underwent two standardized thyroid screening examinations. To evaluate the dose-response relationship, we estimated the excess OR (EOR) using logistic regression. Results: Based on a combined total of eight cases diagnosed at screenings from 2003 to 2006 and 2012 to 2015, we found a markedly elevated, albeit not statistically significant, dose-related risk of thyroid cancer (EOR/Gy = 3.91, 95% CI: -1.49, 65.66). At cycle 2 (n = 1,786), there was a strong and significant association between I-131 thyroid dose and screen-detected large benign nodules (>/=10 mm) (EOR/Gy = 4.19, 95% CI: 0.68, 11.62; P = 0.009), but no significant increase in risk for small nodules (<10 mm) (EOR/Gy = 0.34, 95% CI: -0.67, 2.24; P = 0.604). Conclusions: The dose effect by nodule size, with I-131 risk for large but not small nodules, is similar to that among exposed children and adolescents in Belarus. Based on a small number of cases, there is also a suggestive effect of I-131 dose on thyroid cancer risk.
PubMed-ID: 30445441
http://dx.doi.org/10.1210/jc.2018-00847

Completion Thyroidectomy: Revisited a Quarter of a Century Later.
Ann Surg Oncol, 26(2):694-6.
B. M. Dy, V. Strajina, M. Tuttle and A. R. Shaha. 2019.
PubMed-ID: 30536128
http://dx.doi.org/10.1245/s10434-018-07102-z

Oncologic outcomes in patients with 1-cm to 4-cm differentiated thyroid carcinoma according to extent of thyroidectomy.
Head Neck, 41(1):56-63.
J. B. Choi, S. G. Lee, M. J. Kim, T. H. Kim, E. J. Ban, C. R. Lee, J. Lee, S. W. Kang, J. J. Jeong, K. H. Nam, W. Y. Chung and C. S. Park. 2019.
BACKGROUND: Recent guidelines advocate unilateral thyroidectomy for low-risk 1-cm to 4-cm differentiated thyroid cancer (DTC). This study was designed to examine the association between the extent of thyroidectomy and oncologic outcomes in patients with 1-cm to 4-cm DTC. MATERIALS AND METHODS: From April 1978 to December 2011, 16 057 patients with DTC underwent thyroidectomy at Yonsei University Hospital. Among them, 5266 (32.8%) patients were classified as having 1-cm to 4-cm DTC and were enrolled in this study. Clinicopathologic features and prognostic results (disease-free survival [DFS] and disease-specific survival [DSS] rates) were analyzed by retrospective medical record review. The mean follow-up duration was 57.3 +/- 58.1 months. RESULTS: Of tumor subtypes in the study group, papillary thyroid carcinoma was the most common (97.5%) and follicular thyroid carcinoma occurred at a rate of 2.5%. In this study, the mean tumor size was 1.84 +/- 0.74 cm. Patients had extrathyroidal extension (69.3%), multiplicity (35.1%), bilaterality (26.4%), central lymph node metastasis (53.0%), and lateral neck node metastases (19.9%). Of the 5266 patients, 4292 (81.5%) underwent total thyroidectomy and 974 (18.5%) had lobectomies. Recurrence rates in the total thyroidectomy and lobectomy groups were 5.7% and 9.4%, respectively. The lobectomy group had lower DFS (P = .007) and higher DSS (P = .034) than the total thyroidectomy group. A multivariate analysis for DFS revealed that tumor size, N classification, and extent of thyroidectomy were independent risk factors. On multivariate analysis, independent risk factors for DSS were age, sex, tumor size, and M classifications. CONCLUSION: Although extent of thyroidectomy does not affect DSS, total thyroidectomy is beneficial for reducing recurrence in patients with 1-cm to 4-cm DTC. However, if such tumors have such low-risk features as being unifocal, intrathyroidal, and lymph node metastasis-negative, extent of thyroidectomy does not affect oncologic outcome and lobectomy may be sufficient.
PubMed-ID: 30536465
http://dx.doi.org/10.1002/hed.25356

Superior detection of metastatic cystic lymphadenopathy in patients with papillary thyroid cancer by utilization of thyroglobulin washout.
Head Neck, 41(1):225-9.
H. Khadra, H. Mohamed, Z. Al-Qurayshi, A. Sholl, M. Killackey and E. Kandil. 2019.
BACKGROUND: Fine-needle aspiration (FNA) cytology has been the standard of care in the workup of cervical lymph nodes (LNs) in patients with recurrent papillary thyroid cancer (PTC) and suspicious cervical LNs. Recently, FNA thyroglobulin (TG) washout measurement has been proposed as an adjunct in the management of these patients. We hypothesize that using FNA-TG washout for suspicious cervical LNs would increase the accuracy of diagnosing metastatic disease especially in cystic and highly vascular cervical LN in patients with recurrent PTC. METHODS: This is a retrospective study of a prospectively collected database for patients with thyroid cancer who underwent preoperative FNA followed by selective neck dissection by one surgeon at an academic institution. FNA-cytology and FNA-TG washout were performed simultaneously. A total of 138 patients were included in our study, of which 92 (66.7%) had undergone surgical intervention. Results of both methods were then correlated with the final surgical pathology. RESULTS: FNA-cytology alone showed a sensitivity of 80.0%, specificity of 100.0% with a negative predictive value (NPV) of 60.0%. By contrast, FNA-TG washout had a sensitivity of 95.8%, specificity of 90.5% with a NPV of 86.4%. Combination of the FNA-cytology with FNA-TG washout of cystic/highly vascular LN increased the accuracy of diagnosis with a sensitivity of 98.2%, specificity of 100.00% with a NPV of 95.0%. All 14 malignant cervical LNs with false-negative FNA-cytology showed elevated FNA-TG washout, 10 (71.4%) of which were cystic in nature and 4 were highly vascular on ultrasonography. CONCLUSION: FNA-TG washout increases the diagnostic accuracy in detecting metastatic disease in patients with recurrent thyroid cancer. FNA-TG washout may be of special diagnostic importance in cystic or highly vascular LNs, which might have falsely negative cytology. LEVEL OF EVIDENCE: 2B.
PubMed-ID: 30536535
http://dx.doi.org/10.1002/hed.25488

Virtual evaluation of selected cervical lymph nodes with three-dimensional ultrasound in thyroid cancer patients after thyroidectomy.
Head Neck, 41(3):748-55.
S. J. Frank, S. J. Ahn and M. I. Surks. 2019.
BACKGROUND: We evaluated the usefulness of three-dimensional (3D) ultrasound of cervical lymph nodes (LN), when two-dimensional (2D) ultrasound evaluation is not sufficient to clearly evaluate lymph node characteristics, in thyroid cancer patients being followed after thyroidectomy. METHODS: Two readers retrospectively analyzed 2D and 3D images of 147 LNs; LNs were categorized as normal, reactive, suspicious, or indeterminate, and confidence level was rated. Results were compared to cytological/clinical data. Inter-reader agreement was calculated. RESULTS: Addition of 3D ultrasound significantly increased specificity (0.787 with 2D ultrasound vs 0.905 with 2D + 3D ultrasound for reader 1, P = .009; 0.701 with 2D ultrasound vs 0.898 with 2D + 3D ultrasound for reader 2, P = .01). Addition of 3D ultrasound significantly increased confidence level of readers (P < .001). Inter-reader agreement in LN categorization was almost perfect with 2D + 3D ultrasound. CONCLUSION: 3D ultrasound of cervical LNs enables better demonstration of imaging features that are important in differentiating benign and malignant LNs. These improvements can potentially obviate the need for FNA in post thyroidectomy cancer patients.
PubMed-ID: 30536820
http://dx.doi.org/10.1002/hed.25427

Feasibility of indocyanine green fluorescence imaging for intraoperative identification of parathyroid glands during thyroid surgery.
Head Neck, 41(2):340-8.
J. van den Bos, L. van Kooten, S. M. E. Engelen, T. Lubbers, L. P. S. Stassen and N. D. Bouvy. 2019.
BACKGROUND: This study assessed the feasibility of near-infrared fluorescence imaging with indocyanine green (ICG) to identify the parathyroid glands (PGs) intraoperatively and to assess their perfusion after thyroid resection. METHODS: Patients undergoing elective thyroidectomy were enrolled in this prospective study. An intravenous bolus of 7.5 mg ICG was administered twice: the first bolus to identify the PGs before resection of the thyroid and the second to assess vascularization of the PGs after resection. RESULTS: A total of 30 operations in 26 patients were included. In 17 surgeries (56.7%), fluorescence imaging was of added value, especially to confirm the presence of a suspected PG. No intraoperative or postoperative complications occurred because of the use of ICG. CONCLUSION: Near-infrared fluorescence imaging with the use of ICG for intraoperative identification of the PGs and the assessment of its vascularization is feasible and safe and can provide more certainty about the location of the PGs.
PubMed-ID: 30536963
http://dx.doi.org/10.1002/hed.25451

Increased risk of postoperative complications after total thyroidectomy with Graves' disease.
Head Neck, 41(2):281-5.
H. Kwon, J. K. Kim, W. Lim, B. I. Moon and N. S. Paik. 2019.
BACKGROUND: The effect of Graves' disease on the risk of postoperative complications in patients undergoing total thyroidectomy is unclear. METHODS: The incidence of recurrent laryngeal nerve (RLN) injury and hypoparathyroidism were analyzed between 165 patients with Graves' disease (GD group) and 1:1 matched patients with euthyroid states (control group). RESULTS: The matched cohorts did not differ in age, sex, body mass index, pathologic diagnosis, and extent of operation. Excised thyroid weight was higher in the Graves' disease than in the control group (60.1 g vs 22.6 g; P < .001). Multivariate analysis showed that Graves' disease significantly increased risks of transient RLN injury (odds ratio [OR] = 4.7, 95% confidence interval [CI] = 1.5-15.5; P = .010) and transient hypoparathyroidism (OR = 2.8, 95% CI = 1.3-5.8; P = .007). Rates of permanent complications were comparable in the Graves' disease and control groups. CONCLUSIONS: Graves' disease can be a predictive factor for postoperative RLN injury and hypoparathyroidism after total thyroidectomy.
PubMed-ID: 30537006
http://dx.doi.org/10.1002/hed.25484

Different outcomes in sporadic versus familial medullary thyroid cancer.
Head Neck, 41(1):154-61.
K. Saltiki, G. Simeakis, E. Anagnostou, E. Zapanti, E. Anastasiou and M. Alevizaki. 2019.
BACKGROUND: Medullary thyroid carcinoma (MTC) has varying clinical course with familial cases (fMTC) diagnosed earlier than sporadic MTC (spMTC). METHODS: A total of 273 MTCs (familial: n = 110 [40.3%], males: 38.5%) were followed for 1-35 years (median 5.0 years). Fifty one of the familial cases were operated

because of positive findings at genetic screening. Disease extent at diagnosis and follow-up was recorded. RESULTS: Mean age at diagnosis was: fMTC = 33.85 +/- 16.5 years (range 4-74) and spMTC = 52.6 +/- 14.0 years (range 16-81, P < .001). This difference remained when genetic screening cases were excluded. fMTCs had more frequently multifocality, smaller size, and more favorable stage at diagnosis (stages I and II: 60.9% vs 47.9%, stage III: 30.0% vs 23.9%, stage IV: 9.1% vs 28.9%, P = .01). fMTC had lower preoperative and postoperative calcitonin, more frequently remission (59.1% vs 47.2%) and less frequently progressive disease (8.2% vs 35.0%, P < .001). After excluding genetic screening cases, no difference in stage at diagnosis was observed. Outcome was more favorable in fMTC compared to sporadic (P = .002); the 10-year probability of lack of progression of disease differed significantly between fMTCs and spMTCs (86.4% vs 65.0%, P < .001). CONCLUSION: After excluding genetic screening cases, although stage at diagnosis is similar, disease outcome remains worse in sporadic compared to fMTCs.
PubMed-ID: 30548085
http://dx.doi.org/10.1002/hed.25463

The time point of completion thyroidectomy has no prognostic impact in patients with differentiated thyroid cancer.
Clin Endocrinol (Oxf), 90(3):479-86.
C. Lenschow, U. Mader, C. T. Germer, C. Reiners, N. Schlegel and F. A. Verburg. 2019.
BACKGROUND: After partial resection of the thyroid gland, a second operation referred to as "completion thyroidectomy" may be required if histopathological analysis indicates the presence of differentiated thyroid cancer (DTC). Although there is little evidence, it is assumed that the time point of completion thyroidectomy is not critical for oncological prognosis of patients with DTC. We assessed whether patients with total thyroidectomy (TTx) in a two-step procedure have an equal long-term prognosis with regard to disease-specific survival (DSS) compared to patients immediately undergoing total thyroidectomy in a one-step procedure. METHODS: A database study using the Wurzburg thyroid cancer database with 2258 patients with pT1a-pT4b tumours DTC who were operated between 1980 and 2016 was carried out. RESULTS: A total of 277 patients with papillary microcarcinoma pT1aN0M0 were treated by hemithyroidectomy. TTx as one-step procedure was performed in 1114 patients compared to 867 with TTx as a two-step procedure. Patients with papillary thyroid cancer more frequently had a TTx as one-step procedure than follicular thyroid cancer patients (59.4% vs 47%; P < 0.001). Compared to a one-step thyroidectomy, overall complication rate was not different compared to patients undergoing a single operation. Multivariate analysis showed that the presence of distant metastases, T-stage and age at diagnosis were the only independent determinants for DTC-specific survival, regardless of a one- or two-time thyroidectomy. CONCLUSION: The present study on the largest of such patient collectives provides evidence that a delayed completion operation does not affect DSS in DTC, nor does it lead to a significant increase in complication rates.
PubMed-ID: 30548672
http://dx.doi.org/10.1111/cen.13916

Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma.
Thyroid, 29(1):59-63.
T. Sakai, I. Sugitani, A. Ebina, O. Fukuoka, K. Toda, H. Mitani and K. Yamada. 2019.
BACKGROUND: Prospective trials of active surveillance for asymptomatic papillary microcarcinoma (T1aN0M0) since the 1990s have shown progression rates of only 5-10%. Late rescue surgery after progression had no deleterious effects on mortality and morbidity. The 2015 American Thyroid Association guidelines approved active surveillance for very low-risk papillary thyroid carcinoma (PTC) as an alternative method to immediate surgery. However, there is no study that evaluates long-term active surveillance for T1b tumors. METHODS: A prospective trial of active surveillance with 360 very low-risk PTC (T1aN0M0) patients has been conducted since 1995. Of the 392 T1bN0M0 patients, 61 selected active surveillance over surgery and eventually participated in this trial, while the remaining 331 patients underwent surgery. To find an appropriate management strategy for patients with T1bN0M0 PTC, the outcomes of active surveillance for T1bN0M0 to T1aN0M0 PTC were investigated and compared, and the outcomes of surgery for T1bN0M0 PTC were studied. RESULTS: After a mean of 7.4 years of active surveillance, 29 (8%) T1aN0M0 tumors and four (7%) T1bN0M0 tumors had increased in size (p = 0.69). Development of lymph node metastasis was seen in three (0.8%) patients and two (3%) patients, respectively (p = 0.10). No significant difference in progression rate was seen between groups. Among T1bN0M0 tumors, weak calcification and rich vascularity were risk factors for tumor-size increase, and younger age was a predictor for the development of lymph node metastasis. Mean initial tumor size was significantly greater in T1bN0M0 patients who underwent immediate surgery (14.5 +/- 2.8 mm) than it was in patients who chose observation (11.7 +/- 1.1 mm; p < 0.0001). No postoperative recurrence was seen in patients with tumor <15 mm in diameter. CONCLUSIONS: Active surveillance is an option for selected patients with

T1bN0M0 PTC.
PubMed-ID: 30560718
http://dx.doi.org/10.1089/thy.2018.0462

Remote-Access Thyroidectomy: A Multi-Institutional North American Experience with Transaxillary, Robotic Facelift, and Transoral Endoscopic Vestibular Approaches.
J Am Coll Surg, 228(4):516-22.
J. O. Russell, C. R. Razavi, M. E. Garstka, L. W. Chen, E. Vasiliou, S. W. Kang, R. P. Tufano and E. Kandil. 2019.
BACKGROUND: Many remote-access approaches (RAAs) to the thyroid have been described to circumvent anterior neck scarring, including the transaxillary, robotic facelift, and transoral endoscopic vestibular approaches. These techniques have been popularized in Asia, but adoption has been slow in North America. We aimed to examine multi-institutional North American outcomes with RAA thyroidectomy in the context of these institutions' transcervical approach (TCA) outcomes. STUDY DESIGN: Cases of lobectomy and total thyroidectomy via transaxillary, robotic facelift, and transoral endoscopic vestibular approaches were reviewed. Demographic characteristics, outcomes, and complications were compared with the same measures in patients undergoing lobectomy and total thyroidectomy via TCA by the primary RAA surgeons at each institution. Patients who underwent parathyroidectomy or other concomitant neck dissection procedures were excluded. RESULTS: Two hundred and sixteen RAA thyroidectomies were attempted (92 transoral endoscopic vestibular approaches, 70 transaxillary, and 54 robotic facelift) and 410 TCA thyroidectomies were performed. There was no difference in mean index nodule sizes between RAA (2.8 +/- 1.6 cm) and TCA (2.9 +/- 1.9 cm) cohorts ($p = 0.72$). Median operative times for lobectomy were 146 minutes (range 60 to 343 minutes) and 90 minutes (range 25 to 247 minutes) for the RAA and TCA cohorts, respectively ($p < 0.0001$). Median operative time for total thyroidectomy was 170 minutes (range 100 to 398 minutes) vs 126.5 minutes (range 51 to 260 minutes) for the RAA and TCA cohorts, respectively ($p < 0.0001$). There was no difference in the rates of permanent recurrent laryngeal nerve injury between the RAA (0 of 216 [0%]) and TCA (0 of 410 [0%]) cohorts ($p = 0.99$). CONCLUSIONS: Remote-access approach thyroidectomy can be performed in a select North American patient population with outcomes comparable with TCA.
PubMed-ID: 30586640
http://dx.doi.org/10.1016/j.jamcollsurg.2018.12.005

Evaluation of Parathyroid Glands with Indocyanine Green Fluorescence Angiography After Thyroidectomy.
World J Surg, 43(6):1538-43.
A. V. Rudin, T. J. McKenzie, G. B. Thompson, D. R. Farley and M. L. Lyden. 2019.
BACKGROUND: Indocyanine green fluorescence angiography (ICGA) is a new adjunct that has been used in surgical procedures to assess blood flow. This study evaluated the utility of ICGA compared to visual inspection to predict parathyroid function, guide autotransplantation and potentially decrease permanent hypoparathyroidism. METHODS: This was a retrospective study of patients who underwent total or near-total thyroidectomy (T-NT) between January 2015 and March 2018. Patients with preoperative hyperparathyroidism and those undergoing reoperation were excluded. Patients who had ICGA were compared to T-NT patients without ICGA. Data were analyzed to assess the frequency of autotransplantation and incidence of hypoparathyroidism between groups. RESULTS: In total, 210 patients underwent T-NT: 86 with ICGA and 124 without. Autotransplantation was more common in the ICGA group at 36% compared to 12% in the control ($p = 0.0001$). There was no correlation with at least one normal parathyroid gland on ICGA and postoperative PTH levels ($p = 0.75$). There was a difference in having normal postoperative PTH when there were at least two normal parathyroid glands ($n = 50$) compared to patients with less than two normal ICGA glands ($n = 36$, $p = 0.044$). Visual assessment and ICGA assessment of vascularity were in agreement, 245/281 (87%). There were 19 glands (6.8%) that would have undergone autotransplant based on visual inspection that had adequate blood supply on ICGA. Transient hypoparathyroidism was present in 45 out of 124 controls (36%) and 32 out of 86 (37%) in the ICG group. CONCLUSIONS: ICGA is a novel technique that may improve the assessment of parathyroid gland blood supply compared to visual inspection. ICGA can guide more appropriate autotransplantation without compromising postoperative parathyroid function. At least two vascularized glands on ICGA may predict postoperative parathyroid gland function.
PubMed-ID: 30659346
http://dx.doi.org/10.1007/s00268-019-04909-z

Neck and Shoulder Motor Function following Neck Dissection: A Comparison with Healthy Control Subjects.
Otolaryngol Head Neck Surg, 160(6):1009-18.
E. M. Gane, S. M. McPhail, A. L. Hatton, B. J. Panizza and S. P. O'Leary. 2019.
OBJECTIVE: To compare the neck and shoulder motor function of patients following neck dissection, including comparison with a group of healthy volunteers. STUDY DESIGN: Cross-sectional study. SETTING: Two tertiary hospitals in Brisbane, Australia. SUBJECTS AND METHODS: Participants included patients 0.5 to 5 years after unilateral nerve-sparing neck dissection and healthy control subjects. Demographic and clinical information was collected with cervical and shoulder motor function measures (scapular resting position, active range of motion, and isometric muscle strength). Differences between groups were examined via regression analyses that included statistical adjustment for the potential effect of age, sex, body mass index, and other disease-related variables. RESULTS: The 57 patients (68%, men; median age, 62 years) were typically older than the 34 healthy controls (47%, men; median age, 46 years). There were no differences between types of nerve-preserving neck dissection for any of the motor function measures. When adjusted for age, sex, and body mass index, healthy volunteers (vs patients) had significantly greater cervical range (eg, extension coefficient [95% CI]: 11.04 degrees [4.41 degrees -17.67 degrees]), greater affected shoulder range (eg, abduction: 16.64 degrees [1.19 degrees -31.36 degrees]), and greater isometric strength of the cervical flexors (eg, men: 4.24 kgf [1.56-6.93]) and shoulder flexors (eg, men: 8.00 kgf [1.62-14.38]). CONCLUSIONS: Strength and flexibility of the neck and shoulder are impaired following neck dissection in comparison with healthy controls. Clinicians and researchers are encouraged to consider the neck-and the neck dissection as a whole-as a source of motor impairment for these patients and not just the status of the accessory nerve.
PubMed-ID: 30665326
http://dx.doi.org/10.1177/0194599818821885

Prediction of hypocalcemia after total thyroidectomy using indocyanine green angiography of parathyroid glands: A simple quantitative scoring system.
Am J Surg,
S. Galvez-Pastor, N. M. Torregrosa, A. Rios, B. Febrero, R. Gonzalez-Costea, M. A. Garcia-Lopez, M. D. Balsalobre, P. Pastor-Perez, P. Moreno, J. L. Vazquez-Rojas and J. M. Rodriguez. 2019.
BACKGROUND: Hypocalcemia is one of the most common complications after total thyroidectomy. Recently, indocyanine green (ICG) angiography of the parathyroid glands (PGs) has been suggested as a reliable tool for predicting postoperative hypocalcemia. The aim of our study was to evaluate the performance of a simple quantitative score based on ICG angiography of the PGs (4-ICG score) for predicting postoperative hypocalcemia. METHODS: Thirty nine consecutive patients who underwent total thyroidectomy for multinodular goiter were included. For each patient, the 4-ICG score was calculated, adding the individual viability value of the four PGs. Discrimination and correlation analyses were performed. RESULTS: In 32/39 patients, the four PGs were identified. Patients with postoperative hypocalcemia (n=6, 19%) had a lower 4-ICG score (2.5 [1.8-3.3] vs. 4.0 [3.0-6.0]; p=0.003). The 4-ICG score showed good discrimination in terms of predicting postoperative hypocalcemia (AUC=0.875 (0.710-0.965); p=0.001) and a good correlation with postoperative parathyroid function. CONCLUSIONS: The 4-ICG score predicts postoperative hypocalcemia and correlates well with postoperative parathyroid function in patients undergoing total thyroidectomy for multinodular goiter.
PubMed-ID: 30665612
http://dx.doi.org/10.1016/j.amjsurg.2018.12.074

Relationship of Vitamin D Deficiency and Intraoperative Parathyroid Hormone Elevation in Completion and Total Thyroidectomy.
Otolaryngol Head Neck Surg, 160(4):612-5.
B. R. Lawson, A. M. Hinson, J. C. Lucas, D. L. Bodenner and B. C. Stack, Jr. 2019.
OBJECTIVE: To quantify how frequently intraoperative parathyroid hormone levels increase during thyroid surgery and to explore a possible relationship between secondary hyperparathyroidism due to vitamin D deficiency and elevation in intraoperative parathyroid hormone. STUDY DESIGN: Case series with chart review. SETTING: Tertiary academic center. SUBJECTS AND METHODS: A total of 428 consecutive patients undergoing completion and total thyroidectomy by the senior author over a 7-year period were included for analysis. All patients had baseline and postexcision intraoperative parathyroid hormone levels as well as vitamin D levels from the same laboratory. Institute of Medicine criteria were employed for vitamin D stratification (>30, normal; 20-29.9, insufficient; <20, deficient) . Other data analyzed include sex, age, neck dissection status, and parathyroid autotransplantation. RESULTS: A total of 118 patients (27.6%) had an intraoperative parathyroid hormone elevation above baseline. Patients with vitamin D deficiency were significantly more likely to experience hormone elevation (P = .04). When parathyroid hormone rose, it did so by a mean 32.1 pg/mL. Patients with

vitamin D deficiency demonstrated significantly larger hormone increases (P = .03). CONCLUSION: Elevation in intraoperative parathyroid hormone levels above baseline after completion and total thyroidectomy occurs in over one-fourth of cases and is significantly associated with vitamin D deficiency. This study is the first to report this observation. We hypothesize that vitamin D deficiency in these patients may create a subclinical secondary hyperparathyroidism that leads to intraoperative parathyroid hormone elevation when the glands are manipulated. Additional studies will be needed to explore this physiologic mechanism and its clinical significance.
PubMed-ID: 30668264
http://dx.doi.org/10.1177/0194599818825467

Contralateral surgery in patients scheduled for total thyroidectomy with initial loss or absence of signal during neural monitoring.
Br J Surg, 106(4):404-11.
A. Sitges-Serra, L. Gallego-Otaegui, J. Fontane, L. Trillo, L. Lorente-Poch and J. Sancho. 2019.
BACKGROUND: Staged total thyroidectomy has been advised to prevent bilateral recurrent laryngeal nerve paralysis when loss of the signal from neural monitoring is observed after dissection of the initial thyroid lobe. This is supported by expert opinion but hard evidence is lacking. A lost signal can return during surgery or, even if it persists, its positive predictive value is only in the range 60-70 per cent. The aim of the present study was to investigate the clinical outcome of patients in whom total thyroidectomy was performed following loss of signal after dissection of the first thyroid lobe. METHODS: This was a prospective observational study of adult patients scheduled for neural monitoring during total thyroidectomy. The prevalence of first-side absence or loss of signal was recorded. The contralateral thyroid lobe was approached routinely. The vagus and recurrent laryngeal nerves on the first side were retested during and at the end of the contralateral procedure. RESULTS: Some 462 patients were included. Loss (32 patients) or initial absence (8) of signal at dissection of the first thyroid lobe was noted in 40 patients (8.7 per cent). Total thyroidectomy was completed in 29 patients, and a change of surgical strategy adopted in 11 patients with benign disease. At retesting, 15 of 37 initially silent nerves recovered electromyographic signal after a mean(s.d.) interval of 30(14) min. Postoperative vocal cord palsy/paresis was demonstrated in 24 of 40 patients. One patient developed a bilateral paresis that could be managed conservatively. CONCLUSION: After an absence or loss of signal of the recurrent laryngeal nerve following dissection of the first thyroid lobe, contralateral thyroidectomy can be performed safely, avoiding the expense, psychological burden and potential complications of a second procedure.
PubMed-ID: 30681138
http://dx.doi.org/10.1002/bjs.11067

