EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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

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

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Journals covered

Journal	IF2014	Journal	IF2014
Acta Cytol	1.562‡	J Bone Miner Res	6.832
Am J Kidney Dis	5.900	J Clin Endocrinol Metab	6.209
Am J Nephrol	2.669	J Clin Oncol	18.428
Am J Surg	2.291	J Endocrinol	3.718
Am Surgeon	0.818	J Endocrinol Invest	1.552‡
Ann Surg	8.327	J Nephrol	1.454
Ann Surg Oncol	3.930	J Nucl Med	6.160
ANZ J Surg	1.122	J Surg Oncol	3.244
Br J Surg	5.542	Lancet	45.217
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Chirurg	0.574	Laryngoscope	2.144
Clin Endocrinol Oxf	3.457	N Engl J Med	55.873
Clin Nucl Med	3.931	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	13.281
Curr Opin Oncol	4.466	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	14.180
Endocr Relat Cancer	4.805	Nephrol Dial Transplant	3.577
Endocr Rev	21.059	Nephron Clin Pract	1.402
Eur Arch Otorhinolaryngol	1.545	Neuroendocrinology	4.373
Eur J Endorcrinol	4.069	Oncologist	4.865
Eur J Surg Oncol	3.009	Otolaryngol Head Neck Surg	2.020
Gland Surg	---	Surg Clin North Am	1.879
Head Neck	2.641	Surg Endosc	3.256
Horm Metab Res	2.121	Surg Laparosc Endosc Percutan Tech	1.140
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	1.794	Surg Oncol	3.270
JAMA Surg (*prev:* Arch Surg)	3.936	Surg Oncol Clin N Am	1.806
Int J Cancer	5.085	Surgery	3.380
J Am Coll Surg	5.122	Thyroid	4.493
J Am Soc Nephrol	9.343	Updates In Surgery	---
J Bone Miner Metab	2.460	World J Surg	2.642

Journal names are links to the journal's homepage!, IF2014: Impact factor 2014, ‡IF2013 (IF 2014 not available)

Thyroid

Meta-Analyses

Transoral robotic excision of ectopic lingual thyroid: Case series and literature review.
Head Neck, 37(8):E88-91.
E. Prisman, A. Patsias and E. M. Genden. 2015.
BACKGROUND: Surgical excision of an ectopic lingual thyroid has traditionally been associated with significant morbidity and has therefore been reserved for patients with severe obstructive symptoms or suspected malignancy. Transoral robotic surgery (TORS) has provided a minimally invasive approach to completely and safely excise ectopic lingual thyroid. METHODS: Three index cases were identified from the detailed clinical database of TORS patients. A systematic review of the management of ectopic lingual thyroid in the English literature was performed. RESULTS: TORS-assisted excision of a lingual thyroid gland was successfully performed in 3 patients with excellent functional outcomes CONCLUSION: TORS-assisted excision of an ectopic lingual thyroid is a safe and feasible treatment modality with minimal morbidity, and, in experienced hands, should be offered as a valid treatment for this pathology.
PubMed-ID: 24816912
http://dx.doi.org/10.1002/hed.23757

Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis.
Clin Endocrinol (Oxf), 83(1):124-32.
H. Qu, G. R. Sun, Y. Liu and Q. S. He. 2015.
BACKGROUND: Prophylactic central lymph node dissection (CLND) in clinically node-negative patients remains controversial, and predictive factors for central lymph node metastasis (CLNM) in patients with papillary thyroid carcinoma (PTC) are not well defined. Herein, we conducted a systematic review to quantify the clinicopathologic factors predictive for CLNM in patients with PTC. METHODS: A systematic search of electronic databases (PubMed, Embase, Cochrane CENTRAL, Scopus and Wanfang Database) for studies published until July 2014 was performed. Cohort, case-control studies and randomized controlled trials that examined clinical risk factors of CLNM were included. RESULTS: Twenty-five studies (4 prospective and 21 retrospective studies) involving 7,719 patients met final inclusion criteria. From the pooled analyses, male gender (OR 1.93, 95% CI 1.40 to 2.64), tumour multifocality (OR 1.93, 95% CI 1.62 to 2.30), tumour size >0.5 cm (OR 3.48, 95% CI 2.24 to 5.41), capsular invasion (OR 1.91, 95% CI 1.36 to 2.67), extrathyroidal extension (OR 2.42, 95% CI 1.58 to 3.71), lymphovascular invasion (OR 13.29, 95% CI 5.61 to 31.48) and lateral lymph node metastasis (OR 14.33, 95% CI 5.34 to 38.50) were significantly associated with increased risk of CLNM, while age >45 years (OR 0.65, 95% CI 0.51 to 0.83) and lymphocytic thyroiditis (OR 0.70, 95% CI 0.53 to 0.92) resulted in decreased risk of CLNM. Bilaterality and tumour location were not significantly associated with CLNM development (all P > 0.05). CONCLUSIONS: Our analysis identified several clinicopathologic factors associated with CLNM. These findings may guide the necessity and extent of prophylactic CLND and ultimately improve the outcomes of patients with PTC.
PubMed-ID: 25130203
http://dx.doi.org/10.1111/cen.12583

Endocrine tumours: familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis.
Eur J Endocrinol, 172(6):R253-62.
X. Wang, W. Cheng, J. Li, A. Su, T. Wei, F. Liu and J. Zhu. 2015.
OBJECTIVE: There is controversy as to whether familial nonmedullary thyroid carcinoma (FNMTC) is more aggressive than sporadic NMTC (SNMTC). The aim of the study was to evaluate the biological characteristics of patients with FNMTC by a meta-analysis. METHODS: Four databases (PubMed, EMBASE, the Cochrane library databases, and the Web of Science) were searched to identify studies published before September, 2014. All original studies that compared clinical characteristics and prognosis of patients with FNMTC and SNMTC were included. The pooled effect sizes of interesting parameters were calculated by odds ratio (OR), standard mean difference (SMD), or hazard ratio (HR). RESULTS: Twelve studies with a total of 12 741 participants were included in this analysis. FNMTC patients had an increased rate of recurrence (OR=1.72, 95% CI: 1.34 to 2.20) and decreased disease-free survival (DFS) (HR=1.83, 95% CI: 1.34 to 2.52) in comparison with SNMTC patients. FNMTC possessed more aggressive biological behaviors, characterized by younger age at diagnosis

(SMD=-0.91, 95% CI: -1.59 to -0.22), higher risk of multifocal (OR=1.50, 95% CI: 1.32 to 1.71), bilateral (OR=1.29, 95% CI: 1.00 to 1.66), extrathyroidal invasion (OR=1.20, 95% CI: 1.02 to 1.41), and lymph node metastasis (OR=1.18, 95% CI: 1.01 to 1.38). CONCLUSION: FNMTC is a more aggressive disease and possesses higher recurrence rate and lower DFS. More attention and careful consideration should be paid regarding the decision about treatment for patients with FNMTC.
PubMed-ID: 25637073
http://dx.doi.org/10.1530/EJE-14-0960

Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature.
J Clin Endocrinol Metab, 100(5):1748-61.
L. Lamartina, C. Durante, S. Filetti and D. S. Cooper. 2015.
BACKGROUND: Radioiodine remnant ablation (RRA) has traditionally been one of the cornerstones of differentiated thyroid cancer (DTC) treatment. The decision to use RRA in low-risk (LR) and intermediate-risk (IR) patients is controversial. The aim of this review is to examine the evidence of RRA benefit in the staging, follow-up, and recurrence prevention in LR and IR DTC patients. METHODS: From a PubMed search, we selected original papers (OPs) using the following inclusion criteria: 1) DTC; 2) LR and IR patients; 3) non-RRA-treated patients or RRA-treated vs non-RRA-treated groups; 4) a report of the outcome of cancer recurrence; and 5) publication since 2008. RESULTS: Neck ultrasonography is superior to whole-body scan for disease detection in the neck. A rising or declining serum thyroglobulin level over time provides an excellent positive or negative predictive value, respectively, even in non-RRA-treated patients. No OP demonstrating RRA benefit on recurrence in LR patients was found; two OPs found no evidence of benefit. We found 11 OPs that observed some benefit in reducing recurrence rates with RRA in IR patients and 13 OPs that failed to show benefit from RRA in this group. CONCLUSIONS: Neck ultrasonography and serum thyroglobulin measurement are equivalent or superior in detecting and localizing residual disease compared to post-therapy whole-body scan. There is no evidence of RRA benefit in recurrence prevention for LR patients. There are conflicting data on IR patients and only a few studies with homogenous and properly stratified populations. A careful evaluation of tumor pathological features and patient characteristics and preferences should guide RRA decision making.
PubMed-ID: 25679996
http://dx.doi.org/10.1210/jc.2014-3882

Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid nodules: systematic review including traditional pooling and bayesian network meta-analysis.
J Clin Endocrinol Metab, 100(5):1903-11.
E. J. Ha, J. H. Baek, K. W. Kim, J. Pyo, J. H. Lee, S. H. Baek, H. Dossing and L. Hegedus. 2015.
PURPOSE: To compare the efficacy of radiofrequency ablation (RFA) and laser ablation (LA) for treatment of benign solid thyroid nodules, using a systematic review including traditional pooling and Bayesian network meta-analysis. MATERIALS AND METHODS: A comprehensive literature search in PubMed-MEDLINE, EMBASE, and the Cochrane Library databases identified prospective studies evaluating the percentage mean change [absolute mean change (mL)] in nodule volume after RFA or LA. Studies from January 1, 2000, to November 1, 2013, were included. Review of 128 potential papers, including a full-text review of 33, identified 10 eligible papers covering a total of 184 patients for meta-analysis. The percentage mean change [absolute mean change] in nodule volume over a 6-month follow-up was compared between RFA and LA. RESULTS: Based on the traditional frequentist approach, the pooled percentage mean changes (95% confidence interval) of RFA and LA were 76.1% (70.1-82.1) and 49.9% (41.4-58.5), respectively, and the pooled absolute mean changes (95% confidence interval) of RFA and LA were 8.9 mL (6.6-11.2) and 5.2 mL (4.3-6.1), respectively. Based on the Bayesian network meta-analysis, RFA achieved a larger pooled percentage mean change (95% credible interval) and absolute mean change (95% credible interval) compared to LA [77.8% (67.7-88.0) vs 49.5% (26.7-72.4), and 9.2 mL (5.8-11.9) vs 5.3 mL (2.1-8.5), respectively]. The RFA group has the highest probability of having the most efficacious treatment (98.7%). There were no major complications after either RFA or LA. CONCLUSIONS: RFA appears to be superior to LA in reducing benign solid thyroid nodule volume, despite the smaller number of treatment sessions without major side effects.
PubMed-ID: 25695887
http://dx.doi.org/10.1210/jc.2014-4077

Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies.
Thyroid, 25(5):538-50.
L. R. Remonti, C. K. Kramer, C. B. Leitao, L. C. Pinto and J. L. Gross. 2015.

BACKGROUND: Thyroid nodules are a common finding in the general population, and their detection is increasing with the widespread use of ultrasound (US). Thyroid cancer is found in 5-15% of cases depending on sex, age, and exposure to other risk factors. Some US parameters have been associated with increased risk of malignancy. However, no characteristic seems sufficiently reliable in isolation to diagnose malignancy. The objective of this meta-analysis was to evaluate the diagnostic performance of US features for thyroid malignancy in patients with unselected thyroid nodules and nodules with indeterminate fine-needle aspiration (FNA) cytology. METHODS: Electronic databases were reviewed for studies published prior to July 2012 that evaluated US features of thyroid nodules and reported postoperative histopathologic diagnosis. A manual search of references of review and key articles, and previous meta-analyses was also performed. A separate meta-analysis was performed including only nodules with indeterminate cytology. Analyzed features were solid structure, hypoechogenicity, irregular margins, absence of halo, microcalcifications, central vascularization, solitary nodule, heterogeneity, taller than wide shape, and absence of elasticity. RESULTS: Fifty-two observational studies (12,786 nodules) were included. Nine studies included nodules with indeterminate cytology as a separate category, comprising 1851 nodules. In unselected nodules, all US features were significantly associated with malignancy with an odds ratio varying from 1.78 to 35.7, and microcalcifications, irregular margins, and a taller than wide shape had high specificities (Sp; 87.8%, 83.1%, 96.6%) and positive likelihood ratios (LHR; 3.26, 2.99, 8.07). Absence of elasticity was the single feature with the best diagnostic performance (sensitivity 87.9%, Sp 86.2%, and positive LHR 6.39). The presence of central vascularization was the most specific US feature in nodules with indeterminate cytology (Sp 96% and positive LHR 2.13). CONCLUSIONS: US features in isolation do not provide reliable information to select nodules that should have a FNA performed. A combination of US characteristics with higher likelihood ratios and consequently with higher post-test probabilities of malignancy-microcalcifications, or a taller than wide shape, or irregular margins, or absence of elasticity-will probably identify nodules with an increased risk for malignancy. Further studies are required to standardize elastography techniques and evaluate outcomes, especially in nodules with an indeterminate cytology.
PubMed-ID: 25747526
http://dx.doi.org/10.1089/thy.2014.0353

Procalcitonin for detecting medullary thyroid carcinoma: a systematic review.
Endocr Relat Cancer, 22(3):R157-64.
P. Trimboli, E. Seregni, G. Treglia, M. Alevizaki and L. Giovanella. 2015.
The aim of the present study was to perform a systematic review of published studies to provide a robust estimation of the use of procalcitonin (ProCT) as a diagnostic marker of medullary thyroid carcinoma (MTC), with particular focus on its specificity and negative predictive value in excluding MTC. A comprehensive computer literature search was conducted to find relevant published articles on the topic. We used a search algorithm based on a combination of the terms 'medullary,' 'thyroid,' and 'ProCT.' The search was updated until February 2015. To expand our search, references of the retrieved articles were also screened. A total of 39 articles were retrieved, of which nine original papers published from 2003 to 2014 were selected for the review. Some of these studies used ProCT in the preoperative diagnosis of MTC, whereas others measured ProCT during the follow-up of patients who had been previously treated for MTC. Other laboratory measurements were performed in some of the included studies. The results of the majority of the studies indicate that ProCT measurement appears to be a very promising and reliable serum marker for the diagnosis of MTC, and it is not inferior to calcitonin (CT). The sample handling is less laborious, and in the few CT-negative cases reviewed, the assay had even greater sensitivity. It would be worthwhile to establish cutoff levels using larger patient series, because we speculate that this assay could potentially replace CT measurement in the future.
PubMed-ID: 25934688
http://dx.doi.org/10.1530/ERC-15-0156

Total thyroidectomy versus lobectomy as initial operation for small unilateral papillary thyroid carcinoma: A meta-analysis.
Surg Oncol, 24(2):117-22.
F. I. Macedo and V. K. Mittal. 2015.
INTRODUCTION: Consensus guidelines have recommended total thyroidectomy for papillary thyroid carcinoma (PTC) > 1 cm. However, the optimal surgical approach for small and unilateral (</=1 cm) PTC remains controversial. METHODS: A meta-analysis was performed using MEDLINE and EMBASE databases to identify all studies investigating at thyroid surgery options, total thyroidectomy (TT) versus thyroid lobectomy (TL), for PTC </= 1 cm. The primary endpoints were locoregional recurrence and mortality rates. RESULTS: The initial literature search identified 305 publications (1980-2014). Six studies met the inclusion criteria comprising 2939 patients (2002-2013). Among these patients, 2134 (72.6%) underwent TT and 805 (27.4%) underwent TL. Mean

follow-up was 10.9 +/- 3.4 years (range, 1 month to 54 years). Overall, the recurrence rate was 5.4%: 4.4% in the TT group and 8.3% in the TL group ($p < 0.001$; RR 0.50, 95% CI 0.37-0.67). The mortality rates were 0.3% (8 cases) versus 1.1% (9 cases) in TT and TL groups, respectively ($p = 0.14$; RR 0.43, 95% CI 0.17-1.09). CONCLUSION: TT was associated with lower recurrence rates, possibly due to a more complete nodal dissection of the central neck compartment at the time of initial surgery. Based on these data, it is unclear to establish a definitive correlation between the extent of thyroid resection and long-term survival rates due to the small number of mortality events. However, there is a trend toward lower mortality rates in the TT group. Other factors need to be taken into consideration while planning thyroid resection for small PTC, such as multifocality, locoregional involvement, mode of presentation and age at diagnosis. Refinement of current guidelines for the optimal surgical management of PTC <1 cm may be warranted.
PubMed-ID: 25956302
http://dx.doi.org/10.1016/j.suronc.2015.04.005

Randomized controlled trials

How does high-concentration supplemental perioperative oxygen influence surgical outcomes after thyroid surgery? A prospective, randomized, double-blind, controlled, monocentric trial.
J Am Coll Surg, 220(5):921-33.
M. Schietroma, F. Piccione, E. M. Cecilia, F. Carlei, G. De Santis, F. Sista and G. Amicucci. 2015.
BACKGROUND: Recurrent laryngeal nerve palsy (RLNP) and hypoparathyroidism are complications of thyroid surgery. The convalescence can depend on several factors (ie, pain, fatigue, nausea, and vomiting). Supplemental oxygen improves inflammatory and immune function and decreases nausea and vomiting after surgical procedures. We have investigated whether supplemental perioperative oxygen administration could improve surgical outcomes in patients undergoing thyroid surgery. STUDY DESIGN: Three hundred and sixty patients were randomized to an oxygen/air mixture with a fraction of inspired oxygen (FiO2) of 30% (n = 179) or 80% (n = 181). Administration was commenced after induction of anesthesia and maintained for 6 hours after surgery. The primary end points were temporary or permanent RLNP and transient or definitive hypoparathyroidism. Pain and fatigue scores, nausea, and the number of vomiting episodes were also registered. Preoperatively and at several times during the first 24 postoperative hours, we measured C-reactive protein, interleukin (IL)-6, and IL1beta levels. RESULTS: In the 80% FiO2 group, the rate of temporary RLNP (4.4%) was significantly lower compared with the 30% FiO2 group (9.4%) ($p = 0.040$). In addition, postoperative transient biochemical hypoparathyroidism occurred more frequently in the 30% FiO2 group (48.5%) than in the 80% FiO2 group (16.3%) ($p = 0.046$). Supplemental 80% FiO2 significantly reduced postoperative levels of C-reactive protein ($p < 0.01$), IL6 and IL1beta ($p < 0.05$), fatigue ($p < 0.01$), and overall pain during the first 24 postoperative hours ($p < 0.01$). Supplemental 80% FiO2 also reduced nausea and vomiting on the day of operation ($p = 0.058$). CONCLUSIONS: Supplemental 80% FiO2 reduced postoperative temporary RLNP and hypoparathyroidism rates and reduced pain, fatigue, nausea, and vomiting after thyroid surgery.
PubMed-ID: 25840543
http://dx.doi.org/10.1016/j.jamcollsurg.2015.01.046

Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial.
Thyroid, 25(8):890-6.
M. Deandrea, J. Y. Sung, P. Limone, A. Mormile, F. Garino, F. Ragazzoni, K. S. Kim, D. Lee and J. H. Baek. 2015.
BACKGROUND: Percutaneous radiofrequency thermal ablation (RFA) has been reported as an effective tool for the management of benign thyroid nodules (BTN). However, large, randomized controlled trials (RCTs) are lacking. OBJECTIVE: The aims of this study were to assess the volume reduction of BTN after a single RFA performed using the moving-shot technique and to compare the volume reduction obtained in patients treated in two centers with different experience of the moving-shot technique. METHOD: This study was an international prospective RCT. It was carried out at the Mauriziano Hospital (Turin, Italy) and the Asan Medical Center (Seoul, Korea). Eighty patients harboring solid, compressive, nonfunctioning BTN (volume 10-20 mL) were enrolled. Twenty patients in each country were treated by RFA using a 18-Gauge internally cooled electrode (group A); 20 nontreated patients in each country were followed as controls (group B). RESULTS: At six months, BTN volume significantly decreased in group A (15.1+/-3.1 mL vs. 4.2+/-2.7 mL; $p<0.0001$), whereas it remained unchanged in group B (14.4+/-3.3 mL vs. 15.2+/-3.5 mL). The baseline volume was larger in the Italian series (16.4+/-2.5 mL vs. 13.9+/-3.3 mL, $p=0.009$). However, at six months, there was no significant difference between the Korean group and the Italian group (3.7+/-2.9 mL vs. 5.5+/-2.2 mL). Both cosmetic and compressive symptoms significantly improved (3.6+/-0.5 vs. 1.7+/-0.4 and 3.6+/-1.9 vs. 0.4+/-0.7, respectively; $p<0.001$). No side effects occurred. CONCLUSIONS: RFA was effective in reducing the volume of BTN. The outcome was similar in centers with different experience in the moving-shot technique.
PubMed-ID: 26061686
http://dx.doi.org/10.1089/thy.2015.0133

Consensus Statements/Guidelines

Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*, 25(6):567-610.
S. A. Wells, Jr., S. L. Asa, H. Dralle, R. Elisei, D. B. Evans, R. F. Gagel, N. Lee, A. Machens, J. F. Moley, F. Pacini, F. Raue, K. Frank-Raue, B. Robinson, M. S. Rosenthal, M. Santoro, M. Schlumberger, M. Shah and S. G. Waguespack. 2015.
INTRODUCTION: The American Thyroid Association appointed a Task Force of experts to revise the original Medullary Thyroid Carcinoma: Management Guidelines of the American Thyroid Association. METHODS: The Task Force identified relevant articles using a systematic PubMed search, supplemented with additional published materials, and then created evidence-based recommendations, which were set in categories using criteria adapted from the United States Preventive Services Task Force Agency for Healthcare Research and Quality. The original guidelines provided abundant source material and an excellent organizational structure that served as the basis for the current revised document. RESULTS: The revised guidelines are focused primarily on the diagnosis and treatment of patients with sporadic medullary thyroid carcinoma (MTC) and hereditary MTC. CONCLUSIONS: The Task Force developed 67 evidence-based recommendations to assist clinicians in the care of patients with MTC. The Task Force considers the recommendations to represent current, rational, and optimal medical practice.
PubMed-ID: 25810047
http://dx.doi.org/10.1089/thy.2014.0335

Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*, 25(7):716-59.
G. L. Francis, S. G. Waguespack, A. J. Bauer, P. Angelos, S. Benvenga, J. M. Cerutti, C. A. Dinauer, J. Hamilton, I. D. Hay, M. Luster, M. T. Parisi, M. Rachmiel, G. B. Thompson and S. Yamashita. 2015.
BACKGROUND: Previous guidelines for the management of thyroid nodules and cancers were geared toward adults. Compared with thyroid neoplasms in adults, however, those in the pediatric population exhibit differences in pathophysiology, clinical presentation, and long-term outcomes. Furthermore, therapy that may be recommended for an adult may not be appropriate for a child who is at low risk for death but at higher risk for long-term harm from overly aggressive treatment. For these reasons, unique guidelines for children and adolescents with thyroid tumors are needed. METHODS: A task force commissioned by the American Thyroid Association (ATA) developed a series of clinically relevant questions pertaining to the management of children with thyroid nodules and differentiated thyroid cancer (DTC). Using an extensive literature search, primarily focused on studies that included subjects </=18 years of age, the task force identified and reviewed relevant articles through April 2014. Recommendations were made based upon scientific evidence and expert opinion and were graded using a modified schema from the United States Preventive Services Task Force. RESULTS: These inaugural guidelines provide recommendations for the evaluation and management of thyroid nodules in children and adolescents, including the role and interpretation of ultrasound, fine-needle aspiration cytology, and the management of benign nodules. Recommendations for the evaluation, treatment, and follow-up of children and adolescents with DTC are outlined and include preoperative staging, surgical management, postoperative staging, the role of radioactive iodine therapy, and goals for thyrotropin suppression. Management algorithms are proposed and separate recommendations for papillary and follicular thyroid cancers are provided. CONCLUSIONS: In response to our charge as an independent task force appointed by the ATA, we developed recommendations based on scientific evidence and expert opinion for the management of thyroid nodules and DTC in children and adolescents. In our opinion, these represent the current optimal care for children and adolescents with these conditions.
PubMed-ID: 25900731
http://dx.doi.org/10.1089/thy.2014.0460

Other Articles

Number of tumor foci as predictor of lateral lymph node metastasis in papillary thyroid carcinoma.
Head Neck, 37(5):650-4.
H. J. Kim, H. K. Park, D. W. Byun, K. Suh, M. H. Yoo, Y. K. Min, S. W. Kim and J. H. Chung. 2015.
BACKGROUND: The purpose of this study was to determine the clinicopathologic characteristics of patients with papillary thyroid carcinoma (PTC) by the number of tumor foci. METHODS: A retrospective analysis of 2095 patients with PTC was performed. The study population was divided into 4 groups based on the number of tumor foci: N1 (1 tumor focus), N2 (2 foci), N3 (3 foci), and N4 (4 or more foci). RESULTS: An increasing number of tumor foci was significantly associated with older age at diagnosis (p = .006), cervical lymph node metastasis (p < .001), and advanced TNM stage of disease (p = .001) at initial surgery. The multivariate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the N2, N3, and N4 groups compared to the N1 group for lateral lymph node metastasis were OR 1.53 (95% CI, 1.05-2.22), OR 2.57 (95% CI, 1.50-4.42), and OR 2.88 (95% CI, 1.42-5.84), respectively. CONCLUSION: An increase in the number of tumor foci was strongly associated with older age at diagnosis, cervical lymph node metastasis, and advanced TNM stage of PTC. The number of tumor foci independently predicted lateral lymph node metastasis.
PubMed-ID: 24590814
http://dx.doi.org/10.1002/hed.23650

Differences in the characteristics of papillary thyroid microcarcinoma </=5 mm and >5 mm in diameter.
Head Neck, 37(5):694-7.
E. Kim, J. Y. Choi, H. Koo do, K. E. Lee and Y. K. Youn. 2015.
BACKGROUND: The behavior and optimal management of papillary thyroid microcarcinomas (PTMCs) after thyroidectomy remain unclear. The purpose of this study was to compare the clinicopathologic features and tumor recurrence rates of patients with PTMCs </=5 mm and >5 mm in diameter after total thyroidectomy. METHODS: A group of patients with PTMCs </=5 mm (n=83) has been compared to a group with >5 mm (n=122). All of these patients had conventional type PTMCs and were followed up for 5 years. Both the histology and the outcome have been compared. RESULTS: Sex (p=.014) and extrathyroidal extension (p=.003) of patients in the </=5 mm and >5 mm groups differed significantly. Two and 5 patients from these groups, respectively, experienced tumor recurrence within 5 years (2.4% vs 4.1%; p=.634). CONCLUSION: The clinicopathologic features of PTMCs </=5 mm and >5 mm are similar, except for sex distribution and extrathyroidal extension. The 5-year recurrence rate in the 2 groups did not differ significantly.
PubMed-ID: 24596325
http://dx.doi.org/10.1002/hed.23654

Acute prediction of laryngeal outcome during thyroid surgery by electromyographic laryngeal monitoring.
Head Neck, 37(6):835-9.
Y. Pavier, N. Saroul, B. Pereira, I. Tauveron, L. Gilain and T. Mom. 2015.
BACKGROUND: The purpose of this study was to evaluate the contribution of laryngeal intraoperative nerve monitoring (IONM) during thyroidectomy in predicting postoperative laryngeal mobility. METHODS: Between 2009 and 2012, 127 patients underwent thyroidectomy, during which 216 recurrent laryngeal nerves were stimulated with suprathreshold stimulations. Laryngeal mobility was examined through direct laryngoscopy. Statistical analysis was performed to determine specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and a threshold value in order to define a intraoperative diagnostic test. RESULTS: Nine patients had a unilateral laryngeal palsy. No bilateral laryngeal palsy was observed. The threshold value to assure the postoperative laryngeal mobility is 280 muV. For this value, specificity was 94.06%, sensitivity 100%, NPV 100%, and PPV 47.83%. CONCLUSION: Laryngeal IONM can predict a favorable outcome of laryngeal mobility in cases in which the response exceeds 280 muV. Under this value, the risk of palsy is about 50% suggesting a staged surgery.
PubMed-ID: 24616163
http://dx.doi.org/10.1002/hed.23676

Experimental autotransplantation and cryopreservation of the thyroid gland.
Head Neck, 37(7):940-5.
I. Yuce, H. Okuducu, S. Cagli, A. Vural, R. Gundogdu, U. Abdulrezzak, T. Arli, M. Aydin and E. Guney. 2015.
BACKGROUND: The purpose of this study was to investigate the functionality of autotransplanted thyroid tissues immediately or after cryopreservation in rabbits. METHODS: The study was completed with 12 rabbits randomized in 2 groups. Preoperative scintigraphies were performed for all subjects. The rabbits underwent total

thyroidectomy. The first group underwent immediate thyroid autotransplantation. Thyroid tissues of the second group were cryopreserved and autoimplanted at the eighth postoperative week. The free triiodothyronine (fT3) and thyroxine (fT4) levels were monitored for 8 weeks. Postoperative scintigraphies were performed at the eigth week after autoimplantation. RESULTS: The subjects in the first group reached euthyroid levels at the eighth week while none of the second group reached that level, but all showed continuous increase. Although implanted thyroid tissues of 5 of the 6 rabbits in the first group were demonstrated during the first scintigraphy, the number was only 1 in the second group. CONCLUSION: Thyroid autografts were found to be functional and thought to have a potential preventing postoperative hypothyroidism.
PubMed-ID: 24634027
http://dx.doi.org/10.1002/hed.23691

Statin use and thyroid cancer: a population-based case-control study.
Clin Endocrinol (Oxf), 83(1):111-6.
S. H. Hung, H. C. Lin and S. D. Chung. 2015.
OBJECTIVE: Several observational studies raised the possibility that the use of statins may decrease the overall risk of cancer and of specific cancers. This study aimed to evaluate the association of statin use with thyroid cancer based on a population-based data set. DESIGN: The data for this case-control study were sourced from the Taiwan Longitudinal Health Insurance Database 2000. We included 500 subjects with thyroid cancer as cases and 2500 gender- and age-matched subjects without thyroid cancer as controls. We used a conditional logistic regression to calculate the odds ratio (OR) and its corresponding 95% confidence interval (CI) for having previously used statins between cases and controls. RESULTS: The OR of prior statin use for cases was 1.39 (95% CI = 1.08-1.78) compared to controls, and thyroid cancer was significantly associated with previous regular statin use (OR = 1.40, 95% CI = 1.05-1.86). However, thyroid cancer was not significantly associated with previous irregular statin use (OR = 1.35; 95% CI = 0.88-2.07). Furthermore, the significant association between thyroid cancer and previous statin use only existed for females (OR: 1.43; 95% CI: 1.07-1.90) but not for males (OR: 1.28; 95% CI: 0.75-2.17). CONCLUSIONS: We concluded that statin use was associated with thyroid cancer in female patients.
PubMed-ID: 25074346
http://dx.doi.org/10.1111/cen.12570

RAS mutations in indeterminate thyroid nodules are predictive of the follicular variant of papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 82(5):760-6.
J. H. An, K. H. Song, S. K. Kim, K. S. Park, Y. B. Yoo, J. H. Yang, T. S. Hwang and D. L. Kim. 2015.
OBJECTIVE: RAS mutations are the most common mutations in thyroid nodules with indeterminate cytology by fine-needle aspiration cytology (FNAC), and are mutually exclusive with BRAF mutations. However, the diagnostic utility of RAS mutation analysis is uncertain. We evaluated the diagnostic utility of RAS mutation analysis in indeterminate thyroid nodules. DESIGN, PATIENTS, AND MEASUREMENTS: A total of 155 thyroid nodules (90 benign and 65 indeterminate) negative for BRAF(V) (600E) mutations on FNAC were analysed for mutations in RAS codon 61 using pyrosequencing methods. We evaluated diagnostic accuracy of RAS mutation for predicting thyroid malignancy based on the surgical pathologic diagnosis. RESULTS: Among the 65 BRAF(V) (600E) -negative indeterminate thyroid nodules identified by FNAC, 25 (38.5%) exhibited point mutations in RAS 61 consisting of 18 NRAS 61 (72%), and 7 HRAS 61 (28%) mutations. In contrast, only five of 90 (5.6%) nodules with benign cytology had RAS mutations. Only two of 25 (8.0%) RAS 61(+) indeterminate nodules exhibited malignant ultrasonographic features. Of the 15 patients with RAS 61(+) -indeterminate nodules who underwent thyroid surgery, 14 (93.3%) were diagnosed as malignant, including 13 follicular variant of papillary thyroid carcinomas (FVPTC), and one follicular thyroid carcinoma (FTC). The average tumour size was 1.79 +/- 0.62 cm. Multifocality was seen in 28.6% of cases, with 7.1% exhibiting extrathyroidal extension; no lymph node or distant metastases were evident. Based on the surgical pathologic diagnosis results, preoperative RAS 61 mutation analysis on FNAC exhibited 93.3% sensitivity, 75.0% specificity, 93.3% positive predictive value, 75.0% negative predictive value and 89.5% diagnostic accuracy for predicting malignancies. CONCLUSION: Our results suggest that RAS mutation analysis holds great promise as a preoperative diagnostic tool for predicting FVPTC in cytologically and sonographically indeterminate nodules negative for BRAF mutations.
PubMed-ID: 25109485
http://dx.doi.org/10.1111/cen.12579

The risk of second primary malignancy is increased in differentiated thyroid cancer patients with a cumulative (131)I dose over 37 GBq.
Clin Endocrinol (Oxf), 83(1):117-23.