A Population-Based Study on NIFTP Incidence and Survival: Is NIFTP Really a "Benign" Disease?
Ann Surg Oncol, 26(5):1376-84.
A. Eskander, S. F. Hall, M. Manduch, R. Griffiths and J. C. Irish. 2019.
BACKGROUND: This study aimed to determine the incidence of noninvasive follicular thyroid neoplasm with papillary-like features (NIFTP) in Ontario, Canada and the predictors of disease-free survival (DFS) by comparing patients with follicular variant papillary thyroid cancer (FVPTC) and patients with NIFTP. METHODS: This population-based retrospective cohort study included all patients who had definitive surgery for well-differentiated thyroid cancer (WDTC) in Ontario, Canada between 1990 and 2001 and were followed until 2014. A conservative decision rule was applied to subtype-select FVPTCs into NIFTPs after pathology report review. The primary outcome was DFS, for which Cox proportional hazard regression analysis was performed to assess the impact of FVPTC versus NIFTP. RESULTS: At pathology re-review of the 725 FVPTC cases, 318 were reclassified as potential NIFTP. The median follow-up time was 15.3 years for the entire cohort and 15.9 years for those alive at the last follow-up visit. Disease failure occurred for 109 patients, 79 (19.4%) in the FVPTC group and 30 (9.4%) in the NIFTP group ($p < 0.01$). This effect was sustained in the multivariable analysis, with FVPTC showing significantly worse DFS than NIFTP (hazard ratio, 1.84; 95% confidence interval, 1.17-2.89). After recategorization of certain FVPTCs into NIFTPs, the findings showed that NIFTP accounted for 16.8% (1.461/8.699 per 100,000) of all WDTCs. CONCLUSION: The disease failure rate for NIFTP was 9.4%. The NIFTP diagnosis is challenging for the pathologist and may make tumor behavior difficult to predict for this entity. Caution should be used in the management of patients with an NIFTP.
PubMed-ID: 30690683
http://dx.doi.org/10.1245/s10434-019-07187-0

Prolongation of tumour volume doubling time (midDT) is associated with improvement in disease-specific survival in patients with rapidly progressive radioactive iodine refractory differentiated thyroid cancer selected for molecular targeted therapy.
Clin Endocrinol (Oxf), 90(4):617-22.
M. M. Sabra, E. Sherman and R. M. Tuttle. 2019.
PURPOSE: To assess molecular targeted therapy (MTT)'s ability to affect tumour volume doubling time (TVDT) and disease-specific survival (DSS) in patients presenting with lung metastasis from radioactive iodine refractory progressive thyroid cancer. METHODS: In this retrospective study, we examined the clinical characteristics, average tumour volume doubling times of lung metastasis and disease-specific survival of patients with lung metastasis from differentiated thyroid cancer who were treated with MTT. RESULTS: The 5-year DSS from the distant metastasis (DM) diagnosis was 72% with median survival of 8 years (95% CI: 6.6-9.5). The median survival was 2.9 years after MTT start (95% CI: 2.1-3.6). On MTT, lung average tumour volume doubling time (midDT) was prolonged to midDT >/=3 years in 75% of patients with baseline midDT </=1 year and 100% of patients with midDT 1-3 years. In patients with rapidly progressive thyroid cancer (midDT </=1 year at baseline), the median survival was 4.5 years in those with MTT-achieved midDT >/=3 years (95% CI: 2.9-6.2), as opposed to 2.3 years (95% CI: 0.3-4.3) and 0.7 years (95% CI: 0.2-1.3) in those with MTT-achieved midDT of 1-3 years and MTT-achieved midDT </=1 year, respectively (log rank P < 0.001). CONCLUSION: Lung midDT is a useful and important clinical marker of disease-specific survival for patients with progressive radioactive iodine refractory (RAIR) metastatic thyroid cancer. In patients with rapidly progressive metastatic RAIR thyroid cancer, molecular targeted therapy prolongs lung tumour volume doubling time and is associated with improved disease-specific survival.
PubMed-ID: 30706513
http://dx.doi.org/10.1111/cen.13941

Primary Squamous Cell Carcinoma in the Thyroid Gland: A Population-Based Analysis Using the SEER Database.
World J Surg, 43(5):1249-55.
S. Yang, C. Li, X. Shi, B. Ma, W. Xu, H. Jiang, W. Liu, Q. Ji and Y. Wang. 2019.
OBJECTS: To evaluate prognostic factors and treatment outcomes of primary squamous cell carcinoma in thyroid (PSCCTh) over the past decades using a large national database. METHODS: All patients diagnosed with PSCCTh between 1973 and 2015 were identified with the Surveillance, Epidemiology, and End Results Program (SEER) 18-registry database. Relevant clinical data were collected, and prognostic factors of overall survival (OS) and disease-specific survival (DSS) were analyzed. RESULTS: This cohort study included 242 patients, accounting for 0.12% of all primary thyroid carcinomas from 1973 to 2015 nationwide. Of the patients with PSCCTh, 75% were older than 60 years at diagnosis. Patient age older than 60 years (HR 2.242, 95% CI 1.367-3.676, P = 0.001) and a tumor size larger than or equal to 50 mm (HR 1.479, 95% CI 1.011-2.165, P = 0.044) were independent negative prognostic factors. The univariate analysis suggested that the morphological subtype (OS, P = 0.033; DSS, P = 0.048), clinical treatment modality (OS, P < 0.0001; DSS, P < 0.0001), and T stage (OS, P = 0.004; DSS, P = 0.001) were important predictive factors for OS and DSS. In contrast, gender, race, year of diagnosis, geographic location, N stage, and M stage were not prognostic factors. CONCLUSIONS: PSCCTh is a rare malignancy with an aggressive nature and poor prognosis. Survival is predicted by the treatment modality, patient age, T stage, tumor size, and morphological subtypes. This study showed that early diagnosis and complete surgical resection plus adjuvant radiation therapy were associated with a better outcome.
PubMed-ID: 30719559
http://dx.doi.org/10.1007/s00268-019-04906-2

Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer.
Br J Surg, 106(4):412-8.
A. Machens, K. Lorenz and H. Dralle. 2019.
BACKGROUND: It remains unclear when postoperative serum calcitonin levels should be measured in patients with medullary thyroid cancer (MTC) and, specifically, whether this decision should be based on the preoperative calcitonin level or nodal status. METHODS: A cohort of patients with previously untreated MTC was studied. Kaplan-Meier analyses, stratified by preoperative calcitonin level, nodal status and number of nodal metastases, were performed to determine time to calcitonin normalization after initial surgery, with statistical analysis by means of the log rank test. RESULTS: Some 213 patients with node-negative and 182 with node-positive MTC were included in the study. Postoperative calcitonin levels normalized in a mean of 3.5 versus 3.7 days respectively among patients with preoperative calcitonin levels of 10-100 pg/ml (P = 0.815); 4.8 versus 5.3 days

in those with preoperative calcitonin levels of 100.1-500 pg/ml (P = 0.026); 5.3 versus 9.9 days in patients with preoperative calcitonin levels of 500.1-1000 pg/ml (P = 0.004); and 6.6 versus 57.7 days among those with preoperative calcitonin levels exceeding 1000 pg/ml (P < 0.001). Calcitonin levels normalized in a mean of 4.7 days when nodal metastasis was not present, 5.2 days in those with one to five nodal metastases, 7.0 days in patients with six to ten nodal metastases, and 57.1 days among patients with more than ten nodal metastases. Postoperative calcitonin normalization curves paralleled each other in patients with node-negative MTC, but diverged in those with node-positive disease and with more nodal metastases. CONCLUSION: Calcitonin levels typically normalize within 1 week; and within a fortnight in those with node-positive MTC and preoperative calcitonin levels of 500.1-1000 pg/ml. With node-positive MTC and preoperative calcitonin levels exceeding 1000 pg/ml, and with more than ten nodal metastases, calcitonin normalization takes longer.
PubMed-ID: 30725475
http://dx.doi.org/10.1002/bjs.11071

Autofluorescence in Parathyroidectomy: Signal Intensity Correlates with Serum Calcium and Parathyroid Hormone but Routine Clinical Use is Not Justified.
World J Surg, 43(6):1532-7.
A. DiMarco, R. Chotalia, R. Bloxham, C. McIntyre, N. Tolley and F. F. Palazzo. 2019.
BACKGROUND: The inability to identify the pathological gland at surgery results in failure to cure hyperparathyroidism in 2-5%. The poorly understood characteristic of parathyroid tissue to manifest autofluorescence (AF) under near-infrared (NIR) light has been promoted as an intraoperative adjunct in parathyroid surgery. This study sought to explore potential clinical correlates for AF and assess the clinical utility of AF in parathyroid surgery. METHODS: Consecutive patients undergoing parathyroid surgery for primary and renal disease were included. NIR imaging was used intraoperatively and the degree of AF of parathyroid glands graded by the operating surgeon. Variables assessed for correlation with AF were: pre-operative serum calcium and PTH, SestaMIBI positivity, gland weight and histological composition. RESULTS: Ninety-six patients underwent parathyroidectomy over an 8-month period: 49 bilateral explorations, 41 unilateral and 6 focussed lateral approaches: 284 potentially 'visualisable' glands in total. Two hundred and fifty-seven glands (90.5%) were visualised with NIR. Correlation was found between the degree of fluorescence and pre-operative serum calcium and PTH, but not between gland weight and SestaMIBI positivity. In those with renal hyperparathyroidism, a predominance of oxyphil cells correlated with increased AF. CONCLUSION: Autofluorescence intensity correlates with serum calcium, PTH and gland composition. Further refinements would be required for this information to be of value in a clinical setting. Improvements allowing NIR to visualise the additional 9.5% of parathyroids and overcome the variation in signal intensity due to depth of access are required for the routine adoption of this technology. At present, its routine use in a clinical setting cannot be justified.
PubMed-ID: 30737552
http://dx.doi.org/10.1007/s00268-019-04929-9

Dedicated neck (18) F-FDG PET/CT: An additional tool for risk assessment in thyroid nodules at ultrasound intermediate risk.
Clin Endocrinol (Oxf), 90(5):737-43.
P. Trimboli, A. Piccardo, M. Alevizaki, C. Virili, M. Naseri, S. Sola, G. Paone, G. Russ and L. Giovanella. 2019.
BACKGROUND: Several ultrasound (US) risk stratification systems have been proposed for the assessment of thyroid nodules, and their performance was shown as good. However, the rate of nodules assessed at intermediate risk is not negligible and whether they should be submitted or not to further examination is still under debate. The present study aimed to evaluate the reliability of (18) F-FDG PET/CT in stratifying the risk of malignancy in these lesions. METHODS: Two institutions participated to this retrospective study in which a dedicated (18) F-FDG PET/CT was proposed to patients having a thyroid nodule with US assessment of EU-TIRADS 4 or 5. (18) F-FDG PET/CT did not influence the diagnostic and therapeutic decision. Histology was the gold standard for all patients. RESULTS: Ninety-three patients were included for the study with 48 EU-TIRADS 4 and 45 EU-TIRADS 5 nodules. Of these, 26 underwent thyroidectomy following FNAC suspicious for or consistent with malignancy, 38 for inconclusive cytology, 27 because of large goitre and 2 for high-risk lesion at US. At histology, 35 carcinomas and 58 benign lesions were found. Cancer prevalence was 16.7% in EU-TIRADS 4 and 60% in EU-TIRADS 5. Overall, (18) F-FDG PET/CT was positive in 33/35 cancers (94.5% sensitivity) and negative in 31/58 benign lesions (53.4% specificity). When considering only EU-TIRADS 4, (18) F-FDG PET/CT was positive in 7/8 cancers and negative in 20/40 benign lesions; among these, there were 36 cases with FNAC indication according to dimensional cut-off (ie >1.5 cm), and (18) F-FDG PET/CT showed 85.7% sensitivity and 41.4% specificity. CONCLUSIONS: (18) F-FDG PET/CT may have a role in stratifying the cancer risk of thyroid nodules with an intermediate ultrasound assessment. More specifically, thyroid lesions

classified as EU-TIRADS 4 and with no (18) F-FDG uptake could be ruled out from further examination, similar to other anamnestic and clinical suspicious factors of patients. Further prospective and cost-effectiveness studies are needed.
PubMed-ID: 30740757
http://dx.doi.org/10.1111/cen.13949

Long-Term Efficacy of Lymph Node Reoperation for Persistent Papillary Thyroid Cancer: 13-Year Follow-Up.
Ann Surg Oncol, 26(6):1737-43.
A. E. Onuma, E. W. Beal, F. Nabhan, T. Hughes, W. B. Farrar, J. Phay, M. D. Ringel, R. T. Kloos and L. A. Shirley. 2019.
BACKGROUND: Current recommendations for persistent or recurrent locoregional papillary thyroid cancer (PTC) include consideration of surgical resection versus active surveillance. The purpose of this study is to determine long-term outcomes after surgical resection of recurrent or persistent metastatic PTC in cervical lymph nodes after failure of initial surgery and radioactive iodine therapy using newer validated clinical outcomes measures. METHODS: Outcomes of 70 patients who underwent cervical lymphadenectomy (n = 110) from 1999 to 2013 for recurrent or persistent locoregional PTC metastases were reviewed. Measures included biochemical remission (BCR) based on Tg levels, American Thyroid Association classifications for response to treatment [biochemical incomplete response (BIR), structural incomplete response (SIR), indeterminate response (IR), and excellent response (ER)], need for reoperation, surgical complications, disease progression, and death. RESULTS: The median follow-up was 13.1 years, with only two additional reoperations since 2010, one of which had no metastasis on pathology with the other developing anaplastic thyroid cancer in background PTC. ER was achieved in 31 (44%) patients, all of whom remained in ER at time of last follow-up (median 14.1 years). There were no structural recurrences in patients with persistent BIR or IR after reoperation. Patients with SIR had stable disease, except for one who died due to anaplastic thyroid cancer. CONCLUSIONS: Patients who achieved ER after reoperation had no need for further treatment. Patients with persistent detectable Tg levels after reoperation rarely developed structural recurrence. ATA outcomes can be safely used to guide treatment decisions over a decade after reoperation for PTC.
PubMed-ID: 30820785
http://dx.doi.org/10.1245/s10434-019-07263-5

Individual prediction of lateral neck metastasis risk in patients with unifocal papillary thyroid carcinoma.
Eur J Surg Oncol, 45(6):1039-45.
H. Hei, Y. Song and J. Qin. 2019.
INTRODUCTION: Much controversy exists over whether to perform lateral neck dissection (LND) on patients with papillary thyroid carcinoma (PTC). This study aimed to build predictive nomograms that could individually estimate lateral neck metastasis (LNM) risk and help determine follow up intensity. PATIENTS AND METHODS: Unifocal PTC patients who underwent LND between April 2012 and August 2014 were identified. Clinical and pathological variables were retrospectively evaluated using univariate and stepwise multivariate logistic regression analysis. Variables that had statistical significance in final multivariate logistic models were chosen to build nomograms, which were further corrected using the bootstrap resampling method. RESULTS: In all, 505 PTC patients were eligible for analysis. Among these, 178 patients (35.2%) had lateral neck metastasis. Two nomograms were generated: nomogram (c) and nomogram (c + p). Nomogram (c) incorporated four clinical variables: age, tumor size, tumor site, and extrathyroidal extension (ETE). It had a good discriminative ability, with a C-index of 0.79 (bootstrap-corrected, 0.78). Nomogram (c + p) incorporated two clinical variables and two pathological variables: tumor size, tumor site, extranodal extension (ENE), and number of positive nodes in the central compartment. Nomogram (c + p) showed an excellent discriminative ability, with a C-index of 0.86 (bootstrap-corrected, 0.85). CONCLUSION: Two predictive nomograms were generated. Nomogram (c) is a clinical model, whereas nomogram (c + p) is a clinicopathological model. Each nomogram incorporates only four variables and can give an accurate estimate of LNM risk in unifocal PTC patients, which may assist clinicians in patient counseling and decision making regarding LND.
PubMed-ID: 30824213
http://dx.doi.org/10.1016/j.ejso.2019.02.016

Age-Related Trends of Patients Undergoing Thyroidectomy: Analysis of US Inpatient Data from 2005 to 2013.
Otolaryngol Head Neck Surg, 160(3):457-64.
K. A. Echanique, A. Govindan, O. M. Mohamed, M. Sylvester, S. Baredes, M. Yu-Lan Ying and E. Kalyoussef. 2019.
OBJECTIVES: As the country ages, thyroidectomies can be expected to be performed more frequently among the elderly. In this study, we stratified patients by age to explore demographics and complications of patients undergoing thyroidectomy. STUDY DESIGN: Retrospective study with a national database. SETTING: Nationwide Inpatient Sample. SUBJECTS AND METHODS: A total of 414,079 thyroidectomy cases from 2005 to 2013 were identified. Complications, outcomes, demographics, length of stay, and hospital charges were evaluated among patients and stratified by age into 4 cohorts: younger (<65 years), advanced age (65-74 years), elderly (75-84 years), and superelderly (>/=85 years). RESULTS: Of 414,079 thyroidectomy cases identified, patients aged <65 years accounted for 75.6% of cases, while those aged 65-74, 75-84, and >/=85 years accounted for 16.3%, 7.2%, and 0.9%, respectively (P < .001). There was a significant difference in length of stay, total hospital charges, and mortality throughout the different age groups (P < .001), all trending upward with advancing age. In the aging population, incidence of recurrent laryngeal nerve injury, transfusion of erythrocytes, and acute cardiac complications increased with increasing age (P < .001), while hypoparathyroidism decreased with age >/=65 but </=85 years (P < .001). Patients aged >/=75 years had increased odds of mortality as compared with their younger counterparts (P < .001). CONCLUSION: This study utilized a national database to describe and elucidate trends in older populations undergoing thyroidectomy. Thyroid-related complications, including blood transfusion and recurrent laryngeal nerve injury, increased with increasing patient age. This information will help to guide pre- and postoperative care for aging patients undergoing thyroidectomy.
PubMed-ID: 30829140
http://dx.doi.org/10.1177/0194599818825455

Risk of Recurrence in Differentiated Thyroid Cancer: A Population-Based Comparison of the 7th and 8th Editions of the American Joint Committee on Cancer Staging Systems.
Ann Surg Oncol, 26(9):2703-10.
T. Gan, B. Huang, Q. Chen, H. F. Sinner, C. Y. Lee, D. A. Sloan and R. W. Randle. 2019.
BACKGROUND: Differentiated thyroid cancer (DTC) survival is excellent, making recurrence a more clinically relevant prognosticator. We hypothesized that the new American Joint Committee on Cancer (AJCC) 8th edition improves on the utility of the 7th edition in predicting the risk of recurrence in DTC. METHODS: A population-based retrospective review compared the risk of recurrence in patients with DTC according to the AJCC 7th and 8th editions using the Surveillance, Epidemiology, and End Results-based Kentucky Cancer Registry from 2004 to 2012. RESULTS: A total of 3248 patients with DTC were considered disease-free after treatment. Twenty percent of patients were downstaged from the 7th edition to the 8th edition. Most patients had stage I disease (80% in the 7th edition and 94% in the 8th edition). A total of 110 (3%) patients recurred after a median of 27 months. The risk of recurrence was significantly associated with stage for both editions (p < 0.001). In the 7th edition, there was poor differentiation between lower stages and better differentiation between higher stages (stage II hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.39-2.11; stage III HR 3.72, 95% CI 2.29-6.07; stage IV HR 11.66, 95% CI 7.10-19.15; all compared with stage I). The 8th edition better differentiated lower stages (stage II HR 4.06, 95% CI 2.38-6.93; stage III HR 13.07, 95% CI 5.30-32.22; stage IV 11.88, 95% CI 3.76-37.59; all compared with stage I). CONCLUSIONS: The AJCC 8th edition better differentiates the risk of DTC recurrence for early stages of disease compared with the 7th edition. However, limitations remain, emphasizing the importance of adjunctive strategies to estimate the risk of recurrence.
PubMed-ID: 30830539
http://dx.doi.org/10.1245/s10434-019-07275-1

Long-Term Efficacy of a Single Session of RFA for Benign Thyroid Nodules: A Longitudinal 5-Year Observational Study.
J Clin Endocrinol Metab, 104(9):3751-6.
M. Deandrea, P. Trimboli, F. Garino, A. Mormile, G. Magliona, M. J. Ramunni, L. Giovanella and P. P. Limone. 2019.
CONTEXT: Radiofrequency ablation (RFA) of benign thyroid nodules has been gaining consensus. However, no solid information on its long-term efficacy is available. OBJECTIVE: To analyze the long-term results of single-session RFA. DESIGN: Retrospective longitudinal observational study. SETTING: Primary care center. PATIENTS OR OTHER PARTICIPANTS: Adult outpatients who underwent a single-session RFA and posttreatment follow-up of least 3 years. INTERVENTION: Ultrasound-guided RFA was performed after local

anesthesia by "moving-shot" technique. RFA was performed with a median power of 55W and a median time of 14 minutes with an internally cooled 18-gauge electrode with an active 10-mm tip. MAIN OUTCOME MEASURES: Objective (trend of nodule volume) and subjective (compressive and cosmetic concerns) response to RFA were evaluated. Continuous variables were analyzed by the Wilcoxon and ANOVA test and their correlations by using the Spearman test. Categorical variables were compared by Pearson chi2 test. RESULTS: Two hundred and fifteen patients were included. An early significant reduction of nodule volume was found at 1 year, lasting up to 5 years. A 67% nodule shrinkage was observed at the end of the observation period. The best response was recorded in nodules below 10 mL (79% reduction early and 81% at 5 years). Patients' symptoms were significantly reduced. CONCLUSIONS: This study, by demonstrating a durable shrinkage of benign thyroid nodules treated by RFA with an improvement of subjective symptoms, establishes the reliability of RFA as alternative to surgery in the management of thyroid nodules, thus representing a remarkable novelty for clinical practice.
PubMed-ID: 30860579
http://dx.doi.org/10.1210/jc.2018-02808

The Efficacy and Safety of High-Intensity Focused Ultrasound (HIFU) Therapy for Benign Thyroid Nodules-A Single Center Experience from Singapore.
World J Surg, 43(8):1957-63.
P. S. Prakash, H. B. Oh, W. B. Tan, R. Parameswaran and K. Y. Ngiam. 2019.
BACKGROUND: High-intensity focused ultrasound (HIFU) is a recent noninvasive technique of treating thyroid nodules. Our study aims to investigate the efficacy and safety of HIFU in treating benign thyroid nodules. METHODS: This is a retrospective analysis of consecutive patients who underwent HIFU of benign thyroid nodules at our institution from July 2017-2018. All procedures were performed by a single surgeon. Patients were evaluated immediately post-procedure, and at subsequent intervals of 1 week, 1 month, 3 months, and 6 months. The primary endpoint was thyroid nodule volume reduction at 6 months posttreatment. Secondary endpoints were post-procedure local complications. RESULTS: Ten patients with 13 thyroid nodules were included. The median follow-up period was 426 days (range 238-573). Mean maximum diameter reduced from 2.6 cm (+/-0.8) pretreatment to 1.4 cm (+/-0.7, P < 0.05) 6 months posttreatment. Mean nodule volume reduced from 5.2 cm(3) (+/-4.2) pretreatment to 1.5 cm(3) (+/-1.3, P = 0.01) 6 months posttreatment. Mean volume reduction ratio (VRR) at 6 months posttreatment was 63.2% (+/-22.5, P < 0.05), with volume reduction of >/=50% in 10 of 13 (76.9%) nodules. Two nodules (15.4%) showed size increases from 4 months posttreatment. No patients experienced local skin burns or hematomas. Mean pain scores were 1.5 (+/-1.2) immediate post-procedure, 0.8 (+/-1.5) at 1 week, and 0.6 (+/-1.2) at 1 month post-procedure, respectively, with no reports of pain beyond 1 month. Only two (20.0%) patients had early, temporary posttreatment voice hoarseness. CONCLUSION: Our study shows HIFU ablation to be efficacious and safe-with significant thyroid nodule volume reductions, and no significant or prolonged local complications.
PubMed-ID: 30863871
http://dx.doi.org/10.1007/s00268-019-04976-2

Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer.
Surgery, 166(1):55-60.
H. Zhao, T. Huang and H. Li. 2019.
BACKGROUND: Lymph node metastases from papillary thyroid cancer is believed to disseminate sequentially, first to the central neck and later to the lateral neck. Skip metastases of papillary thyroid cancer, however, are defined as lateral lymph node metastasis without central lymph node metastasis. The aim of this study was to investigate the risk factors for skip metastases and lateral lymph node metastasis of papillary thyroid cancer. METHODS: We reviewed 721 papillary thyroid cancer patients undergoing total thyroidectomy with central lymph node dissection and lateral lymph node dissection during 2013 to 2018. Multivariate logistic regression analysis was performed to identify clinicopathologic risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer. RESULTS: The rate of skip metastases was 7.4% (42 of 567 patients). Multivariate analysis showed that female sex and papillary thyroid microcarcinoma (</= 1 cm) were independent risk factors for skip metastases, with odds ratios ([OR], 95% confidence interval [CI]) of 2.29 (1.02-5.16) and 2.84 (1.46-5.16), respectively. Intrathyroidal spread of papillary thyroid cancer and an increased number of central lymph nodes dissected were inversely associated with skip metastases with ORs (95% CI) of 0.13 (0.02-0.99) and 0.88 (0.83-0.94), respectively. In contrast, a greater tumor size, central lymph node metastasis, an increased number of central lymph nodes dissected, and an increased number of lateral lymph nodes dissected were associated with a lateral lymph node metastasis risk of papillary thyroid cancer, with ORs (95% CI) as follow: 1.67 (1.08-2.59), 3.07 (1.71-5.52), 1.25 (1.14-1.37), and 1.07 (1.04-1.10), respectively, by multivariate analysis. CONCLUSION: Greater tumor size, central lymph node metastasis, and an increased number of both central

lymph nodes and lateral lymph nodes dissected were predictors for lateral lymph node metastasis of papillary thyroid cancer. In addition, papillary thyroid microcarcinoma was an independent risk factor for skip metastases. A complete and comprehensive central compartment dissection may decrease the false-positive detection of skip metastases of papillary thyroid cancer.
PubMed-ID: 30876667
http://dx.doi.org/10.1016/j.surg.2019.01.025

Immune Profiling of Thyroid Carcinomas Suggests the Existence of Two Major Phenotypes: An ATC-Like and a PDTC-Like.
J Clin Endocrinol Metab, 104(8):3557-75.
R. Giannini, S. Moretti, C. Ugolini, E. Macerola, E. Menicali, N. Nucci, S. Morelli, R. Colella, M. Mandarano, A. Sidoni, M. Panfili, F. Basolo and E. Puxeddu. 2019.
OBJECTIVES: The understanding of the mechanisms underlying thyroid cancer immune escape can lead to the identification of new molecular targets and/or efficacy biomarkers. For this purpose, we performed immune expression profiling in thyroid cancers to obtain a comprehensive view on immune mechanisms activated during cancer progression. METHODS: The study was conducted retrospectively in 25 papillary thyroid carcinomas (PTCs), 14 poorly differentiated thyroid carcinomas (PDTC), 13 anaplastic thyroid carcinomas (ATCs), and 7 normal thyroid (NT) tissue samples. Gene expression profiling was obtained on RNA samples using the Nanostring platform and its nCounter PanCancer Immune Profiling Panel. RESULTS: Gene expression comparison of ATC, PTC, and PDTC vs NT showed high number of regulated genes in cancer samples. In detail, immune-related gene sets were significantly upregulated (ATC > PTC > > PDTC). Most ATC and approximately half of PTC showed a microenvironment infiltrated by macrophages and T-cells with CD8+ effector phenotype, part of which appeared to be functionally exhausted. Conversely, most PDTC, as NT samples, as the remaining part of PTC, displayed a poor or absent infiltration by immune cells. Interestingly, an upregulation of inhibitory immune checkpoint mediators, including PDL1, PDL2, PD1, LAG-3, TIM-3, PVR, and TIGIT, could be detected in ATC and PTC. CONCLUSIONS: These data indicated the existence of two major immune phenotypes in thyroid carcinoma: an ATC-like one, including hot and altered-immunosuppressed tumors and a PDTC-like one, including altered-excluded and cold tumors. Confirmation of the findings in locally advanced or metastatic cancer tissues is expected to have important immunotherapeutic implications.
PubMed-ID: 30882858
http://dx.doi.org/10.1210/jc.2018-01167

The Prognosis of Papillary Thyroid Cancer with Initial Distant Metastasis is Strongly Associated with Extensive Extrathyroidal Extension: A Retrospective Cohort Study.
Ann Surg Oncol, 26(7):2200-9.
Y. K. Lee, D. Kim, D. Y. Shin, C. R. Lee, E. J. Lee, S. W. Kang, J. Lee, J. J. Jeong, K. H. Nam, W. Y. Chung and C. S. Park. 2019.
BACKGROUND: Extensive extrathyroidal extension (ETE) has a significant role in the prognosis of papillary thyroid cancer (PTC) without distant metastasis, but its role in PTC with initial distant metastasis has never been studied. This study aimed to evaluate the prognostic significance of extensive ETE regarding disease progression, survival, and remission in PTC patients with initial distant metastasis. METHODS: This retrospective cohort study included PTC patients with initial distant metastasis who underwent total thyroidectomy with a median follow-up period of 6.7 years. The prognostic significance of extensive ETE was assessed in terms of time to tumor progression (TTP), cancer-specific survival (CSS), and cumulative incidence of remission with all-cause death as the competing event. RESULTS: The study enrolled 64 patients. Of these patients, 21 (32.8%) had extensive ETE, which was associated with a shorter TTP (adjusted hazard ratio [HR], 4.10; p = 0.015) and a lower CSS rate (p = 0.002, log-rank), particularly for patients 55 years of age or older with stage 4b disease (10-year CSS rate: 33.3% in those with and 92.3% in those without extensive ETE; p = 0.017). Additionally, remission was observed only in patients without extensive ETE (10-year cumulative incidence of remission: 0.0% in those with and 29.3% in those without extensive ETE; p = 0.013). CONCLUSIONS: Extensive ETE of the primary lesion results in poorer prognoses for PTC patients with initial distant metastasis. The high CSS rate for patients with stage 4b PTC but no extensive ETE indicates that the prognosis of this patient population should be distinguished from that of other stage 4 cases.
PubMed-ID: 30895495
http://dx.doi.org/10.1245/s10434-019-07314-x

Cure and survival of sporadic medullary thyroid carcinoma following systematic preoperative calcitonin screening.
Langenbecks Arch Surg, 404(4):411-9.
F. Torresan, C. Mian, E. Cavedon and M. Iacobone. 2019.
BACKGROUND: The improvement in outcome of sporadic medullary thyroid carcinoma (MTC) during the last decades remains controversial, even if a trend toward a better prognosis has been recently proposed. This study was aimed to determine the time trend cure and survival rates in sporadic MTC according to the use of systematic preoperative calcitonin screening. METHODS: Retrospective analysis of 178 sporadic MTC patients operated between 1980 and 2017 was performed. The impact of prognostic factors on cure and survival following the introduction of routine preoperative calcitonin screening in 2001 was evaluated according to the year of surgery. RESULTS: Since 2001, a significant decline of node-positive tumors (from 56.1 to 34.7%) and advanced stage at diagnosis (stage III/IV from 56.1 to 34.7%) occurred, with a concomitant significant increase in cure rate (64.5% vs 38.6%; $p = 0.0012$) and survival ($p < 0.05$). At univariate analysis, the cure was achieved more frequently in more recently operated patients (64.5% vs 38.6%; $p = 0.0012$), in disease staging I/II (86.5% vs 13.5%; $p < 0.0001$), in patients undergoing preoperative calcitonin screening (63.8% vs 23.5%; $p < 0.0001$) and in the absence of lymph node metastases (86.5% vs 13.5%; $p < 0.0001$). At multivariate analysis, only preoperative calcitonin screening and stage at diagnosis turned out to be significant independent prognostic factors for cure and survival. CONCLUSION: The outcome of sporadic MTC improved in the new millennium; diagnosis was achieved earlier, at a less advanced stage. Routine preoperative calcitonin screening may have contributed to improve cure and survival rates.
PubMed-ID: 30903267
http://dx.doi.org/10.1007/s00423-019-01764-3

Changes in total thyroidectomy versus thyroid lobectomy for papillary thyroid cancer during the past 15 years.
Surgery, 166(1):41-7.
B. C. James, L. Timsina, R. Graham, P. Angelos and D. A. Haggstrom. 2019.
BACKGROUND: The incidence of papillary thyroid cancer has increased substantially during the past 15 years, which is likely related to an increased detection of small, nonlethal cancers. Studies have shown that patients may have a similar prognosis when undergoing less aggressive surgical intervention, such as thyroid lobectomy. The objective of this study is to determine whether surgical treatment patterns for papillary thyroid cancer have changed during the past 15 years. METHODS: We performed a retrospective cohort study evaluating changes in the incidence and proportion of total thyroidectomy versus thyroid lobectomy for histologically confirmed papillary thyroid cancers, using the National Cancer Institute Surveillance, Epidemiology, and End Results cancer registries between 2000 and 2014. RESULTS: During the study period, 44,537 patients underwent surgical treatment for papillary thyroid cancer, of which 77% were female and 81.3% were white. The incidence of papillary thyroid cancer more than doubled: from 6.2 (5.9-6.5) to 13.0 (12.5-13.4) per 100,000. The proportion of total thyroidectomy among all papillary cases increased from 78.16% in 2000 to 85.67% in 2014, and the proportion of thyroid lobectomy dropped from 16.62% to 11.41%. When stratified by tumor size, we observed a sustained and increasing gap in the proportions of total thyroidectomy and thyroid lobectomy. CONCLUSION: The incidence of total thyroidectomy has not decreased despite recommendations encouraging consideration of lobectomy for patients with small papillary thyroid cancers. Although these findings could be attributed to the lag between scientific evidence and clinical practice, further work is warranted to explore any additional patient and provider factors that may explain this lack of change.
PubMed-ID: 30904172
http://dx.doi.org/10.1016/j.surg.2019.01.007

The impact of completion thyroidectomy.
Eur J Surg Oncol, 45(7):1171-4.
R. Sawant, K. Hulse, S. Sohrabi, J. C. L. Yeo, K. Pal, F. W. Gibb, R. Adamson and I. J. Nixon. 2019.
INTRODUCTION: The oncological benefit of completion thyroidectomy (CT) following thyroid lobectomy (TL) is presumed to be similar to that of upfront total thyroidectomy(TT), from a patient's perspective the risk and inconvenience of further surgery adds significantly to the impact of the overall treatment. The aim of this study is to assess the impact of CT in terms of the duration of admission and associated complications. METHODS: A study of consecutive patients with DTC identified from prospective MDT records of South-East Scotland from 2009 to 2015. Surgical data was extracted from electronic medical record. RESULTS: Of 361 patients diagnosed with DTC, 161 (45%) had CT. The median postoperative stay was 1 day (range 1-5days). In total 22 patients (14%)suffered complications. Four patients (3%) developed postoperative haematoma. Two (1%) had an identified permanent nerve palsy on the completion side. 13 patients (8%) remained on calcium supplementation

for more than 6 months postoperatively and three patients (2%) developed wound complications. CONCLUSIONS: Our study confirms that CT is regularly performed (45%). Recent changes in international guidelines recognize increasing number of patients as eligible for a conservative approach but recommend CT based on whether upfront TT would have been recommended if the TL pathology were known from the outset. Such an approach fails to consider the additional risk and inconvenience of CT on the overall patient experience. Due to a relatively high rate of complications, only those patients who are most likely to benefit from further surgery to facilitate adjuvant radioactive iodine should be offered additional surgery.
PubMed-ID: 30910458
http://dx.doi.org/10.1016/j.ejso.2019.03.018

Hypoparathyroidism After Total Thyroidectomy: Importance of the Intraoperative Management of the Parathyroid Glands.
World J Surg, 43(7):1728-35.
G. Ponce de Leon-Ballesteros, D. Velazquez-Fernandez, F. J. Hernandez-Calderon, C. Bonilla-Ramirez, R. H. Perez-Soto, J. P. Pantoja, M. Sierra and M. F. Herrera. 2019.
BACKGROUND: Total thyroidectomy is the most common surgical procedure for the treatment of thyroid diseases. Postoperative hypocalcemia/hypoparathyroidism is the most frequent complication after total thyroidectomy. The aim of this study was to evaluate the rate of postoperative hypocalcemia and permanent hypoparathyroidism after total thyroidectomy in order to identify potential risk factors and to evaluate the impact of parathyroid autotransplantation. PATIENTS AND METHODS: We performed a retrospective analysis of 1018 patients who underwent total thyroidectomy at our institution between 2000 and 2016. Medical records were reviewed to analyze patient features, clinical presentation, management and postoperative complications. Descriptive and inferential statistics were employed based on the natural scaling of each included variable. Statistical significance was set at p </= 0.05. RESULTS: Mean +/- SD age was 46.79 +/- 15.9 years; 112 (11.7%) were males and 844 (88.3%) females. A total of 642 (67.2%) patients underwent surgery for malignant disease. The rate of postoperative hypocalcemia, transient, protracted and permanent hypoparathyroidism was 32.8%, 14.43%, 18.4% and 3.9%, respectively. Permanent hypoparathyroidism was significantly associated with the number of parathyroid glands remaining in situ (4 glands: 2.5%, 3 glands: 3.8%, 1-2 glands: 13.3%; p < 0.0001) [OR for 1-2 glands in situ = 5.32, CI 95% 2.61-10.82]. Other risk factors related to permanent hypoparathyroidism were obesity (OR 3.56, CI 95% 1.79-7.07), concomitant level VI lymph node dissection (OR 3.04, CI 95% 1.46-6.37) and incidental parathyroidectomy without autotransplantation (OR 3.6, CI 95% 1.85-7.02). CONCLUSIONS: Identification and in situ preservation of at least three parathyroid glands were associated with a lower rate of postoperative hypocalcemia (30.4%) and permanent postoperative hypoparathyroidism (2.79%).
PubMed-ID: 30919027
http://dx.doi.org/10.1007/s00268-019-04987-z

Indeterminate nodules by the Bethesda system for reporting thyroid cytopathology in Israel: Frequency, and risk of malignancy after reclassification of follicular thyroid neoplasm with papillary-like features.
Eur J Surg Oncol, 45(7):1182-7.
R. C. Rosenblum, A. Shtabsky, S. Marmor, L. Trejo, I. Yaish, S. Barnes, M. Yehuda, N. Stern, Z. Silman and K. M. Tordjman. 2019.
OBJECTIVE: We aimed to determine the frequency and risk of malignancy (ROM) for indeterminate thyroid nodules, categories III (B3) and IV (B4) of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), at a large institution in Israel. Additionally, we investigated the impact of redefining follicular neoplasm with papillary-like nuclear features (NIFTP) as non-malignant on malignancy rates. METHODS: In this retrospective study of all thyroid fine needle aspirations (FNAs) performed at Tel Aviv-Sourasky Medical Center between January 2013 and December 2015, we assessed ROM for B3 and B4 nodules. Potential risk factors thought to affect a-priori ROM were assessed. Suspected NIFTP lesions were re-examined, and if proven, reclassified as benign. RESULTS: 3701 nodules were sampled in 2919 FNAs performed on 2674 patients. B3 reports comprised 7.7% of all nodules (n=284); B4 represented 3.6% (n=132). In multivariate logistic regression, male gender, being of former Soviet Union origin, and smoking increased ROM for B3 nodules by a factor of 7.97 (P=0.002; CI: 2.2-23.4), 9.15 (P=0.021; CI:1.4-60.0), and 11.0 (P=0.001; CI 2.8-44.8), respectively. Reclassifying NIFTP decreased ROM from 14% to 12.5% for B3, and from 26.7% to 25% for B4 nodules. NIFTP comprised 9.5% of previously diagnosed resected malignant tumors. CONCLUSIONS: The relative frequencies of B3 and B4 nodules and their associated malignancy rates were consistent with previous series. Risk factors identified for malignancy may help characterize patients most likely to benefit from surgery. Reclassifying NIFTP had a substantial impact on the ROM in the resected tumors previously diagnosed as malignant.

PubMed-ID: 30928335
http://dx.doi.org/10.1016/j.ejso.2019.03.015

Completion thyroidectomy-indications and complications.
Eur J Surg Oncol, 45(7):1129-31.
A. R. Shaha and R. Michael Tuttle. 2019.
PubMed-ID: 30935727
http://dx.doi.org/10.1016/j.ejso.2019.03.028

Thyroid Antibody Status is Associated with Central Lymph Node Metastases in Papillary Thyroid Carcinoma Patients with Hashimoto's Thyroiditis.
Ann Surg Oncol, 26(6):1751-8.
X. Wen, B. Wang, Q. Jin, W. Zhang and M. Qiu. 2019.
OBJECTIVE: The aim of this study was to explore the impact of thyroid antibody status on central lymph node metastases (CLNM) in papillary thyroid carcinoma (PTC) patients with Hashimoto's thyroiditis (HT). METHODS: A retrospective analysis was performed on 346 PTC patients with HT who underwent thyroidectomy and ipsilateral central lymph node dissection (CLND). Histopathological characteristics of the tumor and serum levels of thyroid hormone, as well as antibodies, were collected and analyzed. RESULTS: The multivariate logistic regression analysis showed that being male [odds ratio (OR) 3.269, 95% confidence interval (CI) 1.240-8.619], tumor size > 1 cm [1 cm < diameter (D) </= 2 cm: OR 6.947, 95% CI 2.886-16.722; 2 cm < D: OR 5.880, 1.937-17.846], and antibody status [thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) double negative: OR 3.791, 95% CI 1.391-10.331; TPOAb and TgAb double positive: OR 4.047, 95% CI 1.509-10.856; TgAb single positive: OR 6.024, 95% CI 2.019-17.970] were independent risk factors for CLNM. Additionally, a risk-score scale, including sex, antibody status, and tumor size, was established to predict CLNM. The sensitivity, specificity, positive predictive value, and negative predictive value were 55.7%, 84.4%, 74.4%, and 70%, respectively, when the cut-off point was chosen as 3. CONCLUSIONS: Antibody status is a critical independent risk factor for CLNM in PTC patients with HT. For the CLND strategy, a more conservative option could be considered in a low-risk cohort with the following characteristics: female sex, smaller tumor size, and TPOAb single positive.
PubMed-ID: 30937662
http://dx.doi.org/10.1245/s10434-019-07256-4

The Importance of Diagnosing Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) Based on the Defined Criteria.
Ann Surg Oncol, 26(7):2306-7.
P. W. Rosario. 2019.
PubMed-ID: 30989494
http://dx.doi.org/10.1245/s10434-019-07354-3

Risk of incident circulatory disease in patients treated for differentiated thyroid carcinoma with no history of cardiovascular disease.
Clin Endocrinol (Oxf), 91(2):323-30.
K. A. Toulis, D. Viola, G. Gkoutos, D. Keerthy, K. Boelaert and K. Nirantharakumar. 2019.
CONTEXT: The incidence of differentiated thyroid cancer (DTC) is increasing, yet the prognosis is favourable and long-term survival is expected. Exogenous TSH suppression has been used for many years to prevent DTC recurrence and may be associated with increased risks of circulatory diseases. DESIGN: Risks of circulatory disease in patients treated for DTC were compared to randomly matched patients without DTC (controls) up to a 1:5 ratio using age, sex, body mass index (BMI) and smoking as the matching parameters in a population-based, open cohort study using The Health Improvement Network. PATIENTS: A total of 3009 patients treated for DTC with no pre-existing cardiovascular disease were identified and matched to 11 303 controls, followed up to median of 5 years. RESULTS: A total of 1259 incident circulatory events were recorded during the observation period. No difference in the risk of ischaemic heart disease (IHD) (adjusted hazards ratio [aHR]: 1.04, 95% CI: 0.80-1.36) or heart failure (HF) (aHR: 1.27, 95% CI: 0.89-1.81) was detected. The risk of atrial fibrillation (AF) and stroke was significantly higher in patients with DTC (aHR: 1.71, 95% CI: 1.36-2.15 and aHR: 1.34, 95% CI: 1.05-1.72, respectively). In a sensitivity analysis limited to newly diagnosed patients with DTC, only the risk of AF was consistently elevated (aHR: 1.86, 95% CI: 1.33-2.60). CONCLUSIONS: The increased risk of AF in patients who have undergone treatment for DTC but without pre-existing CVD may warrant periodic screening for this arrhythmia. Whereas no evidence of increased risk of IHD or HF was observed, the increased risk of stroke/TIA warrants further investigation.

PubMed-ID: 30993728
http://dx.doi.org/10.1111/cen.13990

Rethinking Malignancy Risk in Indeterminate Thyroid Nodules with Positive Molecular Studies: Southern California Permanente Experience.
Otolaryngol Head Neck Surg:194599819842859.
D. S. Cohen, J. E. Tongson-Ignacio, C. M. Lolachi, V. S. Ghaderi, B. Jahan-Parwar and L. D. R. Thompson.
2019.
OBJECTIVES: To recognize that thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS; Bethesda III) have different risks of malignancy based on genetic mutation and to consider molecular testing of nodules with AUS/FLUS to help avoid unnecessary morbidity or cost. STUDY DESIGN: Retrospective cohort study. SETTING: Multiple locations within Southern California Permanente Medical Group. SUBJECTS AND METHODS: Patients included those with indeterminate thyroid nodules and AUS/FLUS on 2 separate fine-needle aspirations with positive ThyGenX testing from 2014 to 2017 who underwent thyroid surgery. Patients were classified as having benign or malignant disease. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features was considered benign. RESULTS: A total of 231 patients had repeat AUS/FLUS with positive molecular testing and surgery. The most frequent type of malignancy was papillary carcinoma, followed by follicular carcinoma. The overall prevalence of malignancy in nodules with mutations was 74.0%, although there was considerable variation: BRAF = 100%, RET = 100%, PAX8-PPARgamma = 84.6%, HRAS = 70.7%, NRAS = 63.4%, and KRAS = 33%-a statistically significant finding (P < .001). CONCLUSIONS: Not all molecular mutations in thyroid nodules with AUS/FLUS have a high risk of malignancy. Of note, patients with BRAF and RET mutations in our population had a 100% risk of malignancy. Patients with PAX, HRAS, or NRAS mutations had a high risk of malignancy, while patients with KRAS mutations had a lower risk of malignancy. Further studies are needed to determine if the presence of certain molecular mutations can help personalize care and aid in the decision for thyroid surgery.
PubMed-ID: 31013183
http://dx.doi.org/10.1177/0194599819842859

Parathyroids

Meta-Analyses

The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery.
Langenbecks Arch Surg, 404(1):63-70.
D. Taterra, L. M. Wong, J. Vikse, B. Sanna, P. Pekala, J. Walocha, R. Cirocchi, K. Tomaszewski and B. M. Henry. 2019.
PURPOSE: The anatomy of parathyroid glands (PTG) is highly variable in the population. The aim of this study was to conduct a systematic analysis on the prevalence and location of PTG in healthy and hyperparathyroidism (HPT) patients. METHODS: An extensive search of the major electronic databases was conducted to identify all studies that reported relevant data on the number of PTG per patient and location of PTG. The data was extracted from the eligible studies and pooled into a meta-analysis. RESULTS: The overall analysis of 26 studies (n = 7005 patients; n = 23,519 PTG) on the number of PTG showed that 81.4% (95% CI 65.4-85.8) of patients have four PTG. A total of 15.9% of PTG are present in ectopic locations, with 11.6% (95% CI 5.1-19.1) in the neck and 4.3% (95% CI 0.7-9.9) in mediastinum. The subgroup analysis of ectopic PTG showed that 51.7% of ectopic PTG in the neck are localized in retroesophageal/paraesophageal space or in the thyroid gland. No significant differences were observed between the healthy and HPT patients and cadaveric and intraoperative studies. CONCLUSIONS: Knowledge regarding the prevalence, location, and anatomy of PTG is essential for surgeons planning for and carrying out parathyroidectomies, as any unidentified PTG, either supernumerary or in ectopic location, can result in unsuccessful treatment and need for reoperation.
PubMed-ID: 30762091
http://dx.doi.org/10.1007/s00423-019-01751-8

Randomized controlled trials

Effect of Parathyroidectomy on Cardiovascular Risk Factors in Primary Hyperparathyroidism: A Randomized Clinical Trial.
J Clin Endocrinol Metab, 104(8):3223-32.
H. Ejlsmark-Svensson, L. Rolighed and L. Rejnmark. 2019.
CONTEXT: It remains unclear whether risk of cardiovascular diseases is increased in patients with mild (<1.45 mmol/L) to moderate (>/=1.45 to 1.60 mmol/L) primary hyperparathyroidism (PHPT). OBJECTIVE: We aimed to determine the short-term effect of parathyroidectomy (PTX) on arterial stiffness, cholesterol levels, and blood pressure (BP). DESIGN: This study was a clinical trial randomly allocating patients to either PTX or a control group (no surgery). Follow-up was performed 3 months after surgery in the PTX group and 3 months after baseline in the control group. SETTING: University hospital. PARTICIPANTS: We recruited 79 patients with PHPT; 69 participants completed the study. MAIN OUTCOMES: Office and ambulatory 24-hour BP, pulse wave velocity (PWV), augmentation index, and fasting plasma cholesterol levels. RESULTS: At baseline, participants had a median level of ionized calcium of 1.41 mmol/L (range, 1.33 to 1.60 mmol/L) and PTH of 10.4 pmol/L (4.5 to 30.4 pmol/L). Median age was 64 years (range, 18 to 81) and 72% were females. Following PTX, plasma total cholesterol levels decreased significantly compared with the controls (P = 0.04). Changes in PWV, augmentation index, and ambulatory 24-hour BP did not differ between groups, except for an increase in ambulatory diastolic BP following PTX. However, in patients with baseline levels of ionized calcium >/=1.45 mmol/L, PWV decreased significantly in response to PTX compared with the control group (P = 0.03). CONCLUSION: PTX may decrease risk of cardiovascular diseases in PHPT by lowering total cholesterol levels, although ambulatory diastolic BP increases in response to surgery. Patients with moderate to severe hypercalcemia may benefit from PTX by a decrease in PWV.
PubMed-ID: 30860588
http://dx.doi.org/10.1210/jc.2018-02456

Consensus Statements/Guidelines

- None -

Other Articles

Outcomes in patients with renal hyperparathyroidism requiring cinacalcet pre-operatively followed by parathyroidectomy.
Am J Surg, 217(1):146-51.
D. Baker, S. Sevak, R. E. Callahan, P. F. Czako, L. R. Lloyd and S. Nagar. 2019.
BACKGROUND: Cinacalcet is an effective treatment for renal hyperthyroidism when traditional medical therapy has failed. We studied the impact of pre-operative cinacalcet administration on post-surgical outcomes. METHODS: A retrospective analysis was performed of patients from 2002 to 2017 diagnosed with renal hyperparathyroidism requiring parathyroidectomy to evaluate the need for post-operative supplementation and outcomes. RESULTS: 102 patients were identified; 34 patients were treated with cinacalcet prior to undergoing parathyroidectomy. The cinacalcet treatment cohort (CT) demonstrated a greater duration of renal replacement therapy (p=0.03) relative to the untreated cohort (NC). NC had greater proportion receiving peritoneal dialysis (p=<0.0001) compared to other forms of renal replacement, greater pre-operative PTH levels (p=0.001) and greater decrease in PTH after resection (p=0.0086). Post-operative vitamin D supplementation was more frequent in the CT group (p=0.02). After propensity matching for pre-operative PTH and duration of renal replacement therapy, there were no differences in post-operative supplementation or outcomes. CONCLUSIONS: Cinacalcet patients may have advanced disease. These patients have longer duration of renal failure and higher PTH levels. After propensity matching, no significant differences were noted in terms of need for supplementation or outcomes.
PubMed-ID: 29929906
http://dx.doi.org/10.1016/j.amjsurg.2018.06.016

Value of (123)I/(99m)Tc-sestamibi parathyroid scintigraphy with subtraction SPECT/CT in primary hyperparathyroidism for directing minimally invasive parathyroidectomy.
Am J Surg, 217(1):108-13.
P. Asseeva, N. C. Paladino, C. Guerin, F. Castinetti, J. Vaillant-Lombard, A. E. Abdullah, B. Farman-Ara, A. Loundou, F. Sebag and D. Taieb. 2019.
BACKGROUND: Primary hyperparathyroidism/(PHPT) is one of the most common endocrinological conditions. Surgery remains the only curative option. We have evaluated the performance of double isotope (123)I/(99m)Tc-sestamibi parathyroid scintigraphy/(PS) with subtraction SPECT/CT in PHP for identifying uniglandular disease. METHODS: Ninety PHPT patients undergoing parathyroidectomy (December 2015-August 2016) were included. All patients were evaluated with neck ultrasound/(US), PS and SPECT/CT with a new protocol. Outcomes from imaging modalities were reported as: uniglandular disease/(UGD), multiglandular disease/(MGD), or negative, and were compared to post-operative diagnoses. RESULTS: Post-operatively, 72 and 18 patients had true UGD and MGD, respectively. Sensitivities and specificities of US, pinhole scintigraphy with subtraction, pinhole and SPECT/CT with subtraction, and all modalities combined were 91.7%/38.9%, 88.9%/72.2%, 93%/66.7% and 84.72%/77.78%, respectively: specificity of US + PS superior to US alone, p = 0.074. SPECT/CT enables reclassification of doubtful uptake foci. CONCLUSIONS: Combination of neck US and PS with subtraction SPECT/CT offers a higher specificity for guiding towards minimally invasive parathyroidectomy.
PubMed-ID: 29980283
http://dx.doi.org/10.1016/j.amjsurg.2018.06.027

Primary Hyperparathyroidism in Pregnancy: Maternofetal Outcomes at a Quaternary Referral Obstetric Hospital, 2000 Through 2015.
J Clin Endocrinol Metab, 104(3):721-9.
J. Rigg, E. Gilbertson, H. L. Barrett, F. L. Britten and K. Lust. 2019.
Context: Primary hyperparathyroidism (PHPT) in pregnancy has historically been associated with substantial maternofetal morbidity and mortality rates. The optimal treatment and timing of surgical intervention in pregnancy remain contested. Objective: To compare maternofetal outcomes of medically and surgically treated patients with PHPT in pregnancy. Design: Retrospective chart review. Setting: Quaternary referral hospital. Patients: Women with PHPT in pregnancy treated between 1 January 2000 and 31 December 2015. Interventions: Medical therapy or parathyroid surgery. Main Outcomes Measured: Timing of diagnosis; maternal corrected serum calcium concentrations; gestation, indication and mode of delivery; complications attributable to PHPT;

birth weight; and admission to the neonatal intensive care unit (NICU). Results: Twenty-two pregnancies were managed medically, and six patients underwent parathyroidectomy in pregnancy (five in trimester 2, and one at 32 weeks gestation). Most patients treated medically either had a corrected serum calcium concentration <2.85 mmol/L in early pregnancy or had PHPT diagnosed in trimester 3. Of viable medically managed pregnancies, 30% were complicated by preeclampsia, and preterm delivery occurred in 66% of this group. All preterm neonates required admission to the NICU for complications related to prematurity. All surgically treated patients delivered their babies at term, and there were no complications of parathyroid surgery. Conclusion: Maternofetal outcomes have improved relative to that reported in early medical literature in patients treated medically and surgically, but the rates of preeclampsia and preterm delivery were higher in medically treated patients. The study was limited by its retrospective design and small sample sizes.
PubMed-ID: 30247615
http://dx.doi.org/10.1210/jc.2018-01104