A. R. Khang, S. W. Cho, H. S. Choi, H. Y. Ahn, W. S. Yoo, K. W. Kim, K. W. Kang, K. H. Yi, J. Park do, D. S. Lee, J. K. Chung, B. Y. Cho and Y. J. Park. 2015.
BACKGROUND: The aim of this study was to investigate the risk factors for second primary malignancy (SPM) diagnosed after differentiated thyroid cancer (DTC). METHODS: A total of 2468 DTC patients who underwent thyroidectomy were reviewed. SPM was defined as a non-thyroidal malignancy, diagnosed at least 1 year after the diagnosis of thyroid cancer. Patients were divided into five groups according to cumulative (131)I dose: very high-activity (>/= 37.0 GBq), high-activity (22.3-36.9 GBq), intermediate-activity (5.56-22.2 GBq), low-activity (1.1-5.55 GBq) and no RAI. RESULTS: Among the 2468 patients, 61 (2.5%) had SPMs during 7.0 (1.0-33.0) years of median follow-up. Age above 40 years, male sex and very high-activity RAI were independent risk factors for the development of SPM. SPM-related mortality was highest in the very high-activity group, while DTC-related mortality was highest in the high-activity group. The overall mortality both from SPM and DTC was highest in the high-activity group. CONCLUSION: A cumulative (131)I dose <37.0 GBq did not increase the risk of SPM. A cumulative (131) I dose >/= 37.0 GBq increased the risk of SPM and SPM-related mortality and decreased the DTC-specific mortality, resulting in a similar all-cause mortality compared with the low-activity RAI group. Using repeated high-dose RAI for treating RAI-responsive but persistent DTC patients needs careful consideration of the individual benefits from RAI vs the risk of developing SPM.
PubMed-ID: 25115234
http://dx.doi.org/10.1111/cen.12581

CD8+ tumour-infiltrating lymphocytes and COX2 expression may predict relapse in differentiated thyroid cancer.
Clin Endocrinol (Oxf), 83(2):246-53.
L. L. Cunha, M. A. Marcello, S. Nonogaki, E. C. Morari, F. A. Soares, J. Vassallo and L. S. Ward. 2015.
BACKGROUND/OBJECTIVE: There is an increasing rate of papillary thyroid carcinomas that may never progress to cause symptoms or death. Predicting outcome and determining tumour aggressiveness could help diminish the number of patients submitted to aggressive treatments. We aimed to evaluate whether markers of the immune system response and of tumour-associated inflammation could predict outcome of differentiated thyroid cancer (DTC) patients. DESIGN: Retrospective cohort study. PATIENTS: We studied 399 consecutive patients, including 325 papillary and 74 follicular thyroid carcinomas. MEASUREMENTS: Immune cell markers were evaluated using immunohistochemistry, including tumour-associated macrophages (CD68) and subsets of tumour-infiltrating lymphocytes (TIL), such as CD3, CD4, CD8, CD16, CD20, CD45RO, GRANZYME B, CD69 and CD25. We also investigated the expression of cyclooxygenase 2 (COX2) in tumour cells and the presence of concurrent lymphocytic infiltration characterizing chronic thyroiditis. RESULTS: Concurrent lymphocytic infiltration characterizing chronic thyroiditis was observed in 29% of the cases. Among all the immunological parameters evaluated, only the enrichment of CD8+ lymphocytes (P = 0.001) and expression of COX2 (P =0.01) were associated with recurrence. A multivariate model analysis identified CD8+ TIL/COX2 as independent risk factor for recurrence. A multivariate analysis using Cox's proportional-hazards model adjusted for the presence of concurrent chronic thyroiditis demonstrated that the presence of concurrent chronic thyroiditis had no effect on prognostic prediction mediated by CD8+ TIL and COX2. CONCLUSION: In conclusion, we suggest the use of a relatively simple pathology tool to help select cases that may benefit of a more aggressive approach sparing the majority of patients from unnecessary procedures.
PubMed-ID: 25130519
http://dx.doi.org/10.1111/cen.12586

Ultrasound scoring in combination with ultrasound elastography for differentiating benign and malignant thyroid nodules.
Clin Endocrinol (Oxf), 83(2):254-60.
J. Shao, Y. Shen, J. Lu and J. Wang. 2015.
OBJECTIVE: The aim of this study was to evaluate the value of ultrasound scores obtained by conventional ultrasonography and ultrasound elastography in the differentiation of benign and malignant thyroid nodules in Chinese patients. METHODS: This study included 297 patients who were referred for surgery for compressive symptoms or suspicion of malignancy. Five hundred and twelve thyroid nodules were examined by ultrasonography. The final diagnosis was based on histological findings. A seven-point ultrasound scoring system based on conventional ultrasonography and a five-point scoring system based on ultrasound elastography were applied independently or in combination. The receiver operating characteristic (ROC) curves were graphed, and the areas under the curves (AUCs) were compared using the chi(2) -test. RESULTS: Solid composition, hypo-echoic appearance, an irregular or blurred margin, an aspect ratio >/=1, intranodular blood flow and presence of microcalcifications were significant predictors of malignant thyroid nodules. The AUC (95% CI) was 0.9067 (0.8817-0.9318) for the ultrasound scores based on conventional ultrasonography and 0.9080

(0.8842-0.9317) for the elasticity scores. The combination of these two scoring systems provided good accuracy with an AUC (95% CI) of 0.9415 (0.9223-0.9606), which was significantly higher than that obtained with the conventional ultrasound scores (chi(2) = 36.03, P < 0.001) or the elasticity scores (chi(2) = 12.80, P < 0.001) individually. When we set the cut-point to >/=5, the sensitivity and specificity were 85.22% and 87.38%, respectively. CONCLUSIONS: Elastography in combination with conventional ultrasonography is a promising imaging-based approach that can assist in the differential diagnosis of thyroid cancer.
PubMed-ID: 25138622
http://dx.doi.org/10.1111/cen.12589

Survival in anaplastic thyroid cancer in relation to pre-existing goiter: a population-based study.
Am J Surg, 209(6):1013-9.
L. C. Steggink, B. A. van Dijk, T. P. Links and J. T. Plukker. 2015.
BACKGROUND: We investigated whether pre-existent goiter and well-differentiated thyroid cancer (WDTC) are associated with survival in anaplastic thyroid carcinoma (ATC). METHODS: We analyzed medical records from 94 ATC patients, drawn from the Netherlands Cancer Registry, diagnosed in 17 hospitals between 1989 and 2009. RESULTS: The 29 patients (31%) with pre-existent goiter, including 8 with WDTC, were younger than those without (median, 69 vs. 76 years; P = .02). One-year overall survival was 9% (95% confidence interval [CI], 3% to 14%) with no difference between pre-existent goiter or not (overall survival, 14%; 95% CI, 1% to 26% vs overall survival, 6%; 95% CI, 0% to 13%]). Higher age was associated with a worse survival (hazard rate, 1.03; 95% CI, 1.01 to 1.06]), whereas the hazard to die was lower after surgery and/or radiotherapy (hazard rate, .37; 95% CI, .21 to .67 and hazard rate, .22; 95% CI, .12 to .41, respectively). CONCLUSIONS: ATC patients with pre-existent goiter were younger, yet survival was not significantly different between those with or without pre-existent goiter or WDTC.
PubMed-ID: 25242682
http://dx.doi.org/10.1016/j.amjsurg.2014.06.027

Stimulation threshold greatly affects the predictive value of intraoperative nerve monitoring.
Laryngoscope, 125(5):1265-70.
D. L. Faden, L. A. Orloff, T. Ayeni, D. S. Fink and K. Yung. 2015.
OBJECTIVES/HYPOTHESIS: Using a standardized, graded, intraoperative stimulation protocol, we aimed to delineate the effects of various stimulation levels applied to the recurrent laryngeal nerve on the postoperative predictive value of intraoperative nerve monitoring. STUDY DESIGN: A total of 917 nerves at risk were included for analysis. Intraoperatively, patients underwent stimulation of the recurrent laryngeal nerve at 0.3, 0.5, 0.8, and 1.0 mA followed by postoperative laryngoscopy for correlation with intraoperative findings. METHODS: Sensitivity, specificity, positive predictive value, and negative predictive value were calculated at each stimulation level. RESULTS: Sensitivity, specificity, positive predictive value, and negative predicative values ranged from 100% to 37%, 6% to 99%, 2% to 39%, and 100% to 99%, respectively at 0.3 to 1.0 mA. No demographic variables affected sensitivity or specificity. Receiver operating characteristic analysis identified 0.5 mA as the level of stimulation that optimizes sensitivity and specificity. CONCLUSIONS: The predictive value of intraoperative nerve monitoring varies greatly depending on the stimulation levels used. At low amplitudes of stimulation, nerve monitoring has high sensitivity and negative predictive value but low specificity and positive predictive value, related to the high rate of false positives. At high levels of stimulation, specificity and negative predictive value are high, sensitivity is low, and the positive predictive value rises as the rate of false negatives increase and the rate of false positives decrease. A stimulation level of 0.5 mA optimizes the predictive value of nerve monitoring; however, stimulation at multiple levels significantly improves the predictive value of intraoperative nerve monitoring. LEVEL OF EVIDENCE: 2b.
PubMed-ID: 25302692
http://dx.doi.org/10.1002/lary.24960

Use of the Nerve Integrity Monitor during Thyroid Surgery Aids Identification of the External Branch of the Superior Laryngeal Nerve.
Ann Surg Oncol, 22(6):1768-73.
A. R. Glover, O. Norlen, J. S. Gundara, M. Morris and S. B. Sidhu. 2015.
BACKGROUND: The external branch of the superior laryngeal nerve (EBSLN) is at risk during thyroid surgery. Despite meticulous dissection and visualization, the EBSLN can be mistaken for other structures. The nerve integrity monitor (NIM) allows EBSLN confirmation with cricothyroid twitch on stimulation. AIMS: The aim of this study was to assess any difference in identification of EBSLN and its anatomical sub-types by dissection alone compared to NIM-aided dissection. METHODS: Routine intra-operative nerve monitoring (IONM) was used, when available, for 228 consecutive thyroid operations (129 total thyroidectomies, 99 hemi-thyroidectomies) over

a 10-month period. EBSLN identification by dissection alone (with NIM confirmation of cricothyroid twitch) and by NIM-assisted dissection was recorded prospectively. Anatomical sub-types were defined by the Cernea classification. RESULTS: Of 357 nerves at risk, 97.2 % EBSLNs (95 % confidence interval [CI], 95.5-98.9) were identified by visualization and NIM-aided dissection compared to 85.7 % (95 % CI, 82.1-89.3) identified by dissection alone (<0.001). EBSLN frequency was 34 % for type 1, 55 % for type 2a, and 11 % for type 2b. All identified EBSLNs were stimulated to confirm a cricothyroid twitch after superior thyroid vessel ligation. CONCLUSION: Using the NIM and meticulous dissection of the upper thyroid pole improves EBSLN identification. As the EBSLN is at risk during thyroidectomy and can lead to voice morbidity, the NIM can aid identification of the EBSLN and provide a functional assessment of the EBSLN after thyroid resection.
PubMed-ID: 25319580
http://dx.doi.org/10.1245/s10434-014-4142-3

Assessing the Validity of Transcutaneous Laryngeal Ultrasonography (TLUSG) After Thyroidectomy: What Factors Matter?
Ann Surg Oncol, 22(6):1774-80.
K. P. Wong, B. H. Lang, Y. K. Chang, K. C. Wong and F. C. Chow. 2015.
INTRODUCTION: Although transcutaneous laryngeal ultrasound (TLUSG) is an excellent, noninvasive way to assess vocal cord (VC) function after thyroidectomy, some patients simply have "un-assessable" or "inaccurate" examination. Our study evaluated what patient and surgical factors affected assessability and/or accuracy of postoperative TLUSG. METHODS: Five hundred eighty-one consecutive patients were analyzed. All TLUSGs were done by one operator using standardized technique, whereas direct laryngoscopies (DL) were done by an independent endoscopist to confirm TLUSG findings. Their findings were correlated. TLUSG was "unassessable" if >/=1 VC could not be clearly visualized, whereas it was "inaccurate" if the TLUSG and DL findings were discordant. Demographics, body habitus, neck anthropometry, and position of incision were correlated with assessability and accuracy of TLUSG. RESULTS: Twenty-nine (5.0 %) patients had "unassessable" VCs; among the "assessable" patients, 29 (5.3 %) patients had "inaccurate" TLUSG. More than one-third (38.5 %) of VC palsies (VCPs) were "inaccurate." Older age (odds ratio [OR] = 1.055, 95 % confidence interval [CI] 1.016-1.095, p = 0.005), male sex (OR = 13.657, 95 % CI 2.771-67.315, p = 0.001), taller height (OR = 1.098, 95 % CI 1.008-1.195, p = 0.032), and shorter distance from cricoid cartilage to incision (OR = 0.655, 95 % CI 0.461-0.932, p = 0.019) were independent factors for "unassessable" VCs, whereas older age (OR = 1.028, 95 % CI 1.001-1.056, p = 0.040) was the only factor of incorrect assessment. CONCLUSIONS: Older age, male sex, tall in height, and incision closer to the thyroid cartilage were independent contributing factors for unassessable VCs, whereas older age was the only contributing factor for inaccurate postoperative TLUSG. Because more than one-third of VCPs were actually normal, patients labeled as such on TLUSG would benefit from laryngoscopic validation.
PubMed-ID: 25323472
http://dx.doi.org/10.1245/s10434-014-4162-z

Thyroid cancer presentation and treatment in the United States.
Ann Surg Oncol, 22(6):1789-97.
L. Enewold, L. C. Harlan, J. L. Stevens and E. Sharon. 2015.
INTRODUCTION: Thyroid cancer incidence is rising in the United States. Although overall thyroid cancer survival is high, prognostic stratification schemes have been developed to better delineate patients with poor prognoses. METHODS: A random sample that included 1,003 adult papillary thyroid cancer patients diagnosed in 2006 and reported to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program had their medical records re-abstracted and additional risk factor data collected. The distribution of patient demographics, medical histories, tumor characteristics and treatment modalities were assessed. Logistic regression was used to assess factors associated with total thyroidectomy (total, subtotal or near total) and radioiodine therapy. All analyses were conducted stratified by the Age, Metastases, Extent and Size (AMES) low/high-risk classification. RESULTS: Receipt of total thyroidectomy was associated with family history of thyroid disease/cancer and larger tumor size among low-risk patients and smaller tumor size among high-risk patients. Among low-risk patients, the receipt of radioiodine was associated with family history of thyroid disease/cancer, larger tumor size, total thyroidectomy, and positive lymph nodes. Among high-risk patients, the receipt of radioiodine was associated with intermediate tumor and hospital sizes. CONCLUSIONS: This study provides insight into the patterns of papillary thyroid cancer care in the general population. The findings from this study indicate adherence to guideline recommendations in that family history of thyroid disease/cancer, in addition to tumor characteristics, does appear to inform treatment practices, especially among low-risk patients.
PubMed-ID: 25361888
http://dx.doi.org/10.1245/s10434-014-4209-1

A risk model to determine surgical treatment in patients with thyroid nodules with indeterminate cytology.
Ann Surg Oncol, 22(5):1527-32.
C. A. Macias, D. Arumugam, R. L. Arlow, O. S. Eng, S. E. Lu, P. Javidian, T. Davidov and S. Z. Trooskin. 2015.
BACKGROUND: Thyroid nodules are present in 19-67 % of the population and have a 5-10 % risk of malignancy. Fine needle aspiration biopsies are indeterminate in 20-30 % of patients, often necessitating thyroid surgery for diagnosis. We hypothesized that developing a risk model incorporating factors associated with malignancy could help predict the risk of malignancy in patients with indeterminate thyroid nodules. METHODS: We identified 151 patients with a cytologic diagnosis of follicular neoplasm (Bethesda IV) who progressed to surgery. We retrospectively analyzed demographic, clinical, sonographic, and cytological variables in relation to thyroid carcinoma. RESULTS: Of 151 patients, 51 (33.8 %) had a final diagnosis of thyroid carcinoma. Papillary carcinoma was diagnosed in 34 patients (66.7 %), follicular carcinoma in 15 (29.4 %), and Hurthle cell carcinoma in 2 (3.9 %). On univariate analysis, younger age, male gender, tobacco use, larger nodule size, and calcifications on ultrasound, nuclear atypia on cytology, and suspicious frozen section were associated with the presence of malignancy. When determining odds ratios, four factors were most predictive of malignancy: nodule calcification [odds ratio (OR) 6.37, 95 % confidence interval (CI) 1.62-25.1, $p < 0.01$] and nodule size (OR 1.75, 95 % CI 1.19-2.57, $p < 0.01$) on ultrasound, nuclear atypia on cytology (OR 4.91, 95 % CI 1.90-12.66, $p < 0.01$), and tobacco use (OR 4.59, 95 % CI 1.30-16.27, $p < 0.02$). A multivariable model based on these four factors resulted in a c-statistic of 0.82. CONCLUSIONS: A multivariable model based on calcification, nodule size, nuclear atypia, and tobacco use may predict the risk of thyroid cancer requiring a total thyroidectomy in patients with thyroid nodules of indeterminate cytology.
PubMed-ID: 25388058
http://dx.doi.org/10.1245/s10434-014-4190-8

"Scarless" (in the neck) endoscopic thyroidectomy (SET) with ipsilateral levels II, III, and IV dissection via breast approach for papillary thyroid carcinoma: a preliminary report.
Surg Endosc, 29(8):2158-63.
H. Yan, Y. Wang, P. Wang, Q. Xie and Q. Zhao. 2015.
BACKGROUND: Endoscopic thyroidectomy with level II dissection has previously been reported to be performed endoscopically via various approaches. However, very few reports were available regarding level II dissection performed via the breast approach. In this article, we reported a series of 12 papillary thyroid carcinoma (PTC) patients with scarless (in the neck) endoscopic thyroidectomy (SET) via breast approach to level II dissection and evaluated its feasibility and safety. METHODS: Between January 2011 and March 2013, 12 PTC female patients with suspected lymph node metastasis at level II, III, or IV were selected for this procedure. After completing thyroidectomy and central compartment dissection, dissection of ipsilateral levels II, III, and IV was performed. The steps of endoscopic lateral neck dissection were similar to those of conventional surgery except that the lateral cervical compartment was exposed by splitting the sternocleidomastoid muscle (SCM) longitudinally and dividing between the strap muscles and the anterior margin of the SCM. RESULTS: This procedure was carried out in all of the 12 patients (Table 1). Mean operative time was 243 min (range 165-355 min). Nine patients (75 %) had lymph node metastasis in the lateral compartment confirmed on the final pathological report. Mean lymph node yield (LNY) in the lateral compartment (including ipsilateral level II, III, and IV dissection) was 21.8 (range 5-42). Five patients (41.6 %) had lymph node metastasis in the ipsilateral level II. The mean LNY in the ipsilateral level II was 6.7 (range 1-14). In 1 of the 12 patients, bleeding from injury to the internal jugular vein in level II was encountered intraoperatively, and a 4-cm upper neck transverse incision was made to stop the bleeding. Average postoperative hospital stay was 5.0 days (range 3-7 days). Table 1 Original article on endoscopic lateral neck dissection (including level II) by other authors Author (Ref.) Year Mean age (years) Tumor size (cm) No. of patients M:F Tech. Type of operation Mean LNY in lateral zone Mean operative time (min) Postoperative bleeding Chyle leakage Mean PHS (days) Wu et al. [13] 2013 43.2 1.88 26 6:20 VAT SLND 8.3 137.7 None None 3.6 Lee et al. [8] 2013 40.2 1.39 62 5:57 Robot MRND 32.8 271.8 None None 6.9 Kang et al. [5] 2012 35.8 1.14 56 10:46 Robot MRND 31.1 277.4 1 5 6 Kang et al. [6] 2011 NA NA 36 NA Robot MRND 27.7 280.91 1 3 NA Kang et al. [4] 2009 NA NA 13 NA AP MRND/SLND 18.8 286 NA NA 5.3 Current article 31.2 1.67 12 0:12 SET SLND 21.8 243 None None 5 Ref. references, No. number, M male, F female, Tech. technique, LNY lymph node yield, PHS postoperative hospital stay, VAT video-assisted thyroidectomy, SLND selective lateral neck dissection, MRND modified radical neck dissection, AP axillary approach, NA not available CONCLUSIONS: According to the present SET data, level II dissection by SET was a feasible and safe procedure. With reasonable costs and satisfactory cosmetic results, oncoplastic SET via breast approach might gain wider acceptance in the near future.

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Twenty years of lesson learning: how does the RET genetic screening test impact the clinical management of medullary thyroid cancer?
Clin Endocrinol (Oxf), 82(6):892-9.
C. Romei, A. Tacito, E. Molinaro, L. Agate, V. Bottici, D. Viola, A. Matrone, A. Biagini, F. Casella, R. Ciampi, G. Materazzi, P. Miccoli, L. Torregrossa, C. Ugolini, F. Basolo, P. Vitti and R. Elisei. 2015.
OBJECTIVE: Medullary thyroid carcinoma (MTC) is a rare disease that can be inherited or sporadic; its pathogenesis is related to activating mutations in the RET gene. DESIGN: This study describes our 20-year experience regarding RET genetic screening in MTC. PATIENTS AND METHODS: We performed RET genetic screening in 1556 subjects, 1007 with an apparently sporadic MTC, 95 with a familial form and 454 relatives of RET-positive patients with MTC. RESULTS: A germline RET mutation was found in 68 of 1007 (6.7%) patients with sporadic MTC, while 939 patients with MTC were negative for germline RET mutations. We then identified a total of 137 gene carriers (GC). These subjects initiated a clinical evaluation for the diagnosis of MEN 2. A total of 139 MEN 2 families have been followed: 94 FMTC, 33 MEN 2A and 12 MEN 2B. Thirty-three different germline RET mutations were identified. Codon 804 was the most frequently altered codon particularly in FMTC (32/94, 34%), while codon 634 was the most frequently altered codon in MEN 2A (31/33, 94%); MEN 2B cases were exclusively associated with an M918T mutation at exon 16. CONCLUSIONS: Our 20-year study demonstrated that RET genetic screening is highly specific and sensitive, and it allows the reclassification as hereditary of apparently sporadic cases and the identification of GC who require an adequate follow-up. We confirmed that FMTC is the most prevalent MEN 2 syndrome and that it is strongly correlated with noncysteine RET mutations. According to these findings, a new paradigm of follow-up of hereditary MTC cases might be considered in the next future.
PubMed-ID: 25440022
http://dx.doi.org/10.1111/cen.12686

Breach of the thyroid capsule and lymph node capsule in node-positive papillary and medullary thyroid cancer: Different biology.
Eur J Surg Oncol, 41(6):766-72.
A. Machens and H. Dralle. 2015.
AIMS: The higher incidence of extranodal growth (breach of a lymph node capsule) in the presence of extrathyroidal extension (breach of the thyroid capsule) in papillary thyroid cancer prompted conclusions that the biology of thyroid cancer is conferred to the lymph nodes, causing invasion of perinodal tissues. This study aimed at quantifying the independent contributions of clinical-pathological factors to extranodal growth in thyroid cancer. METHODS: Multivariate analyses of 1250 patients operated on for node-positive papillary (PTC; 702 patients) or node-positive medullary thyroid cancer (MTC; 548 patients), 138 and 130 of whom harbored extranodal growth. RESULTS: After correction for multiple testing, extranodal growth correlated with number of lymph node metastases (means of 17.0 vs. 10.1 nodes for PTC, 20.6 vs. 13.4 nodes for MTC; each $P < 0.001$) and male gender (49 vs. 35% for PTC, $P = 0.005$; 62 vs. 46% for MTC; $P = 0.002$); and in MTC also with extrathyroidal extension (46 vs. 30%; $P = 0.002$). On multivariate analysis, independent determinants of extranodal growth were number of lymph node metastases (odds ratios of 2.1, 3.7 and 3.7 for PTC ($P </= 0.01$) and 2.7, 3.3, and 4.0 for MTC ($P </= 0.004$) looking at 6-10, 11-20 and >20 involved nodes against a 1-5 node baseline) and male gender (odds ratio 1.6 for PTC, 1.7 for MTC; each $P = 0.02$), but not extrathyroidal extension. CONCLUSIONS: In PTC and MTC, extranodal growth develops independently from extrathyroidal extension. This finding argues against mere transference of primary tumor characteristics to lymph nodes, pointing more to accrual of invasive properties by nodal tumor deposits.
PubMed-ID: 25468749
http://dx.doi.org/10.1016/j.ejso.2014.10.049

Local recurrence in the neck and survival after thyroidectomy for metastatic renal cell carcinoma.
Ann Surg Oncol, 22(6):1798-805.
I. Iesalnieks, A. Machens, C. Bures, D. Krenz, H. Winter, C. Vorlander, E. Bareck, P. F. Alesina, T. Musholt, T. Steinmuller, M. Anthuber, P. Goretzki, A. Trupka, M. Mayr, T. Weber, H. J. Schlitt, H. Dralle, M. Hermann and A. Agha. 2015.
BACKGROUND: Most investigations of thyroidectomy for metastatic renal cell carcinoma (RCC) are case studies or small series. This study was conducted to determine the contribution of clinical and histopathologic variables to local recurrence in the neck and overall survival after thyroidectomy for RCC metastases.
METHODS: The medical records of 140 patients with thyroidectomy for metastatic RCC performed between

1979 and 2012 at 25 institutions in Germany and Austria were analyzed. RESULTS: The median interval between nephrectomy and thyroidectomy was 120 months. Concurrence of thyroid and pancreatic metastases was present in 23 % of the patients and concurrence of thyroid and adrenal metastases in 13 % of the patients. Clinical outcome data were available for 130 patients with a median follow-up period of 34 months. The 5-year overall survival rate was 46 %, and 28 % of patients developed a local neck recurrence at a median of 12 months after thyroidectomy. Multivariate analysis showed that invasion of adjacent cervical structures (hazard ratio [HR] 3.2; p = 0.001), patient age exceeding 70 years (HR 2.5; p = 0.004), and current or past evidence of metastases to nonendocrine organs (HR 2.4; p = 0.003) were independent determinants of inferior overall survival. Conversely, invasion of adjacent cervical structures (HR 12.1; p < 0.0001) and year of thyroidectomy (HR 5.7 before 2000; p < 0.0001) were shown to be independently associated with local recurrence in the neck by multivariate analysis. CONCLUSIONS: Although significant improvement of local disease control in patients with thyroid metastases of RCC has been achieved during the last decade, overall outcome continues to be poor for patients with locally invasive thyroid metastases.
PubMed-ID: 25472649
http://dx.doi.org/10.1245/s10434-014-4266-5

Thyroid nodules diagnosed as follicular neoplasm: do not forget Doppler US and correlation to previous imaging findings.
Clin Endocrinol (Oxf), 83(2):287-8.
A. Lacout, C. Chevenet and P. Y. Marcy. 2015.
PubMed-ID: 25597327
http://dx.doi.org/10.1111/cen.12723

FDG PET performed at thyroid remnant ablation has a higher predictive value for long-term survival of high-risk patients with well-differentiated thyroid cancer than radioiodine uptake.
Clin Nucl Med, 40(5):378-83.
F. C. Gaertner, S. Okamoto, T. Shiga, Y. M. Ito, Y. Uchiyama, O. Manabe, N. Hattori and N. Tamaki. 2015.
PURPOSE: The predictive value of FDG PET at thyroid remnant ablation was evaluated in comparison to radioiodine uptake in high-risk patients with differentiated thyroid cancer. PATIENTS AND METHODS: One hundred forty-one patients who underwent radioiodine therapy (RIT) after total thyroidectomy and received at least 1 further RIT due to suspected metastases were retrospectively analyzed. Patients had not received RIT previously. FDG PET was performed before thyroid remnant ablation. Thyroid-stimulating hormone-stimulated serum thyroglobulin (Tg) was measured for biochemical response assessment (change of Tg between the first and second RIT, DeltaTg). RESULTS: Biochemical response could be evaluated in 80 patients; survival data could be obtained for 88 patients (maximum, 124 months). Biochemical response was significantly better in patients with radioiodine-positive metastases compared with patients with radioiodine-negative metastases (median DeltaTg I+, 55.8% vs I-, 112.6%; P < 0.01). Regarding survival, deaths occurred later in patients with radioiodine-positive metastases compared with radioiodine-negative patients; however, there was no significant difference regarding overall survival (I+, 61.3% vs I-, 58.2%; P > 0.05). Patients with FDG-positive metastases at thyroid remnant ablation showed a poorer biochemical response compared with patients with FDG-negative metastases (median DeltaTg FDG+, 77.5% vs FDG-, 53.2%; P < 0.05), and these groups also differed significantly regarding survival (overall survival FDG+, 48.5% vs FDG-, 100%, P < 0.05). CONCLUSIONS: At thyroid remnant ablation, FDG PET is more predictive for long-term survival, whereas radioiodine uptake is more important for short-term response. FDG PET performed at thyroid remnant ablation might represent a useful tool for management of high-risk patients with differentiated thyroid cancer.
PubMed-ID: 25608175
http://dx.doi.org/10.1097/RLU.0000000000000699

Day Case Thyroid and Parathyroid Surgery: Time to Replicate Same in Developing Countries.
World J Surg, 39(8):2102-3.
J. L. Miller, A. A. Agarwal, K. R. Singh, A. A. Sonkar, J. K. Kushwaha and A. Shrivastav. 2015.
PubMed-ID: 25609119
http://dx.doi.org/10.1007/s00268-015-2951-6

Ipsilateral Central Neck Dissection Plus Frozen Section Examination Versus Prophylactic Bilateral Central Neck Dissection in cN0 Papillary Thyroid Carcinoma.
Ann Surg Oncol, 22(7):2302-8.
M. Raffaelli, C. De Crea, L. Sessa, G. Fadda, C. Bellantone and C. P. Lombardi. 2015.
BACKGROUND: Ipsilateral central compartment node dissection (IpsiCCD) can reduce the morbidity of

prophylactic bilateral central compartment node dissection (BilCCD) in papillary thyroid carcinoma (PTC) but it carries the risk of contralateral metastases being overlooked. Frozen section examination (FSE) of removed ipsilateral nodes has been proposed to intraoperatively assess nodal status. We compared IpsiCCD plus FSE and BilCCD in clinically unifocal and node negative PTC. METHODS: One hundred patients were prospectively assigned to undergo total thyroidectomy (TT) plus BilCCD or TT plus IpsiCCD. In the IpsiCCD group, removed lymph nodes were sent for FSE. If FSE was positive for metastases, a BilCCD was accomplished. RESULTS: The two groups included 50 patients each. Overall, occult lymph node metastases were found in 41 patients-20 in the IpsiCCD group and 21 in the BilCCD group. FSE correctly identified occult node metastases in 13 of 20 pN1a patients in the IpsiCCD group (overall accuracy 86 %). Seven node metastases were not detected at FSE-five were micrometastases (</=2 mm). Six of 13 patients in the IpsiCCD group who underwent BilCCD and 6 of 21 BilCCD pN1a patients had bilateral metastases. More patients in the BilCCD group showed transient hypocalcemia (27/50 vs. 18/50, respectively) [p = NS]. No patient experienced recurrent disease. CONCLUSIONS: FSE of ipsilateral nodes is accurate in determining nodal status, allowing the extension of the central neck clearance to be reliably modulated. Routine IpsiCCD plus FSE of the ipsilateral nodes could be a valid alternative to prophylactic BilCCD since it allows accurate staging and may reduce morbidity.
PubMed-ID: 25652046
http://dx.doi.org/10.1245/s10434-015-4383-9

A prospective analysis of thyroidectomy outcomes in a resource-limited setting.
World J Surg, 39(7):1708-11.
N. O. Donohoe, R. Kintu-Luwaga, J. Bolger and J. Odubu Fualal. 2015.
BACKGROUND: This study aimed to document thyroidectomy outcomes in the surgical endocrine unit, Mulago Hospital, Kampala, Uganda. The burden of global surgical disease is currently receiving much attention, especially in countries experiencing epidemiological transition. There is a paucity of publications on surgical outcomes from Sub-Saharan Africa. International thyroid guidelines from high-income countries do not factor in the logistical challenges or the advanced pathology faced by the surgeon in resource-limited settings. METHODS: This was a prospective cohort study in 2013. Eight peri-operative variables of poor outcome were analysed statistically against six outcomes variables. Data was collected from 0 to 6 months post-operatively. RESULTS: Forty-two thyroidectomies were performed over a 3-month period (female = 38). Intraoperative events recorded included rebleeding = 10 %, infection = 0 %, transient voice symptoms = 30 %, transient hypocalcaemia = 12.5 %, recurrent laryngeal nerve (RLN) paralysis = 7.5 % and permanent hypocalcaemia = 15 %. There was a weak powered association between RLN paralysis and total thyroidectomy and smaller thyroid size. There were associations between large thyroid size and both permanent hypocalcaemia and rebleeding. Younger patients showed statistically more transient voice changes compared to older patients. Older patients were statistically more likely to develop rebleeding. Shorter operative duration was associated with transient voice change, permanent hypocalcaemia and rebleeding. Airway difficulties and transient hypocalcaemia were statistically significant in prolonged procedures. CONCLUSIONS: Whilst the thyroidectomy outcomes are not equal to international standards, an acceptable standard is achievable in this resource-limited setting. Poor outcomes are multifactorial but extremes of thyroid size, extremes of operation duration and total thyroidectomies all have statistically poorer outcomes in this setting.
PubMed-ID: 25663012
http://dx.doi.org/10.1007/s00268-015-3009-5

Identification of the external branch of the superior laryngeal nerve: an additional argument for neuromonitoring?
Ann Surg Oncol, 22(6):1751-2.
P. Angelos. 2015.
PubMed-ID: 25663590
http://dx.doi.org/10.1245/s10434-014-4254-9

The Author's Reply: 'Thyroid nodules diagnosed as follicular neoplasm: do not forget Doppler US and correlation to previous imaging findings'.
Clin Endocrinol (Oxf), 83(2):288.
C. L. Chng, T. R. Kurzawinski and T. Beale. 2015.
PubMed-ID: 25677653
http://dx.doi.org/10.1111/cen.12743

Initial attributable cost and economic burden of clinically-relevant differentiated thyroid cancer: A health care service provider perspective.

Eur J Surg Oncol, 41(6):758-65.
B. H. Lang, C. K. Wong and C. T. Chan. 2015.
BACKGROUND: Rapid rise in differentiated thyroid cancer (DTC) may impose a heavy economic burden on future healthcare. We aimed to calculate the average first-year monetary cost/patient for DTC and estimate the projected cost burden on our local healthcare system. METHODS: Medical records of 270 clinically-relevant DTC patients were reviewed to calculate the amount of services utilized during the first-year. Only direct costs were included with estimates derived from government gazette. Cancer incidences were derived from the territory-wide cancer registry. Total annual cost equaled to the incidence multiplied by the cost/patient. RESULTS: The average first-year cost of DTC was USD11,560/patient. Initial surgery accounted for 66.9% of total cost. Male and female annual percentage increases for DTC were 4.86% and 4.28%, respectively. Female DTC is projected to surpass rectal cancer in 2019 (20.4/100,000 vs. 20.0/100,000) and colon cancer (47.2/100,000 vs. 46.8/100,000) in 2039. However, the projected incidence of DTC in 2026 would still be about one fourth that of CRC (19.5/100,000 vs. 83.2/100,000). CONCLUSIONS: The average first-year monetary cost of DTC care was relatively low. Initial surgery accounted for most of the cost. Despite a rapid incidence rise, the projected first-year cost for DTC is unlikely to impose substantial economic burden on our local future healthcare system.
PubMed-ID: 25680952
http://dx.doi.org/10.1016/j.ejso.2015.01.019

Surgeon-performed ultrasound-guided FNAC with on-site cytopathology improves adequacy and accuracy.
Laryngoscope, 125(7):1633-6.
R. L. Witt, V. R. Sukumar and F. Gerges. 2015.
OBJECTIVE: To demonstrate that surgeon-performed fine-needle aspiration cytology (FNAC) results in a high percent of satisfactory FNAC results; the number of passes to obtain a satisfactory cytological result with on-site cytopathological interpretation is reduced with ultrasound guidance (comparing FNAC with and without surgeon-performed ultrasound guidance); and immediate triage for indeterminate thyroid nodules can be performed in one setting for molecular testing, potentially improving selection for surgery. STUDY DESIGN: Retrospective cohort comparison. METHODS: A cytopathologist is present for on-site staining adequacy evaluation and molecular testing triage for indeterminate cytology. Overall cytological adequacy and number of passes required to obtain cytological adequacy for 200 consecutive patients are compared with a historical series of 100 consecutive patients from the same surgeon and cytopathologists without ultrasound guidance. RESULTS: The percent of patients with an adequate FNAC with ultrasound guidance was 100%. The mean number of passes with and without ultrasound guidance was 1.7 and 4.0 ($P < 0.001$). Indeterminate FNACs (9%) were triaged to molecular alteration testing and gene expression classifier testing. CONCLUSIONS: Surgeon-performed ultrasound-guided FNAC with an experienced cytopathologist present resulted in a cytologically adequate result in 100% of cases. Significantly fewer passes for a satisfactory result were achieved with ultrasound guidance. Indeterminate FNAC can be triaged for molecular testing in one patient visit, was required in only 9% of carefully selected patients, and improved patient selection for surgery. The percent of patients who went on to surgery was 24 of 200 (12%). The percent of patients who had malignancy was 18 of 24 (75%).
PubMed-ID: 25703413
http://dx.doi.org/10.1002/lary.25214

Thyroid gland: TSHR mutations and subclinical congenital hypothyroidism.
Nat Rev Endocrinol, 11(5):258-9.
N. Schoenmakers and V. K. Chatterjee. 2015.
PubMed-ID: 25707783
http://dx.doi.org/10.1038/nrendo.2015.27

Preablation 131-I scans with SPECT/CT contribute to thyroid cancer risk stratification and 131-I therapy planning.
J Clin Endocrinol Metab, 100(5):1895-902.
A. M. Avram, N. H. Esfandiari and K. K. Wong. 2015.
CONTEXT: The use of preablation diagnostic radioiodine scans for risk stratification and radioiodine therapy planning for differentiated thyroid cancer (DTC) remains controversial. OBJECTIVE: The objective was to assess the contribution of preablation diagnostic 131-I scans with SPECT/CT (Dx 131-I scan) to (1) the risk stratification and (2) the postoperative management of DTC. DESIGN: The study was designed as a prospective sequential patient series. SETTING: The study was conducted at a University hospital. PATIENTS: Three hundred twenty patients (pts) with DTC (219F; 101M, mean age 47.3 +/- 16.4 y, range 10-90) were studied. INTERVENTION:

Using clinical and histopathology information an endocrinologist performed risk stratification and determined postoperative management with respect to radioiodine therapy (RAI) planning. The decision to withhold or to administer RAI, and the recommended low, medium or high therapeutic 131-I activity were recorded. Dx 131-I scans were performed and interpreted by two nuclear medicine physicians as showing thyroid remnant, cervical nodal, or distant metastases. The endocrinologist then reperformed risk stratification and reformulated management after consideration of Dx 131-I scans and stimulated thyroglobulin (Tg) information. MAIN OUTCOME MEASURE: Main outcome measures were changes in risk stratification and management after Dx 131-I scans. RESULTS: Detection of unsuspected nodal and distant metastases and elevated stimulated Tg levels resulted in a change in the estimated risk of recurrence in 15% of patients, and management in 31% of patients, as compared to initial risk stratification and management based on histopathology alone. CONCLUSIONS: Both imaging data and stimulated thyroglobulin levels acquired at the time of Dx 131-I scans are consequential for 131-I therapy planning, providing information that changes risk stratification in 15% of patients as compared to recurrence risk estimation based on histopathology alone. Dx 131-I scans contribute to risk stratification by defining residual nodal and distant metastatic disease, changing clinical management in 29.4% of patients.
PubMed-ID: 25734251
http://dx.doi.org/10.1210/jc.2014-4043

Prognostic value of vascular invasion in well-differentiated papillary thyroid carcinoma.
Thyroid, 25(5):503-8.
V. B. Wreesmann, I. J. Nixon, M. Rivera, N. Katabi, F. Palmer, I. Ganly, A. R. Shaha, R. M. Tuttle, J. P. Shah, S. G. Patel and R. A. Ghossein. 2015.
BACKGROUND: Vascular invasion (VI) is an important predictor of distant metastasis and possible radioactive iodine (RAI) benefit in follicular, Hurthle cell, and poorly differentiated thyroid carcinomas, but its role in well-differentiated papillary thyroid cancer (WDTC) remains unclear. METHODS: Archived pathological material of all differentiated thyroid carcinoma patients undergoing primary surgical treatment at Memorial Sloan-Kettering Cancer Center between 1986 and 2003 was reviewed by two dedicated thyroid pathologists. Only WDTCs were included in the present study. Standard statistical methods were used to assess the relationship between VI and outcomes of interest, including 10-year disease-specific survival (DSS), regional recurrence-free survival (RRFS), and distant recurrence-free survival (DRFS). RESULTS: VI was present in 47 of 698 WDTC (6.7%). VI was significantly associated with tumor size >4.0 cm, extrathyroidal extension, distant metastasis, and RAI treatment. On univariate analysis, VI was predictive of decreased 10-year DRFS, but not DSS or RRFS. On multivariate analysis, VI was not an independent predictor of DRFS. Univariate survival analysis of 422 RAI-naive WDTC showed that both size >4 cm and VI were predictors of outcome, but only size remained independently predictive on multivariate analysis. CONCLUSION: The presence of VI is not an independent predictor of outcome in WDTC.
PubMed-ID: 25748079
http://dx.doi.org/10.1089/thy.2015.0052

Thyroidectomy in the professional singer-neural monitored surgical outcomes.
Thyroid, 25(6):665-71.
G. W. Randolph, N. Sritharan, P. Song, R. Franco, Jr., D. Kamani and G. Woodson. 2015.
BACKGROUND: Voice changes commonly occur from thyroidectomy and may be due to neural or nonneural causes. Such changes can be a source of significant morbidity for any patient, but thyroidectomy in the professional singer carries special significance. We test the hypothesis that the career of singers and professional voice users is not impaired after neural monitored thyroid surgery. METHODS: A quantitative analysis of pre- and postoperative neural monitored thyroid surgery voice outcomes utilizing three validated vocal instruments-Voice Handicap Index (VHI), Singing Voice Handicap Index (SVHI), and Evaluation of Ability to Sing Easily (EASE)-in a unique series of professional singers/voice users was performed. Additional quantitative analysis related to final intraoperative electromyography (EMG) amplitude, the time to return to performance, and vocal parameters affected during this interval was performed. RESULTS: Twenty-seven vocal professionals undergoing thyroidectomy were identified, of whom 60% had surgery for thyroid cancer. Pre- and postsurgery flexible fiberoptic laryngeal exams were normal in all patients. Return to performance rate was 100%, and mean time to performance was 2.26 months (+/-1.61). All three vocal instrument mean scores, pre-op vs. post-op, were unchanged: VHI, 4.15 (+/-5.22) vs. 4.04 (+/-3.85), p=0.9301; SVHI, 11.26 (+/-14.41) vs.12.07 (+/-13.09), p=0.8297; and EASE, 6.19 (+/-9.19) vs. 6.00 (+/-7.72), p=0.9348. The vocal parameters most affected from surgery until first performances were vocal fatigue (89%), high range (89%), pitch control and modulation (74%), and strength (81%). Final mean intraoperative EMG amplitude was within normal limits for intraoperative stimulation and had no relationship with time to first professional performance (p=0.7199).

CONCLUSIONS: Neural monitored thyroidectomy, including for thyroid malignancy, in professional voice users is safe without any changes in three different voice/singing instruments, with 100% return to performance. Intraoperative EMG data at the conclusion of surgery and postoperative laryngeal exam were normal in all patients. Specific vocal parameters are transiently affected during the postoperative recovery phase, which is important to outline in the consent process of this unique patient population and may provide insight into the physiologic state of the larynx subsequent to thyroid surgery.
PubMed-ID: 25790153
http://dx.doi.org/10.1089/thy.2014.0467

The Implementation of the Bethesda System for Reporting Thyroid Cytopathology Improves Malignancy Detection Despite Lower Rate of Thyroidectomy in Indeterminate Nodules.
World J Surg, 39(8):1959-65.
D. Hirsch, E. Robenshtok, G. Bachar, D. Braslavsky and C. Benbassat. 2015.
BACKGROUND: The Bethesda system for reporting thyroid cytopathology (TBSRTC) was developed in 2009 to standardize the terminology for interpreting fine-needle aspiration (FNA) specimens. METHODS: A historical prospective case series design was employed. The study group included patients with a thyroid nodule classified as TBSRTC AUS/FLUS (B3) or FN/SFN (B4) in 2011-2012 in a tertiary university-affiliated medical center. Rates of surgery and malignancy detection were compared to our pre-TBSRTC (1999-2000) study. RESULTS: Of 3927 nodules aspirated, 575 (14.6%) were categorized as B3/B4. Complete data were available for 322. Thyroidectomy was performed in 123 (38.2%) cases: 66/250 (26.4%) B3 and 57/72 (79.2%) B4. Differentiated thyroid cancer was found in 66 (53.7%) patients: 30/66 (45.5%) B3 and 36/57 (63.2%) B4 (p=0.075). Operated patients were younger than the non-operated (B3: 52.4+/-16 vs. 59.7+/-13 years, p=0.009; B4: 51.7+/-15 vs. 60.5+/-14 years, p=0.042), and operated B3 nodules were larger than the non-operated (27.2 vs. 22.2 mm, p=0.014). Additional FNA was done in 160 patients (49.7%): 137/250 (54.8%) B3 and 23/72 (31.9%) B4 (p=0.002). The additional B3 nodules aspirations yielded a diagnosis of B2 in 84 patients (61.3%), B3 in 48 (35%), and B4 in 5 (3.6%). Of the 23 repeated B4 aspirations, B2 was reported in 5 (21.7%), B3 in 12 (52.2%), B4 in 4 (17.4%), and B6 in 2 (8.7%). The number of aspirated nodules was twice that reported in 1999-2000. The rate of indeterminate nodules increased from 6 to 14.6%, the surgery rate decreased from 52.3 to 38.2%, and the accuracy of malignancy diagnosis increased from 25.9 to 53.7%. CONCLUSIONS: The application of TBSRTC significantly improves diagnostic accuracy for indeterminate thyroid nodules, leading to higher rates of malignancy detection despite lower rates of thyroidectomies.
PubMed-ID: 25809059
http://dx.doi.org/10.1007/s00268-015-3032-6

Validation and Comparison of Nomograms in Predicting Disease-Specific Survival for Papillary Thyroid Carcinoma.
World J Surg, 39(8):1951-8.
B. H. Lang and C. K. Wong. 2015.
BACKGROUND: Nomogram could estimate individualized prognosis in papillary thyroid carcinoma (PTC). We aimed to create and validate a new nomogram and compare it with other published nomograms using a large patient cohort. METHODS: Eight-hundred and forty-nine PTC patients with >/=7 years follow-up were randomly assigned to the development (n=425) and validation (n=424) groups. The former was used for developing a nomogram for disease-specific survival (DSS), while the latter was for validating the nomogram by discrimination [or area under curve (AUC)]. AUC of the newly developed nomogram was compared to other published nomograms. RESULTS: The 5- and 10-year risk of dying from PTC were 1.4 and 3.3%, respectively, while dying from non-PTC-related causes were 2.3 and 5.1%, respectively. The new nomogram was developed from age, tumor size, multifocality, nodal status and distant metastases. The discrimination was excellent (AUC (95% CI) for 5- and 10-year DSS were 0.896 (0.683-0.971) and 0.919 (0.871-0.967), respectively). Its predictability was similar to other published nomograms (p>0.05). Based on the new nomogram, a total score of <28 meant 99.72% chance of surviving from PTC at 10 years while a score of >/=28 meant 9.09% chance of dying from PTC at 10 years. CONCLUSIONS: Using variables from the current tumor node metastasis (TNM) staging system, a new nomogram was developed. It exhibited excellent discriminatory ability and accuracy in predicting 10-year DSS relative to other published nomograms. However, given the excellent prognosis of PTC, the new nomogram was better at ruling out than predicting PTC-related death. Further validation by an external cohort is required.
PubMed-ID: 25809064
http://dx.doi.org/10.1007/s00268-015-3044-2

Using diffusion-weighted MRI to predict aggressive histological features in papillary thyroid carcinoma: a novel tool for pre-operative risk stratification in thyroid cancer.
Thyroid, 25(6):672-80.
Y. Lu, A. L. Moreira, V. Hatzoglou, H. E. Stambuk, M. Gonen, Y. Mazaheri, J. O. Deasy, A. R. Shaha, R. M. Tuttle and A. Shukla-Dave. 2015.
BACKGROUND: Initial management recommendations of papillary thyroid carcinoma (PTC) are very dependent on preoperative studies designed to evaluate the presence of PTC with aggressive features. The purpose of this study was to evaluate whether diffusion-weighted magnetic resonance imaging (DW-MRI) before surgery can be used as a tool to stratify tumor aggressiveness in patients with PTC. METHODS: In this prospective study, 28 patients with PTC underwent DW-MRI studies on a three Tesla MR scanner prior to thyroidectomy. Due to image quality, 21 patients were finally suitable for further analysis. Apparent diffusion coefficients (ADCs) of normal thyroid tissues and PTCs for 21 patients were calculated. Tumor aggressiveness was defined by surgical histopathology. The Mann-Whitney U test was used to compare the difference in ADCs among groups of normal thyroid tissues and PTCs with and without features of tumor aggressiveness. Receiver operating characteristic (ROC) analysis was performed to assess the discriminative specificity, sensitivity, and accuracy of and determine the cutoff value for the ADC in stratifying PTCs with tumor aggressiveness. RESULTS: There was no significant difference in ADC values between normal thyroid tissues and PTCs. However, ADC values of PTCs with extrathyroidal extension (ETE; 1.53+/-0.25x10(-3) mm2/s) were significantly lower than corresponding values from PTCs without ETE (2.37+/-0.67x10(-3) mm2/s; p<0.005). ADC values identified 3 papillary carcinoma patients with extrathyroidal extension that would have otherwise been candidates for observation based on ultrasound evaluations. The cutoff value of ADC to discriminate PTCs with and without ETE was determined at 1.85x10(-3) mm2/s with a sensitivity of 85%, specificity of 85%, and ROC curve area of 0.85. CONCLUSION: ADC value derived from DW-MRI before surgery has the potential to stratify ETE in patients with PTCs.
PubMed-ID: 25809949
http://dx.doi.org/10.1089/thy.2014.0419

Correlation of BRAFV600E Mutation and Glucose Metabolism in Thyroid Cancer Patients: An (1)(8)F-FDG PET Study.
J Nucl Med, 56(5):662-7.
J. Nagarajah, A. L. Ho, R. M. Tuttle, W. A. Weber and R. K. Grewal. 2015.
There is significant interest in a better understanding of the genetic underpinnings of the increased glucose metabolic rates of cancer cells. Thyroid cancer demonstrates a broad variability of (18)F-FDG uptake as well as several well-characterized oncogenic mutations. In this study, we evaluated the differences in glucose metabolism of the BRAF(V600E) mutation versus BRAF wild-type (BRAF-WT) in patients with metastatic differentiated thyroid cancer (DTC) and poorly differentiated thyroid cancer (PDTC). METHODS: Forty-eight DTC and 34 PDTC patients who underwent (18)F-FDG PET/CT for tumor staging were identified from a database search. All patients were tested for the BRAF(V600E) mutation and assigned to 1 of 2 groups: BRAF(V600E) mutated and BRAF-WT. (18)F-FDG uptake of tumor tissue was quantified by maximum standardized uptake value (SUVmax) of the hottest malignant lesion in 6 prespecified body regions (thyroid bed, lymph nodes, lung, bone, soft tissue, and other). When there were multiple lesions in 1 of the prespecified body regions, only the 1 with the highest (18)F-FDG uptake was analyzed. RESULTS: In the DTC cohort, 24 tumors harbored a BRAF(V600E) mutation, whereas 24 tumors were BRAF-WT. (18)F-FDG uptake of BRAF(V600E)-positive lesions (median SUVmax, 6.3; n = 53) was significantly higher than that of BRAF-WT lesions (n = 39; median SUVmax, 4.7; P = 0.019). In the PDTC group, only 5 tumors were BRAF(V600E)-positive, and their (18)F-FDG uptake was not significantly different from the BRAF-WT tumors. There was also no significant difference between the SUVmax of all DTCs and PDTCs, regardless of BRAF mutational status (P = 0.90). CONCLUSION: These data suggest that BRAF(V600E)-mutated DTCs are significantly more (18)F-FDG-avid than BRAF-WT tumors. The effect of BRAF(V600E) on tumor glucose metabolism in PDTC needs further study in larger groups of patients.
PubMed-ID: 25814520
http://dx.doi.org/10.2967/jnumed.114.150607

Risk Factors for Re-recurrence After First Reoperative Surgery for Locoregional Recurrent/Persistent Papillary Thyroid Carcinoma.
World J Surg, 39(8):1943-50.
H. S. Lee, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim. 2015.
BACKGROUND: Papillary thyroid carcinoma (PTC) is generally an indolent tumor indicative of favorable prognosis. However, post-treatment recurrences may be problematic, and management strategies for recurrent

disease have not been established. This study investigated risk factors associated with re-recurrence of PTC after reoperative surgery. MATERIALS AND METHODS: This study included 151 patients with pathologically confirmed recurrent/persistent PTC who underwent reoperation. Clinical factors, operative and pathologic findings, serum thyroglobulin levels, postoperative complications, and recurrences were examined. Univariate and multivariate analyses were performed to identify factors associated with re-recurrence-free survival (RFS) after reoperative surgery. RESULTS: Recurrent tumors were found in thyroid remnants or previous resection bed (n=28), central nodes (n=48), and lateral neck nodes (n=102). Biochemical complete remission (stimulated thyroglobulin<1 ng/mL) was achieved in 69 (51.5%) patients after reoperative surgery. Permanent vocal fold paralysis and hypoparathyroidism developed in 6 (4.1%) and 4 (2.8%) patients, respectively. Vocal fold paralysis occurred primarily due to intentional nerve resection following tumor invasion. During a median follow-up of 57.5 months, 41 (27.2%) patients had re-recurrences. Univariate analyses showed that extranodal extension (p=0.028), recurrent laryngeal nerve invasion (p=0.037), as well as stimulated (p=0.001) and unstimulated (p=0.015) serum thyroglobulin were significant predictors of RFS. Multivariate analyses showed that postoperative biochemical remission independently predicted RFS (p=0.014). CONCLUSIONS: Postoperative thyroglobulin after reoperative surgery predicted re-recurrence. Careful follow-up of these patients after reoperation is recommended.
PubMed-ID: 25820911
http://dx.doi.org/10.1007/s00268-015-3052-2

Therapy: Lenvatinib and radioiodine-refractory thyroid cancers.
Nat Rev Endocrinol, 11(6):325-7.
L. Dunn and J. A. Fagin. 2015.
PubMed-ID: 25824678
http://dx.doi.org/10.1038/nrendo.2015.53

Transaxillary thyroidectomies: a comparative learning experience of robotic vs endoscopic thyroidectomies.
Otolaryngol Head Neck Surg, 152(5):820-6.
K. L. Kiong, N. G. Iyer, T. Skanthakumar, J. C. Ng, N. C. Tan, H. N. Tay and H. K. Tan. 2015.
OBJECTIVE: Robotic and endoscopic approaches have become more accepted in thyroid surgery, with current literature documenting the experience of high-volume centers. We adopted both approaches concurrently, and this series presents our initial experience to assess the more practical option for low- to moderate-volume centers starting out with transaxillary thyroidectomies. STUDY DESIGN: Case series with chart review. SETTING: Tertiary academic center. SUBJECTS AND METHODS: Over a period of 4 years, 101 patients underwent transaxillary thyroidectomies, of whom 48 underwent robotic thyroidectomy and 53 underwent endoscopic thyroidectomy. Data analysis includes patient characteristics, procedure time, thyroid pathology, and postoperative complications. A survey was conducted among surgeons to assess the subjective experience. RESULTS: Endoscopic hemithyroidectomies had a significantly shorter duration of operation (145.8 minutes) vs that of robotic hemithyroidectomies (193.6 minutes), P < .001. The mean time taken for the first 5 hemithyroidectomies vs the last 5 hemithyroidectomies showed a greater drop in the endoscopic group (49.1%) vs the robotic group (18.6%). There were 2 cases of transient recurrent laryngeal nerve injury. In the surgeon survey, the endoscopic technique was perceived to have less need for peripheral support, while the robotic technique was preferred for its shorter learning curve. CONCLUSION: In terms of outcome, both techniques are comparable at least in the initial phase. Based on our early experience, the endoscopic technique may be less intuitive with a longer learning curve, although at steady state, it may be the quicker procedure. This is relevant for low- to moderate-volume centers starting their transaxillary thyroidectomy program.
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http://dx.doi.org/10.1177/0194599815573003

Ambulatory thyroidectomy: a multistate study of revisits and complications.
Otolaryngol Head Neck Surg, 152(6):1017-23.
R. K. Orosco, H. W. Lin and N. Bhattacharyya. 2015.
OBJECTIVE: Determine rates and reasons for revisits after ambulatory adult thyroidectomy. STUDY DESIGN: Cross-sectional analysis of multistate ambulatory surgery and hospital databases. SETTING: Ambulatory surgery data from the State Ambulatory Surgery Databases of California, Florida, Iowa, and New York for calendar years 2010 and 2011. SUBJECTS AND METHODS: Ambulatory thyroidectomy cases were linked to state ambulatory, emergency, and inpatient databases for revisit encounters occurring within 30 days. The numbers of revisits, mortality, and associated diagnoses were analyzed. RESULTS: A total of 25,634 cases of ambulatory thyroid surgery were identified: 44.2% total thyroidectomy (TT) and 55.8% partial thyroidectomy (PT).