Degree of hypercalcemia correlates with parathyroidectomy but not with symptoms.
Am J Surg, 217(3):437-40.
H. Yan, N. Calcatera, T. A. Moo-Young, R. A. Prinz and D. J. Winchester. 2019.
BACKGROUND: Primary hyperparathyroidism (HPT) is an undertreated disease. This study's purpose is to determine if the calcium levels correlate with prevalence of symptoms and surgical treatment in patients with primary HPT. METHOD: Patients treated in 2006-2015 with serum calcium>/=10.0mg/dL and PTH>65pg/mL were identified and stratified based on calcium level: 10.0-10.3 (normocalcemia), 10.4-11.2 (moderate), and >/=11.3 (severe) mg/dL. Clinical variables and rates of surgery were compared between the three groups. RESULTS: A total of 2266 patients were identified: 303 with normocalcemia, 1513 with moderate hypercalcemia, and 450 with severe hypercalcemia. All three groups had similar rates of nephrolithiasis (p=0.10), osteoporosis (p=0.82), and reduced GFR (p=0.06). Most patients (85%) had at least one surgical indication, but only 29% underwent parathyroidectomy. Higher calcium levels were correlated with higher surgical rates: 12% for Ca 10.0-10.3, 27% for Ca 10.4-11.2, and 46% for Ca>/=11.3 (p<0.01). CONCLUSION: Prevalence of symptoms does not correlate with calcium levels. Patients with normocalcemia and moderate hypercalcemia were equally likely to have a surgical indication, but normocalcemic patients are less likely to receive surgery.
PubMed-ID: 30262120
http://dx.doi.org/10.1016/j.amjsurg.2018.09.010

Heterogeneous and low-intensity parathyroid autofluorescence: Patterns suggesting hyperfunction at parathyroid exploration.
Surgery, 165(2):431-7.
E. Kose, B. Kahramangil, H. Aydin, M. Donmez and E. Berber. 2019.
BACKGROUND: Although parathyroid glands have been found to exhibit autofluorescence with near-infrared fluorescence imaging, it is unknown if autofluorescence characteristics vary between hyperfunctioning and normofunctioning glands. The hypothesis was that pattern of autofluorescence exhibited by hyperfunctioning versus normofunctioning parathyroid glands would be different. METHODS: This is an Institutional Review Board-approved, prospective clinical study. Patients underwent bilateral neck exploration for primary hyperparathyroidism, during which autofluorescence from each gland was assessed with near-infrared fluorescence imaging. Pattern and intensity of autofluorescence between hyperfunctioning and normofunctioning parathyroid glands were compared. RESULTS: Overall, 199 parathyroid glands were identified in 50 patients (single gland disease, n=31; multigland disease, n=19). Autofluorescence was detected from 96% (n=192) of parathyroid glands, all of which exhibited a higher intensity autofluorescence than the background tissues. Parathyroid gland location was revealed by near-infrared fluorescence imaging before dissection in 26% (n=52). A total of 77 glands that were large or firm were excised and 122 were preserved because of normal appearance. Hyperfunctioning parathyroid glands had a lower mean normalized autofluorescence intensity than normofunctioning parathyroid glands (1.8, and 2.6, respectively, P < .001). Moreover, hyperfunctioning parathyroid glands more often exhibited a heterogeneous pattern of autofluorescence (75% and 5%, respectively, P < .001). On multivariate analysis, only parathyroid gland hyperfunction correlated with normalized autofluorescence intensity. On receiver operative characteristic curve, optimal cutoff of normalized autofluorescence intensity to differentiate hyperfunctioning from normofunctioning parathyroid glands was 2.0. CONCLUSION: Our results indicate that hyperfunctioning and normofunctioning parathyroid glands exhibit different patterns of autofluorescence in hyperparathyroidism. Given these findings, autofluorescence pattern could be implemented as another adjunctive parameter for gland assessment during parathyroid exploration.
PubMed-ID: 30274733
http://dx.doi.org/10.1016/j.surg.2018.08.006

Risk Factors for Readmission After Parathyroidectomy for Renal Hyperparathyroidism.
World J Surg, 43(2):534-9.
J. D. Lee, E. J. Kuo, L. Du, M. W. Yeh and M. J. Livhits. 2019.
BACKGROUND: Patients with renal hyperparathyroidism (RHPT) are susceptible to major electrolyte fluctuations following parathyroidectomy, which may predispose them to early readmission. The purpose of this study is to evaluate risk factors for readmission in patients undergoing parathyroidectomy for RHPT. METHODS: Patients with renal failure who underwent parathyroidectomy were abstracted from the California Office of Statewide Health Planning and Development (1999-2012). Multivariable logistic regression was used to identify risk factors for readmission within 30 days of discharge. RESULTS: The cohort included 4411 patients, of whom 17% were readmitted. Procedures included subtotal parathyroidectomy (74% of cases) and total parathyroidectomy with autotransplantation (26%). Median time to readmission was 9 days (interquartile range 4-16 days). Electrolyte disturbances including hypocalcemia were present in 36% of readmissions and were the most common cause for readmission. Independent risk factors for readmission included Black race [odds ratio (OR) 1.26, 95% confidence interval (CI) 1.00-1.57], Hispanic race (OR 1.38, 95% CI 1.12-1.71), disposition with home health (OR 1.94, 95% CI 1.35-2.77), disposition to a skilled nursing facility (OR 2.30, 95% CI 1.58-3.35), and total parathyroidectomy with autotransplantation (OR 1.27, 95% CI 1.06-1.52). Advancing age (OR 0.98, 95% CI 0.98-0.99) and surgery at a high-volume hospital (OR 0.53, 95% CI 0.36-0.77) were protective against readmission. CONCLUSIONS: Patients undergoing parathyroidectomy for RHPT have a high readmission rate, most frequently for metabolic complications. Increased postoperative vigilance, which may include outpatient laboratory monitoring, may be indicated in patients with risk factors for readmission.
PubMed-ID: 30341470
http://dx.doi.org/10.1007/s00268-018-4823-3

Correlation of surgeon-performed parathyroid ultrasound with the Perrier classification and gland weight.
Langenbecks Arch Surg, 403(7):897-903.
M. Dordea, U. Moore, J. Batty, T. W. J. Lennard and S. R. Aspinall. 2018.
BACKGROUND: Ultrasound localisation of parathyroid glands correlates with gland weight. We hypothesise that gland identification is also dependent on anatomical location. Perrier et al. have described a uniform and reliable nomenclature for parathyroid locations. We aimed to correlate surgeon-performed ultrasound (SUS) with intra-operative Perrier classification and gland weight. METHODS: Review of a prospectively maintained single operator SUS database of 194 patients referred with non-familial primary hyperparathyroidism (PHPT) at a tertiary centre between 2010 and 2015. Patients underwent MIBI localisation as well as on table SUS. Intra-operative pathological gland locations were classified according to the Perrier nomenclature. RESULTS: Mean weight of pathological glands found and missed by SUS was 1.07 +/- 0.1 g and 0.48 +/- 0.08 g respectively ($p = 0.0001$, unpaired t test). The weight of glands identified was greater than that of missed glands for each of the Perrier locations ($p < 0.001$, Mann-Whitney). The proportion of pathological glands found at each Perrier location varied significantly ($p < 0.0001$, Chi Square); so we find proportionally more B-, D-, E- and F-type glands and miss more A- and C-type glands. The median weight of glands missed on SUS varied significantly across the Perrier groups (Kruskal-Wallis, $p = 0.0034$) and suggests that SUS can miss quite large glands (> 0.5 g) in locations B, C and F; whereas missed glands in locations A, D and E were all small (< 0.5 g). CONCLUSION: Whilst gland identification correlates well with gland weight, anatomical location has a significant impact on failure of localisation irrespective of gland weight. For the surgeon operating on PHPT patients with negative US localisation, particular attention should be paid to locations C, D and A as these are the sites where pathological glands are most often missed on pre-operative US.
PubMed-ID: 30343413
http://dx.doi.org/10.1007/s00423-018-1714-x

Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study.
Clin Endocrinol (Oxf), 90(2):285-92.
T. Vadiveloo, P. T. Donnan, C. J. Leese, K. J. Abraham and G. P. Leese. 2019.
OBJECTIVES: A population-based study was undertaken to determine the mortality and morbidity for people with hypoparathyroidism compared to the general population. METHODS: In this study, patients identified with chronic hypoparathyroidism using data linkage from regional datasets were compared with five age- and gender-matched controls from the general population. Data from biochemistry, hospital admissions, prescribing and the demographic dataset were linked. Outcomes for mortality and specified conditions were examined for all patients and subdivided into post-surgical and non-surgical cases of hypoparathyroidism. RESULTS: All patients had an increased risk of epilepsy (HR 1.65 [95% CI 1.12-2.44]) and cataracts (HR 2.10 [1.30-3.39]) but no increased

fracture risk. Only non-surgical hypoparathyroid patients also had increased mortality (HR 2.11 [1.49-2.98]), cardiovascular disease (HR 2.18 [1.41-3.39]), cerebrovascular disease (HR 2.95 [1.46-5.97]), infection (HR 1.87 [1.2-2.92]) and mental illness (HR 1.59 [1.21-2.11]). There was an increased risk of renal failure (HR 10.05 [95% CI 4.71-21.43]) during the first 2000 days (5.5 years) of follow-up. Renal failure and death were associated with increasing serum calcium concentrations. CONCLUSION: Patients with hypoparathyroidism have an increased risk of cataract and epilepsy. Non-surgical hypoparathyroidism is associated with increased mortality and additional morbidities.
PubMed-ID: 30375660
http://dx.doi.org/10.1111/cen.13895

Biochemical and Skeletal Outcomes of Parathyroidectomy for Normocalcemic (Incipient) Primary Hyperparathyroidism.
Ann Surg Oncol, 26(2):539-46.
S. Sho, E. J. Kuo, A. C. Chen, N. Li, M. W. Yeh and M. J. Livhits. 2019.
BACKGROUND: Normocalcemic (incipient) primary hyperparathyroidism (PHPT) is characterized by inappropriately elevated parathyroid hormone (PTH) levels in the setting of normal serum calcium. The biochemical and skeletal outcomes after parathyroidectomy for normocalcemic PHPT are not well-described. METHODS: All patients who underwent parathyroidectomy for normocalcemic PHPT at a single institution were retrospectively reviewed (2006-2016). Pre- and postoperative calcium, PTH, and bone mineral density (BMD) were compared between patients with normalized versus persistently elevated PTH levels > 6 months after parathyroidectomy. Multivariable Cox regression was used to identify risk factors associated with persistently elevated PTH levels after parathyroidectomy. RESULT: Parathyroidectomy was performed in 71 patients with normocalcemic PHPT, of whom 38 (53.5%) had multi-gland disease. No patients became hypercalcemic, with a median follow-up of 23.1 months. Persistently elevated PTH levels were noted in 33 (46.5%) patients. In multivariable analysis, preoperative PTH > 100 pg/mL was associated with persistently elevated PTH levels after parathyroidectomy. In 38 patients with available pre- and postoperative BMD measurements, the mean preoperative BMD improved + 5.6% ($p < 0.01$) in patients with normalized PTH, while no significant change was observed in patients with persistently elevated PTH levels (- 2.2%, $p = 0.47$). CONCLUSIONS: Elevated PTH levels are common after parathyroidectomy for normocalcemic PHPT. Improvements in BMD may be predicated on long-term normalized PTH levels following surgery.
PubMed-ID: 30406488
http://dx.doi.org/10.1245/s10434-018-6998-0

Preoperative calcitriol reduces postoperative intravenous calcium requirements and length of stay in parathyroidectomy for renal-origin hyperparathyroidism.
Surgery, 165(1):151-7.
S. Alsafran, S. K. Sherman, F. S. Dahdaleh, B. Ruhle, F. Mercier, E. L. Kaplan, P. Angelos and R. H. Grogan. 2019.
BACKGROUND: Patients undergoing subtotal parathyroidectomy for renal-origin hyperparathyroidism often develop postoperative hypocalcemia, requiring calcitriol and intravenous calcium (Postop-IVCa). We hypothesized that in subtotal parathyroidectomy for renal-origin hyperparathyroidism, preoperative calcitriol treatment reduces the use of postoperative administration of intravenous calcium. METHODS: A retrospective chart review compared subtotal parathyroidectomy for renal-origin hyperparathyroidism patients who received preoperative calcitriol treatment with those patietns who did not receive preoperative calcitriol treatment at one institution. Preoperative calcitriol treatment loading doses were 0.5 mcg twice daily for 5 days. All patients received postoperative calcitriol and oral calcium carbonate. Postoperative administration of intravenous calcium was given for symptoms, calcium <7.0 mg/dL, or surgeon preference. The Fisher exact test was used to compare proportions. The Wilcoxon test was used to compare continuous data. Multivariable logistic regression adjusted for confounders. RESULTS: Included were 81 patients who received subtotal parathyroidectomy for renal-origin hyperparathyroidism (41 patients who received preoperative calcitriol treatment, 40 patients who did not receive preoperative calcitriol treatment). Preoperative calcitriol treatment use increased over time (0% 2004-2010, 69% 2011-2016). Groups who received preoperative calcitriol treatment and groups who did not receive preoperative calcitriol treatment were similar in preoperative serum calcium, vitamin D, parathyroid hormone, and median age ($P > .05$ for all). Patients who received preoperative calcitriol treatment less often required postoperative administration of intravenous calcium (34% vs 90% of patients who did not receive preoperative calcitriol treatment, $P < .001$). Median length of stay was 2.0 days shorter for patients who received preoperative calcitriol treatment versus patients who did not receive preoperative calcitriol treatment patients ($P < .001$). Factors associated with postoperative administration of intravenous calcium included not receiving preoperative calcitriol treatment, low preoperative calcium, and high preoperative parathyroid hormone. After multivariable

adjustment, preoperative calcitriol treatment remained independently associated with reduced postoperative administration of intravenous calcium (OR 0.02, P < .001). CONCLUSION: Preoperative calcitriol therapy lowered use of postoperative administration of intravenous calcium by 56% and length of stay by 50% in subtotal parathyroidectomy for renal-origin hyperparathyroidism patients. We believe preoperative calcitriol treatment should become standard of care for subtotal parathyroidectomy for renal-origin hyperparathyroidism.
PubMed-ID: 30413326
http://dx.doi.org/10.1016/j.surg.2018.03.029

Outcomes of parathyroidectomy for primary hyperparathyroidism with nonlocalizing preoperative imaging.
Head Neck, 41(3):666-71.
C. Vuong, E. Frank, A. A. Simental, P. Han, M. Perez, M. Staton, B. M. Hanna and P. A. Andrade Filho. 2019.
BACKGROUND: The purpose of this study was to evaluate our surgical experience in patients with primary hyperparathyroidism (PHPT) with nonlocalizing sestimibi and ultrasound scans. METHODS: A retrospective review of 521 patients treated from April 2005 to July 2017 at Loma Linda University Medical Center who received parathyroidectomy for PHPT. One hundred forty-seven patients (28%) had double negative localization (nonlocalizing sestamibi and ultrasound). RESULTS: Surgical cure for PHPT was 97.3% and 99.2% with nonlocalized and localized disease, respectively, and complication rates were similar between groups. Preoperative parathyroid hormone and gland weight were significantly lower with nonlocalization. The incidence of multigland disease (MGD) was greater in patients with nonlocalization on sestamibi and ultrasound. CONCLUSION: Nonlocalization of parathyroid glands was not associated with decreased cure rate or increased morbidity. The presence of MGD and requirement for more extensive surgery were greater in patients with nonlocalizing disease.
PubMed-ID: 30584672
http://dx.doi.org/10.1002/hed.25456

Intraoperative Parathyroid Autofluorescence Detection in Patients with Primary Hyperparathyroidism.
Ann Surg Oncol, 26(4):1142-8.
M. H. Squires, R. Jarvis, L. A. Shirley and J. E. Phay. 2019.
BACKGROUND: Intrinsic near-infrared (NIR) autofluorescence of the parathyroid gland may improve intraoperative gland identification without the need for contrast agent injection. Compared with patients undergoing surgery for thyroid disease, identification of pathologic parathyroid tissue in patients with hyperparathyroidism is essential. This study analyzed the utility of a novel real-time autofluorescence imaging system in patients with primary hyperparathyroidism enrolled in a prospective feasibility clinical trial. METHODS: Data on patients undergoing surgery for primary hyperparathyroidism by two experienced endocrine surgeons were prospectively collected. Intraoperative imaging was performed with a handheld NIR device, and images were captured for analysis. The collected data included the surgeon's confidence in parathyroid identification, both with ambient light and use of NIR imaging, as well as how the imaging affected the surgical procedure. Images were quantified by Image J software, with autofluorescence reported as mean values +/- SD. RESULTS: From 2017 to 2018, 59 consecutive patients with a diagnosis of primary hyperparathyroidism underwent resection of 69 parathyroid glands. Use of NIR imaging increased the intraoperative confidence of parathyroid identification (on a scale of 0-5) from an average of 4.1 to an average of 4.4 (+0.3, p = 0.003), all of which were confirmed pathologically. The addition of autofluorescence helped to identify the parathyroid gland in 12 patients (20%), and to rule out other soft tissue as not parathyroid in an additional 9 patients (15%). The mean autofluorescence for the parathyroid in situ (75.9 +/- 21.3) was significantly greater than that for the thyroid (61.1 +/- 17.4) or soft tissue (53.3 +/- 19.2) (p < 0.001 for both). The mean absolute difference in parathyroid versus background thyroid autofluorescence was +15.2 (range, 2.4-53.1). CONCLUSION: This is the first prospective trial to examine the utility of parathyroid autofluorescence for identifying glands exclusively in patients with parathyroid disease. Intraoperative identification and localization of parathyroid glands by real-time, NIR imaging using their intrinsic autofluorescence is feasible and may provide a useful adjunct during parathyroid surgery.
PubMed-ID: 30675703
http://dx.doi.org/10.1245/s10434-019-07161-w

Bilateral Neck Exploration for Sporadic Primary Hyperparathyroidism: Use Patterns in 5,597 Patients Undergoing Parathyroidectomy in the Collaborative Endocrine Surgery Quality Improvement Program.
J Am Coll Surg, 228(4):652-9.
C. M. Kiernan, T. Wang, N. D. Perrier, E. G. Grubbs and C. C. Solorzano. 2019.
BACKGROUND: For many surgeons, focused parathyroidectomy has become the preferred approach for management of sporadic primary hyperparathyroidism (HPT). This study describes use patterns of bilateral neck

exploration (BE) by endocrine surgeons participating in the Collaborative Endocrine Surgery Quality Improvement Program (CESQIP). STUDY DESIGN: Using the CESQIP parathyroid dataset (2014 to 2017), use trends, demographic and clinical characteristics of patients undergoing BE vs focused vs focused converted to BE parathyroidectomy were compared. Preoperative, intraoperative, and postoperative variables were also analyzed. RESULTS: Among 5,597 patients who underwent initial parathyroidectomy for HPT, BE was used in 2,253 (40%), 613 (11%) of which were converted procedures. Patients with BE were older and more likely female. Ultrasound (87%), sestamibi (66%), and CT scans (20%) were commonly used. Glands were highly localized. Intraoperative-parathyroid hormone (ioPTH) was used in >90%. Operative time >2 hours was more likely in BE (16%) and converted (30%) vs focused (3%) procedures. Two or more glands were removed in 57% of BE cases. Outpatient procedures were more common in focused cases; emergency room visits, readmissions, and complications were more likely in BE and converted cases. Concern for failure and lack of ioPTH decrease was significantly more common in BE and converted cases. CONCLUSIONS: This is the first analysis of parathyroidectomy use trends by high-volume endocrine surgeons in CESQIP. Bilateral neck exploration is a commonly used approach (40%), and conversion from focused to BE was observed in 11% of cases, despite highly localized glands. Bilateral neck exploration remains a complex and frequently used procedure, and surgeons intending to perform parathyroid surgery should be adequately trained and adept at BE.
PubMed-ID: 30677525
http://dx.doi.org/10.1016/j.jamcollsurg.2018.12.034

Recurrent tertiary hyperparathyroidism due to supernumerary parathyroid glands in a patient receiving long-term hemodialysis: a case report.
BMC Endocr Disord, 19(1):16.
T. S. Tai, Y. H. Hsu, J. M. Chang and C. C. Chen. 2019.
BACKGROUND: Renal hyperparathyroidism is a common complication of chronic kidney disease (CKD) or end-stage renal disease (ESRD) characterized by elevated parathyroid hormone levels secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D. Rapid correction of severe and prolonged hyperparathyroidism by surgical parathyroidectomy in long-term hemodialysis patients occasionally causes hungry bone syndrome. These patients then exhibit severe and long-lasting secondary or tertiary hyperparathyroidism with high bone turnover. CASE PRESENTATION: We report a case of recurrent tertiary hyperparathyroidism after total parathyroidectomy due to supernumerary parathyroid gland in a patient with long-term hemodialysis. Supplementation with intravenous calcium, oral calcium, and vitamin D immediately after patient surgery helps to prevent and treat hungry bone syndrome. CONCLUSIONS: We should prompt a search for the supernumerary parathyroid glands in ESRD patients, who have recurrent or persistent hyperparathyroidism after total parathyroidectomy. ESRD patients are more likely to develop hungry bone syndrome after parathyroidectomy. Prevention and treatment of hungry bone syndrome may be required after ectopic parathyroidectomy in clinical practice.
PubMed-ID: 30691427
http://dx.doi.org/10.1186/s12902-019-0346-7

Parathyroidectomy versus cinacalcet for tertiary hyperparathyroidism; a retrospective analysis.
Langenbecks Arch Surg, 404(1):71-9.
R. R. Dulfer, E. Y. Koh, W. Y. van der Plas, A. F. Engelsman, E. van Dijkum, R. A. Pol, L. Vogt, M. H. de Borst, S. Kruijff, A. Schepers, N. M. Appelman-Dijkstra, J. I. Rotmans, D. A. Hesselink, C. H. J. van Eijck, E. J. Hoorn and T. M. van Ginhoven. 2019.
INTRODUCTION: Tertiary hyperparathyroidism (tHPT), i.e., persistent HPT after kidney transplantation, affects 17-50% of transplant recipients. Treatment of tHPT is mandatory since persistently elevated PTH concentrations after KTx increase the risk of renal allograft dysfunction and osteoporosis. The introduction of cinacalcet in 2004 seemed to offer a medical treatment alternative to parathyroidectomy (PTx). However, the optimal management of tHPT remains unclear. METHODS: A retrospective analysis was performed on patients receiving a kidney transplantation (KT) in two academic centers in the Netherlands. Thirty patients undergoing PTx within 3 years of transplantation and 64 patients treated with cinacalcet 1 year after transplantation for tHPT were included. Primary outcomes were serum calcium and PTH concentrations 1 year after KT and after PTx. RESULTS: Serum calcium normalized in both the cinacalcet and the PTx patients. PTH concentrations remained above the upper limit of normal (median 22.0 pmol/L) 1 year after KT, but returned to within the normal range in the PTx group (median 3.7 pmol/L). Side effects of cinacalcet were difficult to assess; minor complications occurred in three patients. Re-exploration due to persistent tHPT was performed in three (10%) patients. CONCLUSION: In patients with tHPT, cinacalcet normalizes serum calcium, but does not lead to a normalization of serum PTH concentrations. In contrast, PTx leads to a normalization of both serum calcium and PTH concentrations. These

findings suggest that PTx is the treatment of choice for tHPT.
PubMed-ID: 30729318
http://dx.doi.org/10.1007/s00423-019-01755-4

Enhancing Parathyroid Gland Visualization Using a Near Infrared Fluorescence-Based Overlay Imaging System.
J Am Coll Surg, 228(5):730-43.
M. A. McWade, G. Thomas, J. Q. Nguyen, M. E. Sanders, C. C. Solorzano and A. Mahadevan-Jansen. 2019.
BACKGROUND: Misidentifying parathyroid glands (PGs) during thyroidectomies or parathyroidectomies could significantly increase postoperative morbidity. Imaging systems based on near infrared autofluorescence (NIRAF) detection can localize PGs with high accuracy. These devices, however, depict NIRAF images on remote display monitors, where images lack spatial context and comparability with actual surgical field of view. In this study, we designed an overlay tissue imaging system (OTIS) that detects tissue NIRAF and back-projects the collected signal as a visible image directly onto the surgical field of view instead of a display monitor, and tested its ability for enhancing parathyroid visualization. STUDY DESIGN: The OTIS was first calibrated with a fluorescent ink grid and initially tested with parathyroid, thyroid, and lymph node tissues ex vivo. For in vivo measurements, the surgeon's opinion on tissue of interest was first ascertained. After the surgeon looked away, the OTIS back-projected visible green light directly onto the tissue of interest, only if the device detected relatively high NIRAF as observed in PGs. System accuracy was determined by correlating NIRAF projection with surgeon's visual confirmation for in situ PGs or histopathology report for excised PGs. RESULTS: The OTIS yielded 100% accuracy when tested ex vivo with parathyroid, thyroid, and lymph node specimens. Subsequently, the device was evaluated in 30 patients who underwent thyroidectomy and/or parathyroidectomy. Ninety-seven percent of exposed tissue of interest was visualized correctly as PGs by the OTIS, without requiring display monitors or contrast agents. CONCLUSIONS: Although OTIS holds novel potential for enhancing label-free parathyroid visualization directly within the surgical field of view, additional device optimization is required for eventual clinical use.
PubMed-ID: 30769112
http://dx.doi.org/10.1016/j.jamcollsurg.2019.01.017

Quality of Life in Hypoparathyroidism Improves With rhPTH(1-84) Throughout 8 Years of Therapy.
J Clin Endocrinol Metab, 104(7):2748-56.
G. Tabacco, Y. D. Tay, N. E. Cusano, J. Williams, B. Omeragic, R. Majeed, M. G. Almonte, M. R. Rubin and J. P. Bilezikian. 2019.
CONTEXT: Calcium and vitamin D treatment does not improve reduced quality of life (QOL) in hypoparathyroidism. Recombinant human (rh) PTH(1-84) therapy improves QOL metrics for up to 5 years. Data on QOL beyond this time point are not available. OBJECTIVES: To evaluate the effects of 8 years of rhPTH(1-84) therapy on QOL and factors associated with long-term benefit. DESIGN: Prospective, open-label trial. SETTING: Referral center. PATIENTS: Twenty patients with hypoparathyoidism. MAIN OUTCOME MEASURES: RAND 36-Item Short Form Health Survey (SF-36). RESULTS: rhPTH therapy led to substantial improvement in five of the eight SF-36 domains [vitality, social functioning (SF), mental health (MH), bodily pain (BP) and general health] and three of these domains (SF, MH, BP) were no longer lower than the reference population. The improvement in the mental component summary (MCS) score was sustained through 8 years, while the physical component summary (PCS) score improved through 6 years. A lower baseline QOL score was associated with greater improvement. A threshold value <238 (MCS) and <245 (PCS) predicted long-term improvement in 90% and 100% of the cohort, respectively. In patients whose calcium supplementation was reduced, MCS and PCS scores improved more than those whose supplementation did not decline to the same extent. Improvement in PCS was greater in patients whose calcitriol dosage was reduced and duration of disease was shorter. CONCLUSIONS: rhPTH(1-84) improves long-term well-being in hypoparathyroidism. The improvements are most prominent in those with impaired SF-36 at baseline and those whose requirements for conventional therapy decreased substantially.
PubMed-ID: 30776291
http://dx.doi.org/10.1210/jc.2018-02430