Common indications for surgery included goiter/cyst (39.5%), benign/uncertain neoplasm (24.2%), and malignant neoplasm (24.0%). The 30-day revisit rate was 7.2% (n = 1858; 61.8% emergency department, 22.4% inpatient admission, and 15.8% ambulatory surgery center). The most common diagnosis at revisit was hypocalcemia (20.8% of revisits), followed by wound hematoma/seroma/bleeding (7.1%). Higher rates of revisit, hypocalcemia, and hematoma/seroma/bleeding were seen in patients undergoing TT (P < .016 for all). Sixteen patients had bleeding less than 24 hours after the index procedure (0.1% overall, 0.9% of revisits). Most hypocalcemia and hematoma/bleeding occurred over the first postoperative week. Three deaths occurred within 30 days of the index procedure. CONCLUSION: In carefully selected patients, ambulatory thyroidectomy demonstrates a good postoperative morbidity and mortality profile. Common reasons for revisits included hypocalcemia and bleeding/seroma/hematoma, which occurred with relatively high frequencies as late as a week after surgery. Quality improvement measures should be targeted at lowering revisit rates and safely managing complications.
PubMed-ID: 25829390
http://dx.doi.org/10.1177/0194599815577603

Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer.
Thyroid, 25(6):681-7.
J. L. Marti, K. S. Jain and L. G. Morris. 2015.
INTRODUCTION: The long-term sequelae of radioactive iodine (RAI) for differentiated thyroid cancer (DTC) in pediatric and young adult patients are not well-defined. Epidemiologic analyses of second primary malignancy (SPM) risk have only been performed in the adult population. Existing data are limited to case series with limited follow-up. The objective of this study was to analyze the elevated risk of SPM attributable to RAI in young patients treated for DTC. METHODS: Population-based analysis of 3850 pediatric and young adult patients (<25 years old) undergoing treatment with surgery with/without RAI for DTC, followed in the Surveillance, Epidemiology, and End Results cancer registry (1973-2008), equating to 54,727 person-years at risk (PYR). The excess risk of SPM was calculated relative to a reference population and expressed as standardized incidence ratio (SIR) and excess absolute risk (EAR) per 10,000 PYR. Excess risk was compared in RAI-treated and non-RAI-treated patients. RESULTS: A total of 1571 patients (40%) received RAI. The percentage of patients treated with RAI increased over time, from 4% in 1973 to 62% in 2008 (p<0.001). Among patients who received RAI, 26 SPMs were observed, and 18.3 were expected. The relative risk of SPM at any site was significantly elevated (SIR=1.42), corresponding to 4.4 excess cases per 10,000 PYR. SPM risk was not elevated in the non-RAI-treated cohort (SIR=1.01, EAR=0). Patients treated with RAI were at dramatically elevated risk for development of a salivary malignancy (SIR=34.1), corresponding to 1.7 excess cases per 10,000 PYR. The risk of leukemia in RAI-treated patients was elevated (SIR=4.0, EAR=0.9) but did not reach statistical significance. There was no elevated risk of salivary cancer or leukemia in the non-RAI-treated cohort. CONCLUSIONS: Pediatric and young adult patients who receive RAI for DTC experience an elevated risk of SPM, mainly salivary gland cancer. These risks appear to be only slightly higher than in adult patients. Over a decade, approximately 1 in 227 RAI-treated patients will develop an SPM, and 1 in 588 RAI-treated patients will develop a salivary cancer, attributable to RAI. Because the expected survival time for young DTC patients is long, it is critical to weigh the benefits of RAI carefully against the small, but real, increase in SPM risk.
PubMed-ID: 25851829
http://dx.doi.org/10.1089/thy.2015.0067

Assessment of Simplified Blood Dose Protocols for the Estimation of the Maximum Tolerable Activity in Thyroid Cancer Patients Undergoing Radioiodine Therapy Using 124I.
J Nucl Med, 56(6):832-8.
W. Jentzen, A. Bockisch and M. Ruhlmann. 2015.
In high-activity radioiodine therapies for differentiated thyroid cancer, blood dosimetry has been developed to estimate the maximum tolerable activity (MTA) of (131)I that can be safely administered without leading to toxic effects. The reference protocol involves a series of both blood sampling (BS) and whole-body counting (WC) over a period of several days. The aim of this retrospective study was to identify simplified protocols without an appreciable loss of accuracy. METHODS: Data from 211 thyroid cancer patients who received (124)I blood dosimetries were retrospectively analyzed. BS and WC acquired at approximately 1-2, 4, 24, 48, and 96 h or longer after (124)I administration were included. This dataset was used to determine the reference MTA and estimations based on a reduced number of combined data from BS and respective WC. MTA estimates were also determined on the basis of either BS or WC alone using some simplifying assumptions in the dosimetry approach. A simplified protocol was considered equivalent to the reference protocol if the estimates of 95% of the MTAs were within the +/-20% range and the absolute maximum percentage deviation did not exceed the

limit of 30% in a few cases. Lin's concordance correlation analysis was applied to assess the protocol's agreements. RESULTS: Two equivalent protocols were identified that included both BS and respective WC acquired at only 3 time points (1-2, 24 or 48, and >/=96 h). Further equivalent protocols with only 3 blood samples drawn at similar time points were discovered for patients, who had undergone at least 1 radioiodine therapy. For all equivalent protocols, deviations of the mean absolute percentage MTA were below 9% and Lin's concordance correlation coefficients of 0.95 or greater were found, indicating almost excellent agreement (according to Partik's criteria). CONCLUSION: The pretherapy blood dosimetry protocol can be substantially shortened and may be beneficial to patients and patient management while reducing the radiation exposure to medical staff.
PubMed-ID: 25858042
http://dx.doi.org/10.2967/jnumed.114.153031

Parathyroid Reimplantation in Forearm Subcutaneous Tissue During Thyroidectomy: A Simple and Effective Way to Avoid Hypoparathyroidism.
World J Surg, 39(8):1936-42.
G. Cavallaro, O. Iorio, M. Centanni, N. Porta, A. Iossa, L. Gargano, S. Del Duca, A. Gurrado, M. Testini, V. Petrozza and G. Silecchia. 2015.
INTRODUCTION: Parathyroid autotransplantation plays an important role in preventing hypoparathyroidism following thyroidectomy. The preferred reimplantation site is still the sternocleidomastoid muscle, but this approach does not permit to check graft vitality postoperatively. The authors report the first prospective evaluation of normal parathyroid gland reimplantation in forearm subcutaneous tissue (using the same technique proposed during parathyroidectomy for hyperplasia) in case of devascularized or inadvertently removed glands during thyroid surgery. MATERIALS AND METHODS: From January 2013 to August 2014, we performed 348 consecutive thyroidectomies for various disease, both benign and malignant. In 25 cases, due to inadvertent parathyroid removal or evidence of insufficient blood supply, we removed and fragmented the gland into 0.5-1 mm slices (one for frozen section) and reimplanted it into two subcutaneous pockets on the non-dominant forearm. After surgery we checked grafted gland function by evaluation of serum parathormone gradient between reimplanted versus non-reimplanted arm (considering significant a ratio of 1.5 or more), at 1 week, 1 and 3 months after surgery. RESULTS: We observed recovery of reimplanted graft function in 48, 88 and 96% of patients respectively at 1 week, 1 and 3 months after surgery. All patients showed normal parathormone levels in peripheral blood (non-reimplanted arm). In one case we observed post-operative wound hematoma on graft-site. This patient showed no graft functionality in post-operative period (even at 3 months follow-up). CONCLUSIONS: Parathyroid gland reimplantation in forearm subcutaneous tissue during thyroid surgery is a safe, easy and effective procedure; furthermore, it allows a good control of graft functionality and would allow an easy grafted gland removal if needed.
PubMed-ID: 25862025
http://dx.doi.org/10.1007/s00268-015-3070-0

High Diagnostic Accuracy Based on CLDN10, HMGA2, and LAMB3 Transcripts in Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 100(6):E890-9.
M. C. Barros-Filho, F. A. Marchi, C. A. Pinto, S. R. Rogatto and L. P. Kowalski. 2015.
CONTEXT: Thyroid nodules are common in adult population and papillary thyroid carcinoma (PTC) is the most frequent malignant finding. The natural history of PTC remains poorly understood and current diagnostic methods limitations are responsible for a significant number of potentially avoidable surgeries. OBJECTIVE: This study aimed to identify molecular markers to improve the diagnosis of thyroid lesions. DESIGN: Gene expression profiling was performed using microarray in 61 PTC and 13 surrounding normal tissues (NT). A reliable gene list was established using cross-study validation (138 matched PTC/NT from external databases). Results were collectively interpreted by in silico analysis. A panel of 28 transcripts was evaluated by RT-qPCR, including benign thyroid lesions (BTL) and other follicular cell-derived thyroid carcinomas (OFDTC). A diagnostic algorithm was developed (training set: 23 NT, 8 BTL, and 86 PTC), validated (independent set: 10 NT, 140 BTL, 120 PTC, and 12 OFDTC) and associated with clinical features. RESULTS: GABRB2 was ranked as the most frequently up-regulated gene in PTC (cross-study validation). Altered genes in PTC suggested a loss of T4 responsiveness and dysregulation of retinoic acid metabolism, highlighting the putative activation of EZH2 and histone deacetylases (predicted in silico). An algorithm combining CLDN10, HMGA2, and LAMB3 transcripts was able to discriminate tumors from BTL samples (94% sensitivity and 96% specificity in validation set). High algorithm scores were associated with regional lymph node metastases. CONCLUSIONS: A promising tool with high performance for PTC diagnosis based on three transcripts was designed with the potential to predict lymph node metastasis risk.

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http://dx.doi.org/10.1210/jc.2014-4053

Tall cell papillary thyroid carcinoma: new diagnostic criteria and mutations in BRAF and TERT.
Endocr Relat Cancer, 22(3):419-29.
M. S. Dettmer, A. Schmitt, H. Steinert, D. Capper, H. Moch, P. Komminoth and A. Perren. 2015.
The tall cell (TC) variant of papillary thyroid carcinoma (PTC) has an unfavorable prognosis. The diagnostic criteria remain inconsistent, and the role of a minor TC component is unclear. Molecular diagnostic markers are not available; however, there are two potential candidates: BRAF V600E and telomerase reverse transcriptase (TERT) promoter mutations. Using a novel approach, we enriched a collective with PTCs that harbored an adverse outcome, which overcame the limited statistical power of most studies. This enabled us to review 125 PTC patients, 57 of which had an adverse outcome. The proportion of TCs that constituted a poor prognosis was assessed. All of the tumors underwent sequencing for TERT promoter and BRAF V600E mutational status and were stained with an antibody to detect the BRAF V600E mutation. A 10% cutoff for TCs was significantly associated with advanced tumor stage and lymph node metastasis. Multivariate analysis showed that TCs above 10% were the only significant factor for overall, tumor-specific, and relapse-free survival. Seven percent of the cases had a TERT promoter mutation, whereas 61% demonstrated a BRAF mutation. The presence of TC was significantly associated with TERT promoter and BRAF mutations. TERT predicted highly significant tumor relapse (P<0.001). PTCs comprised of at least 10% TCs are associated with an adverse clinical outcome and should be reported accordingly. BRAF did not influence patient outcome. Nevertheless, a positive status should encourage the search for TCs. TERT promoter mutations are a strong predictor of tumor relapse, but their role as a surrogate marker for TCs is limited.
PubMed-ID: 25870252
http://dx.doi.org/10.1530/ERC-15-0057

Predictive factors of contralateral paratracheal lymph node metastasis in unilateral papillary thyroid carcinoma.
Eur J Surg Oncol, 41(6):746-50.
T. Wei, R. Chen, X. Zou, F. Liu, Z. Li and J. Zhu. 2015.
BACKGROUND: Most of unilateral papillary thyroid carcinoma (PTC) metastasize to ipsilateral paratracheal lymph nodes (LNs) while some had contralateral paratracheal LN involved. The aim of this study was to analyze the predictive factors of contralateral paratracheal LN metastasis in unilateral PTC. METHODS: Data on 332 patients with unilateral PTC who underwent total/near total thyroidectomy and bilateral central neck dissection (CND) with/without lateral neck dissection were collected retrospectively. Patients' demographics, the extent of surgeries, and the pathological status of LNs and primary tumor were analyzed. RESULTS: A total of 332 patients (67 male and 265 female) were included. Contralateral paratracheal LN metastasis was found in 68 (68/332, 20.5%) patients. Tumor size (>1 cm) (P < .001), capsular/extracapsular invasion (P < .001), pretracheal/prelaryngeal LN metastasis (P < .001), lateral neck LN metastasis (P < .001) and ipsilateral paratracheal LN metastasis (P < .001) was significantly associated with contralateral paratracheal LN metastasis on univariate analysis. Multivariate analysis showed that tumor size (>1 cm) (P = .013), capsular/extracapsular invasion (P = .009), pretracheal/prelaryngeal LN metastasis (P = .021) and lateral neck LN metastasis (P = .002) were independent risk factors of contralateral paratracheal LN metastasis. CONCLUSION: Primary tumor size >1 cm, capsular/extracapsular invasion, pretracheal/prelaryngeal LN metastasis and lateral neck LN metastasis are predictive factors of contralateral paratracheal LN metastasis in unilateral PTC, which may help to determine the optimal extent of CND in patients with PTC.
PubMed-ID: 25882035
http://dx.doi.org/10.1016/j.ejso.2015.02.013

Preoperative Serum Thyrotropin to Thyroglobulin Ratio Is Effective for Thyroid Nodule Evaluation in Euthyroid Patients.
Otolaryngol Head Neck Surg, 153(1):15-9.
L. Wang, H. Li, Z. Yang, Z. Guo and Q. Zhang. 2015.
OBJECTIVE: This study was designed to assess the efficiency of the serum thyrotropin to thyroglobulin ratio for thyroid nodule evaluation in euthyroid patients. STUDY DESIGN: Cross-sectional study. SETTING: Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China. SUBJECTS AND METHODS: Retrospective analysis was performed for 400 previously untreated cases presenting with thyroid nodules. Thyroid function was tested with commercially available radioimmunoassays. The receiver operating characteristic curves were constructed to determine cutoff values. The efficacy of the thyrotropin:thyroglobulin ratio and thyroid-stimulating hormone for thyroid nodule evaluation was evaluated in terms of sensitivity,

specificity, positive predictive value, positive likelihood ratio, negative likelihood ratio, and odds ratio. RESULTS: In receiver operating characteristic curve analysis, the area under the curve was 0.746 for the thyrotropin:thyroglobulin ratio and 0.659 for thyroid-stimulating hormone. With a cutoff point value of 24.97 IU/g for the thyrotropin:thyroglobulin ratio, the sensitivity, specificity, positive predictive value, positive likelihood ratio, and negative likelihood ratio were 78.9%, 60.8%, 75.5%, 2.01, and 0.35, respectively. The odds ratio for the thyrotropin:thyroglobulin ratio indicating malignancy was 5.80. With a cutoff point value of 1.525 microIU/mL for thyroid-stimulating hormone, the sensitivity, specificity, positive predictive value, positive likelihood ratio, and negative likelihood ratio were 74.0%, 53.2%, 70.8%, 1.58, and 0.49, respectively. The odds ratio indicating malignancy for thyroid-stimulating hormone was 3.23. CONCLUSION: Increasing preoperative serum thyrotropin:thyroglobulin ratio is a risk factor for thyroid carcinoma, and the correlation of the thyrotropin:thyroglobulin ratio to malignancy is higher than that for serum thyroid-stimulating hormone.
PubMed-ID: 25883100
http://dx.doi.org/10.1177/0194599815579877

Surgical Management of Familial Papillary Thyroid Microcarcinoma: A Single Institution Study of 94 Cases.
World J Surg, 39(8):1930-5.
T. Y. Sung, Y. M. Lee, J. H. Yoon, K. W. Chung and S. J. Hong. 2015.
BACKGROUND: Familial papillary thyroid carcinoma (familial PTC) is well known to present with aggressiveness; however, the characteristics and the prognostic outcomes of familial papillary thyroid microcarcinoma (familial micro-PTC) are not well established. The overall aim of this study was to analyze the clinicopathological outcomes of familial micro-PTC. METHODS: Between 1996 and 2006, 2071 patients underwent thyroid surgery for papillary thyroid carcinoma. The clinicopathological outcomes for familial PTC and sporadic PTC were compared, and familial micro-PTC data were sub-analyzed. RESULTS: There were significant differences in multifocality, bilaterality, extent of surgery, and recurrence between familial PTC and sporadic PTC ($p<0.05$). There was no significant difference in the number of affected family members in the familial PTC group. In patients with familial micro-PTC, less aggressiveness was noted in multifocality, extrathyroidal invasion, tumor stage at time of initial surgery, central lymph node metastasis, and recurrence than in those with familial PTC tumors>1 cm in diameter ($p<0.05$). The multivariate analysis including recurrence showed no significant difference between familial micro-PTC patients and sporadic micro-PTC patients. CONCLUSION: When familial PTC was compared with sporadic PTC, our results support the recommendation for more invasive familial PTC surgery. However, familial micro-PTC outcomes differed from familial PTC tumors>1.0 cm in diameter. It was similar to sporadic micro-PTC, illustrating that familial micro-PTC is less aggressive and that a less invasive surgical treatment could be considered.
PubMed-ID: 25894401
http://dx.doi.org/10.1007/s00268-015-3064-y

Thyroid cancer in patients with toxic nodular goiter--is the incidence increasing?
Am J Surg, 209(6):974-6.
K. C. Choong and C. R. McHenry. 2015.
BACKGROUND: There has been a dramatic increase in the incidence of thyroid cancer, but it is unclear if this has occurred in patients with toxic nodular goiter (TNG). METHODS: TNG was defined as one or more thyroid nodules in combination with a low serum TSH level. Patients who underwent thyroidectomy for TNG were identified from a prospectively maintained database. The rates of incidental thyroid cancer were compared over the intervals 1990 to 1999, 2000 to 2009, and 2010 to 2014. RESULTS: There was no significant difference in cancer rate between the 3 time periods. Overall, 7 (4.7%) of the 148 patients had thyroid cancer; similarly, 1 (3.2%) of the 31 patients from 1990 to 1999, 3 (4.2%) of 72 patients from 2000 to 2009, and 3 (6.7%) of the 45 patients from 2010 to 2014 ($P > .05$) had thyroid cancer. CONCLUSIONS: No significant increase in the rate of carcinoma was observed in patients with TNG. As a result, the risk benefit analysis should not change when considering therapeutic options for TNG.
PubMed-ID: 25896315
http://dx.doi.org/10.1016/j.amjsurg.2014.12.033

Mortality after thyroid surgery, insignificant or still an issue?
Langenbecks Arch Surg, 400(4):517-22.
J. Gomez-Ramirez, A. Sitges-Serra, P. Moreno-Llorente, A. R. Zambudio, J. Ortega-Serrano, M. T. Rodriguez and J. V. del Moral. 2015.
BACKGROUND: Thyroidectomy is considered to be a safe procedure. Although very uncommon, death may occur after thyroid resection. The aim of this study was to investigate the prevalence and causes of death after

thyroidectomy and the associated risk factors in the modern era of thyroid surgery. PATIENTS AND METHODS: A structured questionnaire was sent to all endocrine surgery units in Spain to report all deaths that occurred after thyroidectomy in recent years. RESULTS: Twenty-six surgical units, encompassing 30.495 thyroidectomies, returned the questionnaire. A total of 20 deaths (0.065%) were recorded: 12 women (60%) and 8 men (40%) with a median age of 65 years (range 32-86). Half of the patients had a retrosternal goiter with a median weight of 210 g. The median operative time was 185 min. Histological diagnoses were benign goiter (35%) or thyroid carcinoma (65%): differentiated (30%), medullary (20%), poorly differentiated/anaplastic (10%), and colorectal cancer metastasis (5%). Causes of death were cervical hematoma (30%), respiratory distress/pneumonia due to prolonged endotracheal intubation (25%), tracheal injury (15%), heart failure (15%), sepsis (wound infection/esophageal perforation) (10%) and mycotic aneurysm (5%). The median time from surgery to death was 14 days (range 1-85). CONCLUSIONS: Death after thyroidectomy is very uncommon, and most often results from a combination of advanced age, giant goiters, and upper airway complications.
PubMed-ID: 25900848
http://dx.doi.org/10.1007/s00423-015-1303-1

Variation in cost of total thyroidectomy across the United States, 2007 to 2008.
Am J Surg, 210(2):302-8.
C. E. Reinke, E. M. Sonnenberg, G. C. Karakousis, D. L. Fraker and R. R. Kelz. 2015.
BACKGROUND: Variation in cost of surgical care across state lines is poorly understood. We sought to examine state-level variation in wage-adjusted total cost (WATC) of a common surgical procedure. METHODS: We performed a retrospective cohort study of patients undergoing total thyroidectomy in the Nationwide Inpatient Sample (2007 to 2008). WATC was calculated from charges and adjusted for the area wage index. Hierarchical linear modeling was used to investigate the variation in WATC explained by variables at the patient, hospital, and state levels. RESULTS: We identified 11,058 eligible patients from 35 states. The overall mean WATC was $8,132; 37% of the WATC variance was because of differences across hospitals, whereas 28% was explained by patient-level factors and 8% because of differences across states. CONCLUSIONS: More than a quarter of the variation in cost of total thyroidectomy was not explained by patient-, hospital-, or state-level factors. Further research is needed to understand the unexplained residual variation.
PubMed-ID: 25936247
http://dx.doi.org/10.1016/j.amjsurg.2014.12.039

IL-14 and IL-16 are expressed in the thyroid of patients with either Graves' disease or Hashimoto's thyroiditis.
Clin Endocrinol (Oxf),
E. Helen Kemp, R. A. Ajjan, R. A. Metcalfe, P. F. Watson and A. P. Weetman. 2015.
OBJECTIVES: Cytokines have an important role in orchestrating the pathophysiology in autoimmune thyroid disease. The aim of the current study was to analyse the expression of interleukin (IL)-14 and IL-16 in the thyroid tissue of patients with Graves' disease (GD), Hashimoto's thyroiditis (HT) or multinodular goitre (MNG) and in that of normal individuals, in patients' intrathyroidal CD4+ and CD8+ T cells, and in patient and normal cultured thyroid follicular cells. METHODS: The expression of IL-14 and IL-16 mRNA and protein was investigated using reverse transcription-polymerase chain reaction (RT-PCR) amplification, and Western blotting and ELISAs, respectively. RESULTS: IL-14 mRNA expression was detected in thyroid tissue from 8/9 GD, 3/4 HT and 3/13 MNG patients and 1/6 normal individuals, and IL-16 mRNA expression in thyroid tissue from 9/9 GD, 4/4 HT and 9/13 MNG patients and 4/6 normal individuals. IL-14 mRNA expression was detected in intrathyroidal CD4+ and CD8+ T cells from 2/2 GD and 2/2 HT patients, while IL-16 mRNA was detected in samples from 1/2 HT patients but not in those from either patient with GD. IL-14 and IL-16 mRNA expression was found in thyroid follicular cells derived from 2/2 patient with GD and 1/1 normal individual. IL-14 protein was detected in thyroid tissue from 6/6 GD, 1/1 HT and 0/6 MNG patients and 0/6 normal individuals, and IL-16 protein in thyroid tissue from 6/6 GD, 1/1 HT and 1/6 MNG patients and 0/6 normal individuals. Expression of IL-14 protein was stimulated in thyroid follicular cells derived from two patients with GD and one normal individual by peripheral blood mononuclear cell (PBMC)-conditioned medium. Treatment of thyrocytes from two patients with GD and one normal individual with PBMC-conditioned medium and tumour necrosis factor (TNF)-alpha stimulated IL-16 protein expression. In normal thyrocytes, IL-16 protein synthesis was induced also by IL-1beta, IL-17A, IL-4 and transforming growth factor (TGF)-beta. CONCLUSIONS: The data provide evidence that the intrathyroidal production of IL-14 and IL-16 is associated with the pathogenesis of autoimmune thyroid disease. Thyroid follicular cells display the ability to express IL-14 and IL-16 mRNA and can be stimulated to express IL-16 protein, by a panel of cytokines, and IL-14 protein, by as yet unidentified factors.
PubMed-ID: 25940130
http://dx.doi.org/10.1111/cen.12810

Electrophysiologic identification and monitoring of the external branch of superior laryngeal nerve during thyroidectomy.
Laryngoscope, 125(8):1996-2000.
E. Kandil, S. E. Mohamed, A. Deniwar, H. Mohamed, P. Friedlander, R. Aslam, A. Saeed, I. Musa and G. Randolph. 2015.
OBJECTIVE: The aim of the study is to examine the correlation between weight, gender, and race with external branch of superior laryngeal nerve (EBSLN) visualization. Furthermore, we compared normative EBSLN neural-monitoring values to those of the recurrent laryngeal nerve (RLN). STUDY DESIGN: Retrospective study. SETTING: North American tertiary academic hospital. SUBJECTS AND METHODS: A retrospective, institutional review board-approved review was carried out on patients undergoing thyroid surgery by a single surgeon over 3.5 years. Preoperative and postoperative laryngoscopy was done on all patients in accordance with recently published American Academy of Otolaryngology voice optimization at thyroidectomy guidelines, and patients' clinical and operative relevant data were collected. RESULTS: A total of 447 nerves were at risk in 371 thyroidectomy patients. Of these nerves at risk, 237 (53.02%) were visualized and stimulated. The average amplitude and latency for the EBSLN were significantly lower when compared to the amplitude and the latency of RLN stimulation ($P < 0.0001$, $P < 0.0001$, respectively). There was no gender or racial disparity. Out of our study population, the EBSLN was identified in 64.56% in nonobese patients, whereas it was only 40.00% in obese patients ($P < 0.001$). Additionally, of the 56 patients in whom the EBSLN was visualized on one side and who further underwent bilateral neck exploration, 41 (73%) had visualization of the nerve on the contralateral side as well. CONCLUSION: EBSLN is less likely to be visualized in obese patients; however, there was no gender or racial disparity. Stimulation of EBSLN was felt to be a useful adjunct during superior pole dissection to assure the nerve integrity. LEVEL OF EVIDENCE: 4. Laryngoscope, 125:1996-2000, 2015.
PubMed-ID: 25942675
http://dx.doi.org/10.1002/lary.25139

Reference range of serum calcitonin in pediatric population.
J Clin Endocrinol Metab, 100(5):1780-4.
M. G. Castagna, L. Fugazzola, F. Maino, D. Covelli, S. Memmo, F. Sestini, C. Fioravanti, C. Ferraris Fusarini, C. Scapellato, F. Macchini, G. Cevenini and F. Pacini. 2015.
BACKGROUND: Children belonging to the multiple endocrine neoplasia type 2 (MEN 2) pedigree and carrying germline RET mutations are candidates for prophylactic thyroidectomy, the timing of which is based on the mutation-associated risk and the calcitonin (CT) levels. DESIGN: The aim of this study was to establish the reference range for serum CT in a pediatric population. The study included 2740 subjects (1339 females and 1401 males) ranging in age from 1 day to 16 years and undergoing blood testing for any medical condition not affecting serum CT. RESULTS: Overall, serum CT was undetectable in 61.5% of the samples and detectable in 38.5%. Detectable samples were more frequent in the first 2 years of life. Thereafter, undetectable samples became more frequent, particularly in females. Mean serum CT concentrations were higher in the first year of life (9.81 +/- 8.8 pg/mL; range, 2.0-48.9 pg/mL) and the second year of life (4.56 +/- 2.64 pg/mL; range, 2.0-14.7 pg/mL). A significant decrease of serum CT levels was observed thereafter ($P < .001$), and starting from the third year of life serum CT levels were similar to those found in adults. No gender difference was found in any age group. Based on these results, age-specific CT reference ranges are needed in the pediatric population, and especially in the first 2 years of life. CONCLUSIONS: This is the first study defining the reference range for serum CT in the pediatric population and large enough to be statistically meaningful. Our proposal may facilitate the process of decision making when dealing with gene carriers of MEN 2.
PubMed-ID: 25955324
http://dx.doi.org/10.1210/jc.2014-4508

Increased and safer detection of nonrecurrent inferior laryngeal nerve after preoperative ultrasonography.
Laryngoscope, 125(7):1743-7.
M. Iacobone, M. Citton, G. Pagura, G. Viel and D. Nitti. 2015.
OBJECTIVES/HYPOTHESIS: Right nonrecurrent inferior laryngeal nerve (NRLN) is an anatomical variant reported with a variable prevalence (0.3%-6%). It is associated with some arterial abnormalities (absence of the brachiocephalic trunk and presence of a right aberrant subclavian lusorian artery) that may be identified by preoperative ultrasonography (pUS). NRLN represents a major morbidity risk factor during neck surgery. The aim of this study was to verify pUS accuracy in predicting NRLN and to assess the impact of this technique on NRLN detection rate and laryngeal morbidity. STUDY DESIGN: Retrospective. METHODS: The study included 1,477 patients undergoing thyroid and parathyroid surgery with right-side inferior laryngeal nerve exploration.

pUS was performed in 878 patients (pUS group); no preoperative attempts were performed in the remaining 599 patients (controls). Demographics, disease type, intraoperative inferior laryngeal nerve anatomy, and laryngeal morbidity were compared. RESULTS: No differences occurred between the two groups concerning demographics and disease type. NRLN was detected in 17 patients (1.9%) of the pUS group and in four patients (0.6%) of controls ($P < 0.05$). pUS predicted NRLN in all cases, with an overall accuracy > 98%. Overall laryngeal nerves morbidity was 1.8% in the pUS group and 4.2% in the controls ($P < 0.05$). NRLN palsy never occurred in the pUS group, whereas it occurred three times in the controls ($P < 0.005$). CONCLUSION: NRLN is accurately predicted by pUS. It occurs more frequently than expected because it may be misdiagnosed when no preoperative suspicion is available. Preoperative NRLN detection by pUS prevents inferior laryngeal nerve injuries.
PubMed-ID: 25960168
http://dx.doi.org/10.1002/lary.25093

Carfilzomib is an effective anticancer agent in anaplastic thyroid cancer.
Endocr Relat Cancer, 22(3):319-29.
A. Mehta, L. Zhang, M. Boufraqech, Y. Zhang, D. Patel, M. Shen and E. Kebebew. 2015.
Anaplastic thyroid cancer (ATC) is one of the most aggressive human malignancies. Currently, there is no standard or effective therapy for ATC. Drug repurposing for cancer treatment is an emerging approach for identifying compounds that may have antineoplastic effects. The aim of this study was to use high-throughput drug library screening to identify and subsequently validate novel therapeutic agents with anticancer effects in ATC. We performed quantitative high-throughput screening (qHTS) in ATC cell lines (SW-1736, 8505C, and C-643), using a compound library of 3282 drugs. qHTS identified 100 compounds that were active in all three ATC cell lines. Proteasome inhibitors were one of the most active drug categories according to enrichment analysis. Of the three proteasome inhibitors screened, a second-generation proteasome inhibitor, carfilzomib, was the most active. Treatment of ATC cells with carfilzomib significantly inhibited cellular proliferation and induced G2/M cell cycle arrest and caspase-dependent apoptosis. Mechanistically, carfilzomib increased expression of p27 (CDKN1B) and decreased expression of the anti-apoptotic protein ATF4. Pretreatment with carfilzomib reduced in vivo metastases (lung, bone, liver, and kidney) and disease progression, and decreased N-cadherin expression. Carfilzomib treatment of mice with established, widely metastatic disease significantly increased their survival, without significant toxicity. Our findings support the use or clinical study of carfilzomib as a therapeutic option in patients with advanced and metastatic ATC.
PubMed-ID: 25972243
http://dx.doi.org/10.1530/ERC-14-0510

Evaluation of the Clinical Usefulness of BRAF(V600E) Mutation Analysis of Core-Needle Biopsy Specimens in Thyroid Nodules with Previous Atypia of Undetermined Significance or Follicular Lesions of Undetermined Significance Results.
Thyroid, 25(8):897-903.
S. H. Choi, J. H. Baek, J. H. Lee, Y. J. Choi, D. E. Song, K. W. Chung, T. Y. Kim and Y. K. Shong. 2015.
BACKGROUND: The accurate diagnosis of thyroid nodules is important for making management decisions. The purpose of this study is to evaluate the clinical usefulness of BRAF(V600E) mutation analysis with core-needle biopsy (CNB+BRAF(V600E)) in thyroid nodules with previous atypia of undetermined significance (AUS) or follicular lesions of undetermined significance (FLUS) results. MATERIALS AND METHODS: From January 2011 to December 2012, 590 CNB+BRAF(V600E) mutation analyses were performed. We analyzed 200 nodules from 200 patients with previous AUS/FLUS results (22 men, 178 women; mean age, 48.6 years). The clinical usefulness of CNB+BRAF(V600E) was assessed by comparing the rates of conclusive results, the additional value of BRAF(V600E) mutation analysis, diagnostic performances, and therapeutic/diagnostic surgery results with those of CNB alone. For the subgroup analysis, the study patients were divided into those with nodules with previous AUS results and those with previous FLUS results. RESULTS: All CNB+BRAF(V600E) procedures were well-tolerated. CNB+BRAF(V600E) did not show significantly better diagnostic performance than CNB alone in thyroid nodules with previous AUS/FLUS results. However, the conclusive result rate of CNB+BRAF(V600E) was improved in thyroid nodules with previous AUS/FLUS results (76.5% vs. 73.0%, p=0.016), especially with previous AUS results (81.1% vs. 76.4%, p=0.031). Of the 56 previous AUS result thyroid nodules with surgical management, BRAF(V600E) mutation analysis led to therapeutic surgery in 5.4% by decreasing unnecessary diagnostic surgery. CONCLUSIONS: In general, CNB+BRAF(V600E) did not show significantly higher diagnostic accuracy than CNB alone. Although CNB+BRAF(V600E) may add additional value in nodules with previous AUS results, routinely adding BRAF(V600E) mutation analysis to CNB is not recommended.

PubMed-ID: 25978151
http://dx.doi.org/10.1089/thy.2014.0606

A low incidence of iodine-induced hyperthyroidism following administration of iodinated contrast in an iodine-deficient region.
Clin Endocrinol (Oxf),
C. Jarvis, K. Simcox, J. A. Tamatea, K. McAnulty, G. Y. Meyer-Rochow, J. V. Conaglen and M. S. Elston. 2015.
OBJECTIVE: There are limited data on the incidence of iodinated contrast-induced thyrotoxicosis, particularly in iodine-deficient regions. The aim of this study was to determine the incidence of iodinated contrast-induced thyrotoxicosis and to determine whether thyrotoxicosis was more common in patients >/=70 years compared to those <70 years of age. DESIGN: A prospective study of adult patients undergoing an outpatient CT with iodinated contrast was performed. MEASUREMENTS: Thyroid function tests (TFTs) and urine iodine measurements were performed prior to the scan. TFTs were repeated at 4- and 8-weeks postscan. Changes in TFTs from baseline were analysed. RESULTS: A total of 102 patients were included in the final analysis. Overall, TSH levels dropped (P = 0.0002), and free T3 (FT3) levels increased (P = 0.04) between baseline and week 4 with normalization by week 8; however, these changes were not considered clinically significant. No significant differences in free T4 (FT4) occurred in the overall group (P = 0.82). There were no differences in TFTs between baseline and 4 or 8 weeks for those patients aged <70 compared to >/=70 years. Two patients developed new subnormal TSH values. Of these, one had a 90-mm follicular variant papillary thyroid carcinoma diagnosed while the other had a normal thyroid assessment and TSH spontaneously normalized by 12 weeks. CONCLUSIONS: Only 2% of patients developed subclinical hyperthyroidism following a standard dose of iodinated contrast for CT investigations. Given the low incidence of iodine-induced thyrotoxicosis, there is no indication for routine pre- and post-CT thyroid function testing in our region.
PubMed-ID: 25982929
http://dx.doi.org/10.1111/cen.12818

Variations in single/two stage thyroidectomies for cancer may be due to differences in thyroid fine needle cytology provision.
Eur J Surg Oncol, 41(8):1033-8.
A. Gandhi, B. Ranganathan, S. A. Thiryayi, M. Rowland and B. K. Yap. 2015.
BACKGROUND & AIMS: Recommended treatment for thyroid cancers >10 mm is single stage total thyroidectomy (SST). Cancers diagnosed by diagnostic lobectomy may need completion surgery resulting in two stage thyroidectomies (TST). We noticed significant variation in numbers of SST and TST between hospitals within our cancer network and explored reasons for this using a prospective database containing all cases from 2004 to 2011 (n = 1030). We therefore conducted a survey of thyroid cytology provision across the network during 2010-2011. METHODS: A central university hospital with the largest caseload (21.5% of total) was chosen as "benchmark". Of 14 remaining hospitals 3 were excluded from analysis due to low thyroid operation numbers and the remaining compared with benchmark. We used individual chi-squared tests with Bonferroni correction to explore variation in expected and observed numbers of SST/TST. Analysis of variance (ANOVA) was used to examine reasons for observed differences. RESULTS: Significant variance in SST/TST was seen between hospitals (p < 0.00001). Three hospitals had frequencies of SST statistically similar to reference hospital; each reported 201-300 thyroid cytology cases during the survey period. The remaining 8 had lower rates of SST, the 2 lowest performing hospitals having SST rates of 11% (p = 0.0004) and 9% (p < 0.0001). These eight hospitals reported fewer than 200 cytology cases each, shared amongst 4-7 pathologists per site. Differences were unrelated to patient age, gender, tumour histology or stage (ANOVA). Only the reference hospital had specialist cytopathologists. CONCLUSION: Variation in thyroid cytology provision may increase TST rates. Thyroid cytology should be concentrated in high volume centres with specialist thyroid cytopathologists.
PubMed-ID: 25983241
http://dx.doi.org/10.1016/j.ejso.2015.04.010

Identifying the most appropriate age threshold for TNM stage grouping of well-differentiated thyroid cancer.
Eur J Surg Oncol, 41(8):1028-32.
J. Hendrickson-Rebizant, H. Sigvaldason, R. W. Nason and K. A. Pathak. 2015.
OBJECTIVE: Age is integrated in most risk stratification systems for well-differentiated thyroid cancer (WDTC). The most appropriate age threshold for stage grouping of WDTC is debatable. The objective of this study was to evaluate the best age threshold for stage grouping by comparing multivariable models designed to evaluate the independent impact of various prognostic factors, including age based stage grouping, on the disease specific

survival (DSS) of our population-based cohort. METHODS: Data from population-based thyroid cancer cohort of 2125 consecutive WDTC, diagnosed during 1970-2010, with a median follow-up of 11.5 years, was used to calculate DSS using the Kaplan Meier method. Multivariable analysis with Cox proportional hazard model was used to assess independent impact of different prognostic factors on DSS. The Akaike information criterion (AIC), a measure of statistical model fit, was used to identify the most appropriate age threshold model. Delta AIC, Akaike weight, and evidence ratios were calculated to compare the relative strength of different models. RESULTS: The mean age of the patients was 47.3 years. DSS of the cohort was 95.6% and 92.8% at 10 and 20 years respectively. A threshold of 55 years, with the lowest AIC, was identified as the best model. Akaike weight indicated an 85% chance that this age threshold is the best among the compared models, and is 16.8 times more likely to be the best model as compared to a threshold of 45 years. CONCLUSION: The age threshold of 55 years was found to be the best for TNM stage grouping.
PubMed-ID: 25986855
http://dx.doi.org/10.1016/j.ejso.2015.04.014

Papillary thyroid carcinoma: prognostic significance of cancer presentation.
Am J Surg, 210(2):298-301.
H. Choi, K. Kasaian, A. Melck, K. Ong, S. J. Jones, A. White and S. M. Wiseman. 2015.
BACKGROUND: The objective of this study was to evaluate whether the clinical presentation of papillary thyroid carcinoma (PTC) has prognostic significance. METHODS: Retrospective evaluation was carried out of sequential, primary presentation, >1 cm diameter, PTC cases treated at a single center. PTC cases were grouped into 3 groups: (1) incidental detection by imaging, (2) incidental detection by physical examination, and (3) detection because of complaints related to a thyroid mass. The MACIS (metastasis, age, completeness of resection, invasion, and size) system was used to determine cancer prognosis for each group. RESULTS: Of the 168 PTC cases, 28 patients (17%) were in group 1, 60 patients (36%) were in group 2, and 80 patients (47%) were in group 3. Overall, 53% of differentiated thyroid cancers were detected incidentally. The difference in the proportion of patients in each MACIS score groups among the 3 clinical presentation categories, and for each component of the MACIS score, was not statistically significant (P = .36). CONCLUSION: The manner in which PTC initially clinically presents has no relationship with cancer prognosis.
PubMed-ID: 25997714
http://dx.doi.org/10.1016/j.amjsurg.2014.12.047

Robotic Thyroidectomy: Is it a Futile Surgical Approach?
Surg Laparosc Endosc Percutan Tech, 25(3):268.
G. B. Levi Sandri, M. Coluzzi, D. Caporilli, A. de Luca and F. Guerra. 2015.
PubMed-ID: 26018051
http://dx.doi.org/10.1097/SLE.0000000000000160

[Learning curve for transaxillary endoscopic thyroidectomy].
Chirurg, 86(6):606.
H. Dralle and P. N. Thanh. 2015.
PubMed-ID: 26041149
http://dx.doi.org/10.1007/s00104-015-0019-7

Vitamin D level is not a predictor of hypocalcemia after total thyroidectomy.
Langenbecks Arch Surg, 400(5):617-22.
G. H. Lee, Y. H. Ku, H. I. Kim, M. C. Lee and M. J. Kim. 2015.
PURPOSE: As the incidence of thyroid cancer has increased, hypocalcemia, a common complication of thyroid surgery, has become a serious problem. However, no definite predictor of postoperative hypocalcemia is known. In this study, our purpose was to investigate the potential role of vitamin D as a predictor of postoperative hypocalcemia. METHODS: A prospective observational study was performed on patients who underwent total thyroidectomy for thyroid cancer performed by a single experienced surgeon between October 2013 and September 2014. MEASUREMENTS: Their serum 25-OH vitamin D levels were measured preoperatively. On the day after surgery, serum calcium and intact parathyroid hormone levels were measured, and symptoms of hypocalcemia were recorded. RESULTS: Of the 134 patients, laboratory and symptomatic hypocalcemia developed in 52 patients (39 %) and 25 patients (19 %), on the day after surgery. The preoperative vitamin D level was 16.5 +/- 9.2 ng/mL, and this value did not differ according to laboratory or symptomatic hypocalcemia (p = 0.94). The incidence of laboratory or symptomatic hypocalcemia did not differ according to vitamin D deficiency. Only incidental parathyroidectomy was associated with symptomatic hypocalcemia (p = 0.03). CONCLUSIONS: Vitamin D level is not a predictor of hypocalcemia after total thyroidectomy for thyroid cancer.

Thus, routine preoperative screening for vitamin D is not recommended.
PubMed-ID: 26050997
http://dx.doi.org/10.1007/s00423-015-1311-1

Association between single nucleotide polymorphisms of upstream transcription factor 1 (USF1) and susceptibility to papillary thyroid cancer.
Clin Endocrinol (Oxf),
Q. Yuan, Q. Bu, G. Li, J. Zhang, T. Cui, R. Zhu and D. Mu. 2015.
BACKGROUND: Thyroid cancer, predominantly by papillary thyroid cancer (PTC), is a malignant tumour of endocrine system with increasing incidence rate worldwide. Upstream transcription factor 1 (USF1) regulates a variety of biological processes by transactivation of functional genes. In this study, we investigated the association between USF1 polymorphisms and PTC risk. MATERIAL & METHODS: A total of 334 patients with PTC, 186 patients with benign nodules (BN) and 668 healthy controls were enrolled in our study. Tag-SNPs were identified in Chinese Han in Beijing (CHB) from International HapMap Project Databases. Genomic DNAs were extracted by TaqMan Blood DNA kits. SNPs of USF1 were genotyped by TaqMan SNPs genotyping assay. Odds ratios (OR) and corresponding 95% confidence interval (CI) were used to assess the association between USF1 genetic variants and PTC risk. The statistical analyses were carried out with spss 13.0 software. RESULTS: Five tag-SNPs were retrieved to capture all the genetic variants of USF1. Among the five tag-SNPs, genetic variants in rs2516838, rs3737787 and rs2516839 have significant association with PTC risk. The rs2516838 polymorphisms dominant model (CG+GG vs CC: OR = 0.71; 95% CI: 0.52-0.97; P = 0.033) and allelic model (C vs G: OR = 0.031; 95% CI: 0.56-0.97; P = 0.031) indicated it may act as a protective factor against PTC. On the contrary, the results of rs3737787 polymorphisms: dominant model (CT+TT vs CC: OR = 1.55; 95%CI: 1.09-2.02; P = 0.001) and allelic model (C vs T: OR = 1.35; 95%CI: 1.10-1.64; P = 0.003), as well as the results of rs2516839 polymorphisms: dominant model (GA+AA vs GG: OR = 1.77; 95%CI: 1.31-2.38; P < 0.001) and allelic model (G vs A: OR = 1.36; 95%CI: 1.13-1.63; P = 0.014), revealed that they may act as risk factors for PTC. CONCLUSION: In this study, we found the SNPs of rs2516838 (mutant G alleles vs wild C alleles), rs3737787 (mutant T alleles vs wild C alleles) and rs2516839 (mutant A alleles vs wild G alleles) were significantly associated with PTC risk. Further large-scale studies with different ethnicities are still needed to validate our findings and explore the underlying mechanism of USF1 in PTC development.
PubMed-ID: 26052935
http://dx.doi.org/10.1111/cen.12832

American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making.
Thyroid, 25(7):760-8.
R. L. Ferris, Z. Baloch, V. Bernet, A. Chen, T. J. Fahey, 3rd, I. Ganly, S. P. Hodak, E. Kebebew, K. N. Patel, A. Shaha, D. L. Steward, R. P. Tufano, S. M. Wiseman and S. E. Carty. 2015.
BACKGROUND: Recent advances in research on thyroid carcinogenesis have yielded applications of diagnostic molecular biomarkers and profiling panels in the management of thyroid nodules. The specific utility of these novel, clinically available molecular tests is becoming widely appreciated, especially in perioperative decision making by the surgeon regarding the need for surgery and the extent of initial resection. METHODS: A task force was convened by the Surgical Affairs Committee of the American Thyroid Association and was charged with writing this article. RESULTS/CONCLUSIONS: This review covers the clinical scenarios by cytologic category for which the thyroid surgeon may find molecular profiling results useful, particularly for cases with indeterminate fine-needle aspiration cytology. Distinct strengths of each ancillary test are highlighted to convey the current status of this evolving field, which has already demonstrated the potential to streamline decision making and reduce unnecessary surgery, with the accompanying benefits. However, the performance of any diagnostic test, that is, its positive predictive value and negative predictive value, are exquisitely influenced by the prevalence of cancer in that cytologic category, which is known to vary widely at different medical centers. Thus, it is crucial for the clinician to know the prevalence of malignancy within each indeterminate cytologic category, at one's own institution. Without this information, the performance of the diagnostic tests discussed below may vary substantially.
PubMed-ID: 26058403
http://dx.doi.org/10.1089/thy.2014.0502

Is Preoperative Vitamin D Deficiency a Risk Factor for Postoperative Symptomatic Hypocalcemia in Thyroid Cancer Patients Undergoing Total Thyroidectomy Plus Central Compartment Neck Dissection?
Thyroid, 25(8):911-8.
W. W. Kim, S. H. Chung, E. J. Ban, C. R. Lee, S. W. Kang, J. J. Jeong, K. H. Nam, W. Y. Chung and C. S. Park.

2015.
BACKGROUND: Although some studies have reported that preoperative vitamin D deficiency (VDD) is a risk factor for hypocalcemia after total thyroidectomy (TT) in patients with nontoxic multinodular goiter or Graves' disease, the association between VDD and postoperative hypocalcemia in thyroid cancer patients undergoing TT plus central compartment neck dissection (CCND) remains unclear. This study evaluated whether preoperative VDD was associated with postoperative symptomatic hypocalcemia. MATERIALS AND METHODS: Data were collected prospectively between September 2012 and May 2013. A total of 267 consecutive thyroid cancer patients who underwent TT with CCND were analyzed. Patients were divided into two groups-VDD or non-VDD-by preoperative vitamin D level of <10 or >/=10 ng/mL. Symptomatic hypocalcemia was defined as serum calcium <8.2 mg/dL and symptoms or signs of hypocalcemia. The rates of postoperative symptomatic hypocalcemia and clinicopathological features were compared between the two patient groups. RESULTS: The rate of postoperative symptomatic hypocalcemia was higher in the VDD group than in the non-VDD group (43.8% vs. 30.4%, p=0.043). By logistic regression analysis, predictive factors for postoperative symptomatic hypocalcemia included a preoperative vitamin D level of <10 ng/mL (p=0.007; odds ratio=3.00). In patients who had postoperative intact parathyroid hormone (iPTH) levels <15 pg/mL, symptomatic hypocalcemia was more common in the VDD group than in the non-VDD group (77.5% vs. 53.2%, p=0.008). The findings show that a preoperative vitamin D threshold level of >20 ng/mL reduced the risk of symptomatic hypocalcemia by 72% when compared with patients with VDD (p=0.003). CONCLUSION: VDD is significantly associated with postoperative symptomatic hypocalcemia in thyroid cancer patients undergoing TT plus CCND. VDD was predictive for symptomatic hypocalcemia when patients had postoperative serum iPTH levels <15 pg/mL. Thus, preoperative supplementation with oral vitamin D should be considered to minimize postoperative symptomatic hypocalcemia.
PubMed-ID: 26061175
http://dx.doi.org/10.1089/thy.2014.0522

Not all DTC patients with N positive disease deserve the attribution "high risk". Contribution of the MSDS trial.
J Surg Oncol, 112(1):9-14.
A. Vrachimis, C. Wenning, J. Gerss, H. Dralle, M. Vaez Tabassi, O. Schober and B. Riemann. 2015.
BACKGROUND AND OBJECTIVES: To investigate if patients with thyroid carcinoma having N1a disease are at the same risk with N1b using the collective of the well-defined European prospective Multicentre Study Differentiated Thyroid Cancer (MSDS). METHODS: Overall (OS) and event free survival (EFS) were calculated. Cox multivariable regression analysis was performed in order to calculate Hazard ratios (HR). RESULTS: EFS was significantly decreased only in patients with N1b metastasis as compared to N0 patients and became worse when N1a was concomitantly affected. A superior survival in favor of N1a patients as compared to N1b patients with regard to EFS was also observed. The patients having N1a disease showed no differences in the EFS as compared to N0. OS did not differ significantly in any of the groups. There was an increased HR for events with regards to histology, T-stage, tumor size, UICC stage and cervical lymph node metastasis. Tumor size showed a significantly increased risk for OS. CONCLUSIONS: Patients with pT3b and pT4a tumors with N1b are of higher risk for relapse, albeit not affecting overall survival. Patients with N1a are of no higher risk. The risk stratification of these patients may be adapted accordingly. J. Surg. Oncol. 2015 111:9-14. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26074402
http://dx.doi.org/10.1002/jso.23948

Clinicopathological Significance of Minimal Extrathyroid Extension in Solitary Papillary Thyroid Carcinomas.
Ann Surg Oncol,
C. G. Woo, C. O. Sung, Y. M. Choi, W. G. Kim, T. Y. Kim, Y. K. Shong, W. B. Kim, S. J. Hong and D. E. Song. 2015.
BACKGROUND: The definitive diagnosis of minimal extrathyroid extension (ETE) is subjective because a well-defined true capsule is absent in the thyroid gland. We subclassified the extent of minimal ETE and investigated the clinicopathological significance of the presence of minimal ETE in patients with solitary papillary thyroid carcinomas (PTCs) and solitary papillary thyroid microcarcinomas (PTMCs). METHODS: A series of 546 patients with solitary PTCs, including 144 patients with solitary PTMCs, were retrospectively analyzed. Whether the presence of minimal ETE had an effect on recurrence-free survival (RFS) along with other clinicopathological parameters was investigated. RESULTS: The only independent prognostic factor found to be associated with recurrence was the presence of LN metastasis in solitary PTC (p = 0.002) but not in solitary PTMC groups (p = 0.073). The presence of minimal ETE had no effect on RFS in both solitary PTC (p = 0.053) and solitary PTMC (p = 0.816). CONCLUSIONS: The presence of minimal ETE has no significant influence on RFS in solitary PTC

and PTMC. There is a risk of overrepresenting the T3 category in solitary PTC and PTMC patients with minimal ETE.
PubMed-ID: 26077913
http://dx.doi.org/10.1245/s10434-015-4659-0

Therapy of Endocrine Disease: Central Neck Dissection: A Step Forward in the Treatment of Papillary Thyroid Cancer.
Eur J Endocrinol,
A. Sitges-Serra, L. Lorente, G. Mateu and J. Sancho. 2015.
Since its introduction in the 70's and 80's, CND for papillary cancer is here to stay. Compartment VI should always be explored during surgery for PTC in search for obvious lymph node metastasis. These can be easily spotted by an experienced surgeon or, eventually, by frozen section. No doubt, obvious nodal disease in the delphian, paratracheal and subithsmic areas should be dissected in a comprehensive manner (therapeutic central neck dissection), avoiding selective removal of suspicious nodes. Available evidence for routine prophylactic CND is not completely satisfactory. Our group bias, however, is that it reduces, even eliminates, the need for redo surgery in the central neck, better defines the extent (and stage) of the disease and adds a further argument against routine radioiodine ablation. Thus, PTC is becoming more and more a surgical disease that can be cured by optimized surgery alone in the majority of cases. Prophylactic CND, however, involves a higher risk for the parathyroid function and should be skilfully performed, preferably only on the same side as the primary tumour and preserving the cervical portion of the thymus.
PubMed-ID: 26088823
http://dx.doi.org/10.1530/EJE-15-0481

[Vocal cord paralysis after thyroid surgery : Current medicolegal aspects of intraoperative neuromonitoring].
Chirurg, 86(7):698-706.
H. Dralle, R. Schneider, K. Lorenz, N. T. Phuong, C. Sekulla and A. Machens. 2015.
Intraoperative neuromonitoring (IONM) has been commercially available for approximately 15 years and is highly predictive in thyroid gland surgery concerning either postoperative vocal fold mobility in the case of an intact signal for muscle action electromyogram (EMG, > 99 % right negative) or vocal fold dysfunction in the case of loss of signal (> 70 % right positive). The use of IONM improves the intraoperative identification of recurrent laryngeal nerve function and due to the high predictive value with respect to the expected vocal cord function the result of IONM has to be integrated into the surgical concept of thyroidectomy. Unilateral loss of function of the recurrent laryngeal nerve cannot be completely avoided despite correct application of IONM; however, bilateral vocal fold palsy can be safely avoided when contralateral surgery is cancelled after a loss of signal occurs during resection of the first side in planned bilateral surgery (alternative strategy). Patients have to be informed preoperatively about the limitations of IONM and potential strategy changes during planned bilateral surgery. Surgeons should apply IONM according to the published current recommendations and by selecting a risk-oriented intraoperative strategy in the case of loss of signal from the recurrent laryngeal nerve.
PubMed-ID: 26099288
http://dx.doi.org/10.1007/s00104-015-0033-9