Timing of Parathyroidectomy Does Not Influence Renal Function After Kidney Transplantation.
World J Surg, 43(8):1972-80.
W. Y. van der Plas, M. El Moumni, P. J. von Forstner, E. Y. Koh, R. R. Dulfer, T. M. van Ginhoven, J. I. Rotmans, N. M. Appelman-Dijkstra, A. Schepers, E. J. Hoorn, J. T. M. Plukker, L. Vogt, A. F. Engelsman, E. J. M. Nieveen van Dijkum, S. Kruijff, R. A. Pol and M. H. de Borst. 2019.
BACKGROUND: Parathyroidectomy (PTx) is the treatment of choice for end-stage renal disease (ESRD)

patients with therapy-resistant hyperparathyroidism (HPT). The optimal timing of PTx for ESRD-related HPT-before or after kidney transplantation (KTx)-is subject of debate. METHODS: Patients with ESRD-related HPT who underwent both PTx and KTx between 1994 and 2015 were included in a multicenter retrospective study in four university hospitals. Two groups were formed according to treatment sequence: PTx before KTx (PTxKTx) and PTx after KTx (KTxPTx). Primary endpoint was renal function (eGFR, CKD-EPI) between both groups at several time points post-transplantation. Correlation between the timing of PTx and KTx and the course of eGFR was assessed using generalized estimating equations (GEE). RESULTS: The PTxKTx group consisted of 102 (55.1%) and the KTxPTx group of 83 (44.9%) patients. Recipient age, donor type, PTx type, and pre-KTx PTH levels were significantly different between groups. At 5 years after transplantation, eGFR was similar in the PTxKTx group (eGFR 44.5 +/- 4.0 ml/min/1.73 m(2)) and KTxPTx group (40.0 +/- 6.4 ml/min/1.73 m(2), p = 0.43). The unadjusted GEE model showed that timing of PTx was not correlated with graft function over time (mean difference -1.0 ml/min/1.73 m(2), 95% confidence interval -8.4 to 6.4, p = 0.79). Adjustment for potential confounders including recipient age and sex, various donor characteristics, PTx type, and PTH levels did not materially influence the results. CONCLUSIONS: In this multicenter cohort study, timing of PTx before or after KTx does not independently impact graft function over time.
PubMed-ID: 30798418
http://dx.doi.org/10.1007/s00268-019-04952-w

Is calcium supplementation always needed in patients with hypoparathyroidism?
Clin Endocrinol (Oxf), 90(6):775-80.
A. Al-Sharefi, E. Glenister, M. Morris and R. Quinton. 2019.
Oral calcium salts are recommended for the treatment of chronic hypoparathyroidism (HypoPT), although dosimetry is variable between individual patients and clinicians. However, patient feedback on calcium salts can be negative, particularly due to gastrointestinal side effects and hypercalciuria-related complications. We begin with a clinical case of a HypoPT patient taking oral calcium salts following thyroid surgery, who requested support in reducing her dose of these with a view to stopping entirely. To evaluate her request, we first describe the usual treatment of HypoPT according to current guidance and then present data from (a) a case note review of a cohort of 24 HypoPT patients managed with a "no calcium" treatment regimen by single physician (b) a comprehensive online survey of HypoPT patients' treatment and experiences (n = 330). The case note review found that target range serum calcium levels were successfully achieved in all 24 patients since transitioning to a "no calcium" regimen, without any breakthrough hypocalcaemia-related symptoms, the development of new renal stones, the occurrence of calcium-related hospital admissions or the finding of significant hypercalciuria. The online survey identified 36% of HypoPT patients who continued to take activated vitamin D, but had discontinued calcium supplements. HypoPT patients not currently taking calcium reported a significantly lower prevalence of adverse effects and outcomes, both compared with their previous experiences whilst taking calcium and also compared with the 64% of patients who continued to take oral calcium. We conclude that, subject to methodological limitations, there are significant issues of tolerability arising from conventional calcium-based treatment regimens for patients with chronic HypoPT. For selected patients, it may be reasonable to facilitate a managed therapeutic transition to "no calcium" regimen, and we also propose that calcium-based regimes be prospectively evaluated against calcium-free (or calcium-low) alternatives.
PubMed-ID: 30801749
http://dx.doi.org/10.1111/cen.13955

Normocalcemic Primary Hyperparathyroidism in Adults Without a History of Nephrolithiasis or Fractures: A Prospective Study.
Horm Metab Res, 51(4):243-7.
P. W. Rosario and M. R. Calsolari. 2019.
The prevalence and the diagnostic criterion of "normocalcemic" primary hyperparathyroidism (NPHPT) are still uncertain and there is no consensual definition. This prospective study evaluated the prevalence of NPHPT in 676 adults without a history of fractures or nephrolithiasis and who would be submitted to thyroidectomy, the impact of adopting different cut-off values for 25-hydroxyvitamin D and estimated glomerular filtration rate (eGFR), and the agreement between biochemical diagnosis and the surgical finding of altered parathyroid glands. NPHPT was diagnosed in patients with normal total and ionized calcium and elevated PTH (in 2 measurements) and without a known cause of secondary HPT, including eGFR<40 ml/min/1.73 m(2) and 25-hydroxyvitamin D<20 ng/dl. The 4 parathyroid glands were fully explored in these patients. Forty-six patients (6.8%) had a laboratory diagnosis of NPHPT. Altered parathyroid glands were detected in only 4 patients, corresponding to 0.6% of all patients and to 8.7% of those with a biochemical diagnosis of NPHPT. The latter was confirmed in 0/174 men, 1/252 premenopausal women, and 3/250 postmenopausal women. Among the 42 patients with elevated PTH and without altered parathyroid glands, 25 had 25-hydroxyvitamin D between 20 and

30 ng/dl, 7 had eGFR between 40 and 60 ml/min/1.73 m(2), and 9 had both. The prevalence of NPHPT was 0.74% in this adult population without a history of nephrolithiasis or fractures. The diagnostic criterion using eGFR>60 ml/min/1.73 m(2) and 25-hydroxyvitamin D>30 ng/dl was more appropriate considering the agreement with the surgical finding of altered parathyroid glands.
PubMed-ID: 30840998
http://dx.doi.org/10.1055/a-0859-1020

Minimally Invasive Parathyroidectomy without Intraoperative PTH Performed after Positive Ultrasonography as the only Diagnostic Method in Patients with Primary Hyperparathyroidism.
World J Surg, 43(6):1525-31.
R. Schneider, J. Hinrichs, B. Meier, M. K. Walz and P. F. Alesina. 2019.
BACKGROUND: A positive and concordant result of at least two diagnostic modalities is generally recommended prior to focused parathyroidectomy. The aim of this study was to analyze the results of surgery and the accurateness of preoperative ultrasonography (US) as single localization modality in patients who underwent parathyroidectomy without the adjunct of intraoperative Parathormone (PTH) measurement. METHODS: The cases with a preoperative US as the only localization technique, who underwent parathyroidectomy between 10/1999 and 12/2017, were selected from a prospectively maintained database. Therefore, a total number of 242 patients with a mean age of 58.6 +/- 13.7 years were included in the present study. US was performed by referral endocrinologist or by the surgeon during office visits. RESULTS: The overall "cure rate" was 99.2% (240 out of 242 patients). In 228/242 patients (94.2%), a drop of perioperative PTH levels consistent with the definition of cure was observed on the day of surgery. In four of the remaining 14 patients, healing was confirmed by PTH level dropping into the normal range on the first postoperative day. Eight patients were cured after a reoperation was performed at our department. Postoperative complications included one case of permanent recurrent laryngeal nerve palsy (0.4%). CONCLUSIONS: If performed by an experienced endocrinologist and/or endocrine surgeon, a positive US could be the only preoperative localization study in patients with pHPT. Moreover, the add-value of intraoperative PTH is limited. Major advantages of US are a very high accuracy, the ease of performance (accessibility) and its cost-effectiveness compared with Sesta-MIBI scintigraphy.
PubMed-ID: 30847526
http://dx.doi.org/10.1007/s00268-019-04944-w

Predictors of Nephrolithiasis, Osteoporosis, and Mortality in Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 104(9):3692-700.
L. J. Reid, B. Muthukrishnan, D. Patel, J. R. Seckl and F. W. Gibb. 2019.
CONTEXT: Primary hyperparathyroidism (PHPT) has a prevalence of 0.86% and is associated with increased risk of nephrolithiasis and osteoporosis. PHPT may also be associated with increased risk of cardiovascular disease and mortality. OBJECTIVE: To identify risk factors for nephrolithiasis, osteoporosis, and mortality in PHPT. DESIGN: Retrospective cohort study. SETTING: University teaching hospital. PATIENTS: Presented with PHPT between 2006 and 2014 (n = 611). MAIN OUTCOME MEASURE: Assessment of nephrolithiasis, osteoporosis, and mortality. RESULTS: Of patients with PHPT, 13.9% had nephrolithiasis. Most had previously documented stone disease, and only 4.7% of asymptomatic patients who were screened for renal stones had calculi identified, not very dissimilar to the rate in the non-PHPT population. Younger age ($P < 0.001$) and male sex ($P = 0.003$) were the only independent predictors of nephrolithiasis. Of patients with dual-energy X-ray absorptiometry data, 48.4% had osteoporosis (223/461). Older age ($P < 0.001$), lower body mass index ($P = 0.002$), and lower creatinine ($P = 0.006$) were independently associated with a diagnosis of osteoporosis. Higher PTH was independently associated with lower z score at the hip ($P = 0.009$); otherwise, calcium and PTH were not associated with lower z scores. Mortality in PHPT was associated with older age ($P < 0.008$), social deprivation ($P = 0.028$), and adjusted calcium ($P = 0.009$) but not independently with PTH at diagnosis. CONCLUSIONS: Screening for nephrolithiasis has a low yield, particularly in lower risk patients. Osteoporosis is only minimally associated with biochemical indices of PHPT. Mortality is associated with higher calcium (and possibly vitamin D deficiency) but not PTH.
PubMed-ID: 30916764
http://dx.doi.org/10.1210/jc.2018-02483

Practice Patterns in Parathyroid Surgery: A Survey of Asia-Pacific Parathyroid Surgeons.
World J Surg, 43(8):1964-71.
R. Chen, H. B. Oh, R. Parameswaran, A. Gorelik and J. A. Miller. 2019.
BACKGROUND: Practice variations exist amongst parathyroid surgeons depending on their expertise and resources. Our study aims to elucidate the choice of surgical techniques and adjuncts used in parathyroid

surgery by surgeons in the Asia-Pacific region. METHODS: A 25-question online survey was sent to members of five endocrine surgery associations. Questions covered training background, practice environment and preferred techniques in parathyroid surgery. Respondents were divided into three regions: Australia/New Zealand, South/South East Asia and East Asia, and responses were analysed according to region, specialty, case volume and years in practice. RESULTS: One hundred ninety-six surgeons returned the questionnaire. Most surgeons (98%) routinely perform preoperative imaging, with 75% preferring dual imaging with (99m)Tcsestamibi and ultrasound. Ten per cent of surgeons use parathyroid 4DCT as first-line imaging, more commonly in East Asia ($p = 0.038$). Minimally invasive parathyroidectomy is the favoured technique of choice (97%). Most surgeons reporting robotic or endoscopic approaches are from East Asia. Rapid intraoperative parathyroid hormone is accessible to just under half of the surgeons but less available in Australian/New Zealand ($p < 0.001$). The use of intraoperative neuromonitoring is not commonly used, even less so amongst Asian surgeons ($p = 0.048$) and surgeons with low case load ($p = 0.013$). CONCLUSION: Dual localisation techniques are the preferred choice of investigations in preparation for parathyroid surgery, with minimally invasive surgery without neuromonitoring the preferred approach. Use of adjuncts is sporadic and limited to certain centres.
PubMed-ID: 30941454
http://dx.doi.org/10.1007/s00268-019-04990-4

Mild sporadic primary hyperparathyroidism: high rate of multiglandular disease is associated with lower surgical cure rate.
Langenbecks Arch Surg, 404(4):431-8.
E. Trebouet, S. Bannani, M. Wargny, C. Leux, C. Caillard, F. Kraeber-Bodere, K. Renaudin, L. Chaillous, E. Mirallie and C. Ansquer. 2019.
BACKGROUND: Mild primary hyperparathyroidism (serum calcium </= 2.85 mmol/L) is the most representative form of pHPT nowadays. The aim of this study was to evaluate its subtypes and the multiglandular disease (MGD) rate as it may lower the sensitivity of preoperative parathyroid scintigraphy and the surgical cure rate. METHODS: We retrospectively included patients with mild pHPT who underwent parathyroid dual-tracer scintigraphy with (99m)Tc-MIBI SPECT/CT and surgery between January 2013 and December 2015. Cure was defined as normalization of serum calcium (or PTH in the normocalcemic form) at 6 months. MGD was defined by either two abnormal resected glands or persistent disease after resection of at least one abnormal gland. RESULTS: We included 121 patients. Median preoperative serum calcium was 2.68 mmol/L and median PTH was 83.4 pg/mL. A total of 141 glands were resected (95 adenomas, 33 hyperplasias). The subtypes were 57% classic, 32.2% normohormonal, and 10.7% normocalcemic. MGD occurred in 23.5% of patients divided as 13%, 30%, and 64% respectively ($p = 0.0011$). The surgical cure rate was 85.2%. The normocalcemic form had lower cure rate than the normohormonal (45% vs 84%, $p = 0.018$) and classic forms (45% vs 93%, $p = 0.0006$). MIBI scintigraphy identified at least one abnormal lesion, later confirmed by the pathologist in 90/98 patients, making the sensitivity per patient 91.8% (95% CI 84.1-96.2%). CONCLUSIONS: MGD is strongly associated with mild pHPT, especially the normocalcemic form where it accounts for 64% of cases. Bilateral neck exploration should be performed in this population to improve the cure rate, even if the scintigraphy shows a single focus.
PubMed-ID: 30955085
http://dx.doi.org/10.1007/s00423-019-01782-1

Parathyroid Computed Tomography Angiography: Early Experience with a Novel Imaging Technique in Primary Hyperparathyroidism.
Otolaryngol Head Neck Surg, 161(2):251-6.
I. E. Schwartz, G. G. Capra, D. P. Mullin, T. E. Johnson and G. E. Boswell. 2019.
OBJECTIVES: To describe parathyroid computed tomography angiography (PCTA), determine its accuracy, and, as a secondary objective, calculate its mean radiation dosimetry. STUDY DESIGN: Retrospective chart review of patients who underwent parathyroidectomy for primary hyperparathyroidism from 2007 to 2015. SETTING: Single-center tertiary care academic military hospital. SUBJECTS AND METHODS: PCTA is a 2-phase computed tomography imaging technique that uses individualized timing of contrast infusion and novel patient positioning to accurately identify parathyroid adenomas. Consecutive patients who underwent parathyroidectomy for primary hyperparathyroidism from 2007 to 2015 were reviewed; 55% of patients were women. The mean age was 50.9 years (range, 26-68 years). Sensitivity and specificity were calculated as well as mean radiation dosimetry and timing of contrast. RESULTS: A total of 108 procedures were performed during the study period. Twenty-one patients undergoing 22 PCTAs after prior sestamibi scans were nonlocalizing or equivocal. In this group, there were 15 true-positive, 3 false-positive, 4 true-negative, and 0 false-negative PCTAs. This represents a sensitivity of 100% (95% CI, 74.7%-100%) and a specificity of 57% (95% CI, 20%-88%). The mean calculated radiation dose was 5.15 mSv. In the most recent studies, a mean dose of 4.1 mSv was calculated. The ideal time of image acquisition contrast administration varied from 20 to 30 seconds after

contrast infusion. CONCLUSIONS: PCTA is a new technique in anatomic imaging for hyperparathyroidism. In a single-center, single-radiologist retrospective study, it demonstrates excellent accuracy for patients with parathyroid adenomas that are otherwise difficult to localize preoperatively. Preliminary experience suggests that its use may be indicated as a primary imaging modality in the future.
PubMed-ID: 30964739
http://dx.doi.org/10.1177/0194599819842106

Intraoperative parathyroid hormone levels </=40 pg/mL are associated with the lowest persistence rates after parathyroidectomy for primary hyperparathyroidism.
Surgery, 166(1):50-4.
J. Claflin, A. Dhir, N. M. Espinosa, A. G. Antunez, M. S. Cohen, P. G. Gauger, B. S. Miller and D. T. Hughes. 2019.
BACKGROUND: Intraoperative parathyroid hormone (IOPTH) monitoring is used to predict biochemical cure during parathyroidectomy for primary hyperparathyroidism; however, there is variability in the intraoperative parathyroid hormone criteria used by surgeons to predict normocalcemia after parathyroidectomy. This study sought to determine the intraoperative parathyroid hormone criteria correlated with the lowest rates of persistent hyperparathyroidism after parathyroidectomy for primary hyperparathyroidism. MATERIALS AND METHODS: This is a retrospective cohort study of 2,654 patients with primary hyperparathyroidism who underwent parathyroidectomy with intraoperative parathyroid hormone monitoring at a single institution from 1999 to 2014. Multivariate logistic regression analysis was used to measure the association between the lowest intraoperative parathyroid hormone level and the persistence of primary hyperparathyroidism after parathyroidectomy. RESULTS: A total of 66 patients (2.5%) had persistent hyperparathyroidism after parathyroidectomy. Using the traditional intraoperative parathyroid hormone criteria of a >/=50% decrease from the baseline level, the rate of persistent primary hyperparathyroidism was greater when intraoperative parathyroid hormone did not decrease to >/=50% from the baseline level (17 of 180 patients [9.4%] vs 49 of 2,474 [2.0%], [OR 5.9, 95% CI 3.2-10.5, P < .001]). Regardless of whether intraoperative parathyroid hormone decreased >/=50%, patients with a lowest intraoperative parathyroid hormone above the normal range (10-65 pg/mL) had greater persistence rates compared with patients with an intraoperative parathyroid hormone <65 pg/mL (30 of 350 [8.6%] vs 36 of 2,304 [1.6%], [OR 6.6, 95% CI 3.4-12.7, P < .001]). Furthermore, patients with a lowest intraoperative parathyroid hormone 40 to 65 pg/mL had increased rates of adjusted persistence compared with patients with lowest intraoperative parathyroid hormone </=40 pg/mL (13 of 385 [3.4%] vs 23 of 1,919 [1.2%], [OR 4.2, 95% CI 2.0-8.7, P < .001]). Patients with lowest intraoperative parathyroid hormone <5 to 20 pg/mL did not have decreased rates of persistence compared with patients with lowest intraoperative parathyroid hormone 20 to 40 pg/mL (9 of 996 [0.9%] vs 14 of 923 [1.5%], [OR 0.5, 95% CI 0.2-1.2, P = .14]). CONCLUSION: Patients with a lowest intraoperative parathyroid hormone </=40 pg/mL compared with the traditional criteria of a >/=50% decrease from baseline and a final parathyroid hormone in the normal range (<65 pg/mL) had the lowest rates of persistent primary hyperparathyroidism after parathyroidectomy for primary hyperparathyroidism. The single criteria of a lowest intraoperative parathyroid hormone level </=40 pg/mL may best predict the lowest persistent disease rates after parathyroidectomy for primary hyperparathyroidism.
PubMed-ID: 30975497
http://dx.doi.org/10.1016/j.surg.2019.01.024

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

Surgical therapy of adrenal tumors: guidelines from the German Association of Endocrine Surgeons (CAEK).
Langenbecks Arch Surg, 404(4):385-401.
K. Lorenz, P. Langer, B. Niederle, P. Alesina, K. Holzer, C. Nies, T. Musholt, P. E. Goretzki, N. Rayes, M. Quinkler, J. Waldmann, D. Simon, A. Trupka, R. Ladurner, K. Hallfeldt, A. Zielke, D. Saeger, T. Poppel, G. Kukuk, A. Hotker, P. Schabram, S. Schopf, C. Dotzenrath, P. Riss, T. Steinmuller, I. Kopp, C. Vorlander, M. K. Walz and D. K. Bartsch. 2019.
BACKGROUND AND AIMS: Previous guidelines addressing surgery of adrenal tumors required actualization in adaption of developments in the area. The present guideline aims to provide practical and qualified recommendations on an evidence-based level reviewing the prevalent literature for the surgical therapy of adrenal tumors referring to patients of all age groups in operative medicine who require adrenal surgery. It primarily addresses general and visceral surgeons but offers information for all medical doctors related to conservative, ambulatory or inpatient care, rehabilitation, and general practice as well as pediatrics. It extends to interested patients to improve the knowledge and participation in the decision-making process regarding indications and methods of management of adrenal tumors. Furthermore, it provides effective medical options for the surgical treatment of adrenal lesions and balances positive and negative effects. Specific clinical questions addressed refer to indication, diagnostic procedures, effective therapeutic alternatives to surgery, type and extent of surgery, and postoperative management and follow-up regime. METHODS: A PubMed research using specific key words identified literature to be considered and was evaluated for evidence previous to a formal Delphi decision process that finalized consented recommendations in a multidisciplinary setting. RESULTS: Overall, 12 general and 52 specific recommendations regarding surgery for adrenal tumors were generated and complementary comments provided. CONCLUSION: Effective and balanced medical options for the surgical treatment of adrenal tumors are provided on evidence-base. Specific clinical questions regarding indication, diagnostic procedures, alternatives to and type as well as extent of surgery for adrenal tumors including postoperative management are addressed.
PubMed-ID: 30937523
http://dx.doi.org/10.1007/s00423-019-01768-z

Other Articles

Preoperative 18F-FDG PET/CT in Pheochromocytomas and Paragangliomas Allows for Precision Surgery.
Ann Surg, 269(4):741-7.
P. Nockel, M. El Lakis, A. Gaitanidis, R. Merkel, D. Patel, N. Nilubol, T. Prodanov, K. Pacak and E. Kebebew. 2019.
BACKGROUND: Fluorodeoxyglucose (F-FDG) positron emission tomography/computed tomography (PET/CT) imaging is recommended in patients with metastatic pheochromocytoma (PC) and paraganglioma (PGL). There are no data on whether routine preoperative F-FDG PET/CT in all patients with PC/PGL impacts surgical management. OBJECTIVE: The aim of this study was to determine whether routine preoperative F-FDG PET/CT imaging affects the surgical management of patients with PC/PGLs. METHODS: We analyzed clinical,

biochemical, genetic, and anatomic imaging data in 93 consecutive patients with PC/PGL who collectively underwent a total of 100 operations and who had preoperative F-FDG PET/CT imaging. RESULTS: Of 100 operations, preoperative F-FDG PET/CT showed additional lesions compared to anatomic imaging in 15 cases. These patients were more likely to undergo an open surgical approach ($P < 0.05$). Presence of genetic mutation, redo operations, sex, age, or tumor size had no significant association with finding additional lesions on F-FDG PET/CT. CONCLUSIONS: Additional lesions detected on preoperative F-FDG-PET/CT imaging have an impact on the surgical approach in patients with PC/PGLs. Therefore, surgeons should routinely obtain F-FDG-PET/CT imaging in patients with PC/PGL to allow for a more precise surgical intervention.
PubMed-ID: 29334561
http://dx.doi.org/10.1097/SLA.0000000000002671

Pheochromocytoma in Children and Adolescents With Multiple Endocrine Neoplasia Type 2B.
J Clin Endocrinol Metab, 104(1):7-12.
A. Makri, S. Akshintala, C. Derse-Anthony, J. Del Rivero, B. Widemann, C. A. Stratakis, J. Glod and M. Lodish. 2019.
Context: Multiple endocrine neoplasia type 2B (MEN2B) is characterized by early-onset medullary thyroid cancer in virtually all cases and a 50% lifetime risk of pheochromocytoma (PHEO) development. The literature on PHEO in patients with MEN2B is limited with most data being reported from adult studies that primarily address MEN2A. Objective: The aim of the current study is to describe PHEO development in a cohort of pediatric patients with MEN2B. Design: Retrospective chart review of patients with MEN2B evaluated at the National Institutes of Health in the period between July 2007 and February 2018. Results: A total of 38 patients were identified (21 males and 17 females). Mean age at MEN2B diagnosis was 10.6 +/- 3.9 years. Eight patients (21%) developed PHEO in the course of follow-up to date, all of whom were sporadic cases with the classic M918T RET mutation. PHEO was diagnosed based on biochemical and/or imaging screening studies in five patients, whereas three patients presented with symptoms of excess catecholamines. PHEO was diagnosed at a mean age 15.2 +/- 4.6 (range, 10 to 25) years and 4.0 +/- 3.3 years after MEN2B diagnosis. Only one patient was diagnosed with PHEO as the initial manifestation of MEN2B after she presented with hypertension and secondary amenorrhea. Conclusion: Undiagnosed PHEO can be associated with substantial morbidity. Current American Thyroid Association guidelines recommend PHEO screening starting at age 11 for the high-/highest risk group. The youngest patient diagnosed with PHEO in our cohort was an asymptomatic 10-year-old, suggesting that PHEO development may begin before the screening-recommended age of 11, though remains clinically undetectable and thus the current screening guidelines seem appropriate.
PubMed-ID: 30113649
http://dx.doi.org/10.1210/jc.2018-00705

Adrenal Vein Sampling Lateralization Despite Mineralocorticoid Receptor Antagonists Exposure in Primary Aldosteronism.
J Clin Endocrinol Metab, 104(2):487-92.
A. T. Nanba, T. Wannachalee, J. J. Shields, J. B. Byrd, W. E. Rainey, R. J. Auchus and A. F. Turcu. 2019.
Context: Many antihypertensive medications modulate the renin-angiotensin-aldosterone system, possibly skewing the diagnosis and subtyping of primary aldosteronism (PA). Particularly, mineralocorticoid receptor antagonists (MRA) might raise renin and stimulate aldosterone synthesis from nonautonomous areas, potentially obscuring lateralization on adrenal vein sampling (AVS). Withdrawal of MRA in severe PA, however, can precipitate hypokalemia and/or hypertension and therefore is not always practical. Objective: To assess the effects of MRA on the interpretation of AVS data. Design and Participants: A cohort study of all PA patients who underwent AVS at University of Michigan between January 2009 and January 2018 was conducted. Demographics, diagnostic, AVS, surgical pathology, and follow-up data were collected retrospectively. Results: Of 191 patients who underwent AVS, 51 (27%) were exposed to MRA at the time of the procedure. Plasma aldosterone concentration and the daily defined dose of antihypertensives were higher in patients taking vs those not taking MRA. Unilateral PA was more frequent in the MRA group, both precosyntropin and postcosyntropin ($P < 0.05$). The MRA group included two patients with unsuppressed renin, who demonstrated unequivocal AVS lateralization. To date, 86 patients underwent unilateral adrenalectomy, including 30 patients taking MRA during AVS. The proportion of clinical and biochemical success was not statistically different between patients exposed to and those not exposed to MRA during AVS ($P = 0.17$ and 0.65, respectively). Conclusion: Our data suggest that conclusive AVS lateralization is often achieved in patients with severe PA despite MRA use.
PubMed-ID: 30239792
http://dx.doi.org/10.1210/jc.2018-01299