Identification of occult tumors by whole-specimen mapping in solitary papillary thyroid carcinoma.
Endocr Relat Cancer, 22(4):679-86.
S. Y. Park, Y. S. Jung, C. H. Ryu, C. Y. Lee, Y. J. Lee, E. K. Lee, S. K. Kim, T. S. Kim, T. H. Kim, J. Jang, D. Park, S. M. Dong, J. G. Kang, J. S. Lee and J. Ryu. 2015.
We undertook this study to estimate an accurate incidence and spread patterns of occult papillary thyroid carcinoma (PTC) in patients with a preoperative diagnosis of solitary PTC by using whole-specimen mapping of all specimens after a total thyroidectomy. Enrolled prospectively in this whole-thyroid mapping study are 82 consecutive patients who underwent a total thyroidectomy under a preoperative diagnosis of solitary PTC. All thyroidectomy specimens were serially sectioned in 2 mm thickness and whole-thyroid mapping was carried out for additional foci of occult PTC. The frequencies of occult lesions detected in the whole and contralateral lobe were determined, and clinicopathologic factors associated with multifocality were assessed. Whole-thyroid mapping revealed 66 occult PTC lesions missed by preoperative ultrasound in 37 (45.1%) of the 82 patients. The great majority (92.5%) of the occult PTC was smaller than 3 mm in size and 25 patients (30.5%) had contralateral lesions. We found that the male sex was an independent predictor of multifocality (odds ratio (OR), 3.00; 95% CI, 1.11-8.14), adjusting for preoperative findings. Analysis with pathologic parameters showed that the male sex (OR, 5.03; 95% CI, 1.68-15.08) and extrathyroidal extensions (OR, 3.03; 95% CI, 1.03-8.95) were associated with multifocal PTC. However, none of the clinicopathologic factors evaluated predicted contralateral

PTC. Our study demonstrates the diagnostic limitations of ultrasound for the detection of multifocal PTC and the need to consider the possibility of occult lesions in the management of solitary PTC, especially in male patients.
PubMed-ID: 26113610
http://dx.doi.org/10.1530/ERC-15-0152

Comparison of differentiated thyroid cancer in children and adolescents (</=20 years) with young adults.
Clin Endocrinol (Oxf),
A. S. Alzahrani, D. Alkhafaji, M. Tuli, H. Al-Hindi and B. B. Sadiq. 2015.
CONTEXT: Age is a major prognostic factor in differentiated thyroid cancer (DTC). It is not clear if paediatric DTC has a different histopathological profile and outcome than DTC in adult patients <45 years of age. OBJECTIVE: To assess whether DTC in children and adolescents differs from young age group by comparing paediatric DTC (age </= 20) with DTC in patients >20 to <45 years of age. PATIENTS AND METHODS: We studied all cases of paediatric DTC seen during the period 1998-2011. We compared this group with a large sample of 213 consecutive adult patients in the age group >20 to <45 years seen during the period 1998-1999 in terms of their pathological features, extent of the disease and long-term outcome. Both groups were managed by the same team at a single institution. RESULTS: A total of 310 DTC were studied including 97 paediatric patients [median age 17 years (range, 8-20)] and 213 young adult patients [median age 33 years (range, 20.5-44.9)]. There was no difference in gender distribution, tumour subtypes, size and tumour multifocality, but there was a significantly higher rate of extrathyroidal extension [40/75 (53.3%) vs 81/213 (38.0%), P = 0.03], lymph node [57/73 (78%) vs 102/183 (55.7%), P < 0.0001] and distant metastases [16/97 (16.5%) vs 8/213 (3.8%), P < 0.0001] in the paediatric than the adult groups. Kaplan-Meier analysis showed a higher risk of persistent/recurrent disease in the paediatric group than adults (log-rank test 0.03). However, there was no mortality secondary to DTC in both groups. CONCLUSION: Paediatric DTC is distinct from DTC in the young adults (age >20 to <45 years). It is characterized by a higher rate of extrathyroidal extension, lymph node and distant metastases and a higher risk of persistent/recurrent DTC.
PubMed-ID: 26118454
http://dx.doi.org/10.1111/cen.12845

Low iodine diet in differentiated thyroid cancer: a review.
Clin Endocrinol (Oxf),
J. H. Li, Z. H. He, V. Bansal and J. V. Hennessey. 2015.
Radioactive iodine (RAI) ablation is a beneficial, adjuvant therapy for the management of differentiated thyroid cancer (DTC) after thyroidectomy. The goal of RAI is to destroy remnant thyroid and microscopic cancerous tissue. Radioactive iodine uptake is enhanced by elevating TSH levels and initiating a low iodine diet (LID) prior to ablation. An ideal LID should preferably not exceed 50 mcg/day of dietary iodine for 1-2 weeks, although the duration may be shortened to a week with a structured patient education programme. A pre-ablation spot urinary iodine concentration (UIC) of <100 mcg/l and/or a urinary iodine to creatinine ratio (UICR) of <100 mcg/gCr would support an adequate LID preparation. Hyponatraemia, most likely due to iatrogenic hypothyroidism, is a potential side effect associated with LID and occurs during and a few days after the LID. Although the overall incidence of hyponatraemia is low, patients at high risk (older age, female sex, use of thiazide diuretics) may benefit from serum sodium monitoring. The existing evidence on the impact of LID on RAI ablation has been largely inconsistent due to retrospective study designs and the lack of an objective measurement of urinary iodine levels. Future large prospective randomized control trials are needed to elucidate and confirm the crucial role of LID in achieving successful RAI ablation and greater disease-free survival in DTC.
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http://dx.doi.org/10.1111/cen.12846

Microscopic Positive Margins in Differentiated Thyroid Cancer Is Not an Independent Predictor of Local Failure.
Thyroid, 25(9):993-8.
L. Y. Wang, R. Ghossein, F. L. Palmer, I. J. Nixon, R. M. Tuttle, A. R. Shaha, J. P. Shah, S. G. Patel and I. Ganly. 2015.
BACKGROUND: In contrast to other head and neck cancers, the impact of histological thyroid specimen margin status in differentiated thyroid cancer (DTC) is not well understood. The aim of this study was to investigate the prognostic value of margin status on local recurrence in DTC. METHOD: The records of 3664 consecutive patients treated surgically for DTC between 1986 and 2010 were identified from an institutional database. Patients with less than total thyroidectomy, unresectable or gross residual disease, or M1 disease at presentation and those with unknown pathological margin status were excluded from analysis. In total, 2616 patients were included in the study; 2348 patients (90%) had negative margins and 268 patients (10%) had

positive margins. Microscopic positive margin status was defined as tumor present at the specimen's edge on pathological analysis. Patient, tumor, and treatment characteristics were compared by Pearson's chi-squared test. Local recurrence free survival (LRFS) was calculated for each group using the Kaplan Meier method. RESULTS: The median age of the cohort was 48 years (range 7-91 years) and the median follow-up was 50 months (range 1-330 months). Age, sex, and histology types were similar between groups. As expected, patients who had positive margins were more likely to have larger tumors (p<0.001), extrathyroidal extension (ETE) (p<0.001), multicentric disease (p<0.001), or nodal disease (p<0.001) and were more likely to receive adjuvant radioactive iodine therapy (p<0.001) as well as external beam radiotherapy (p<0.001). The LRFS at 5 years for patients with positive margins status was slightly poorer compared with patients with negative margins (98.9% vs. 99.5%, p=0.018). Twelve patients developed local recurrence-8/2348 (0.34%) patients with negative margins and 4/263 (1.52%) patients with positive margins. Univariate predictors of LRFS were sex (p=0.006), gross ETE (<0.001), and positive margins (p=0.018). However, when controlling for presence of gross ETE on multivariate analysis, microscopic positive margin status was not an independent predictor of LRFS (p=0.193). CONCLUSION: Patients with resectable, M0 disease that undergo total thyroidectomy have an excellent five year LRFS of 99.4%. Microscopic positive margin status was not a significant predictor for local failure after adjusting for ETE or pathological tumor (pT) stage.
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Implementing the Modified 2009 American Thyroid Association Risk Stratification System in Thyroid Cancer Patients with Low and Intermediate Risk of Recurrence.
Thyroid,
F. Pitoia, F. Jerkovich, C. Urciuoli, A. Schmidt, E. Abelleira, F. Bueno, G. Cross and R. M. Tuttle. 2015.
OBJECTIVE: The primary purpose of this study was to validate the proposed modified 2009 American Thyroid Association Risk Stratification System (M-2009-RSS) in patients with thyroid cancer and to compare the findings with those of the 2009 ATA Risk of Recurrence (2009 ATA-RR) and the Ongoing Risk of recurrence system. The secondary purpose was to assess which risk stratification system had the best predictive value to foresee the probability of structural incomplete response or the no evidence of disease (NED) status at the end of follow-up. SUBJECTS AND METHODS: This retrospective review included 149 patients with differentiated thyroid cancer who had low and intermediate 2009 ATA-RR and were treated at a single experienced center and followed-up for a median of 6 years (range 3-12 years). Each patient was risk stratified using both the 2009 ATA-RR and the M-2009-RSS. The primary endpoints were 1) the best response to initial therapy defined as either excellent response, biochemical or structural incomplete response, or indeterminate response; 2) clinical status at final follow-up defined as either NED, biochemical incomplete response, structural incomplete response, indeterminate response, or recurrence (biochemical or structural disease identified after a period of NED), and 3) ongoing RR defined as low or high risk according several outcomes after initial treatment. RESULTS: Mean age of included patients was 45.3+/-13 years. Both the ATA 2009-RR and the M-2009-RSS provided clinically meaningful graded estimates with regard to the status of NED at the end of follow-up in low-risk patients (84% for 2009 ATA-RR and 74% for M-2009-RSS) or the likelihood of having persistent structural disease (0% for 2009 ATA RR and 3.6% for the M-2009-RSS). When patients were classified as low risk, the positive predictive value (PPV) and negative predictive value (NPV) to predict structural disease was 0% and 88.7% for the 2009 ATA-RR, 3.6% and 86.5% for the M-2009-RSS, and 1.6% and 68.2% for the ongoing RR (p=0.022 and 0.055 of chi-square test for PPV and NPV, respectively). CONCLUSIONS: Despite expanding the definition of low risk to include small-volume lymph node metastases, minor extrathyroidal extension, and minimally invasive follicular thyroid cancer, the M-2009-RSS predicts clinical outcomes (structural incomplete response and NED at the end of follow-up) that are very similar to the previously validated 2009 ATA RR classification system.
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Evaluating Positron Emission Tomography Use in Differentiated Thyroid Cancer.
Thyroid, 25(9):1026-32.
J. L. Wiebel, N. H. Esfandiari, M. Papaleontiou, F. P. Worden and M. R. Haymart. 2015.
BACKGROUND: Using the Surveillance, Epidemiology, and End Results-Medicare database, a substantial increase was found in the use of positron emission tomography (PET) scans after 2004 in differentiated thyroid cancer (DTC) patients. The reason for the increased utilization of the PET scan was not clear based on available the data. Therefore, the indications for and outcomes of PET scans performed at an academic institution were evaluated. METHODS: A retrospective cohort study was performed of DTC patients who underwent surgery at the University of Michigan Health System from 2006 to 2011. After identifying patients who underwent a PET scan, indications, rate of positive PET scans, and impact on management were evaluated. For positive scans,

the location of disease was characterized, and presence of disease on other imaging was determined. RESULTS: Of the 585 patients in the cohort, 111 (19%) patients had 200 PET scans performed for evaluation of DTC. Indications for PET scan included: elevated thyroglobulin and negative radioiodine scan in 52 scans (26.0%), thyroglobulin antibodies in 13 scans (6.5%), rising thyroglobulin in 18 scans (9.0%), evaluation of abnormality on other imaging in 22 scans (11.0%), evaluation of extent of disease in 33 scans (16.5%), follow-up of previous scan in 57 scans (28.5%), other indications in two scans (1.0%), and unclear indications in three scans (1.5%). The PET scan was positive in 124 studies (62.0%); positivity was identified in the thyroid bed on 25 scans, cervical or mediastinal lymph nodes on 105 scans, lung on 28 scans, bone on four scans, and other areas on 14 scans. Therapy following PET scan was surgery in 66 cases (33.0%), chemotherapy or radiation in 23 cases (11.5%), observation in 110 cases (55.0%), and palliative care in one case (0.5%). Disease was identifiable on other imaging in 66% of cases. PET scan results changed management in 59 cases (29.5%). CONCLUSIONS: In this academic medical center, the PET scan was utilized in 19% of patients. Indications for the PET scan included conventional indications, such as elevated thyroglobulin with noniodine avid disease, and more controversial uses, such as evaluation of extent of disease or abnormalities on other imaging tests. PET scan results changed management in about 30% of cases.
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Postoperative biochemical remission of serum calcitonin is the best predictive factor for recurrence-free survival of medullary thyroid cancer: a large-scale retrospective analysis over 30 years.
Clin Endocrinol (Oxf),
K. Y. Jung, S. M. Kim, W. S. Yoo, B. W. Kim, Y. S. Lee, K. W. Kim, K. E. Lee, J. J. Jeong, K. H. Nam, S. H. Lee, J. H. Hah, W. Y. Chung, K. H. Yi, D. J. Park, Y. K. Youn, M. W. Sung, B. Y. Cho, C. S. Park, Y. J. Park and H. S. Chang. 2015.
CONTEXT: The increase in thyroid screening in the general population may lead to earlier detection of medullary thyroid carcinoma (MTC). OBJECTIVE: We aimed to evaluate secular trends in clinicopathological characteristics and long-term prognosis of MTC and its prognostic factors. DESIGN: This was a retrospective analysis from 1982 to 2012. PATIENTS: Three hundred and thirty-one patients with MTC were included and grouped based on the year of diagnosis (1982-2000, 2001-2005, 2006-2010 and 2011-2012). MEASUREMENTS: These included recurrence and mortality as well as biochemical remission (BCR) of serum calcitonin. RESULTS: Mean tumour size (from 2.5 cm to 1.7 cm, $P < 0.001$) and percentage of extrathyroidal extension (from 52.0% to 26.0%, $P = 0.026$) decreased. The percentage of patients achieving BCR within six postoperative months (po-BCR) increased with time (from 39.6% to 76.1%, $P < 0.001$). The 5-year overall recurrence rate significantly decreased in 2006-2012 compared to 1982-2005 (10% vs 18%, respectively, $P = 0.031$), although the 5-year survival rate did not improve (92% vs 92%, $P = 0.929$). Failure to achieve po-BCR was the strongest predictive factor associated with recurrence (hazard ratio [HR] = 58.04, 95% CI 7.14-472.11; $P < 0.001$). Male gender (HR = 3.18, 95% CI 1.18-8.56; $P = 0.022$), tumour size >2 cm (HR = 18.33, 95% CI 2.35-143.06; $P = 0.006$) and distant metastasis (HR = 4.00, 95% CI 1.31-12.21; $P = 0.015$) were significant prognostic factors for mortality. CONCLUSIONS: Clinicopathological characteristics and recurrence of MTC improved with time. Po-BCR was the best predictive factor for recurrence-free survival.
PubMed-ID: 26175307
http://dx.doi.org/10.1111/cen.12852

BRAF (V600E) mutation in isthmic malignant thyroid nodules.
Clin Endocrinol (Oxf),
A. Campenni, L. Giovanella, A. Alibrandi, M. Siracusa, R. M. Ruggeri and S. Baldari. 2015.
PubMed-ID: 26190162
http://dx.doi.org/10.1111/cen.12858

Clinicopathological features and prognosis of familial papillary thyroid carcinoma - a large-scale, matched, case-control study.
Clin Endocrinol (Oxf),
J. Cao, C. Chen, C. Chen, Q. L. Wang and M. H. Ge. 2015.
OBJECTIVE: It remains controversial whether or not the aggressiveness of familial nonmedullary thyroid cancer (FNMTC) differs from sporadic carcinoma. The aim of this study was to determine the clinicopathological features and prognosis of FNMTC. DESIGN: A matched-case comparative study. METHODS: Three hundred and seventy-two patients with familial papillary thyroid carcinoma (FPTC) were enrolled as the study group, and another 372 patients with sporadic PTC were enrolled as controls and matched for gender, age, tumour/node/metastasis (TNM) staging and approximate duration of follow-up. We compared the differences in

the clinicopathological features and prognosis between the subgroups. RESULTS: Compared with sporadic PTC, patients with FPTC were more likely to present tumour multicentricity, bilateral growth and a concomitant nodular goitre (P < 0.05). In papillary thyroid microcarcinoma (PTMC), a higher recurrence rate was noted in patients with a family history of PTC, and this remained independently predictive on multivariate analysis. The patients with FPTC in the second generation showed an earlier age of onset, more frequent Hashimoto's thyroiditis and a higher recurrence rate than the first generation, while the first-generation offspring of patients had a higher incidence of nodular goitre than the second generation. CONCLUSIONS: The presence of familial history in PTC indicates an increase in biological aggressiveness, and patients in the second generation may exhibit the 'genetic anticipation' phenomenon. At present, the available data are not sufficient to support a more aggressive approach for FPTC. However, a family history of PTC is an independent risk factor for recurrence in patients with PTMC.
PubMed-ID: 26191611
http://dx.doi.org/10.1111/cen.12859

Reassessing the NTCTCS Staging Systems for Differentiated Thyroid Cancer, Including Age at Diagnosis.
Thyroid,
D. S. McLeod, J. Jonklaas, J. D. Brierley, K. B. Ain, D. S. Cooper, H. G. Fein, B. R. Haugen, P. W. Ladenson, J. Magner, D. S. Ross, M. C. Skarulis, D. L. Steward, M. Xing, D. R. Litofsky, H. R. Maxon and S. I. Sherman. 2015.
BACKGROUND: Thyroid cancer is unique for having age as a staging variable. Recently, the commonly used age cut-point of 45 years has been questioned. OBJECTIVE: This study assessed alternate staging systems on the outcome of overall survival, and compared these with current National Thyroid Cancer Treatment Cooperative Study (NTCTCS) staging systems for papillary and follicular thyroid cancer. METHODS: A total of 4721 patients with differentiated thyroid cancer were assessed. Five potential alternate staging systems were generated at age cut-points in five-year increments from 35 to 70 years, and tested for model discrimination (Harrell's C-statistic) and calibration (R2). The best five models for papillary and follicular cancer were further tested with bootstrap resampling and significance testing for discrimination. RESULTS: The best five alternate papillary cancer systems had age cut-points of 45-50 years, with the highest scoring model using 50 years. No significant difference in C-statistic was found between the best alternate and current NTCTCS systems (p = 0.200). The best five alternate follicular cancer systems had age cut-points of 50-55 years, with the highest scoring model using 50 years. All five best alternate staging systems performed better compared with the current system (p = 0.003-0.035). There was no significant difference in discrimination between the best alternate system (cut-point age 50 years) and the best system of cut-point age 45 years (p = 0.197). CONCLUSIONS: No alternate papillary cancer systems assessed were significantly better than the current system. New alternate staging systems for follicular cancer appear to be better than the current NTCTCS system, although they require external validation.
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Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer.
Ann Surg Oncol,
I. J. Nixon, D. Kuk, V. Wreesmann, L. Morris, F. L. Palmer, I. Ganly, S. G. Patel, B. Singh, R. M. Tuttle, A. R. Shaha, M. Gonen and J. P. Shah. 2015.
BACKGROUND: Age 45 years is used as a cutoff in the staging of well-differentiated thyroid cancer (WDTC) as it represents the median age of most datasets. The aim of this study was to determine a statistically optimized age threshold using a large dataset of patients treated at a comprehensive cancer center. METHODS: Overall, 1807 patients with a median follow-up of 109 months were included in the study. Recursive partitioning was used to determine which American Joint Committee on Cancer (AJCC) variables were most predictive of disease-specific death, and whether a different cutoff for age would be found. From the resulting tree, a new age cutoff was picked and patients were restaged using this new cutoff. RESULTS: The 10-year disease-specific survival (DSS) by Union for International Cancer Control (AJCC/UICC) stage was 99.6, 100, 96, and 81 % for stages I-IV, respectively. Using recursive partitioning, the presence of distant metastasis was the most powerful predictor of DSS. For M0 patients, age was the next most powerful predictor, with a cutoff of 56 years. For M1 patients, a cutoff at 54 years was most predictive. Having reviewed the analysis, age 55 years was selected as a more robust age cutoff than 45 years. The 10-year DSS by new stage (using age 55 years as the cutoff) was 99.2, 98, 100, and 74 % for stages I-IV, respectively. CONCLUSION: A change in age cutoff in the AJCC/UICC staging for WDTC to 55 years would improve the accuracy of the system and appropriately prevent low-risk patients being overstaged and overtreated.

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Association Between Obesity and BRAFV600E Mutation Status in Patients with Papillary Thyroid Cancer.
Ann Surg Oncol,
J. Lee, C. R. Lee, C. R. Ku, S. W. Kang, J. J. Jeong, D. Y. Shin, K. H. Nam, S. G. Jung, E. J. Lee, W. Y. Chung and Y. S. Jo. 2015.
BACKGROUND: The prevalence of papillary thyroid cancer (PTC) is thought to be related to obesity, which affects the prognosis for PTC patients. However, the mechanisms implicated in the relationship between obesity and PTC is a matter for debate. In this study, we aimed to gain insight into the relationship between obesity and the clinicopathological features of PTC, including the BRAFV600E mutation. METHODS: The medical records of 1121 PTC patients were reviewed and the relationships between anthropometric factors, biochemical parameters, and clinicopathological parameters, including BRAFV600E mutation status, were analyzed. RESULTS: Body mass index (BMI) showed a strong association with advanced TNM stage ($p < 0.001$) and BRAFV600E mutation status ($p = 0.008$). We also found that BRAFV600E (+) patients had a higher body weight ($p = 0.024$) and a higher BMI ($p = 0.003$) than patients with BRAFV600E (-) PTC. In addition, BRAFV600E (+) PTC patients had a significantly higher incidence of extrathyroidal extension ($p = 0.025$) and more advanced T, N, TNM stage ($p < 0.001$) than BRAFV600E (-) PTC patients. Consistent with this observation, female BRAFV600E (+) PTC patients had a higher BMI ($p = 0.011$) and more aggressive tumor behaviors than female BRAFV600E (-) PTC patients. In multivariate analysis, BMI was persistently associated with BRAFV600E mutation in the entire cohort (odds ratio [OR] 1.387; 95 % CI 1.036-1.859; $p = 0.028$) and in the female subcohort (OR 1.221; 95 % CI 1.014-1.631; $p = 0.046$). CONCLUSION: The positive association between BMI and BRAFV600E supports the hypothesis that excessive bodyweight influences tumor progression.
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Initial clinical experience with BRAF mutation analysis of core-needle biopsy specimens from thyroid nodules.
Clin Endocrinol (Oxf),
S. H. Choi, J. H. Baek, J. H. Lee, Y. J. Choi, E. J. Ha, D. E. Song, J. K. Kim, K. W. Chung, T. Y. Kim, W. B. Kim and Y. K. Shong. 2015.
OBJECTIVE: The accurate diagnosis of thyroid nodules is important for making management decisions. The purpose of this study was to evaluate the feasibility of core-needle biopsy with BRAFV600E mutation analysis (CNB + BRAFV600E) and to compare the clinical usefulness of CNB + BRAFV600E and fine-needle aspiration with BRAFV600E mutation analysis (FNA + BRAFV600E) in the diagnosis of thyroid malignancy. DESIGN, PATIENTS AND MEASUREMENTS: The results of BRAFV600E mutation analyses of 820 nodules from 820 patients (153 men, 667 women; mean age, 51.1 years), who underwent CNB + BRAFV600E (n = 256) or FNA + BRAFV600E (n = 564) between January 2011 and March 2012 were retrospectively evaluated. The feasibility of CNB + BRAFV600E was assessed by comparing its rate of detection of BRAFV600E mutations and positive predictive value with those of FNA + BRAFV600E . The clinical usefulness of CNB + BRAFV600E was determined by comparing rates of inconclusive results, the additional value of BRAFV600E mutation analysis, diagnostic surgery and diagnostic performance with those of FNA + BRAFV600E . RESULTS: CNB + BRAFV600E and FNA + BRAFV600E had similar rates of BRAFV600E mutation detection (66.3% vs 64.4%, P = 0.883) and positive predictive value (100.0% vs 96.6%, P = 0.135). CNB + BRAFV600E had a significantly higher diagnostic accuracy rate (95.7% vs 85.9%, P < 0.001), and significantly lower rates of inconclusive results (8.2% vs 51.8%, P < 0.001), and diagnostic surgery (8.9% vs 22.3%, P = 0.006), than FNA + BRAFV600E . CONCLUSIONS: The greater diagnostic performance of CNB + BRAFV600E and its lower rate of inconclusive results than FNA + BRAFV600E suggest that CNB + BRAFV600E can reduce rates of preventable diagnostic surgery.
PubMed-ID: 26215382
http://dx.doi.org/10.1111/cen.12866

Anaplastic Thyroid Cancer: Large Database, Cautious Interpretations.
Ann Surg Oncol,
A. R. Shaha. 2015.
PubMed-ID: 26219238
http://dx.doi.org/10.1245/s10434-015-4744-4

Germline HABP2 Mutation Causing Familial Nonmedullary Thyroid Cancer.
N Engl J Med, 373(5):448-55.
S. K. Gara, L. Jia, M. J. Merino, S. K. Agarwal, L. Zhang, M. Cam, D. Patel and E. Kebebew. 2015.
Familial nonmedullary thyroid cancer accounts for 3 to 9% of all cases of thyroid cancer, but the susceptibility genes are not known. Here, we report a germline variant of HABP2 in seven affected members of a kindred with familial nonmedullary thyroid cancer and in 4.7% of 423 patients with thyroid cancer. This variant was associated with increased HABP2 protein expression in tumor samples from affected family members, as compared with normal adjacent thyroid tissue and samples from sporadic cancers. Functional studies showed that HABP2 has a tumor-suppressive effect, whereas the G534E variant results in loss of function.
PubMed-ID: 26222560
http://dx.doi.org/10.1056/NEJMoa1502449

Treatment options in the young patient with Graves' disease.
Clin Endocrinol (Oxf),
T. Cheetham and R. Bliss. 2015.
The treatment options in the young patient with Graves' disease are the same as in adults, namely anti-thyroid drug (ATD), surgery (partial or total thyroidectomy) and radio-iodine. However the emphasis and expectation is different in the young person, reflecting a range of considerations including age, pubertal status, disease natural history, likely impact of ATD on disease course and the implications of radiation exposure. New therapeutic strategies that could increase the likelihood of long term remission are being explored. This article is protected by copyright. All rights reserved.
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http://dx.doi.org/10.1111/cen.12871

Benign thyroid nodules with RAS mutation grow faster.
Clin Endocrinol (Oxf),
A. Puzziello, A. Guerra, A. Murino, G. Izzo, M. Carrano, E. Angrisani, P. Zeppa, V. Marotta, A. Faggiano and M. Vitale. 2015.
CONTEXT: The management of a benign thyroid nodule includes follow-up until its size requires a surgical or alternative treatment. To date, it is difficult or impossible to predict the size changes of a benign nodule in a given patient because no specific growth parameters exist. RAS mutations have been described in thyroid adenomas and hyperplastic benign nodules. OBJECTIVE: The aim of this study was to establish whether the volume changes of benign nodules are associated withthe presence of RAS mutation. PATIENTS AND METHODS: Genomic DNA obtained by fine-needle aspiration of 78 thyroid noduleswith benign cytologywasanalyzed by pyrosequencing for the presence of NRAS61 and KRAS13 mutations.Ultrasonographic features were obtained. The volume of nodules at baseline and their changes after a mean follow-up of 25 months were evaluated according to the presence of RAS mutation. RESULTS: A RAS mutation was found in 24 thyroid aspirates (30.8%, 8 NRAS61 and 16 KRAS13). RAS mutation was not associated with ultrasonographic features, butwas significantly associated with a larger size at baseline (p = 0.017). After a 25 months mean follow-up, RAS mutation positive nodules displayed faster growth (RAS mutation positive vs. negative % annual growth 27.6% +/- 32.2% vs. 1.0% +/- 17.0%, p <0.001). CONCLUSIONS: Benign thyroid nodules bearing RAS mutation grow more rapidly than those with wild type RAS. Searching for RAS mutations in thyroid nodules with benign cytology might be useful to the clinician in choosing a more appropriate and timely surgical management. This article is protected by copyright. All rights reserved.
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Cancer incidence and mortality in patients treated with RAI or thyroidectomy for hyperthyroidism - a nation-wide cohort study with a long-term follow-up.
J Clin Endocrinol Metab:jc20151874.
R. Essi, M. Saara, J. Pia, H. Heini, S. Rauni, V. Matti and A. Anssi. 2015.
CONTEXT: Some previous studies have suggested increased cancer risk in hyperthyroid patients treated with radioiodine (RAI). It is unclear, whether the excess cancer risk is attributable to hyperthyroidism, its treatment, or the shared risk factors of the two diseases. OBJECTIVE: To assess cancer morbidity and mortality in hyperthyroid patients treated either with RAI or surgery. PATIENTS: We identified 4,334 patients treated surgically for hyperthyroidism in Finland during 1986-2007 from the Hospital Discharge Registry and 1,814 patients treated with RAI for hyperthyroidism at Tampere University Hospital. For each patient, three age- and gender-matched controls were chosen. Information on cancer diagnoses was obtained from the Cancer Registry. The follow-up began three months after the treatment and ended at cancer diagnosis, death,

emigration, or the common closing day December 31st 2009. RESULTS: The overall cancer incidence was not increased among the hyperthyroid patients compared to their controls (RR 1.05, 95% CI 0.96-1.15). However, the risk of cancers of the respiratory tract (RR 1.46, 95% CI 1.05-2.02) and the stomach (RR 1.64, 95% CI 1.01-2.68) was increased among the patients. The overall cancer mortality did not differ between the patients and the controls (RR 1.08, 95% CI 0.94-1.25). The type of treatment did not affect the overall risk of cancer (HR for RAI vs. thyroidectomy 1.03, 95% CI 0.86-1.23) or cancer mortality (HR 1.04, 95% CI 0.91-1.21). CONCLUSIONS: In this cohort of Finnish patients with hyperthyroidism treated with thyroidectomy or RAI, the overall risk of cancer was not increased, although an increased risk of gastric and respiratory tract cancers was seen in hyperthyroid patients. Based on this large-scale, long term follow-up study, the increased cancer risk in hyperthyroid patients is attributable to hyperthyroidism and shared risk factors, not the treatment modality.
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http://dx.doi.org/10.1210/jc.2015-1874

Bone marrow function after I therapy in patients with differentiated thyroid carcinoma.
J Clin Endocrinol Metab:jc20152124.
H. T. Prinsen, E. N. Klein Hesselink, A. H. Brouwers, J. T. Plukker, W. J. Sluiter, A. N. van der Horst-Schrivers, G. W. van Imhoff and T. P. Links. 2015.
PURPOSE: Primary aim was to evaluate the short- and long-term toxic effects of radioiodine (131I) therapy on bone marrow function in differentiated thyroid carcinoma (DTC) patients. Secondary aim was to define characteristics of patients at risk for impaired bone marrow function after 131I treatment. PATIENTS AND METHODS: DTC patients treated with 131I between 1989 and 2013 were included. We excluded patients with morbidities or treatments that could have influenced blood count parameters. Baseline platelets, leukocytes and haemoglobin were compared with blood counts at three and six months, and at one and five years post-treatment. Logistic multivariate regression analyses were performed to determine patient characteristics associated with thrombocytopenia. RESULTS: We included 331 patients. Mean+/-SD age was 47.5+/-17.2 years, 74.0% were female. Post-treatment platelets were significantly decreased at six months and one year, as compared with baseline. Leukocyte counts were also decreased, at three and six months, and at one year post-treatment. No decreases in haemoglobin were found. Five years post-treatment, platelet and leukocyte counts were comparable to baseline. Fourteen patients (4.2%) developed transient post-treatment thrombocytopenia. Risk factors for thrombocytopenia were older age, T4 tumour stage, male gender and cumulative dose 131I. After multivariate regression analysis, cumulative dose 131I remained independently associated with thrombocytopenia. CONCLUSION: Post-treatment platelets and leukocytes were transiently decreased compared to pre-treatment values in a general DTC population. Cumulative 131I dose was independently associated with thrombocytopenia. Platelets and leukocytes normalized to baseline levels five years post-treatment, implying that in most patients clinical effects of bone marrow toxicity are limited.
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http://dx.doi.org/10.1210/jc.2015-2124

Impact of Timeliness of Resection and Thyroidectomy Margin Status on Survival for Patients with Anaplastic Thyroid Cancer: An Analysis of 335 Cases.
Ann Surg Oncol,
P. Goffredo, S. M. Thomas, M. A. Adam, J. A. Sosa and S. A. Roman. 2015.
BACKGROUND: Controversies regarding anaplastic thyroid cancer (ATC) surround aggressiveness of tumor resection in the presence of extrathyroidal extension and the impact of delayed surgery on patient survival. Our goal was to analyze the survival implications of complete and timely resections. METHODS: Adult patients with ATC were culled from the National Cancer Data Base for the years 2003-2006. Kaplan-Meier curves and Cox proportional hazard regression analyses were used for univariate and multivariate survival analyses, respectively. RESULTS: A total of 680 ATC patients were identified. In the surgical cohort (n = 335), the female-to-male ratio was 1.6:1; mean age was 68.6 years. Patients with ATCs were staged as IVA in 42.7 % of cases, IVB in 32.2 %, and IVC in 25.1 %. Median time from diagnosis to surgery was 15 days. Negative margin status was more often achieved in patients diagnosed with stage IVA disease ($p < 0.001$). Compared to surgical patients, those who did not receive thyroid resections were older and had a more advanced stage of disease (both $p < 0.001$). In multivariable analyses, positive margin status was associated with increased mortality in stage IVA ATC ($p = 0.017$) but had no survival impact in stages IVB and IVC ($p > 0.05$). After adjustment for possible confounders, increasing time from diagnosis to surgery was not found to be associated with compromised survival outcomes for any disease stage. CONCLUSIONS: Timely and aggressive surgical management should be pursued in patients with intrathyroidal disease; however, aggressive resections may not be recommended for patients with stage IVB and IVC disease when morbidity and operative risks outweigh the limited benefits of surgery.

PubMed-ID: 26271394
http://dx.doi.org/10.1245/s10434-015-4742-6

Robotic trans-axillary and retro-auricular thyroid surgery.
J Surg Oncol,
H. E. Mohamed and E. Kandil. 2015.
Remote access approaches for thyroid surgery using surgical incisions placed outside the neck, including the axillary, chest and the retro-auricular region have gained interest due to the social stigmatization of young females with a visible neck scar. These novel approaches have been reported to be safe and feasible approaches for thyroid surgery in a select group of patients. Herein, we will discuss different aspects of the current robotic approaches. J. Surg. Oncol. 2015;9999:XX-XX. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26274340
http://dx.doi.org/10.1002/jso.23955

PTCSC3 is involved in papillary thyroid carcinoma development by modulating S100A4 gene expression.
J Clin Endocrinol Metab:jc20152247.
J. Jendrzejewski, A. Thomas, S. Liyanarachchi, A. Eiterman, J. Tomsic, H. He, H. S. Radomska, W. Li, R. Nagy, K. Sworczak and A. de la Chapelle. 2015.
CONTEXT: We previously showed that a long non-coding RNA (lncRNA) gene (PTCSC3) located close to the variant rs944289 that predisposes to papillary thyroid carcinoma (PTC) might target the S100A4 gene. OBJECTIVE: The aim was to investigate the impact of PTCSC3 on S100A4 expression and its role in cancer development. DESIGN: S100A4 abundance was analyzed by qPCR in unaffected and tumor tissue from n=73 PTC patients. The expression of PTCSC3 and S100A4 was studied in BCPAP and TPC-1 cell lines with forced expression of PTCSC3 by quantitative PCR (qPCR). Expression of S100A4 target genes (VEGF and MMP-9) was studied in the BCPAP cell lines with forced expression of PTCSC3 by qPCR, reverse transcriptase PCR and Western blot. The impact of PTCSC3 on BCPAP motility and invasiveness was analyzed by the Transwell and Matrigel assays, respectively. SETTING: This was a laboratory-based study using cells from clinical samples and thyroid cancer cell lines. MAIN OUTCOME MEASURES: Evidence for a link between the expression of PTCSC3 and thyroid carcinogenesis. RESULTS: Expression data from PTC cell lines pinpointed S100A4 as the most significantly downregulated gene in the presence of PTCSC3. S100A4 was upregulated in tumor tissue (p=9.33x10-7) while PTCSC3 was strongly downregulated (p=2.2x10-16). S100A4 transcription was moderately correlated with PTCSC3 expression in unaffected thyroid tissue (r=0.429, p=0.0001), and strongly in unaffected tissue of patients with the risk allele of rs944289 (r=0.685, p=7.88x10-5). S100A4, VEGF and MMP-9 were suppressed in the presence of PTCSC3 (p=0.0051, p=0.0090 and p=0.0037, respectively). PTC cells expressing PTCSC3 showed reduction in motility and invasiveness (p=4.52x10-5 and p=1.0x10-4, respectively). CONCLUSION: PTCSC3 downregulates S100A4 leading to a reduction in cell motility and invasiveness. We propose that PTCSC3 impacts PTC predisposition and carcinogenesis through the S100A4 pathway.
PubMed-ID: 26274343
http://dx.doi.org/10.1210/jc.2015-2247

Comparison of Secondary and Primary Thyroid Cancers: Patient Characteristics and Postoperative Outcomes : A Cross-Sectional Analysis of Patients with Primary and Secondary Thyroid Cancers.
Ann Surg Oncol,
Z. Al-Qurayshi, H. Mohamed, P. Bhatia, S. Srivastav, R. Aslam and E. Kandil. 2015.
BACKGROUND: Secondary thyroid cancer is believed to lead to a more aggressive clinical course than primary thyroid cancer. We aim to examine the difference between primary and secondary thyroid cancer in terms of patient characteristics and perioperative outcomes at the national level. METHODS: A cross-sectional study utilizing the Nationwide Inpatient Sample database for 2003-2010 was merged with County Health Rankings Data. International Classification of Diseases, Ninth Revision (ICD-9) codes were used to identify adult patients with thyroid cancer. RESULTS: A total of 21,581 discharge records were included. Overall, 16,625 (77.0 %) patients had primary cancer, while the rest (23.0 %) had secondary cancer. Younger (<45 years) and older (>65 years) patients, males, and those of White or Hispanic background were more likely to have secondary cancers ($p < 0.05$ each). The prevalence of secondary cancer was higher in communities of low health risk (24.0 % vs. 21.1 %; $p < 0.024$). Secondary cancer was more likely to be managed by total thyroidectomy (odds ratio [OR] 2.40, 95 % CI 2.12-2.73) and to require additional radical neck dissection (OR 12.51, 95 % CI 10.98-14.25). Patients with secondary thyroid cancers were at higher risk of postoperative complications ($p < 0.01$ each). The cost of secondary cancer management was significantly higher than primary cancer (US$12,449.00 +/- 302.07 vs. US$7848.12 +/- 149.05; $p < 0.001$). However, compared with intermediate-volume surgeons, the complication risk was lower for high-volume (OR 0.47, 95 % CI 0.24-0.92; $p = 0.026$). CONCLUSIONS:

Secondary thyroid cancer is associated with a higher risk of perioperative complications and higher cost and distinct demographic profile. Patients managed by higher-volume surgeons were less likely to experience disadvantageous outcomes.
PubMed-ID: 26282905
http://dx.doi.org/10.1245/s10434-015-4800-0

Concomitant High Expression of BRAFV600E, P-cadherin and cadherin 6 is Associated with High TNM Stage and Lymph Node Metastasis in Conventional Papillary Thyroid Carcinoma.
Clin Endocrinol (Oxf),
L. Zhao, R. Jiang, M. Xu, P. Zhu, X. M. Mo, N. Wang, G. G. Chen and Z. M. Liu. 2015.
CONTEXT AND OBJECTIVE: BRAFV600E mutation is the most common activating mutation associated with aggressive behaviors in human tumors including conventional papillary thyroid carcinoma (cPTC). P-cadherin and cadherin 6 have been shown to be mesenchymal-associated cadherins and promote cancer cell invasion and metastasis. The purpose of this study was to examine BRAFV600E, P-cadherin and cadherin 6 expression in cPTC and to assess the association of their expression with clinicopathological indicators. METHODS: BRAFV600E, P-cadherin and cadherin 6 protein expression in 80 cPTCs, 61 nodular hyperplasia and 76 normal thyroid tissues were examined by immunohistochemistry. The correlation of their protein expression with clinicopathological indicators of cPTC was statistically analyzed. RESULTS: rotein expression of BRAFV600E, P-cadherin and cadherin 6 was upregulated in cPTC. High protein expression of BRAFV600E, P-cadherin and cadherin 6 was significantly correlated with high TNM stage and lymph node metastasis (LNM) ($P < 0.001$). Furthermore, BRAFV600E, P-cadherin and cadherin 6 protein expression were correlated with one another. BRAFV600E high expression combined with both P-cadherin and cadherin-6 high expression had stronger correlation with high TNM stage and LNM when compared with BRAFV600E high expression combined with either P-cadherin or cadherin-6 high expression ($P = 0.042$, 0.017 for TNM stage and $P = 0.003$, 0.006 for LNM, respectively) and only BRAFV600E high expression ($P < 0.001$ for both TNM stage and LNM). CONCLUSIONS: Concomitant high expression of BRAFV600E, P-cadherin and cadherin 6 is strongly associated with high TNM stage and LNM in cPTC. This article is protected by copyright. All rights reserved.
PubMed-ID: 26285159
http://dx.doi.org/10.1111/cen.12878

Low population selenium status is associated with increased prevalence of thyroid disease.
J Clin Endocrinol Metab:jc20152222.
Q. Wu, M. P. Rayman, H. Lv, L. Schomburg, B. Cui, C. Gao, P. Chen, G. Zhuang, Z. Zhang, X. Peng, H. Li, Y. Zhao, X. He, G. Zeng, F. Qin, P. Hou and B. Shi. 2015.
CONTEXT: Epidemiological studies have supported the premise that an adequate selenium intake is essential for thyroid-gland function Objective: To investigate whether the prevalence of thyroid disease differed in two areas, similar except for very different soil/crop selenium concentrations. DESIGN: Cross-sectional observational study. SETTING: Two counties of Shaanxi Province, China, here defined as adequate- and low-selenium. PARTICIPANTS: 6152 participants selected by stratified cluster-sampling. MAIN OUTCOME MEASURES: Participants completed demographic and dietary questionnaires and underwent physical and thyroid-ultrasound examinations. Serum samples were analysed for thyroid-function parameters and selenium concentration. Serum selenium was compared between different demographic, dietary and lifestyle categories in the two counties. The relationship between selenium status, dietary factors and pathological thyroid conditions was explored by logistic regression. RESULTS: Complete data sets were available from 3,038 adequate-selenium and 3,114 low-selenium participants in whom median (IQR) selenium concentrations differed almost two-fold [103.6 (79.7, 135.9) vs. 57.4 (39.4, 82.1) mug/L; P=0.001]. The prevalence of pathological thyroid conditions (hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, enlarged thyroid) was significantly lower in the adequate-selenium than in the low-selenium county (18.0% vs. 30.5%; P<0.001). Higher serum selenium was associated with lower odds (OR; 95% CI) of autoimmune thyroiditis (0.47; 0.35, 0.65), subclinical hypothyroidism (0.68; 0.58, 0.93), hypothyroidism (0.75; 0.63, 0.90) and an enlarged thyroid (0.75; 0.59, 0.97). CONCLUSIONS: Low selenium status is associated with increased risk of thyroid disease. Increased selenium intake may reduce the risk in areas of low selenium intake which exist not only in China but in many other parts of the world.
PubMed-ID: 26305620
http://dx.doi.org/10.1210/jc.2015-2222

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

Cinacalcet normalizes serum calcium in a double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery.
Eur J Endocrinol, 172(5):527-35.
A. Khan, J. Bilezikian, H. Bone, A. Gurevich, P. Lakatos, W. Misiorowski, L. Rozhinskaya, M. L. Trotman and M. Toth. 2015.
OBJECTIVE: Primary hyperparathyroidism (PHPT) is diagnosed by the presence of hypercalcemia and elevated or nonsuppressed parathyroid hormone (PTH) levels. Although surgery is usually curative, some individuals fail or are unable or unwilling to undergo parathyroidectomy. In such individuals, targeted medical therapy may be of value. Cinacalcet normalized calcium level and lowered PTH in patients with PHPT in several phase 2 and open-label studies. We compared cinacalcet and placebo in subjects with PHPT unable to undergo parathyroidectomy. DESIGN: Phase 3, double-blind, multi centere, randomized, placebo-controlled study. METHODS: Sixty-seven subjects (78% women) with moderate PHPT were randomized (1:1) to cinacalcet or placebo for </=28 weeks. MAIN OUTCOME MEASURE: Achievement of a normal mean corrected total serum calcium concentration of </=10.3 mg/dl (2.575 mmol/l). RESULTS: Baseline median (quartile 1 (Q1), Q3) serum PTH was 164.0 (131.0, 211.0) pg/ml and mean (s.d.) serum Ca was 11.77 (0.46) mg/dl. Serum Ca normalized (</=10.3 mg/dl) in 75.8% of cinacalcet- vs 0% of placebo-treated subjects (P<0.001). Corrected serum Ca decreased by >/=1.0 mg/dl from baseline in 84.8% of cinacalcet- vs 5.9% of placebo-treated subjects (P<0.001). Least squares mean (s.e.m.) plasma PTH change from baseline was -23.80% (4.18%) (cinacalcet) vs -1.01% (4.05%) (placebo) (P<0.001). Similar numbers of subjects in the cinacalcet and placebo groups reported adverse events (AEs) (27 vs 20) and serious AEs (three vs four). Most commonly reported AEs were nausea and muscle spasms. CONCLUSIONS: These results demonstrate that cinacalcet normalizes serum calcium in this PHPT population and appears to be well tolerated.
PubMed-ID: 25637076
http://dx.doi.org/10.1530/EJE-14-0877

Consensus Statements/Guidelines

European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults.
Eur J Endocrinol, 173(2):G1-20.
J. Bollerslev, L. Rejnmark, C. Marcocci, D. M. Shoback, A. Sitges-Serra, W. van Biesen and O. M. Dekkers. 2015.
Hypoparathyroidism (HypoPT) is a rare (orphan) endocrine disease with low calcium and inappropriately low (insufficient) circulating parathyroid hormone levels, most often in adults secondary to thyroid surgery. Standard treatment is activated vitamin D analogues and calcium supplementation and not replacement of the lacking hormone, as in other hormonal deficiency states. The purpose of this guideline is to provide clinicians with guidance on the treatment and monitoring of chronic HypoPT in adults who do not have end-stage renal disease. We intend to draft a practical guideline, focusing on operationalized recommendations deemed to be useful in the daily management of patients. This guideline was developed and solely sponsored by The European Society of Endocrinology, supported by CBO (Dutch Institute for Health Care Improvement) and based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles as a methodological base. The clinical question on which the systematic literature search was based and for which available evidence was synthesized was: what is the best treatment for adult patients with chronic HypoPT? This systematic search found 1100 articles, which was reduced to 312 based on title and abstract. The working group assessed these for eligibility in more detail, and 32 full-text articles were assessed. For the final

recommendations, other literature was also taken into account. Little evidence is available on how best to treat HypoPT. Data on quality of life and the risk of complications have just started to emerge, and clinical trials on how to optimize therapy are essentially non-existent. Most studies are of limited sample size, hampering firm conclusions. No studies are available relating target calcium levels with clinically relevant endpoints. Hence it is not possible to formulate recommendations based on strict evidence. This guideline is therefore mainly based on how patients are managed in clinical practice, as reported in small case series and based on the experiences of the authors.
PubMed-ID: 26160136
http://dx.doi.org/10.1530/EJE-15-0628

Other Articles

What Can We Learn from Intraoperative Parathyroid Hormone Levels that Do Not Drop Appropriately?
Ann Surg Oncol, 22(6):1781-8.
H. Wachtel, I. Cerullo, E. K. Bartlett, R. R. Kelz, G. C. Karakousis and D. L. Fraker. 2015.
BACKGROUND: Parathyroidectomy remains the only definitive treatment for primary hyperparathyroidism. We studied our large series of parathyroidectomies to identify factors predictive of failure to meet intraoperative parathyroid hormone (IOPTH) monitoring criteria. METHODS: We performed a retrospective cohort review of patients who underwent initial parathyroidectomy for primary hyperparathyroidism with IOPTH monitoring. Primary outcome was intraoperative failure, defined as failure to decrease IOPTH by >/=50 % and into normal range. Univariate and multivariate analyses were performed to determine factors associated with intraoperative failure. A subset analysis evaluated 6-month outcomes. RESULTS: Of 2,185 subjects, 5.0 % (n = 110) experienced intraoperative failure. The intraoperative failure group had more multigland disease (35.2 vs. 16.6 %, p < 0.001) and smaller glands (1.3 vs. 1.5 cm, p = 0.048) compared to patients who experienced intraoperative success. On multivariate analysis, PTH level was statistically, but not clinically, significantly associated with intraoperative failure (odds ratio 1.0, 95 % confidence interval 1.000-1.003). Persistent hyperparathyroidism was identified in 2.5 % (n = 15) of 592 patients with >/=6 month follow-up. Median IOPTH decrease was lower in patients with persistent hyperparathyroidism (67.1 vs. 85.8 %, p < 0.001). IOPTH criteria were 93.7 % sensitive and 40.0 % specific for eucalcemia 6 months postoperatively. Of 15 patients with persistent hyperparathyroidism, 7 underwent reoperation with a 100 % cure rate. Reoperative diagnoses included ectopic mediastinal glands (n = 3), hyperplasia (n = 3), and missed second adenoma (n = 1). CONCLUSIONS: Intraoperative failure is associated with higher rates of multigland disease and smaller parathyroid glands. Patients with persistent disease had significantly lower decreases in IOPTH, but half of patients who experienced failure by IOPTH criteria were eucalcemic 6 months postoperatively. All patients undergoing reoperation experienced successful cure.
PubMed-ID: 25354574
http://dx.doi.org/10.1245/s10434-014-4201-9

F18-Choline PET/CT: a novel tool to localize parathyroid adenoma?
Clin Endocrinol (Oxf), 82(6):910-2.
D. H. van Raalte, M. C. Vlot, A. Zwijnenburg and R. W. ten Kate. 2015.
PubMed-ID: 25410059
http://dx.doi.org/10.1111/cen.12681

Morbidity Associated with Concomitant Thyroid Surgery in Patients with Primary Hyperparathyroidism.
Ann Surg Oncol, 22(8):2707-13.
P. Riss, M. Kammer, A. Selberherr, C. Scheuba and B. Niederle. 2015.
BACKGROUND: Recurrent laryngeal nerve (RLN) palsy and hypoparathyroidism are serious complications in thyroid and parathyroid surgery. The extent to which incidentally detected thyroid nodules should be treated concomitantly is a matter of debate. METHODS: This analysis was based on 1,065 patients who underwent consecutive surgery for primary hyperparathyroidism at a single institution. Together with the surgical strategy, histologic and follow-up examinations were documented prospectively and analyzed retrospectively regarding the occurrence and course of RLN palsy, hypoparathyroidism, and thyroid carcinoma. RESULTS: Altogether, RLN palsy occurred for 38 patients (3.6 %) and proved to be permanent for 1 patient (0.1 %). Postoperative calcium substitution was necessary for 191 patients (17.9 %), with 3 patients showing permanent hypoparathyroidism (0.3 %). Procedures other than open minimally invasive exploration were accompanied by a significantly increased risk for temporary RLN paresis (odds ratio [OR], 6.136) and temporary

hypoparathyroidism (OR 3.306). Concomitant thyroid surgery was performed for 502 patients (47.1 %). Compared with open minimally invasive parathyroid exploration, patients undergoing unilateral exploration and hemithyroidectomy (OR 5.827) or bilateral neck exploration (BNE) and thyroidectomy (OR 8.047) had a significantly increased risk for RLN paresis. Patients administered BNE with hemithyroidectomy (OR 2.380) or thyroidectomy (OR 7.233) had a significantly increased risk for hypoparathyroidism. Thyroid malignancy was incidentally detected in 86 patients (8.1 %). CONCLUSION: Patients undergoing concomitant thyroid procedures have a significantly higher risk for temporary RLN palsy and hypoparathyroidism. However, the high rate of incidentally detected thyroid carcinoma in an iodine-replete endemic goiter area indicates hemithyroidectomy in the presence of thyroid nodules incidentally identified in preoperative ultrasounds.
PubMed-ID: 25480411
http://dx.doi.org/10.1245/s10434-014-4283-4

No need to abandon focused parathyroidectomy: a multicenter study of long-term outcome after surgery for primary hyperparathyroidism.
Ann Surg, 261(5):991-6.
O. Norlen, K. C. Wang, Y. K. Tay, W. R. Johnson, S. Grodski, M. Yeung, J. Serpell, S. Sidhu, M. Sywak and L. Delbridge. 2015.
OBJECTIVE: The aim of this study was to investigate long-term outcomes after focused parathyroidectomy (FPTX) and open 4-gland parathyroid exploration (OPTX) for primary hyperparathyroidism (pHPT). BACKGROUND: Concerns about increased long-term recurrence rates after FPTX in conjunction with decreased operative times for OPTX have led some groups to abandon FPTX in favor of routine 4-gland exploration. METHODS: This is a multicenter retrospective cohort study of patients undergoing parathyroidectomy for pHPT from 1990 to 2013. The patient cohort was divided into 2 groups, FPTX and OPTX, based on intention-to-treat analysis. The primary outcome measure was the persistence of pHPT. Secondary outcome measures were differences in the long-term recurrence rate of persisting pHPT and surgical complications. RESULTS: A total of 4569 patients (3585 females) were included. The overall persistence and recurrence rates were 2.2% and 0.9%, respectively, after a median follow-up of 6.5 years. There were 2531 FPTX cases and 2038 OPTX cases. The initial persistence rate was higher for FPTX than for OPTX (2.7% vs 1.7%, P = 0.036); however, the long-term recurrence rate was not different (5-year 0.6% vs 0.4%, log-rank P = 0.08). Complications were more common in OPTX than in FPTX (7.6% vs 3.6%, P < 0.001). CONCLUSIONS: FPTX was associated with fewer operative complications and an equivalent rate of long-term recurrence than with OPTX. Although initial persistence rates were higher after FPTX than after OPTX, most were readily resolved with subsequent early reoperation. FPTX should not be abandoned in patients with positive preoperative localization.
PubMed-ID: 25565223
http://dx.doi.org/10.1097/SLA.0000000000000715

Low 24-hour urine calcium levels in patients with sporadic primary hyperparathyroidism: is further evaluation warranted prior to parathyroidectomy?
Am J Surg, 210(1):123-8.
K. O'Connell, T. W. Yen, J. Shaker, S. D. Wilson, D. B. Evans and T. S. Wang. 2015.
BACKGROUND: Low 24-hour urine calcium (uCa) levels in patients with primary hyperparathyroidism (pHPT) raise concern for familial hypocalciuric hypercalcemia. This study evaluated patients with a low 24-hour uCa level for potential differences that may guide the extent of preoperative evaluation needed. METHODS: A retrospective review was conducted of 1,139 sporadic pHPT patients who underwent parathyroidectomy between December 1999 and May 2011. RESULTS: Of the 54 (5%) patients with greater than or equal to one low 24-hour uCa (<100 mg), 28 (52%) patients had only one low level, 9 (17%) had multiple low levels, and 17 (31%) had a repeat 24-hour uCa greater than 100. In the latter group, 4 of the 9 (53%) patients were on a thiazide and had normalization after cessation. Among the groups, differences existed only in serum creatinine (P = .0011) and glomerular filtration rate (P = .0007). CONCLUSION: This study suggests that sporadic pHPT patients with low 24-hour uCa levels may not require further evaluation with genetic testing for familial hypocalciuric hypercalcemia, especially if previous eucalcemia is documented.
PubMed-ID: 25595714
http://dx.doi.org/10.1016/j.amjsurg.2014.09.030

Preoperative imaging for focused parathyroidectomy: making a good strategy even better.
Eur J Endocrinol, 172(5):519-26.
C. Guerin, A. Lowery, S. Gabriel, F. Castinetti, M. Philippon, J. Vaillant-Lombard, A. Loundou, J. F. Henry, F. Sebag and D. Taieb. 2015.