Suppressed ACTH Is Frequently Unrelated to Autonomous Cortisol Secretion in Patients With Adrenal Incidentalomas.
J Clin Endocrinol Metab, 104(2):506-12.
H. Olsen, A. Kjellbom, M. Londahl and O. Lindgren. 2019.
Objective: ACTH is considered a weak marker for autonomous cortisol secretion (ACS) in patients with adrenal incidentalomas (AIs). Our aim was to investigate suppressed basal ACTH as a marker of ACS and to elucidate why this criterion is of limited value. Methods: Basal ACTH and cortisol after overnight dexamethasone suppression test (cortisolONDST) were measured in 198 patients with unilateral AI and at 2-year follow-up. Basal ACTH was measured in 100 control subjects. Results: In patients with cortisolONDST <50 nmol/L (n = 145), ACTH was <2 pmol/L in 19%, compared with 4% in control subjects (P < 0.001). ACTH and size of AI correlated negatively (P = 0.002). Among patients with cortisolONDST >/=50 nmol/L, ACTH was <2 pmol/L in 53%. The patients were grouped according to whether cortisolONDST was <50 or >/=50 nmol/L and whether ACTH was <2.0 or >/=2.0 or pmol/L. At follow-up, these four groups were still separated with statistically significant differences in ACTH and cortisolONDST. Conclusions: This study identifies a previously unrecognized group of patients defined by suppressed ACTH despite normal cortisolONDST. This suppression of ACTH by a factor other than ACS may explain the limitation of suppressed ACTH as a marker for ACS. We suggest increased cortisol secretion in response to ACTH by the AI to be an additional factor.
PubMed-ID: 30265354
http://dx.doi.org/10.1210/jc.2018-01029

Is Prophylactic Steroid Treatment Mandatory for Subclinical Cushing Syndrome After Unilateral Laparoscopic Adrenalectomy?
Surg Laparosc Endosc Percutan Tech, 29(1):31-5.
D. Wang, H. Z. Li, Y. S. Zhang, L. Wang and Z. G. Ji. 2019.
OBJECTIVE: This study aimed to provide rational guidelines for patients with subclinical Cushing syndrome (SCS), who are undergoing laparoscopic adrenalectomy, in order to avoid the risk of overtreatment. METHODS: A total of 59 patients diagnosed with SCS caused by unilateral adrenal adenoma, who underwent laparoscopic adrenalectomy from 2010 to 2017, were included into the study. These patients did not receive prophylactic steroid treatment. After discharge, patients with adrenal insufficiency (AI) were treated with glucocorticoid. Then, cortisol levels were reevaluated at three months after surgery by morning serum cortisol. RESULTS: No severe perioperative complications occurred. After unilateral laparoscopic adrenalectomy, no patient developed AI and was readmitted. In the first week after surgery, 10 patients (16.9%) received steroid therapy at the clinic because of mild symptoms of AI. The probability of developing AI was greater in patients with 1-mg dexamethasone midnight suppression test (1 mg-DST) >5 mug/dL than patients with mg-DST ranging within 1.8 to 5.0 mug/dL (P=0.042). The initial dose of hydrocortisone was 20.00+/-6.67 mg/d (range, 10 to 30), and the duration of treatment was 6.90+/-3.51 weeks (range, 3 to 12 wk). At three months after surgery, morning cortisol was >5 mug/dL in all patients. CONCLUSIONS: After laparoscopic adrenalectomy, the probability of AI is small in patients with adrenal SCS, and the symptoms of AI were mild. Meanwhile, the HPA axis rapidly recovered. Therefore, prophylactic steroid treatment is not mandatory. Given that AI is more frequent in patients with higher cut-offs of 1 mg-DST, a more precise definition of SCS is necessary to better manage these patients.
PubMed-ID: 30300254
http://dx.doi.org/10.1097/SLE.0000000000000585

Laparoscopic hand-assisted adrenalectomy for tumours larger than 5 cm.
Clin Endocrinol (Oxf), 90(1):74-8.
J. Buxton, S. H. Vun, D. van Dellen, R. Wadsworth and T. Augustine. 2019.
OBJECTIVE: Adrenal surgery remains a distinct surgical challenge. Technical challenges associated with laparoscopic adrenalectomy are tumour size, haemorrhage control and oncological compromise. Hand-assisted laparoscopic (HAL) adrenalectomy, utilizing a hand-port device, offers minimally invasive surgery with the advantages and safety of tactile feedback. We aimed to assess the efficacy of HAL for patients requiring adrenalectomy for tumours over 5 cm in size. CONTEXT: Hand-assisted laparoscopic surgery is used in several surgical specialities over totally laparoscopic surgery to manage sizeable pathology, reduce operating time and conversion rates. HAL adrenalectomy is demonstrated in this series as a safe alternative to laparoscopic adrenalectomy for large adrenal tumours. DESIGN: A retrospective analysis of all HAL adrenalectomies performed over 8 years (October 2006-May 2015) by a single surgeon was performed. This case series is the largest study of this technique. PATIENTS: All patients who were fit for surgery with adrenal tumours (over 5 cm) were included. ANALYSIS: Primary endpoints were overall mortality, operating time, hospital stay, complications and conversion to open surgery. RESULTS: A total of 56 patients underwent the procedure. A total of 43 had unilateral and 13 bilateral lesions. Most lesions (45) were histologically benign. These included functioning and

non-functioning tumours. Median tumour size was 8 cm (range 5-19 cm). There was one (1.8%) intra-operative conversion and no peri-operative mortality. Postoperative complications occurred in 8 (14%) patients, all self-limiting. The median length of stay was 6 days (range 2-21). There was one recurrence of pathology with repeat surgery. CONCLUSION: Hand-assisted laparoscopic surgery offers a safe reproducible approach to adrenal surgery combining minimally invasive surgery with tactile integration. Although previously described in small numbers, this represents the largest case series to date. HAL is a safe minimally invasive surgical option for larger tumours, including malignancies. The HAL technique may additionally offer a shorter learning curve for trainee adrenal surgeons.
PubMed-ID: 30346641
http://dx.doi.org/10.1111/cen.13883

CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma.
J Clin Endocrinol Metab, 104(2):312-8.
L. Canu, J. A. W. Van Hemert, M. N. Kerstens, R. P. Hartman, A. Khanna, I. Kraljevic, D. Kastelan, C. Badiu, U. Ambroziak, A. Tabarin, M. Haissaguerre, E. Buitenwerf, A. Visser, M. Mannelli, W. Arlt, V. Chortis, I. Bourdeau, N. Gagnon, M. Buchy, F. Borson-Chazot, T. Deutschbein, M. Fassnacht, A. Hubalewska-Dydejczyk, M. Motyka, E. Rzepka, R. T. Casey, B. G. Challis, M. Quinkler, L. Vroonen, A. Spyroglou, F. Beuschlein, C. Lamas, W. F. Young, I. Bancos and H. Timmers. 2019.
Background: Up to 7% of all adrenal incidentalomas (AIs) are pheochromocytomas (PCCs). In the evaluation of AI, it is generally recommended that PCC be excluded by measurement of plasma-free or 24-hour urinary fractionated metanephrines. However, recent studies suggest that biochemical exclusion of PCC not be performed for lesions with CT characteristics of an adrenocortical adenoma (ACA). Aim: To determine the proportion of PCCs with ACA-like attenuation or contrast washout on CT. Methods: For this multicenter retrospective study, two central investigators independently analyzed the CT reports of 533 patients with 548 histologically confirmed PCCs. Data on tumor size, unenhanced Hounsfield units (HU), absolute percentage washout (APW), and relative percentage washout (RPW) were collected in addition to clinical parameters. Results: Among the 376 PCCs for which unenhanced attenuation data were available, 374 had an attenuation of >10 HU (99.5%). In the two exceptions (0.5%), unenhanced attenuation was exactly 10 HU, which lies just within the range of </=10 HU that would suggest a diagnosis of ACA. Of 76 PCCs with unenhanced HU > 10 and available washout data, 22 (28.9%) had a high APW and/or RPW, suggestive of ACA. Conclusion: Based on the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%) of PCCs with an attenuation of 10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation of </=10 HU. The assessment of contrast washout, however, is unreliable for ruling out PCC.
PubMed-ID: 30383267
http://dx.doi.org/10.1210/jc.2018-01532

Changes of computed tomography-based body composition after adrenalectomy in patients with endogenous hypercortisolism.
Clin Endocrinol (Oxf), 90(2):267-76.
N. Hong, J. Lee, C. R. Ku, K. Han, C. R. Lee, S. W. Kang and Y. Rhee. 2019.
CONTEXT: Data on longitudinal changes of computed tomography (CT)-determined visceral fat area (VFA), skeletal muscle area (SMA) and skeletal muscle radiodensity (SMD) after adrenalectomy are limited in patients with hypercortisolism. OBJECTIVE: To examine the association of severity of cortisol excess and improvement of CT-based muscle and fat parameters after adrenalectomy. DESIGN: Retrospective observational cohort study. PATIENTS: One hundred thirty-four patients with overt Cushing's syndrome (CS; n = 39), mild autonomous cortisol excess (MACE; n = 57), or nonfunctioning adrenal tumour (NFAT; n = 38) at a tertiary endocrinology institution between 2006 and 2017 were included. MEASUREMENTS: Changes in CT-determined VFA, visceral-to-subcutaneous fat ratio (VSR), SMA, skeletal muscle index (SMI), and SMD measured at the third lumbar vertebra (L3). RESULTS: At baseline, CS patients had higher VFA, lower SMA, SMI and SMD values, compared to NFAT or MACE patients. Compared to NFAT, significant decreases in VFA and increases in SMA, SMI and SMD was observed in CS 1 year after adrenalectomy. In MACE, adjusted mean changes of SMD but not VFA, SMA or SMI differ significantly compared to NFAT (+8.9% vs -3.4%, P = 0.032). In a multivariate linear regression model, the increase by 1 mug/dL of post-dexamethasone serum cortisol at baseline was independently associated with greater reduction of VFA (-3.95%), VSR (-3.07%), and increase in SMD (+0.92%, P < 0.05 for all) after adrenalectomy. CONCLUSIONS: The severity of cortisol excess was associated with greater improvement of L3 VFA, VSR and SMD 1 year after adrenalectomy. These CT-based markers may allow more objective assessment of treatment benefit at earlier stage.

PubMed-ID: 30428502
http://dx.doi.org/10.1111/cen.13902

Patterns of Lymph Node Recurrence in Adrenocortical Carcinoma: Possible Implications for Primary Surgical Treatment.
Ann Surg Oncol, 26(2):531-8.
J. Reibetanz, B. Rinn, A. S. Kunz, S. Flemming, C. L. Ronchi, M. Kroiss, T. Deutschbein, A. Pulzer, S. Hahner, A. Kocot, C. T. Germer, M. Fassnacht and C. Jurowich. 2019.
BACKGROUND: In the surgical treatment of adrenocortical carcinoma (ACC), lymphadenectomy may improve oncologic outcome. However, patterns of metastatic lymphatic spread in ACC are unknown. METHODS: Clinical data of patients included in the European Network for the Study of Adrenal Tumors (ENSAT) registry were retrospectively reviewed. Inclusion criteria were: nonmetastatic ACC, complete resection of the primary tumor, a disease-free time of > 3 months, and lymph node metastases as the first disease relapse. The retroperitoneal lymphatic drainage area was evaluated by using follow-up imaging. RESULTS: Of 971 patients from the ENSAT registry, 56 patients were included. In left-sided ACC (n = 36), lymphatic recurrence was detected in the left renal hilum (50%), in the perirenal fat tissue cranial to the renal hilum (ventral, 47%; dorsal, 55%), para-aortic (47%), interaorto-caval (22%), and/or in the perirenal fat tissue caudal to the renal hilum (ventral, 20%; dorsal, 17%). In right-sided ACC (n = 20), lymph node metastases were detected in the perirenal fat tissue cranial to the renal hilum (dorsal, 55%; ventral, 45%), interaorto-caval (35%), in the area of the right renal artery (10%), and/or paracaval (15%). Patients with right-sided ACC showed left-paraaortic lymph node recurrences in 10% of cases. CONCLUSION: Metastatic lymphatic spread appears to be more extensive than previously thought. The distribution pattern of lymph node metastases described in our study could be used as a guide for a more extended lymph node dissection.
PubMed-ID: 30443830
http://dx.doi.org/10.1245/s10434-018-6999-z

Comparison of Technical Details and Short-term Outcomes of Single-incision Versus Multiport Laparoscopic Adrenalectomy.
Surg Laparosc Endosc Percutan Tech, 29(1):49-52.
O. Agcaoglu, B. Sengun, K. Senol, B. Gurbuz, E. Ozoran, S. Carilli and S. Tezelman. 2019.
To date, the single-incision laparoscopic surgery (SILS) technique has been applied to a wide range of general surgical procedures; however, there are still scant data and debates on adrenal procedures. The aim of this study was to compare surgical outcomes of single-incision versus laparoscopic multiport adrenalectomy. The patients were divided into 2 study groups on the basis of the surgical approach: SILS (group 1) and multiport laparoscopic surgery (group 2). Patient demographics and their perioperative and postoperative results were evaluated retrospectively from the medical records. A total of 80 patients were included in the study. There were 44 patients in group 1 and 36 patients in group 2. The average operative time, estimated blood loss, and tumor size were similar between the study groups. There were no mortalities in both groups and the mean duration of hospital stay was 3 days for both groups. Without using any single-incision access trocars and articulated instrumentation, we achieved the same surgical outcomes in our SILS adrenalectomy series compared with conventional multiport laparoscopy series in terms of postoperative short-term outcomes and cost-effectivity.
PubMed-ID: 30605138
http://dx.doi.org/10.1097/SLE.0000000000000596

Clinical outcomes and cortical reserve in adrenal histoplasmosis-A retrospective follow-up study of 40 patients.
Clin Endocrinol (Oxf), 90(4):534-41.
M. Singh, D. D. Chandy, T. Bharani, R. S. K. Marak, S. Yadav, P. Dabadghao, S. Gupta, S. K. Sahoo, R. Pandey and E. Bhatia. 2019.
OBJECTIVE: Detailed studies of Addison's disease resulting from disseminated adrenal histoplasmosis (AH) are not available. We describe the presentation and prognosis of AH and cortisol status before and after antifungal therapy. DESIGN: Single-centre retrospective hospital-based study of 40 consecutive adults with AH [39 males; age (mean +/- SD) 53 +/- 11 years] was conducted between 2006 and 2018. The median duration of follow-up was 2.5 years (range 0.2-12 years). PATIENTS AND METHODS: AH was diagnosed by bilateral adrenal enlargement on CT scan and presence of Histoplasma by histology and/or culture of biopsied adrenal tissue. All patients received oral itraconazole and, if required, amphotericin B as per guidelines. ACTH-stimulated serum cortisol (normal > 500 nmol/L) was measured in 38 patients at diagnosis and re-tested after one year of antifungal therapy in 21 patients. RESULTS: Seventy-three per cent of patients had primary adrenal insufficiency (PAI) and one-third had an adrenal crisis at presentation. HIV antibody was negative in all patients. Of the 29

patients who completed antifungal therapy, 25 (86%) were in remission at last follow-up. Overall, 8 (20%) patients died: three had a sudden death, four had severe histoplasmosis and one died due to adrenal crisis. No patient with PAI became eucortisolemic on re-testing after one year of antifungal therapy. Of the eight patients with normal cortisol at diagnosis, two developed adrenal insufficiency on follow-up. CONCLUSION: All patients with AH tested negative for HIV antibody. While patients achieved a high rate of clinical remission after antifungal therapy, overall mortality was significant. Cortisol insufficiency did not normalize despite treatment.
PubMed-ID: 30656706
http://dx.doi.org/10.1111/cen.13935

Positive Impact of Genetic Test on the Management and Outcome of Patients With Paraganglioma and/or Pheochromocytoma.
J Clin Endocrinol Metab, 104(4):1109-18.
A. Buffet, L. Ben Aim, S. Leboulleux, D. Drui, D. Vezzosi, R. Libe, C. Ajzenberg, D. Bernardeschi, B. Cariou, F. Chabolle, O. Chabre, V. Darrouzet, B. Delemer, R. Desailloud, B. Goichot, A. Esvant, L. Offredo, P. Herman, S. Laboureau, H. Lefebvre, P. Pierre, I. Raingeard, Y. Reznik, J. L. Sadoul, J. Hadoux, A. Tabarin, I. Tauveron, D. Zenaty, J. Favier, J. Bertherat, E. Baudin, L. Amar and A. P. Gimenez-Roqueplo. 2019.
CONTEXT: Pheochromocytomas and paragangliomas (PPGLs) are characterized by a strong genetic component, with up to 40% of patients carrying a germline mutation in a PPGL susceptibility gene. International guidelines recommend that genetic screening be proposed to all patients with PPGL. OBJECTIVE: Our objective was to evaluate how a positive genetic test impacts the management and outcome of patients with SDHx or VHL-related PPGL. DESIGN: We performed a multicentric retrospective study involving 221 propositi carrying an SDHB, SDHD, SDHC, or VHL germline mutation. Patients were divided into two groups: genetic patients, who were informed of their genetic status within the year following the first PPGL diagnosis, and historic patients, who only benefited from the genetic test several years after initial PPGL diagnosis. RESULTS: Genetic patients had better follow-up than historic patients, with a greater number of examinations and a reduced number of patients lost to follow-up (9.6% vs 72%, respectively). During follow-up, smaller (18.7 vs 27.6 mm; P = 0.0128) new PPGLs and metastases as well as lower metastatic spread were observed in genetic patients. Of note, these differences were reversed in the historic cohort after genetic testing. Genetic patients who developed metachronous metastases had a better 5-year survival rate than historic patients (P = 0.0127). CONCLUSION: Altogether, our data suggest that early knowledge of genetic status had a positive impact on the management and clinical outcome of patients with a germline SDHx or VHL mutation.
PubMed-ID: 30698717
http://dx.doi.org/10.1210/jc.2018-02411

Prognosis of Malignant Pheochromocytoma and Paraganglioma (MAPP-Prono Study): A European Network for the Study of Adrenal Tumors Retrospective Study.
J Clin Endocrinol Metab, 104(6):2367-74.
S. Hescot, M. Curras-Freixes, T. Deutschbein, A. van Berkel, D. Vezzosi, L. Amar, C. de la Fouchardiere, N. Valdes, F. Riccardi, C. Do Cao, J. Bertherat, B. Goichot, F. Beuschlein, D. Drui, L. Canu, P. Niccoli, S. Laboureau, A. Tabarin, S. Leboulleux, B. Calsina, R. Libe, A. Faggiano, M. Schlumberger, F. Borson-Chazot, M. Mannelli, A. P. Gimenez-Roqueplo, P. Caron, H. Timmers, M. Fassnacht, M. Robledo, I. Borget and E. Baudin. 2019.
BACKGROUND: Malignant pheochromocytoma and paraganglioma (MPP) are characterized by prognostic heterogeneity. Our objective was to look for prognostic parameters of overall survival (OS) in MPP patients. PATIENTS AND METHODS: Retrospective multicenter study of MPP characterized by a neck-thoraco-abdomino-pelvic CT or MRI at the time of malignancy diagnosis in European centers between 1998 and 2010. RESULTS: One hundred sixty-nine patients from 18 European centers were included. Main characteristics of patients with MPP were: primary pheochromocytoma in 53% of patients; tumor- or hormone-related symptoms in 57% or 58% of cases; positive plasma or urine hormones in 81% of patients; identification of a mutation in SDHB in 42% of cases. Metastatic sites included bone (64%), lymph node (40%), lung (29%), and liver (26%); mean time between initial and malignancy diagnosis was 43 months (range, 0 to 614). Median follow-up was 68 months and median survival 6.7 years. Using univariate analysis, better survival was associated with head and neck paraganglioma, age <40 years, metanephrines less than fivefold the upper limits of the normal range, and low proliferative index. In multivariate analysis, hypersecretion [hazard ratio 3.02 (1.65 to 5.55); P = 0.0004] was identified as an independent significant prognostic factor of worst OS. CONCLUSIONS: Our results do not confirm SDHB mutations as a major prognostic parameter in MPP and suggest additional key molecular events involved in MPP tumor progression. Aside from SDHB mutation, the biology of aggressive MPP remains to be understood.

PubMed-ID: 30715419
http://dx.doi.org/10.1210/jc.2018-01968

(11) C-Metomidate PET/CT is a useful adjunct for lateralization of primary aldosteronism in routine clinical practice.
Clin Endocrinol (Oxf), 90(5):670-9.
P. M. O'Shea, D. O'Donoghue, W. Bashari, R. Senanayake, M. B. Joyce, A. S. Powlson, D. Browne, G. J. O'Sullivan, H. Cheow, I. Mendichovszky, D. Quill, A. Lowery, D. Lappin, M. Gurnell and M. C. Dennedy. 2019.
OBJECTIVE: To describe clinical practice experience of (11) C-Metomidate PET/CT as an adjunct to adrenal vein sampling (AVS) in the lateralization of aldosterone-producing adenomas (APA) in primary aldosteronism (PA). CONTEXT: Accurate lateralization of APA in the setting of PA offers the potential for surgical cure and improved long-term cardiovascular outcomes. Challenges associated with AVS, the current gold standard lateralization modality, mean that only a small proportion of potentially eligible patients currently make it through to surgery. This has prompted consideration of alternative strategies for lateralization, including the application of novel molecular PET tracers such as (11) C-Metomidate. DESIGN: Clinical Service Evaluation/Retrospective audit. PATIENTS: Fifteen individuals with a confirmed diagnosis of PA, undergoing lateralization with (11) C-Metomidate PET/CT prior to final clinical decision on surgical vs medical management. MEASUREMENTS: All patients underwent screening aldosterone renin ratio (ARR), followed by confirmatory testing with the seated saline infusion test, according to Endocrine Society Clinical Practice Guidelines. Adrenal glands were imaged using dedicated adrenal CT. (11) C-Metomidate PET/CT was undertaken due to equivocal or failed AVS. Management outcomes were assessed by longitudinal measurement of blood pressure, ARR, number of hypertensive medications following adrenalectomy or institution of medical therapy. RESULTS: We describe the individual lateralization and clinical outcomes for 15 patients with PA. CONCLUSION: (11) C-Metomidate PET/CT in conjunction with adrenal CT and AVS provided useful information which aided clinical decision-making for PA within a multidisciplinary hypertension clinic.
PubMed-ID: 30721535
http://dx.doi.org/10.1111/cen.13942

Association of Outcome Definitions With Success Following Adrenalectomy for Primary Aldosteronism.
JAMA Surg, 154(4):e185843.
H. Wachtel and R. R. Kelz. 2019.
PubMed-ID: 30810721
http://dx.doi.org/10.1001/jamasurg.2018.5843

Clinical Outcomes After Unilateral Adrenalectomy for Primary Aldosteronism.
JAMA Surg, 154(4):e185842.
W. Vorselaars, S. Nell, E. L. Postma, R. Zarnegar, F. T. Drake, Q. Y. Duh, S. D. Talutis, D. B. McAneny, C. McManus, J. A. Lee, S. B. Grant, R. H. Grogan, M. A. Romero Arenas, N. D. Perrier, B. J. Peipert, M. N. Mongelli, T. Castelino, E. J. Mitmaker, D. N. Parente, J. D. Pasternak, A. F. Engelsman, M. Sywak, G. D'Amato, M. Raffaelli, V. Schuermans, N. D. Bouvy, H. H. Eker, H. J. Bonjer, N. M. Vaarzon Morel, E. J. M. Nieveen van Dijkum, O. M. Vrielink, S. Kruijff, W. Spiering, I. H. M. Borel Rinkes, G. D. Valk and M. R. Vriens. 2019.
Importance: In addition to biochemical cure, clinical benefits after surgery for primary aldosteronism depend on the magnitude of decrease in blood pressure (BP) and use of antihypertensive medications with a subsequent decreased risk of cardiovascular and/or cerebrovascular morbidity and drug-induced adverse effects. Objective: To evaluate the change in BP and use of antihypertensive medications within an international cohort of patients who recently underwent surgery for primary aldosteronism. Design, Setting, and Participants: A cohort study was conducted across 16 referral medical centers in Europe, the United States, Canada, and Australia. Patients who underwent unilateral adrenalectomy for primary aldosteronism between January 2010 and December 2016 were included. Data analysis was performed from August 2017 to June 2018. Unilateral disease was confirmed using computed tomography, magnetic resonance imaging, and/or adrenal venous sampling. Patients with missing or incomplete preoperative or follow-up data regarding BP or corresponding number of antihypertensive medications were excluded. Main Outcomes and Measures: Clinical success was defined based on postoperative BP and number of antihypertensive medications. Cure was defined as normotension without antihypertensive medications, and clear improvement as normotension with lower or equal use of antihypertensive medications. In patients with preoperative normotensivity, improvement was defined as postoperative normotension with lower antihypertensive use. All other patients were stratified as no clear success because the benefits of surgery were less obvious, mainly owing to postoperative, persistent hypertension. Clinical outcomes were assessed at follow-up closest to 6 months after surgery. Results: On the basis of inclusion and exclusion criteria, a total of 435 patients (84.6%) from a cohort of 514 patients who

underwent unilateral adrenalectomy were eligible. Of these patients, 186 (42.3%) were women; mean (SD) age at the time of surgery was 50.7 (11.4) years. Cure was achieved in 118 patients (27.1%), clear improvement in 135 (31.0%), and no clear success in 182 (41.8%). In the subgroup classified as no clear success, 166 patients (91.2%) had postoperative hypertension. However, within this subgroup, the mean (SD) systolic and diastolic BP decreased significantly by 9 (22) mm Hg (P < .001) and 3 (15) mm Hg (P = .04), respectively. Also, the number of antihypertensive medications used decreased from 3 (range, 0-7) to 2 (range, 0-6) (P < .001). Moreover, in 75 of 182 patients (41.2%) within this subgroup, the decrease in systolic BP was 10 mm Hg or greater. Conclusions and Relevance: In this study, for most patients, adrenalectomy was associated with a postoperative normotensive state and reduction of antihypertensive medications. Furthermore, a significant proportion of patients with postoperative, persistent hypertension may benefit from adrenalectomy given the observed clinically relevant and significant reduction of BP and antihypertensive medications.
PubMed-ID: 30810749
http://dx.doi.org/10.1001/jamasurg.2018.5842

A novel clinical nomogram to predict bilateral hyperaldosteronism in Chinese patients with primary aldosteronism.
Clin Endocrinol (Oxf), 90(6):781-8.
L. Xiao, Y. Jiang, C. Zhang, L. Jiang, W. Zhou, T. Su, G. Ning and W. Wang. 2019.
CONTEXT: Adrenal venous sampling (AVS) is recommended as the gold standard for subtype classification in primary aldosteronism (PA); however, this approach has limited availability. OBJECTIVE: We aimed to develop a novel clinical nomogram to predict PA subtype based on routine variables, thereby reducing the number of candidates for AVS. PATIENTS AND METHOD: Patients were randomly divided into a training set (n = 185) and a validation set (n = 79). Risk factors for idiopathic hyperaldosteronism (IHA) differentiating from aldosterone-producing adenoma (APA) were identified using logistic regression analysis. A nomogram was constructed to predict the probability of IHA. A receiver operating characteristic (ROC) curve and a calibration plot were applied to assess the predictive value. Then, 115 patients were prospectively enrolled, and a nomogram was used to predict the subtypes before AVS. RESULTS: Body mass index (BMI), serum potassium and computed tomography (CT) finding were adopted in the nomogram. The nomogram presented an area under the ROC (AUC) of 0.924 (95% CI: 0.875-0.957), sensitivity of 86.59% and specificity of 87.38% in the training set and an AUC of 0.894 (95% CI: 0.804-0.952), sensitivity of 82.86% and specificity of 84.09% in the validation set. Predicted probability and actual probability matched well in the nomogram (Hosmer-Lemeshow test: P > 0.05). Using the nomogram as a surrogate to predict IHA in the prospective set before AVS, the specificity reached 100% when we increased the threshold to a probability of 90%. CONCLUSION: We have developed a tool that is able to predict IHA in patients with PA and potentially avoid AVS.
PubMed-ID: 30820995
http://dx.doi.org/10.1111/cen.13962

Impact of 123 I-MIBG scintigraphy on clinical decision making in pheochromocytoma and paraganglioma.
J Clin Endocrinol Metab,
D. Rao, A. van Berkel, I. Piscaer, W. F. Young, L. Gruber, T. Deutschbein, M. Fassnacht, F. Beuschlein, A. Spyroglou, A. Prejbisz, K. Hanus, G. Eisenhofer, M. Manelli, L. Canu, J. W. M. Lenders, I. Bancos and H. Timmers. 2019.
CONTEXT: Cross sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is regarded as a first-choice modality for tumor localization in patients with pheochromocytoma and paraganglioma (PPGL). 123I-labeled metaiodobenzylguanidine (123I-MIBG) is widely used for functional imaging but the added diagnostic value is controversial. OBJECTIVE: To establish the virtual impact of adding 123I-MIBG scintigraphy to CT or MRI on diagnosis and treatment of PPGL. DESIGN: International multicenter retrospective study. INTERVENTION: None. PATIENTS: 236 unilateral adrenal, 18 bilateral adrenal, 48 unifocal extra-adrenal, 12 multifocal and 26 metastatic PPGL. MAIN OUTCOME MEASURES: Patients underwent both anatomical imaging (CT and/or MRI) and 123I-MIBG scintigraphy. Local imaging reports were analyzed centrally by two independent observers who were blinded to the diagnosis. Imaging-based diagnoses determined by CT/MRI only, 123I-MIBG only, and CT/MRI combined with 123I-MIBG scintigraphy were compared with the correct diagnoses. RESULTS: The rates of correct imaging-based diagnoses determined by CT/MRI only versus CT/MRI plus 123I-MIBG scintigraphy were similar: 89.4 versus 88.8%, respectively, (P=0.50). Adding 123I-MIBG scintigraphy to CT/MRI resulted in a correct change in the imaging-based diagnosis and ensuing virtual treatment in four cases (1.2%: two metastatic instead of non-metastatic, one multifocal instead of single, one unilateral instead of bilateral adrenal) at the cost of an incorrect change in seven cases (2.1%: four metastatic instead of non-metastatic, two multifocal instead of unifocal and one bilateral instead of unilateral adrenal).

CONCLUSIONS: For the initial localization of PPGL, the addition of 123I-MIBG scintigraphy to CT/MRI rarely improves the diagnostic accuracy at the cost of incorrect interpretation in others, even when 123I-MIBG scintigraphy is restricted to patients who are at risk for metastatic disease. In this setting, the impact of 123I-MIBG scintigraphy on clinical decision-making appears very limited.
PubMed-ID: 30822354
http://dx.doi.org/10.1210/jc.2018-02355

Long-Term Outcome of Primary Bilateral Macronodular Adrenocortical Hyperplasia After Unilateral Adrenalectomy.
J Clin Endocrinol Metab, 104(7):2985-93.
A. Osswald, M. Quinkler, G. Di Dalmazi, T. Deutschbein, G. Rubinstein, K. Ritzel, S. Zopp, J. Bertherat, F. Beuschlein and M. Reincke. 2019.
CONTEXT: Unilateral adrenalectomy has been proposed in selected patients with primary bilateral macronodular adrenocortical hyperplasia (PBMAH), but its long-term outcome is unclear. OBJECTIVE: The aim of this study was to analyze long-term clinical and biochemical outcomes of unilateral adrenalectomy vs bilateral adrenalectomy in patients with PBMAH in comparison with the outcome of cortisol-producing adenoma (CPA) treated with unilateral adrenalectomy. DESIGN: Retrospective observational study in three German and one Italian academic tertiary care center. PATIENTS AND METHODS: Twenty-five patients with PBMAH after unilateral adrenalectomy (unilat-ADX-PBMAH), nine patients with PBMAH and bilateral adrenalectomy (bilat-ADX-PBMAH), and 39 patients with CPA and unilateral adrenalectomy (unilat-ADX-CPA) were included. RESULTS: Baseline clinical and biochemical parameters were comparable in patients with unilat-ADX-PBMAH, bilat-ADX-PBMAH, and unilat-ADX-CPA. Directly after surgery, 84% of the patients with unilat-ADX-PBMAH experienced initial remission of Cushing syndrome (CS). In contrast, at last follow-up (median, 50 months), 32% of the patients with unilat-ADX-PBMAH were biochemically controlled compared with nearly all patients in the other two groups (P = 0.000). Adrenalectomy of the contralateral side had to be performed in 12% of the initial patients with unilat-ADX-PBMAH. Three of 20 patients with unilat-ADX-PBMAH (15%) died during follow-up, presumably of CS-related causes; no deaths occurred in the other two groups (P = 0.008). Deaths occurred exclusively in patients who were not biochemically controlled after unilateral ADX. CONCLUSIONS: Our data suggest that unilateral adrenalectomy of patients with PBMAH leads to clinical remission and a lower incidence of adrenal crisis but in less sufficient biochemical control of hypercortisolism, potentially leading to higher mortality.
PubMed-ID: 30844071
http://dx.doi.org/10.1210/jc.2018-02204

Minimally Invasive Surgery for Primary and Metastatic Adrenal Malignancy.
Surg Oncol Clin N Am, 28(2):309-26.
C. M. Kiernan and J. E. Lee. 2019.
Since the first description of laparoscopic adrenalectomy (LA) for pheochromocytoma and Cushing syndrome in 1992, the utilization of and indications for a minimally invasive approach to the adrenal gland have vastly expanded. Although minimally invasive adrenalectomy has been established as the preferred approach for patients with benign tumors of the adrenal gland, minimally invasive adrenalectomy for cancer remains controversial. In this article, the authors review the indications for minimally invasive adrenalectomy for adrenal nodules suspicious for, or established to represent, a primary malignancy or a site of metastatic cancer.
PubMed-ID: 30851831
http://dx.doi.org/10.1016/j.soc.2018.11.011

A synonymous VHL variant in exon 2 confers susceptibility to familial pheochromocytoma and von Hippel-Lindau disease.
J Clin Endocrinol Metab,
S. K. Flores, Z. Cheng, A. M. Jasper, K. Natori, T. Okamoto, A. Tanabe, K. Gotoh, H. Shibata, A. Sakurai, T. Nakai, X. Wang, M. Zethoven, S. Balachander, Y. Aita, W. Young, S. Zheng, K. Takekoshi, E. Nakamura, R. W. Tothill, R. C. T. Aguiar and P. L. M. Dahia. 2019.
CONTEXT: von Hippel-Lindau disease, comprising renal cancer, hemangioblastoma and/or pheochromocytoma (PHEO) is caused by missense or truncating variants of the VHL tumor suppressor gene, which is involved in degradation of hypoxia inducible factors (HIFs). However, the role of synonymous VHL variants in the disease is unclear. OBJECTIVE: We evaluated a synonymous VHL variant in patients with familial PHEO or VHL disease without a detectable pathogenic VHL mutation. DESIGN: We performed genetic and transcriptional analyses of leukocytes and/or tumors from affected and unaffected individuals and evaluated VHL splicing in existing cancer

databases. RESULTS: We identified a synonymous VHL variant(c.414A>G, p.Pro138Pro) as the driver event in five independent individuals/families with PHEOs or VHL syndrome. This variant promotes exon 2 skipping and, hence, abolishes expression of the full-length VHL transcript. Exon 2 spans the HIF binding domain, required for HIF degradation by VHL. Accordingly, PHEOs carrying this variant display HIF hyperactivation typical of VHL loss. Moreover, other exon 2 VHL variants from the TCGA pan-cancer datasets are biased toward expression of a VHL transcript that excludes this exon, supporting a broader impact of this spliced variant. CONCLUSION: A recurrent synonymous VHL variant (c.414A>G, p.Pro138Pro) confers susceptibility to PHEO and VHL disease through splice disruption, leading to VHL dysfunction. This finding indicates that certain synonymous VHL variants may be clinically relevant and should be considered in genetic testing and surveillance settings. The observation that other coding VHL variants can exclude exon 2 suggests that dysregulated splicing may be an underappreciated mechanism in VHL-mediated tumorigenesis.
PubMed-ID: 30946460
http://dx.doi.org/10.1210/jc.2019-00235

Surgery for adrenal angiomyelolipoma: an individualized concept.
Langenbecks Arch Surg, 404(4):403-9.
F. Weber, A. Shaibekov, F. Nensa, X. Zeng and H. Dralle. 2019.
BACKGROUND: Because adrenal angiomyelolipoma (AAML) is rare and uniformly benign, the indications for surgery are ill defined. METHODS: Among a series of 156 patients with adrenal pathologies surgically treated between 2013 and 2018, 12 patients were operated with the diagnosis of an AAML. The clinical as well as imaging parameters forming the individual indications for surgery were analyzed. RESULTS: Preoperative diagnosis consistent with AAML was made in all 12 patients. The mean size of surgically removed AAML was 82.3 mm (45-150 mm). Gender and affected side were evenly distributed. Local symptoms but lack of radiological signs suspicious for malignancy or size increase were observed in 4 of 12 patients (group 1, 33%). In contrast, 4 of 12 patients (group 2, 33%) showed radiological signs suspicious for malignancy but lacked local symptoms. Additional 4 of 12 patients (group 3, 33%) showed both local symptoms and radiological signs suspicious for malignancy. Patients with local symptoms harbored significantly larger tumors compared to those patients that lacked local symptoms (93.9 mm +/- 32.8 vs. 59.3 mm +/- 2.7, p = 0.021). Patients with radiologically suspicious signs were older (60 years +/- 9.9 vs. 53 years +/- 5.4, p > 0.05), and time to surgery was shorter (4.4 months +/- 3 vs. 6.0 months +/- 3.0, p > 0.05). Importantly, surgical approach was not influenced by tumor size (p = 0.65). However, patients with suspicious imaging were more likely to be operated by conventional open approach (4 of 8 vs. 0 of 4, p = 0.08). The minimal invasive approach was associated with shorter hospital stay (7 days, +/- 1.3 vs. 14.2 days, +/- 8.8, p = 0.038). All lesions that showed radiological signs suspicious for malignancy proved benign in final histology. CONCLUSION: Large AAML present a clinical challenge. The presence of local symptoms and/or radiological signs suspicious for malignancy identifies three groups of patients that define the concept of an individualized indication for surgery in AAML. A minimal invasive approach can be advocated even for large AAML with radiological signs suspicious for malignancy.
PubMed-ID: 30972487
http://dx.doi.org/10.1007/s00423-019-01783-0

NET

Meta-Analyses

Management of carcinoid syndrome: a systematic review and meta-analysis.
Endocr Relat Cancer,
J. Hofland, A. D. Herrera Martinez, W. T. Zandee and W. W. de Herder. 2019.
Carcinoid syndrome (CS) is a debilitating disease caused by functional neuroendocrine tumors. Several treatment options are available to alleviate the hormonal symptoms, but their relative efficacy is unknown. Online databases were searched for publications on the treatment of CS symptoms. Independent reviewers assessed relevant publications for study quality and outcome. Meta-analysis of the outcomes of the intervention on CS-related symptoms was stratified by type of treatment. We found 3682 therapeutic interventions on CS-specific outcomes collected from 93 studies. Overall, the study qualities were poor with only six randomized controlled clinical trials. The somatostatin analogs octreotide and lanreotide induced symptomatic improvement in 65-72% and biochemical response in 45-46% of patients. An increase in dose or frequency or interclass switch led to a reduction of flushes and/or diarrhea in 72-84% of cases. Retrospective, institutional series showed that liver-directed therapy can improve symptoms in 82% of CS patients with liver-dominant disease. The serotonin synthesis inhibitor telotristat ethyl reduced bowel movements in 40% of patients with diarrhea refractory to somatostatin analogs. Interferon-alpha controlled CS symptoms in 45-63% of cases. Favorable response has been noted after radionuclide therapy in subgroup analyses of studies not specifically involving CS patients. Chemotherapy and everolimus did not induce significant response in the CS. We conclude that several treatment lines can be offered to patients suffering from the carcinoid syndrome. Initiation of randomized controlled trials with a primary outcome on carcinoid syndrome symptoms is strongly recommended.
PubMed-ID: 30608900
http://dx.doi.org/10.1530/ERC-18-0495

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Treatment challenges in and outside a specialist network setting: Pancreatic neuroendocrine tumours.
Eur J Surg Oncol, 45(1):46-51.
P. M. Lykoudis, S. Partelli, F. Muffatti, M. Caplin, M. Falconi and G. K. Fusai. 2019.
Pancreatic Neuroendocrine Neoplasms comprise a group of rare tumours with special biology, an often indolent behaviour and particular diagnostic and therapeutic requirements. The specialized biochemical tests and radiological investigations, the complexity of surgical options and the variety of medical treatments that require individual tailoring, mandate a multidisciplinary approach that can be optimally achieved through an organized network. The present study describes currents concepts in the management of these tumours as well as an insight into the challenges of delivering the pathway in and outside a Network.
PubMed-ID: 29126671
http://dx.doi.org/10.1016/j.ejso.2017.08.019

The Evolution of Surgical Strategies for Pancreatic Neuroendocrine Tumors (Pan-NENs): Time-trend and Outcome Analysis From 587 Consecutive Resections at a High-volume Institution.
Ann Surg, 269(4):725-32.
L. Landoni, G. Marchegiani, T. Pollini, S. Cingarlini, M. D'Onofrio, P. Capelli, R. De Robertis, M. V. Davi, A. Amodio, H. Impellizzeri, A. Malpaga, M. Miotto, L. Boninsegna, L. Crepaz, C. Nessi, C. C. Zingaretti, S. Paiella, A. Esposito, L. Casetti, G. Malleo, M. Tuveri, G. Butturini, R. Salvia, A. Scarpa, M. Falconi and C. Bassi. 2019.
OBJECTIVE: The objective of the present analysis is 2-fold: first, to define the evolution of time trends on the surgical approach to pancreatic neuroendocrine neoplasms (Pan-NENs); second, to perform a complete analysis of the predictors of oncologic outcome. BACKGROUND: Reflecting their rarity and heterogeneity, Pan-NENs represent a clinical dilemma. In particular, there is a scarcity of data regarding their long-term follow-up after surgical resection. METHODS: From the Institutional Pan-NEN database, 587 resected cases from 1990 to 2015 were extracted. The time span was arbitrarily divided into 3 discrete clusters enabling a balanced comparison between patient groups. Analyses for predictors of recurrence and survival were performed, together with conditional survival analyses. RESULTS: Among the 587 resected Pan-NENs, 75% were nonfunctioning tumors, and 5% were syndrome-associated tumors. The mean age was 54 years (+/-14 years), and 51% of the patients were female. The median tumor size was 20 mm (range 4 to 140), 62% were G1, 32% were G2, and 4% were G3 tumors. Time trends analysis revealed that the number of resected Pan-NENs constantly increased, while the size (from 25 to 20 mm) and G1 proportion (from 65% to 49%) decreased during the study period. After a mean follow-up of 75 months, recurrence analysis revealed that nonfunctioning tumors, tumor grade, N1 status, and vascular invasion were all independent predictors of recurrence. Regardless of size, G1 nonfunctioning tumors with no nodal involvement and vascular invasion had a negligible risk of recurrence at 5 years. CONCLUSIONS: Pan-NENs have been increasingly diagnosed and resected during the last 3 decades, revealing reliable predictors of outcome. Functioning and nodal status, tumor grade, and vascular invasion accurately predict survival and recurrence with resulting implications for patient follow-up.
PubMed-ID: 29189384
http://dx.doi.org/10.1097/SLA.0000000000002594

Treatment challenges in and outside a network setting: Gastrointestinal neuroendocrine tumours.
Eur J Surg Oncol, 45(1):52-9.
F. M. Laskaratos and M. Caplin. 2019.
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are relatively rare neoplasms arising from the enterochromaffin cells of the gastrointestinal tract. They comprise a heterogeneous group of tumours with a diverse natural history, variable biological behaviour and different clinical outcomes. Their management is often complex and may include a combination of surgery, systemic treatments and locoregional approaches. A multidisciplinary team approach is therefore essential for the optimal care of patients with GEP NETs. In this article, the authors review the role and structure of multidisciplinary care models, the importance of regional centres of expertise and institutional networks for the management of these rare neoplasms, as well as the multidisciplinary therapeutic challenges that NET clinicians are often faced with.
PubMed-ID: 29685756
http://dx.doi.org/10.1016/j.ejso.2018.03.012

Implementation of Current ENETS Guidelines for Surgery of Small (</=2 cm) Pancreatic Neuroendocrine Neoplasms in the German Surgical Community: An Analysis of the Prospective DGAV StuDoQ|Pancreas Registry.
World J Surg, 43(1):175-82.
I. Mintziras, T. Keck, J. Werner, S. Fichtner-Feigl, U. Wittel, N. Senninger, T. Vowinkel, J. Koninger, M. Anthuber, B. Geissler and D. K. Bartsch. 2019.
BACKGROUND: ENETS guidelines recommend parenchyma-sparing procedures without formal lymphadenectomy, ideally with a minimally invasive laparoscopic approach for sporadic small pNENs (</=2 cm). Non-functioning (NF) small pNENs can also be observed. The aim of the study was to evaluate how these recommendations are implemented in the German surgical community. METHODS: Data from the prospective StuDoQ|Pancreas registry of the German Society of General and Visceral Surgery were analyzed regarding patient's demographics, tumor characteristics, surgical procedures, histology and perioperative outcomes. RESULTS: Eighty-four (29.2%) of 287 patients had sporadic pNENs </=2 cm. Forty-three (51.2%) patients were male, and the mean age at diagnosis was 58.8 +/- 15.6 years. Twenty-five (29.8%) pNENs were located in the pancreatic head. The diagnosis pNEN was preoperatively established in 53 (65%) of 84 patients. Sixty-two (73.8%) patients had formal pancreatic resections, including partial pancreaticoduodenectomy or total pancreatectomy (21.4%). Only 22 (26.2%) patients underwent parenchyma-sparing resections and 23 (27.4%) patients had minimally invasive procedures. A lymphadenectomy was performed in 63 (75.4%) patients, and

lymph node metastases were diagnosed in 6 (7.2%) patients. Eighty-two (97.7%) patients had an R0 resection. Sixty (72%) tumors were classified G1, 24 (28%) tumors G2. Twenty-seven (32.2%) of 84 patients had postoperative relevant Clavien-Dindo grade >/=3 complications. Thirty- and 90-day mortalities were 2.4% and 3.6%. CONCLUSIONS: ENETS guidelines for surgery of small pNENs are yet not well accepted in the German surgical community, since the rate of formal resections with standard lymphadenectomy is high and the minimally invasive approach is underused. The attitude to operate small NF tumors seems to be rather aggressive.
PubMed-ID: 30097704
http://dx.doi.org/10.1007/s00268-018-4751-2

Hepatic Resection for Non-functional Neuroendocrine Liver Metastasis: Does the Presence of Unresected Primary Tumor or Extrahepatic Metastatic Disease Matter?
Ann Surg Oncol, 25(13):3928-35.
J. X. Xiang, X. F. Zhang, E. W. Beal, M. Weiss, L. Aldrighetti, G. A. Poultsides, T. W. Bauer, R. C. Fields, S. K. Maithel, H. P. Marques and T. M. Pawlik. 2018.
OBJECTIVES: The objective of this study was to assess the impact of unresected primary tumor, as well as extrahepatic metastasis, on the long-term prognosis of patients undergoing hepatic resection for non-functional neuroendocrine liver metastasis (NF-NELM). METHODS: Patients who underwent hepatic resection for NF-NELM were identified from a multi-institutional database. Data on clinical and pathological details, as well as the long-term overall survival (OS) were obtained and compared. Propensity score matching was performed to generate matched pairs of patients. RESULTS: Among the 332 patients with NF-NELM, 281 (84.6%) underwent primary tumor resection, while 51 (15.4%) did not. Patients who underwent primary resection were more likely to have a pancreatic primary and metachronous NELM. The long-term OS of patients who did and did not have the primary neuroendocrine tumor (NET) resected was comparable on both unmatched (10-year survival rate 66.8% vs. 54.0%, p = 0.192) and matched (10-year survival rate 75.7% vs. 60.4%, p = 0.271) analyses. In contrast, patients with NF-NELM and extrahepatic metastasis had a worse OS following resection compared with patients who had intrahepatic-only metastasis on unmatched (10-year survival rate 37.5% vs. 69.3%, p = 0.002) and matched (10-year survival rate 37.5% vs. 86.3%, p = 0.011) analyses. On multivariable analysis, while resection of the primary NET was not associated with OS (hazard ratio [HR] 0.7, 95% confidence interval [CI] 0.4-1.2, p = 0.195), the presence of extrahepatic metastasis was independently associated with long-term risk of death (HR 3.9, 95% CI 1.7-9.2, p = 0.002). CONCLUSIONS: While surgery should be considered for patients with NF-NELM who have an unresectable primary tumor, operative resection of NF-NELM may not be as beneficial in patients with extrahepatic disease.
PubMed-ID: 30218247
http://dx.doi.org/10.1245/s10434-018-6751-8

Exploring the surgical landscape of pancreatic neuroendocrine neoplasia in Austria: Results from the ASSO pNEN study group.
Eur J Surg Oncol, 45(2):198-206.
F. Primavesi, E. Klieser, B. Cardini, K. Marsoner, U. Froschl, S. Thalhammer, I. Fischer, A. Hauer, R. Urbas, T. Kiesslich, D. Neureiter, M. Zitt, R. Klug, H. Wundsam, F. Sellner, J. Karner, R. Fugger, F. Cakar-Beck, P. Kornprat, D. Ofner and S. Stattner. 2019.
INTRODUCTION: Pancreatic neuroendocrine neoplasia (pNEN) show increasing incidence and management is complex due to biological heterogeneity. Most publications report isolated high-volume single-centre data. This Austrian multi-centre study on surgical management of pNENs provides a comprehensive real-life picture of quality indicators, recurrence-patterns, survival factors and systemic treatments. METHODS: Retrospective, national cohort-study from 7 medium-/high-volume centres in Austria, coordinated under the auspices of the Austrian Society of Surgical Oncology (ASSO). RESULTS: Two-hundred patients underwent resection for pNEN, 177 had non-functioning tumours and 31 showed stage 4 disease. Participating centres were responsible for 2/3 of pNEN resections in Austria within the last years. The mean rate of completeness of variables was 98.6%. Ninety-days mortality was 3.5%, overall rate of complications was 42.5%. Morbidity did not influence long-term survival. The 5-year overall-survival (OS) was 81.3%, 10-year-OS 52.5% and 5-year recurrence-free-survival (RFS) 69.8%. Recurrence was most common in the liver (68.1%). Four out of five patients with recurrence underwent further treatment, most commonly with medical therapy or chemotherapy. Multivariable analysis revealed grading (HR:2.7) and metastasis (HR:2.5) as significant factors for relapse. Tumours-size >/=2cm (HR:5.9), age >/=60 years (HR:3.1), metastasis (HR:2.3) and grading (HR:2.0) were associated with OS. Tumours <2cm showed 93.9% 10-year-OS, but 33% had G2/G3 grading, 12.5% positive lymph-nodes and 4.7% metastasis at diagnosis, each associated with significant worse survival. CONCLUSION: Resection of pNENs in Austria is performed with internationally comparable safety. Analysed factors allow for risk-stratification in clinical

treatment and future prospective trials. A watch-and-wait strategy purely based on tumour-size cannot be recommended.
PubMed-ID: 30262324
http://dx.doi.org/10.1016/j.ejso.2018.08.016

Radioguided Surgery With Gallium for Neuroendocrine Tumors.
JAMA Surg, 154(1):45-6.
J. R. Howe. 2019.
PubMed-ID: 30267062
http://dx.doi.org/10.1001/jamasurg.2018.3480

Radioguided Surgery With Gallium 68 Dotatate for Patients With Neuroendocrine Tumors.
JAMA Surg, 154(1):40-5.
M. El Lakis, A. Gianakou, P. Nockel, D. Wiseman, A. Tirosh, M. A. Quezado, D. Patel, N. Nilubol, K. Pacak, S. M. Sadowski and E. Kebebew. 2019.
Importance: Neuroendocrine tumors (NETs) express somatostatin receptors, which can be targeted with radiolabeled peptides. In a variety of solid tumors, radioguided surgery (RGS) has been used to guide surgical resection. Gallium 68 (68Ga) dota peptides have been shown to be more accurate than other radioisotopes for detecting NETs. A pilot study previously demonstrated the feasibility and safety of 68Ga-dotatate RGS for patients with NETs. Objective: To evaluate what intraoperative techniques and thresholds define positive lesions that warrant resection during 68Ga-dotatate RGS. Design, Setting, and Participants: This prospective cohort study, conducted between October 23, 2013, and February 14, 2018, included 44 patients with NETs who underwent 68Ga-dotatate RGS. Intervention: Gallium 68-dotatate RGS. Main Outcomes and Measures: The in vivo and ex vivo tumor to background ratio (TBR) was assessed for resected lesions and correlated with the histopathologic findings. Results: Forty-four patients (22 women and 22 men; mean [SD] age, 51.0 [13.7] years) had 133 lesions detected on preoperative imaging scans, with a diagnosis of a pancreatic NET (19 of 44 [43%]), gastrointestinal NET (22 of 44 [50%]), and pheochromocytoma or paraganglioma (3 of 44 [7%]). The TBR was obtained by normalizing to the omentum (106 of 133 [79.7%]) or other solid organs (27 of 133 [20.3%]). The omentum had a significantly lower mean (SD) count than other solid organs for background count activity 3 hours after injection (22.1 [17.0] vs 34.5 [39.0]; P < .001). The lesions containing NETs had a higher TBR than those that did not contain NETs (18.9 vs 4.4; P < .001). On a receiver operating characteristic curve analysis, a TBR of 2.5 had a sensitivity of 90% and a specificity of 25%, and a TBR of 16 had a sensitivity of 54% and a specificity of 81%. Conclusions and Relevance: A TBR of 2.5 or greater is a highly sensitive threshold for indicating a lesion to be consistent with a NET on histologic findings and thus warranting surgical resection. The omentum should be used as the background count activity for 68Ga-dotatate RGS for patients with abdominal NETs.
PubMed-ID: 30267071
http://dx.doi.org/10.1001/jamasurg.2018.3475

The impact of failure to achieve symptom control after resection of functional neuroendocrine tumors: An 8-institution study from the US Neuroendocrine Tumor Study Group.
J Surg Oncol, 119(1):5-11.
M. Y. Zaidi, A. G. Lopez-Aguiar, G. A. Poultsides, M. Dillhoff, F. G. Rocha, K. Idrees, H. Nathan, E. R. Winslow, R. C. Fields, K. Cardona and S. K. Maithel. 2019.
BACKGROUND: The goals of resection of functional neuroendocrine tumors (NETs) are two-fold: Oncological benefit and symptom control. The interaction between the two is not well understood. METHODS: All patients with functional NETs of the pancreas, duodenum, and ampulla who underwent curative-intent resection between 2000 and 2016 were identified. Using Cox regression analysis, factors associated with reduced recurrence-free survival (RFS) were identified. RESULTS: Two-hundred and thirty patients underwent curative-intent resection. Fifty-three percent were insulinomas, 35% gastrinomas, and 12% were other types. Twenty-one percent had a known genetic syndrome, 23% had lymph node (LN) positivity, 80% underwent an R0 resection, and 14% had no postoperative symptom improvement (SI). Factors associated with reduced RFS included noninsulinoma histology, the presence of a known genetic syndrome, LN positivity, R1 margin, and lack of SI. On multivariable analysis, only the failure to achieve SI following resection was associated with reduced RFS. Considering only those patients with an R0 resection, failure to achieve SI was associated with worse 3-year RFS compared with patients having SI (36% vs 80%; P = 0.006). CONCLUSIONS: Failure to achieve symptomatic improvement after resection of functional NETs is associated with worse RFS. These patients may benefit from short-interval surveillance imaging postoperatively to assess for earlier radiographical disease recurrence.

PubMed-ID: 30481383
http://dx.doi.org/10.1002/jso.25306

Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors.
J Clin Endocrinol Metab, 104(4):1336-44.
W. T. Zandee, T. Brabander, A. Blazevic, B. L. R. Kam, J. J. M. Teunissen, R. A. Feelders, J. Hofland and W. W. de Herder. 2019.
PURPOSE: Peptide receptor radionuclide therapy (PRRT) with the radiolabeled somatostatin analogue [Lutetium-177-DOTA0-Tyr3]octreotate (177Lu-DOTATATE) is widely applied for inoperable metastatic small intestinal and nonfunctioning pancreatic neuroendocrine tumors (pNETs). The aim of this study is to describe the safety and efficacy of the treatment of functioning pNETs. METHODS: Patients were treated with up to four cycles of 177Lu-DOTATATE with an intended dose of 7.4 Gbq per cycle. Radiological (Response Evaluation Criteria in Solid Tumors 1.1), symptomatic, and biochemical response were analyzed retrospectively for all patients with a functioning pNET (insulinoma, gastrinoma, VIPoma, and glucagonoma) treated with 177Lu-DOTATATE. Quality of life (QOL) was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module questionnaire. RESULTS: Thirty-four patients with a metastatic functioning pNET (European Neuroendocrine Tumor Society grade 1 or 2) were included: 14 insulinomas, 5 VIPomas, 7 gastrinomas, and 8 glucagonomas. Subacute hematological toxicity, grade 3 or 4 occurred in 4 patients (12%) and a hormonal crisis in 3 patients (9%). PRRT resulted in partial or complete response in 59% of patients and the disease control rate was 78% in patients with baseline progression. 71% of patients with uncontrolled symptoms had a reduction of symptoms and a more than 80% decrease of circulating hormone levels was measured during follow-up. After PRRT, median progression-free survival was 18.1 months (interquartile range: 3.3 to 35.7) with a concurrent increase in QOL. CONCLUSION: Treatment with 177Lu-DOTATATE is a safe and effective therapy resulting in radiological, symptomatic and biochemical response in a high percentage of patients with metastatic functioning pNETs. Hormonal crises occur relatively frequent and preventive therapy should be considered before and/or during PRRT.
PubMed-ID: 30566620
http://dx.doi.org/10.1210/jc.2018-01991

Neuroendocrine neoplasms: current and potential diagnostic, predictive and prognostic markers.
Endocr Relat Cancer, 26(3):R157-R79.
A. D. Herrera-Martinez, L. J. Hofland, M. A. Galvez Moreno, J. P. Castano, W. W. de Herder and R. A. Feelders. 2019.
Some biomarkers for functioning and non-functioning neuroendocrine neoplasms (NENs) are currently available. Despite their application in clinical practice, results should be interpreted cautiously. Considering the variable sensitivity and specificity of these parameters, there is an unmet need for novel biomarkers to improve diagnosis and predict patient outcome. Nowadays, several new biomarkers are being evaluated and may become future tools for the management of NENs. These biomarkers include (1) peptides and growth factors; (2) DNA and RNA markers based on genomics analysis, for example, the so-called NET test, which has been developed for analyzing gene transcripts in circulating blood; (3) circulating tumor/endothelial/progenitor cells or cell-free tumor DNA, which represent minimally invasive methods that would provide additional information for monitoring treatment response and (4) improved imaging techniques with novel radiolabeled somatostatin analogs or peptides. Below we summarize some future directions in the development of novel diagnostic and predictive/prognostic biomarkers in NENs. This review is focused on circulating and selected tissue markers.
PubMed-ID: 30615596
http://dx.doi.org/10.1530/ERC-18-0354

Large Cell Neuroendocrine Tumor Size >3 cm Negatively Impacts Long-Term Outcomes After R0 Resection.
World J Surg, 43(7):1712-20.
M. Cattoni, E. Vallieres, L. M. Brown, A. A. Sarkeshik, S. Margaritora, A. Siciliani, P. L. Filosso, F. Guerrera, A. Imperatori, N. Rotolo, F. Farjah, G. Wandell, K. Costas, C. Mann, M. Hubka, S. Kaplan, A. S. Farivar, R. W. Aye and B. E. Louie. 2019.
BACKGROUND: Minimal knowledge exists regarding the outcome, prognosis and optimal treatment strategy for patients with pulmonary large cell neuroendocrine carcinomas (LCNEC) due to their rarity. We aimed to identify factors affecting survival and recurrence after resection to inform current treatment strategies. METHODS: We retrospectively reviewed 72 patients who had undergone a curative resection for LCNEC in 8 centers between 2000 and 2015. Univariable and multivariable analyses were performed to identify the factors influencing

recurrence, disease-specific survival and overall survival. These included age, gender, previous malignancy, ECOG performance status, symptoms at diagnosis, extent of resection, extent of lymphadenectomy, additional chemo- and/or radiotherapy, tumor location, tumor size, pT, pleural invasion, pN and pStage. RESULTS: Median follow-up was 47 (95%CI 41-79) months; 5-year disease-specific and overall survival rates were 57.6% (95%CI 41.3-70.9) and 47.4% (95%CI 32.3-61.1). There were 22 systemic recurrences and 12 loco-regional recurrences. Tumor size was an independent prognostic factor for systemic recurrence [HR: 1.20 (95%CI 1.01-1.41); p = 0.03] with a threshold value of 3 cm (AUC = 0.71). For tumors </=3 cm and >3 cm, 5-year freedom from systemic recurrence was 79.2% (95%CI 43.6-93.6) and 38.2% (95%CI 20.6-55.6) (p < 0.001) and 5-year disease-specific survival was 60.7% (95%CI 35.1-78.8) and 54.2% (95%CI 32.6-71.6) (p = 0.31), respectively. CONCLUSIONS: A large proportion of patients with surgically resected LCNEC will develop systemic recurrence after resection. Patients with tumors >3 cm have a significantly higher rate of systemic recurrence suggesting that adjuvant chemotherapy should be considered after complete resection of LCNEC >3 cm, even in the absence of nodal involvement.
PubMed-ID: 30783763
http://dx.doi.org/10.1007/s00268-019-04951-x

Surgery for Pancreatic Neuroendocrine Tumor G3 and Carcinoma G3 Should be Considered Separately.
Ann Surg Oncol, 26(5):1385-93.
T. Yoshida, S. Hijioka, W. Hosoda, M. Ueno, M. Furukawa, N. Kobayashi, M. Ikeda, T. Ito, Y. Kodama, C. Morizane, K. Notohara, H. Taguchi, M. Kitano, K. Yane, Y. Tsuchiya, I. Komoto, H. Tanaka, A. Tsuji, S. Hashigo, T. Mine, A. Kanno, G. Murohisa, K. Miyabe, T. Takagi, N. Matayoshi, M. Sakaguchi, H. Ishii, Y. Kojima, K. Matsuo, H. Yoshitomi, S. Nakamori, H. Yanagimoto, Y. Yatabe, J. Furuse and N. Mizuno. 2019.
BACKGROUND: The role of surgery in pancreatic neuroendocrine neoplasm grade 3 (pNEN-G3) treatment remains unclear. We aimed to clarify the role of surgery for pNEN-G3, which has recently been reclassified as pancreatic neuroendocrine tumor-G3 (pNET-G3) and pancreatic neuroendocrine carcinoma-G3 (pNEC-G3), with and without metastases, respectively. METHODS: We analyzed a subgroup of patients from the Japanese pancreatic NEC study, a Japanese multicenter case-series study of pNEN-G3. Pathologists subclassified 67 patients as having pNET-G3 or pNEC-G3 based on morphological features. We compared the overall survival (OS) rates among patients who were grouped according to whether they had undergone tumor-targeted surgery for tumors without (SwoM) or with (SwM) metastases, or non-surgical procedures (NS). RESULTS: Data from 21 patients with pNET-G3 (SwoM, n = 6; SwM, n = 5; NS, n = 10) and 46 patients with pNEC-G3 (SwoM, n = 8; SwM, n = 5; NS, n = 33) were analyzed. OS of patients with pNET-G3 was significantly longer after SwoM and SwM than with NS (p = 0.018 and p = 0.022). In contrast, OS did not significantly differ between either SwoM or SwM and NS (p = 0.093 and p = 0.489) among patients with pNEC-G3. CONCLUSION: The role of surgery should be considered separately for pNET-G3 and pNEC-G3. Although SwoM and SwM can be considered for pNET-G3, caution is advised before considering SwM and SwoM for pNEC-G3.
PubMed-ID: 30863939
http://dx.doi.org/10.1245/s10434-019-07252-8

Outcomes of laparoscopic tumor ablation for neuroendocrine liver metastases: a 20-year experience.
Surg Endosc,
E. Kose, B. Kahramangil, H. Aydin, M. Donmez, H. Takahashi, F. Aucejo, A. Siperstein and E. Berber. 2019.
BACKGROUND: Since neuroendocrine tumors have an indolent behavior, studies looking at oncologic outcomes should report a long-term follow-up. Over the years, we have been treating selected patients with neuroendocrine liver metastases (NELM) with laparoscopic ablation (LA) and reported favorable local tumor control. The aim of this study is to see whether this local efficacy translates into long-term oncologic outcomes. METHODS: This was an IRB-approved study of patients who underwent LA for NELM at a single center. Overall and progression-free survivals were analyzed using Kaplan-Meier and Cox proportional hazards model. RESULTS: Study included 58 women and 71 men with a median age of 58 (IQR 47-67) years. Tumor type included carcinoid (n = 92), pancreatic islet cell (n = 28), and medullary thyroid cancer (n = 9). There was a median of 6 (IQR 3-8) tumors, measuring 1.6 (IQR 1.1-2.4) cm. At a median follow-up of 73 (IQR 34-135) months, local liver recurrence per patient, new liver recurrence, and new extrahepatic recurrence rates were 22, 68, and 33%, respectively. Local tumor recurrence per lesion was 5% (n = 42/770). Median overall survival was 125 months, with 5-year, and 10-year overall survivals being, 76%, and 59%, respectively; and median disease-free survival was 13 months, with 5-year, and 10-year progression-free survivals being 26%, and 6%, respectively. On Cox proportional hazards model, overall survival was independently predicted by tumor size, grade, and resection status of primary. CONCLUSION: To our knowledge, this is the largest single-center experience with the longest follow-up regarding the utilization of LA for NELM. Our results demonstrate that in selected patients, LA achieves a 95% local tumor control and 59% 10-year overall survival.

PubMed-ID: 30945061
http://dx.doi.org/10.1007/s00464-019-06759-1

Defining the Role of Lymphadenectomy for Pancreatic Neuroendocrine Tumors: An Eight-Institution Study of 695 Patients from the US Neuroendocrine Tumor Study Group.
Ann Surg Oncol, 26(8):2517-24.
A. G. Lopez-Aguiar, M. Y. Zaidi, E. W. Beal, M. Dillhoff, J. G. D. Cannon, G. A. Poultsides, Z. S. Kanji, F. G. Rocha, P. Marincola Smith, K. Idrees, M. Beems, C. S. Cho, A. V. Fisher, S. M. Weber, B. A. Krasnick, R. C. Fields, K. Cardona and S. K. Maithel. 2019.
BACKGROUND: Preoperative factors that reliably predict lymph node (LN) metastases in pancreatic neuroendocrine tumors (PanNETs) are unclear. The number of LNs needed to accurately stage PanNETs has not been defined. METHODS: Patients who underwent curative-intent resection of non-functional PanNETs at eight institutions from 2000 to 2016 were analyzed. Preoperative factors associated with LN metastases were identified. A procedure-specific target for LN retrieval to accurately stage patients was determined. RESULTS: Of 695 patients who underwent resection, 33% of tumors were proximal (head/uncinate) and 67% were distal (neck/body/tail). Twenty-six percent of patients (n = 158) had LN-positive disease, which was associated with a worse 5-year recurrence-free survival (RFS; 60% vs. 86%; p < 0.001). The increasing number of positive LNs was not associated with worse RFS. Preoperative factors associated with positive LNs included tumor size >/= 2 cm (odds ratio [OR] 6.6; p < 0.001), proximal location (OR 2.5; p < 0.001), moderate versus well-differentiation (OR 2.1; p = 0.006), and Ki-67 >/= 3% (OR 3.1; p < 0.001). LN metastases were also present in tumors without these risk factors: < 2 cm (9%), distal location (19%), well-differentiated (23%), and Ki-67 < 3% (16%). Median LN retrieval was 13 for pancreatoduodenectomy (PD), but only 9 for distal pancreatectomy (DP). Given that PD routinely includes a complete regional lymphadenectomy, a minimum number of LNs to accurately stage patients was not identified. However, for DP, removal of less than seven LNs failed to discriminate 5-year RFS between LN-positive and LN-negative patients (less than seven LNs: 72% vs. 83%, p = 0.198; seven or more LNs: 67% vs. 86%; p = 0.002). CONCLUSIONS: Tumor size >/= 2 cm, proximal location, moderate differentiation, and Ki-67 >/= 3% are preoperative factors that predict LN positivity in resected non-functional PanNETs. Given the 9-23% incidence of LN metastases in patients without such risk factors, routine regional lymphadenectomy should be considered. PD inherently includes sufficient LN retrieval, while DP should aim to remove seven or more LNs for accurate staging.
PubMed-ID: 31004295
http://dx.doi.org/10.1245/s10434-019-07367-y

Robotic Central Pancreatectomy for Well-Differentiated Neuroendocrine Tumor: Parenchymal-Sparing Procedure.
Ann Surg Oncol, 26(7):2121.
T. Wakabayashi, E. Felli, Z. Cherkaoui, D. Mutter, J. Marescaux and P. Pessaux. 2019.
BACKGROUND: The frequency of pancreatic neuroendocrine tumors (pNETs), representative of benign and borderline malignant pancreatic tumors, has been increasing. For pNETs, pancreas-preserving pancreatectomy can be an appropriate option. Conversely, some articles have recently shown that robotic central pancreatectomy (RCP) is feasible and safe. METHODS: We demonstrated our standardized technique of RCP. In our technique, pancreaticoenteric reconstruction is performed via a pancreaticogastrostomy to manage the distal pancreatic remnant. We also evaluated our initial experience with four consecutive RCPs for well-differentiated pNETs, retrospectively. RESULTS: In our evaluation, two men and two women had a median age of 45 years (range 36-64). Median tumor size was 2.1 cm (range 1-5), and median operative time was 315 min (range 268-630). No transfusion was given perioperatively. Median hospital stay was 17 days (range 13-22). Grade A postoperative pancreatic fistula was identified in two patients, while grade B was identified in the other two patients. One of the patients was managed using an additional percutaneous drainage. No operative mortality was observed. Pathological findings confirmed R0 resection for all well-differentiated pNETs (pT1: two patients; pT2: two patients). CONCLUSIONS: Central pancreatectomy can be carefully selected as a relevant surgical option for well-differentiated pNETs circumscribed in the pancreatic isthmus and body. Our robotic procedure might overcome the complexity of central pancreatectomy, a parenchymal-preserving procedure, with adequate oncological outcomes.
PubMed-ID: 31020502
http://dx.doi.org/10.1245/s10434-019-07387-8

Endoscopic Ultrasound-Guided Radiofrequency Ablation: A New Therapeutic Approach for Pancreatic Neuroendocrine Tumors.
J Clin Endocrinol Metab, 104(7):2637-47.
K. Oleinikov, A. Dancour, J. Epshtein, A. Benson, H. Mazeh, I. Tal, S. Matalon, C. A. Benbassat, D. M. Livovsky, E. Goldin, D. J. Gross, H. Jacob and S. Grozinsky-Glasberg. 2019.
CONTEXT: Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is rapidly emerging as feasible therapy for patients with pancreatic neuroendocrine tumors (pNETs) in selected cases, as a result of its favorable safety profile. OBJECTIVE: To assess the feasibility, safety, and efficacy of EUS-RFA in a cohort of patients with functional and nonfunctional pNETs (NF-pNETs). DESIGN: Data on pNET patients treated with EUS-RFA between March 2017 and October 2018 at two tertiary centers was retrospectively analyzed. RESULTS: The cohort included 18 adults (eight women, 10 men), aged 60.4 +/- 14.4 years (mean +/- SD), seven insulinoma patients, and 11 patients with NF-pNETs. Twenty-seven lesions with a mean diameter of 14.3 +/- 7.3 mm (range 4.5 to 30) were treated. Technical success defined as typical postablative changes on a surveillance imaging was achieved in 26 out of 27 lesions. Clinical response with normalization of glucose levels was observed in all (seven of seven) insulinoma cases within 24 hours of treatment. Overall, there were no major complications 48 hours postprocedure. No clinically significant recurrences were observed during mean follow-up of 8.7 +/- 4.6 months (range 2 to 21 months). CONCLUSIONS: EUS-guided RFA of pNETs is a minimally invasive, safe, and technically feasible procedure for selected patients.
PubMed-ID: 31102458
http://dx.doi.org/10.1210/jc.2019-00282

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Financial implications of telemedicine visits in an academic endocrine surgery program.
Surgery, 165(3):617-21.
F. Zheng, K. W. Park, W. J. Thi, C. C. Ro, B. L. Bass and M. W. Yeh. 2019.
BACKGROUND: Telemedicine is an emerging medium for the delivery of ambulatory care, but the reimbursement profile of telemedicine visits in the surgical setting has not been well studied. METHODS: A retrospective assessment of telemedicine encounters for thyroid and parathyroid conditions occurring from April 2015 to April 2017 was performed. Financial reimbursement from commercial payers for new and established patient visits were compared between telemedicine visits and in-person visits. Patient "savings" in terms of travel distance and drive time were calculated. RESULTS: A total of 290 telemedicine encounters were conducted; 7% were initial consultations, 47% were postoperative visits, and 45% were follow-up visits. The median patient age was 57 years. The median round-trip travel distance saved was 123.6 miles with estimated drive time of 2.4 hours per encounter. In 2% of cases, a second in-person visit within the 90-day global period occurred after a postoperative telemedicine encounter. Charges were filed for 67 encounters. The initial unpaid claims rate was 6%, which was consistent with the unpaid claims rate for in-person visits. The charge-to-collection ratio was comparable to that of in-person visits. There was a higher ratio of level 2 visits in the telemedicine encounters. Over the study period, 70 clinic hours were liberated via the use of telemedicine. CONCLUSION: Endocrine surgery telemedicine visits have the same level for level reimbursement profile as in-person visits. Down-coding and elimination of components of in-office physical examinations may lead to modest decreases in overall reimbursement. Other advantages include reallocation of clinic resources and decreased travel burden for patients.
PubMed-ID: 30245125
http://dx.doi.org/10.1016/j.surg.2018.08.017

Controversies in Vitamin D: Summary Statement From an International Conference.
J Clin Endocrinol Metab, 104(2):234-40.
A. Giustina, R. A. Adler, N. Binkley, R. Bouillon, P. R. Ebeling, M. Lazaretti-Castro, C. Marcocci, R. Rizzoli, C. T. Sempos and J. P. Bilezikian. 2019.
Context: Vitamin D is classically recognized as a regulator of calcium and phosphorus metabolism. Recent advances in the measurement of vitamin D metabolites, diagnosis of vitamin D deficiency, and clinical observations have led to an appreciation that along with its role in skeletal metabolism, vitamin D may well have an important role in nonclassical settings. Measurement of the circulating form of vitamin D that best describes total body stores, namely 25-hydroxyvitamin D, can be unreliable despite many sophisticated methodologies that have been proposed and implemented. Likewise, evidence from clinical studies showing a beneficial role of vitamin D in different disease states has been controversial and at times speculative. Moreover, the target concentrations of 25-hydroxyvitamin D to address a number of putative links between vitamin D inadequacy and nonskeletal diseases are further areas of uncertainty. Setting: To address these issues, an international

conference on "Controversies in Vitamin D" was held in Pisa, Italy, in June 2017. Three main topics were addressed: (i) vitamin D assays and the definition of hypovitaminosis D; (ii) skeletal and extraskeletal effects of vitamin D; (iii) therapeutics of vitamin D. Results: This report provides a summary of the deliberations of the expert panels of the conference. Conclusions: Despite great advances in our appreciation of vitamin D metabolism, measurements, biological actions on classical and nonclassical tissues, and therapeutics, all of which this report summarizes, much more work remains to be done so that our knowledge base can become even more secure.
PubMed-ID: 30383226
http://dx.doi.org/10.1210/jc.2018-01414

Evacuation of postoperative hematomas after thyroid and parathyroid surgery: An analysis of the CESQIP Database.
Surgery, 165(1):250-6.
S. D. Talutis, F. T. Drake, T. Sachs, S. R. Rao and D. McAneny. 2019.
BACKGROUND: A feared complication after thyroid and parathyroid operations is postoperative hematoma that threatens the airway. The aim of this study was to identify factors associated with postoperative hematoma. METHODS: Patients undergoing thyroidectomy or parathyroidectomy were evaluated for postoperative hematoma requiring operative intervention using the database of the Collaborative Endocrine Surgery Quality Improvement Program. Associations between perioperative factors and postoperative hematoma were evaluated with bivariate methodologies and multivariable logistic regression. RESULTS: Among 19,356 patients, 60.4% underwent thyroidectomy +/- lymph node dissection, 34.9% parathyroidectomy, and 4.7% concurrent thyroidectomy/parathyroidectomy. Postoperative hematoma occurred in 0.6% overall: 0.7% of thyroidectomies, 0.3% of parathyroidectomies, and 1.3% of combined thyroid/parathyroid operations (P < .001). The incidence of postoperative hematoma was greater among men (P < .001) and after greater operative times (P < .001) but was not influenced by body mass index, prior neck surgery, or reoperations. Multivariable logistic regression determined that operative complexity, operation >1 hour, male sex, and age were independently associated with postoperative hematoma. Postoperative hematoma were associated with greater rates of other complications as well. CONCLUSION: Large databases such as Collaborative Endocrine Surgery Quality Improvement Program are useful to evaluate rare complications. The risk of postoperative hematoma is associated with extent of operation, greater operative times, age, and male sex. These data may be beneficial in counseling patients and may serve as a benchmark for surgeons to evaluate their practices.
PubMed-ID: 30413321
http://dx.doi.org/10.1016/j.surg.2018.04.087

Continuous Vagal Neuromonitoring Using the Laryngeal Adductor Reflex: Can Preincision Dyssynchrony Predict Intraoperative Nerve Behavior?
Otolaryngol Head Neck Surg, 161(1):118-22.
M. Roldan, M. J. Tellez, S. Ulkatan and C. F. Sinclair. 2019.
OBJECTIVE: The laryngeal adductor reflex (LAR) is an airway-protective response triggered by sensory laryngeal receptors and resulting in bilateral vocal fold adduction. The normal morphology of the early R1 response resembles that of the compound muscle action potential (CMAP). However, in a small subset of patients, the morphology is dyssynchronous with multiple peaks. This study investigates whether preoperative LAR dyssynchrony predicts intraoperative nerve behavior during thyroid surgeries. STUDY DESIGN: Retrospective case-control study. SETTING: US academic health center. SUBJECTS AND METHODS: Opening and closing LAR waveforms from 200 patients with normal preoperative laryngeal examinations monitored continuously during thyroid surgeries using the LAR were analyzed. Area under the curve (AUC) and number of "events" during surgery (defined as any transient decline in AUC >50% baseline) were determined for patients who demonstrated opening dyssynchronous LAR traces compared to demographically matched controls. RESULTS: Six patients had opening dyssynchronous LAR traces. These patients had significantly greater declines in R1 AUC than demographically matched patients with opening synchronized R1 traces (P = .007). Upon thyroid removal, 1 patient converted from a dyssynchronous to synchronous trace. CONCLUSIONS: Preincision dyssynchronous LAR waveforms may indicate subclinical, potentially reversible, neuropathy of the recurrent laryngeal nerve (RLN) and predict intraoperative RLN behavior. Preincision knowledge of R1 dyssynchrony can facilitate surgical planning as such patients may glean particular benefit from continuous intraoperative nerve monitoring, frequent tissue relaxation, and saline irrigation as means to minimize nerve stress intraoperatively.
PubMed-ID: 30857469
http://dx.doi.org/10.1177/0194599819835781

The role of 68Ga-DOTA-Octreotate (GaTate) PET/CT in follow-up of SDH-associated pheochromocytoma and paraganglioma (PPGL).
J Clin Endocrinol Metab,
G. Kong, T. Schenberg, C. J. Yates, A. Trainer, N. Sachithanandan, A. Iravani, A. Ravi Kumar, M. S. Hofman, T. Akhurst, M. Michael and R. J. Hicks. 2019.
PURPOSE: Germline succinate dehydrogenase (SDHx) mutation carriers, especially SDHB, are at increased malignancy risk and require life-long surveillance. Current guidelines recommend periodic whole-body MRI imaging. We assessed the incremental value of GaTate PET/CT compared to conventional imaging in such patients. METHODS: SDHx mutation carriers who had GaTate PET/CT were retrospectively reviewed. Detection of lesions were compared to MRI or CT on a per-patient and per-lesion basis. Proof of lesions were based on histopathology or clinical/imaging follow-up. RESULTS: Twenty consecutive patients (median age 46 years, 10 males) were reviewed. Fourteen patients had SDHB, 4 SDHD, 1 SDHC and 1 SDHA mutation. Fifteen had prior surgery +/- radiotherapy. Indications for PET/CT: 7 patients for surveillance for previously treated disease, 9 residual disease, 2 asymptomatic mutation carriers and 2 for raised catecholamines. Median time between modalities 1.5 months.GaTate PET/CT had higher sensitivity and specificity than conventional imaging. On a per-patient basis: PET/CT sensitivity 100%, specificity 100%; MRI/CT 85% and 50%. Per-lesion basis: PET/CT sensitivity 100%, specificity 75%; MRI/CT 80% and 25%. PET/CT correctly identified additional small nodal and osseous lesions. MRI/CT had more false positive findings. Change of management resulted in 40% (8/20 pts): 3 received localised treatment instead of observation, 1 changed to observation given extra disease detected, 4 with metastases had radionuclide therapy. CONCLUSIONS: GaTate PET/CT provided incremental diagnostic information with consequent management impact in SDHx-PPGL. Incorporating this modality as part of a surveillance program seems prudent. Further research is needed to define the optimal surveillance strategy including use of MRI.
PubMed-ID: 30977831
http://dx.doi.org/10.1210/jc.2019-00018