OBJECTIVE: Surgical treatment for primary hyperparathyroidism (pHPT) has undergone a major paradigm shift during the last decades from bilateral cervicotomy with four-gland neck exploration to image-guided focused approaches. The primary objective of the present study was to compare the performances of parathyroid scintigraphy (PS), parathyroid ultrasonography (US), and the combination of both procedures for guiding a focused approach on the basis of modified interpretation criteria. METHODS: Data from 199 patients operated for apparent sporadic pHPT and evaluated with US and PS using dual-isotope (123)I/(99m)Tc-sestamibi planar pinhole and single-photon emission computed tomography (SPECT) acquisitions were evaluated. RESULTS: A total of 127 patients underwent a focused approach and the remainder had bilateral cervicotomy. In 42 cases, a focused approach was not performed due to the absence of concordant results between US and PS for a single-gland abnormality. Four patients had persistent disease and three had recurrent disease. A localizing preoperative PS had a sensitivity of 93.3%, positive predictive value of 85.8%, negative predictive value of 73.0%, and accuracy of 83.4% for predicting uniglandular disease. Additional SPECT images accurately localize posterior adenomas that are often missed by US. Compared with PS, US had a lower sensitivity (P<0.01). Our imaging protocol also enabled diagnosis of multiglandular disease in 60.6%. CONCLUSIONS: PS using a highly sensitive dual-tracer subtraction method is the most accurate technique for directing a focused approach. PS could be sufficient for directing a focused approach in the presence of a negative US in two major circumstances: posterior locations due to acquired ectopia that could be missed by US, and previous history of thyroidectomy due to interpretation difficulties.
PubMed-ID: 25637075
http://dx.doi.org/10.1530/EJE-14-0964

Accuracy of early-phase versus dual-phase single-photon emission computed tomography/computed tomography in the localization of parathyroid disease.
Laryngoscope, 125(6):1496-501.
R. Mandal, A. Muthukrishnan, R. L. Ferris, J. R. de Almeida and U. Duvvuri. 2015.
OBJECTIVES/HYPOTHESIS: Preoperative localization for parathyroid disease has improved in recent years with the advent of dual-phase (99m) Tc-sestamibi single-photon emission computed tomography/computed tomography (SPECT/CT) imaging. However, dual-phase imaging is associated with increased cost, time, and radiation dose. The aim of this study was to investigate the need for late-phase imaging when using SPECT/CT for the preoperative localization of parathyroid disease. STUDY DESIGN: Retrospective chart analysis. METHODS: A retrospective review of 75 patients who underwent preoperative imaging localization and subsequent surgical resection for parathyroid disease at a tertiary referral center was performed. Of these, 50 patients met study criteria including preoperative SPECT/CT imaging and specific reporting of early- and late-phase focal radiotracer uptake. Localization accuracy was verified with definitive surgical findings confirmed by histological analysis and evidence of biochemical cure. RESULTS: Accurate localization of adenoma(s) was seen in 78.0% of patients using dual-phase SPECT/CT. Early-phase imaging alone localized 76.0%, whereas late-phase imaging alone localized 74.0%. Sensitivity and specificity for dual-phase imaging was 84.8% and 89.6%, respectively. In comparison, early-phase localization alone was found to have a sensitivity/specificity of 84.4%/89.4%; sensitivity/specificity of late-phase scanning alone was found to be 80.4%/89.1%. Dual-phase SPECT/CT scanning did not provide a statistically significant improvement in adenoma localization when compared to early-phase scanning alone. CONCLUSIONS: Although further investigation is needed, the results of this study suggest that early-phase SPECT/CT scanning alone may obviate the need for dual-phase SPECT/CT scanning in the initial preoperative localization workup of parathyroid disease. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25645695
http://dx.doi.org/10.1002/lary.25020

The Weight of the Resected Gland Predicts Rate of Success After Image-Guided Focused Parathyroidectomy.
World J Surg, 39(8):1922-7.
O. Norlen, A. Glover, N. Zaidi, A. Aniss, M. Sywak, S. Sidhu and L. Delbridge. 2015.
BACKGROUND: A recent study of focused minimally invasive parathyroidectomy (FPTX) in sporadic primary hyperparathyroidism (pHPT) using intraoperative parathyroid hormone (ioPTH) measurements shows that inadequate ioPTH drop and multiglandular disease are more commonly found when a first gland<200 mg is resected. Our aim was to study if a resected gland that weighed <200 mg was associated with an increased persistence rate after FPTX. METHODS: This is a cohort study of FPTX for pHPT performed in the period 1998-2013. FPTX was performed in patients with pHPT where Sestamibi and Ultrasound imaging localized single-gland disease, only one gland was excised and the weight recorded. IoPTH was not used routinely. Two groups were composed according to the weight of the resected gland: Group A<200 mg and Group B>/=200 mg.

Persistent or recurrent disease was defined if it occurred within, or after 6 months. The primary outcome measure was the rate of persisting pHPT. RESULTS: A total of 3,511 parathyroidectomies were performed, and a total 1,745 FPTX (1,347 female) met inclusion criteria. There were 245 and 1,500 patients in groups A and B, respectively. The rate of persistent pHPT was higher in Group A, 6.1 versus 2.0% (p<0.001). Findings at re-operative surgery showed that the ipsilateral gland was diseased in 47% (7/15) of persistent cases in group A. CONCLUSION: The risk of persistent disease after MIP was higher if the resected gland weighed </=200 mg, and this corroborates the findings of a recent study. A heightened awareness of the possibility of multigland disease should be raised, and ioPTH monitoring, identification of the ipsilateral gland or bilateral exploration may be advisable in such cases.
PubMed-ID: 25677011
http://dx.doi.org/10.1007/s00268-015-3017-5

What Should We Tell Our Patients? Lifetime Guarantee or is it 5- to 10-year Warranty on a Parathyroidectomy for Primary Hyperparathyroidism?
World J Surg, 39(8):1928-9.
J. L. Pasieka. 2015.
PubMed-ID: 25804550
http://dx.doi.org/10.1007/s00268-015-3043-3

Parathyroid Localization and Preservation during Transcervical Resection of Substernal Thyroid Glands.
Otolaryngol Head Neck Surg, 152(6):1024-8.
T. E. Heineman, P. Kadkade, D. I. Kutler, M. A. Cohen and W. I. Kuhel. 2015.
OBJECTIVE: The feasibility of parathyroid preservation during thyroidectomy has not been well documented for cases in which the thyroid gland extends into the mediastinum. STUDY DESIGN: Retrospective chart review. SETTING: Tertiary academic referral center. SUBJECTS AND METHODS: In this retrospective cohort study, 70 consecutive patients who had substernal thyroid glands treated with a transcervical thyroidectomy between 1993 and 2013 were compared with 286 thyroidectomies that did not entail substernal extension within that same time period. All localized parathyroid glands were confirmed histologically. RESULTS: Of 160 possible parathyroid glands in the substernal cases, 119 (74%) were histologically confirmed intraoperatively (67 superior and 52 inferior). In nonsubsternal cases, 725 (89%) were histologically confirmed (372 superior and 353 inferior). There was a statistically significant difference between the substernal and nonsubsternal cases in the total number of glands found (P < .0001) and the number of superior and inferior glands that were identified (P = .009 and < 0.0001). CONCLUSIONS: Even when the thyroid gland extends into the mediastinum, it is often possible, although with reduced efficiency, to identify and preserve the parathyroid glands.
PubMed-ID: 25847147
http://dx.doi.org/10.1177/0194599815578105

The role of radionuclide imaging in the surgical management of primary hyperparathyroidism.
J Nucl Med, 56(5):737-44.
E. Hindie, P. Zanotti-Fregonara, A. Tabarin, D. Rubello, I. Morelec, T. Wagner, J. F. Henry and D. Taieb. 2015.
Primary hyperparathyroidism is a frequent and potentially debilitating endocrine disorder for which surgery is the only curative treatment. The modalities of parathyroid surgery have changed over the last 2 decades, as conventional bilateral neck exploration is no longer the only surgical approach. Parathyroid scintigraphy plays a major role in defining the surgical strategy, given its ability to orient a targeted (focused) parathyroidectomy and to recognize ectopic locations or multiglandular disease. This review, which represents a collaborative effort between nuclear physicians, endocrinologists, and endocrine surgeons, emphasizes the importance of performing imaging before any surgery for primary hyperparathyroidism, even in the case of conventional bilateral neck exploration. We discuss the advantages and drawbacks of targeted parathyroidectomy and the performance of various scintigraphic protocols to guide limited surgery. We also discuss the optimal strategy to localize the offending gland before reoperation for persistent or recurrent hyperparathyroidism. Finally, we describe the potential applications of novel PET tracers, with special emphasis on (18)F-fluorocholine.
PubMed-ID: 25858040
http://dx.doi.org/10.2967/jnumed.115.156018

Real-Time Super Selective Venous Sampling in Remedial Parathyroid Surgery.
J Am Coll Surg, 220(6):994-1000.
A. H. Lebastchi, J. E. Aruny, P. I. Donovan, C. E. Quinn, G. G. Callender, T. Carling and R. Udelsman. 2015.
BACKGROUND: Remedial cervical exploration for persistent or recurrent primary hyperparathyroidism can be technically difficult, but is expedited by accurate preoperative localization. We investigated the use of real-time

super selective venous sampling (sSVS) in the setting of negative noninvasive imaging modalities. STUDY DESIGN: We performed a retrospective analysis of a prospective database incorporating real-time sSVS in a tertiary academic medical center. Between September 2001 and April 2014, 3,643 patients were referred for surgical treatment of primary hyperparathyroidism. Of these, 31 represented remedial patients who had undergone one (n=28) or more (n=3) earlier cervical explorations and had noninformative, noninvasive preoperative localization studies. RESULTS: We extended the use of the rapid parathyroid hormone assay in the interventional radiology suite, generating near real-time data facilitating onsite venous localization by a dedicated interventional radiologist. The predictive value of real-time sSVS localization was investigated. Overall, sSVS correctly predicted the localization of the affected gland in 89% of cases. Of 31 patients who underwent sSVS, a significant rapid parathyroid hormone gradient was identified in 28 (90%), localizing specific venous drainage of a culprit gland. All patients underwent subsequent surgery and were biochemically cured, with the exception of one who had metastatic parathyroid carcinoma. Three patients with negative sSVS were also explored and cured. CONCLUSIONS: Preoperative parathyroid localization is of paramount importance in remedial cervical explorations. Real-time sSVS is a sensitive localization technique for patients with persistent or recurrent primary hyperparathyroidism, when traditional noninvasive imaging studies fail. These results validate the utility and benefit of real-time sSVS in guiding remedial parathyroid surgery.
PubMed-ID: 25868412
http://dx.doi.org/10.1016/j.jamcollsurg.2015.01.004

TERT promoter mutations are rare in parathyroid tumors.
Endocr Relat Cancer, 22(3):L9-L11.
F. Haglund, C. C. Juhlin, T. Brown, M. Ghaderi, T. Liu, A. Stenman, A. Dinets, M. Prasad, R. Korah, D. Xu, T. Carling and C. Larsson. 2015.
PubMed-ID: 25876648
http://dx.doi.org/10.1530/ERC-15-0121

An epigenetic cause of seizures and brain calcification: pseudohypoparathyroidism.
Lancet, 385(9979):1802.
C. Ritter, C. H. Gobel, T. Liebig, E. Kaminksy, G. R. Fink and H. C. Lehmann. 2015.
PubMed-ID: 25943944
http://dx.doi.org/10.1016/S0140-6736(15)60451-2

Hypercalciuria May Persist After Successful Parathyroid Surgery and It Is Associated With Parathyroid Hyperplasia.
J Clin Endocrinol Metab, 100(7):2734-42.
S. Palmieri, C. Eller-Vainicher, E. Cairoli, V. Morelli, V. V. Zhukouskaya, U. Verga, M. Filopanti, L. Vicentini, S. Ferrero, A. Spada and I. Chiodini. 2015.
CONTEXT: Hypercalciuria is frequently found in primary hyperparathyroidism (1HPT) and, although it generally normalizes after successful parathyroidectomy, may persist in some patients. The factors associated with persistent calcium renal leak (cRL) have not been clarified. OBJECTIVE: The purpose of this study was to determine the prevalence of cRL in our 1HPT population and investigate cRL-related factors. DESIGN: This was a retrospective longitudinal study. SETTING: The study was conducted in an outpatient setting. PATIENTS/INTERVENTION: The participants were 95 patients with 1HPT successfully operated on who had a normal estimated glomerular filtration rate. MAIN OUTCOME MEASURES: The biochemical parameters of calcium metabolism and bone mineral density (BMD) measured by dual-X-ray absorptiometry before and 24 months after surgery were assessed. All histological findings were recorded. RESULTS: The prevalence of hypercalciuria before and after surgery was 74% and 32%, respectively. Before, surgery patients with cRL showed lower calcium and higher phosphate levels than those without cRL (10.9 +/- 0.6 vs 11.4 +/- 0.8 mg/dL [2.7 +/- 0.2 vs 2.8 +/- 0.2 mmol/L], P = .01 and 2.6 +/- 0.5 vs 2.4 +/- 0.4 mg/dL [0.84 +/- 0.2 vs 0.77 +/- 0.1 mmol/L], P = .04, respectively), whereas 24-h calciuria levels and the prevalence of 1HPT complications (osteoporosis, renal stones, and hypertension) were comparable. After surgery, serum calcium, phosphate, and PTH levels were comparable between patients with and without cRL. The prevalence of the histological finding of parathyroid hyperplasia was higher in patients with cRL (50%) than in patients without cRL (22%) (P = .01). The presence of cRL was independently associated with presurgery hypercalciuria (odds ratio, 4.71; 95% confidence interval, 1.18-18.8; P = .03) and parathyroid hyperplasia (odds ratio, 3.52; 95% confidence interval, 1.31-9.43; P = .01). Only patients without cRL had improved BMD at the spine (P = .04), total femur (P = .01), and femoral neck (P = .01). CONCLUSIONS: cRL is present in 30% of patients with 1HPT after successful surgery, and it is associated with parathyroid hyperplasia before surgery and the lack of improvement in BMD after surgery.

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http://dx.doi.org/10.1210/jc.2014-4548

Intraoperative guidance in parathyroid surgery using near-infrared fluorescence imaging and low-dose Methylene Blue.
Surgery,
Q. R. Tummers, A. Schepers, J. F. Hamming, J. Kievit, J. V. Frangioni, C. J. van de Velde and A. L. Vahrmeijer. 2015.
BACKGROUND: Identification of diseased and normal parathyroid glands during parathyroid surgery can be challenging. The aim of this study was to assess whether near-infrared (NIR) fluorescence imaging using administration of a low-dose Methylene Blue (MB) at the start of the operation could provide optical guidance during parathyroid surgery and assist in the detection of parathyroid adenomas. METHODS: Patients diagnosed with primary hyperparathyroidism planned for parathyroidectomy were included. Patients received 0.5 mg/kg MB intravenously directly after start of anesthesia. During the operation, NIR fluorescence imaging was performed to identify parathyroid adenomas. Imaging results were compared with a previous published feasibility study in which 12 patients received MB after intraoperative identification of the adenoma. RESULTS: A total of 13 patients were included in the current study. In 10 of 12 patients with a histologically proven adenoma, the adenoma was fluorescent. Mean signal to background ratio was 3.1 +/- 2.8. Mean diameter of the resected lesions was 17 +/- 9 mm (range 5-28 mm). Adenomas could be identified up to 145 minutes after administration, which was the longest timespan until resection. Interestingly, in 3 patients, a total of 6 normal parathyroid glands (median diameter 2.5 mm) with a signal to background ratio of 1.8 +/- 0.4 were identified using NIR fluorescence imaging. CONCLUSION: Early administration of low-dose MB provided guidance during parathyroidectomy by identifying both parathyroid adenomas and normal parathyroid glands. In patients in whom difficult identification of the parathyroid adenoma is expected or when normal glands have to be identified, the administration of MB may improve surgical outcome.
PubMed-ID: 25958068
http://dx.doi.org/10.1016/j.surg.2015.03.027

Improvement in patient-reported physical and mental health after parathyroidectomy for primary hyperparathyroidism.
Surgery, 158(3):837-45.
K. Zanocco, Z. Butt, D. Kaltman, D. Elaraj, D. Cella, J. L. Holl and C. Sturgeon. 2015.
BACKGROUND: The majority of patients with primary hyperparathyroidism (PHPT) are diagnosed without the classic signs of renal or osseous complications. Vague and subjective symptoms have been attributed to PHPT but have been difficult to measure during the medical encounter. The Patient-Reported Outcomes Measurement Information System (PROMIS) of the National Institutes of Health contains validated measures of physical and mental health that can be administered by the use of computer-adaptive testing (CAT). The objective of this study was to evaluate the feasibility of PROMIS assessment in the clinical setting to measure changes in patient-reported health before and after parathyroidectomy. We hypothesized that patients undergoing parathyroidectomy for PHPT would report greater improvement in mental and physical health compared with control patients. METHODS: Adult PHPT patients scheduled for parathyroidectomy and control patients requiring diagnostic thyroid operation were enrolled prospectively during a 6-month period. Patients were administered clinically relevant PROMIS health domains via CAT at a preoperative visit and 3 weeks after operation. A change in score of 5 or greater for each PROMIS instrument was defined as clinically important. Statistical significance of pre/post-surgery changes in scores was determined using paired t tests. RESULTS: A total of 35 patients with PHPT and 9 control patients completed the study. The mean number of PROMIS items answered during an assessment was 67 (range 51-121, SD 15.4). Median completion time was 8.2 minutes (range 3.4-38.4, SD 4.7). Clinically important improvement after parathyroidectomy in the PHPT group was greater than in the control group in 5 PROMIS domains. The score improvement experienced by PHPT patients was 8.8 in Fatigue, 6.7 in Sleep-Related Impairment, 5.0 in Anxiety, 7.0 in Applied Cognition, and 6.2 in Depression (all $P < .05$). CONCLUSION: PROMIS is an efficient clinical assessment platform for measuring patient-reported outcomes in PHPT via CAT. Several domains of physical and mental health in patients with PHPT show statistically and clinically important improvement after parathyroidectomy.
PubMed-ID: 26032828
http://dx.doi.org/10.1016/j.surg.2015.03.054

Parathyroid surgery: correlation between pre-operative localization studies and surgical outcomes.
Clin Endocrinol (Oxf),
Y. Ebner, Y. Garti-Gross, A. Margulis, Y. Levy, D. Nabrisky, D. Ophir and P. Rotman-Pikielny. 2015.

OBJECTIVE: Pre-operative imaging techniques have enabled minimally invasive parathyroid surgery to supersede the traditional approach to hyperparathyroidism (HPT) surgery, which included cervical exploration. Cervical ultrasound (US) and sestamibi scan (MIBI) are commonly performed, but the results of these localization tests do not always match. This study correlated surgical outcomes with pre-operative localization findings, including matched positive US and MIBI studies, one positive study (US or MIBI), conflicting studies or negative results. DESIGN: Retrospective medical record review. PATIENTS: A hundred and sixty nine consecutive patients who underwent parathyroidectomy from January 2005 to December 2012. MEASUREMENTS: Correlation between surgical outcomes and pre-operative localization tests. RESULTS: All patients (134F/35M, 59.6 +/- 13.5 years of age) had primary HPT. US and MIBI localization studies matched in 76%, whereas 10.7% had positive MIBI only and 8.3% US only. Studies were negative in 3.6% and contradictory in 1.8%. Minimally invasive parathyroidectomy was performed in 87% of the matched group and 89% of the MIBI-only group. Surgical success rate, defined as postoperative normalization of calcium and PTH levels, was similar in patients with a single positive study (MIBI or US) vs double-matched studies (MIBI and US). Patients were followed up for 6 weeks. Overall, pathology was consistent with adenoma in 95%. DISCUSSION: Parathyroidectomy success rate was similar in patients with primary HPT and MIBI-only or US-only positive localization studies compared to those with matched US/MIBI studies. The results support a clinical algorithm in which positive results from one imaging technique, either MIBI or US, are sufficient to refer a patient for parathyroid surgery.
PubMed-ID: 26053249
http://dx.doi.org/10.1111/cen.12835

Long-term effectiveness of localization studies and intraoperative parathormone monitoring in patients undergoing reoperative parathyroidectomy for persistent or recurrent hyperparathyroidism.
Am J Surg, 210(1):117-22.
P. P. Parikh, J. C. Farra, B. J. Allan and J. I. Lew. 2015.
BACKGROUND: Reoperative parathyroidectomy (RPTX) for persistent or recurrent hyperparathyroidism is associated with a high rate of operative failure. The long-term effectiveness of RPTX using localization studies and intraoperative parathormone monitoring (IPM) was examined. METHODS: Retrospective analysis of prospectively collected data from patients undergoing targeted RPTX with IPM for persistent or recurrent hyperparathyroidism was performed. Persistent hyperparathyroidism was defined as elevated calcium and parathormone (PTH) levels above normal range less than 6 months after parathyroidectomy. Recurrent hyperparathyroidism was defined as elevated calcium and PTH levels greater than 6 months after successful parathyroidectomy. Sensitivity and positive predictive value (PPV) for sestamibi, surgeon-performed ultrasound, intraoperative PTH dynamics, and surgical outcomes were evaluated. RESULTS: Of the 1,064 patients, 69 patients underwent 72 RPTXs with localizing studies and IPM. Sestamibi (n = 69) had a sensitivity of 74% and a PPV of 83%, whereas surgeon-performed ultrasound (n = 38) had a sensitivity of 55% and a PPV of 76%. IPM had a sensitivity of 100% and a PPV of 98%. An intraoperative PTH drop greater than or equal to 50% was predictive of operative success (P < .01). Overall, operative success and recurrence were 94% and 1.4%, with a mean patient follow-up of 59 +/- 12.8 months. CONCLUSION: RPTX can be performed in a targeted approach using preoperative localization studies and IPM, leading to a low rate of complications and a high rate of long-term operative success.
PubMed-ID: 26072281
http://dx.doi.org/10.1016/j.amjsurg.2014.09.039

Robotic parathyroidectomy.
J Surg Oncol,
A. K. Okoh, S. Sound and E. Berber. 2015.
Robotic parathyroidectomy has recently been described. Although the procedure eliminates the neck scar, it is technically more demanding than the conventional approaches. This report is a review of the patients' selection criteria, technique, and outcomes. J. Surg. Oncol. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26073748
http://dx.doi.org/10.1002/jso.23911

Parathyroid Carcinoma: An Update on Treatment Outcomes and Prognostic Factors from the National Cancer Data Base (NCDB).
Ann Surg Oncol,
E. A. Asare, C. Sturgeon, D. J. Winchester, L. Liu, B. Palis, N. D. Perrier, D. B. Evans, D. P. Winchester and T. S. Wang. 2015.
BACKGROUND: Parathyroid carcinoma is a rare disease. Conflicting results on prognostic factors and extent of

surgical resection for patients with parathyroid carcinoma have been made based on small sample sizes. A large, robust dataset is needed to help address some of the controversies. METHODS: A retrospective review of patients with parathyroid carcinoma in the National Cancer Data Base from 1985 to 2006 was performed. Characteristics of the cohort and type of treatment were evaluated. Prognostic factors were assessed with Cox proportional hazards regression models and 5- and 10-year OS rates were determined. RESULTS: There were 733 evaluable patients with a mean age of 56.1 +/- 15.3 years (median 57, range 15-89) and mean tumor size of 29.6 +/- 18.4 mm (median 25.0 mm, range 10.0-150.0). Tumor size, age at diagnosis, male sex, positive nodal status, and complete tumor resection had hazard ratios for death of 1.02 (1.01-1.02, p < 0.0001), 1.06 (1.05-1.07, p < 0.0001), 1.67 (1.24-2.25, p = 0.0008), 1.25 (0.57-2.76, p = 0.6), and 0.42 (0.22-0.81, p = 0.01), respectively, on multivariable analysis. Patients who had removal of the parathyroid tumor with concomitant resection of adjacent organs had HR for death of 0.70 (0.35-1.41, p = 0.3). The 5- and 10-year OS rates were 82.3 and 66 % respectively. CONCLUSIONS: Patient age, tumor size, and sex have modest effects on survival in patients with parathyroid carcinoma. A staging system with prognostic value for parathyroid carcinoma should include at least these pertinent prognostic factors.
PubMed-ID: 26077914
http://dx.doi.org/10.1245/s10434-015-4672-3

Vitamin D in Primary Hyperparathyroidism: Effects on Clinical, Biochemical, and Densitometric Presentation.
J Clin Endocrinol Metab, 100(9):3443-51.
M. D. Walker, E. Cong, J. A. Lee, A. Kepley, C. Zhang, D. J. McMahon and S. J. Silverberg. 2015.
CONTEXT: Vitamin D (25-hydroxyvitamin D [25OHD]) deficiency (<20 ng/mL) and insufficiency (20-29 ng/mL) are common in primary hyperparathyroidism (PHPT), but data regarding their skeletal effects in PHPT are limited. OBJECTIVE: The objective was to evaluate the association between 25OHD levels and PHPT severity. DESIGN, SETTINGS, AND PARTICIPANTS: This is a cross-sectional analysis of 100 PHPT patients with and without 25OHD insufficiency and deficiency from a university hospital setting. OUTCOME MEASURES: We measured calciotropic hormones, bone turnover markers, and bone mineral density (BMD) by dual x-ray absorptiometry. RESULTS: Lower 25OHD was associated with some (PTH: r = -0.42; P < .0001; 1,25-dihydroxyvitamin D: r = -0.27; P = .008; serum PO4: r = 0.31; P = .002) but not all (serum/urine calcium) indicators of PHPT severity. Lower 25OHD was also associated with younger age, higher body mass index, male gender, better renal function, and lower vitamin D intake. Comparison of those with deficient (<20 ng/mL; 19%) vs insufficient (20-29 ng/mL; 35%) vs replete (>/=30 ng/mL; 46%) 25OHD demonstrated more severe PHPT as reflected by higher PTH (mean +/- SEM, 126 +/- 10 vs 81 +/- 7 vs 72 +/- 7 pg/mL; P < .0001) but no difference in nephrolithiasis, osteoporosis, fractures, serum or urinary calcium, bone turnover markers, or BMD after adjustment for age and weight. In women, T-scores at the 1/3 radius were lower in those with 25OHD of 20-29 ng/mL, compared to those who were vitamin D replete (P = .048). In multiple regression modeling, 25OHD (but not PTH) was an independent predictor of 1/3 radius BMD. CONCLUSION: Vitamin D deficiency is associated with more severe PHPT as reflected by PTH levels, but effects on BMD are limited to the cortical 1/3 radius and are quite modest. These data support international guidelines that consider PHPT patients with 25OHD <20 ng/mL to be deficient. However, in this cohort with few profoundly vitamin D-deficient patients, vitamin D status did not appear to significantly impact clinical presentation or bone density.
PubMed-ID: 26079779
http://dx.doi.org/10.1210/jc.2015-2022

Parathyroidectomy Halts the Deterioration of Renal Function in Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 100(8):3069-73.
F. Tassone, A. Guarnieri, E. Castellano, C. Baffoni, R. Attanasio and G. Borretta. 2015.
OBJECTIVE: Decreased renal function has been consistently included among factors prompting recommendation for surgery in primary hyperparathyroidism (PHPT). However, most retrospective studies addressing this issue did not show an improvement in renal function after parathyroidectomy (PTX). The aim of this study was to investigate changes in renal function after PTX in PHPT patients subdivided according to renal function at diagnosis. DESIGN: This was a retrospective cross-sectional study. PATIENTS AND METHODS: We studied 109 consecutive PHPT patients before and after PTX. Biochemical evaluation included fasting total and ionized serum calcium, phosphate, creatinine, immunoreactive intact PTH, and 25-hydroxyvitamin D3 levels. Glomerular filtration rate (GFR) was assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. RESULTS: Mean (+/- SD) CKD-EPI estimated GFR (eGFR) at diagnosis was 82.4 +/- 19.3 mL/min/1.73 m(2) (median, 84.8 mL/min/1.73 m(2); interquartile range, 68.5-94.2 mL/min/1.73 m(2)). Patients with eGFR equal to or higher than 60 mL/min/1.73 m(2) (group 1, n = 95) were significantly younger than patients with eGFR lower than 60 mL/min/1.73 m(2) (group 2, n = 14; P < .0003). After PTX, eGFR did not

change in patients of group 2 (P = .509), whereas it was significantly reduced in patients of group 1 (P < .0002). The difference in eGFR between baseline and post-PTX values was correlated negatively with baseline serum creatinine (R = -0.27; P = .0052) and positively with baseline CKD-EPI eGFR (R = 0.32; P = .00062). At multiple regression analysis, only systolic blood pressure and baseline CKD-EPI eGFR were independent predictors of GFR variation. CONCLUSION: Surgical cure of PHPT halts renal function deterioration in patients with coexisting renal disease. Our study thus supports the indication for surgery in patients with eGFR less than 60 mL/min/1.73 m(2), as recommended by current guidelines. Moreover, our data show that presurgical renal function is a relevant predictor of renal function after PTX.
PubMed-ID: 26079781
http://dx.doi.org/10.1210/jc.2015-2132

Parathyroid Carcinoma: Is It Time for Change?
Ann Surg Oncol,
D. F. Schneider. 2015.
PubMed-ID: 26100817
http://dx.doi.org/10.1245/s10434-015-4673-2

No Need to Abandon Focused Unilateral Exploration for Primary Hyperparathyroidism with Intraoperative Monitoring of Intact Parathyroid Hormone.
J Am Coll Surg, 221(2):518-23.
K. M. Day, M. Elsayed and J. M. Monchik. 2015.
BACKGROUND: We investigated the rate of persistent and recurrent hyperparathyroidism after focused unilateral exploration (UE) with intraoperative monitoring of intact parathyroid hormone (IOPTH). STUDY DESIGN: A prospective cohort of 915 patients with primary hyperparathyroidism (PHP) underwent parathyroid surgery by a single surgeon from January 2003 to September 2013. A total of 556 patients with at least a single positive preoperative localization by ultrasound (US) and/or sestamibi scan (STS) underwent UE with IOPTH. The criterion for completion of surgery was an IOPTH fall of 50% from the highest intraoperative level and into the normal range 5 to 10 minutes after resection of the localized gland. RESULTS: Fifteen patients had either persistent or recurrent PHP, yielding a 2.7% (95% CI 1.6% to 4.4%) overall recurrence rate based on the refined Wilson method with continuity correction. Four patients had persistent PHP. Three of these patients were cured with reoperation, and the fourth patient was followed nonoperatively. Eleven patients had recurrent PHP, with 5 corrected by surgery and 6 patients followed nonoperatively. The mean postoperative serum calcium (Ca) level was 9.4 mg/dL over a mean follow-up interval of 44.0 months. Preoperative localization rates by each localization study were: US 74.3% (n = 413), STS 86.9% (n = 483), and US and STS 71.4% (n = 397). There was no difference in the preoperative study that localized the hyperfunctional parathyroid gland in recurrent vs nonrecurrent patients by the Fisher's exact test (US, p =1.00; STS, p =0.65; US and STS, p =1.00). CONCLUSIONS: The low rate of recurrent PHP after focused unilateral exploration with IOPTH suggests that this procedure should not be abandoned.
PubMed-ID: 26122588
http://dx.doi.org/10.1016/j.jamcollsurg.2015.04.013

Is Intraoperative Parathyroid Hormone Monitoring Warranted in Cases of 4D-CT/Ultrasound Localized Single Adenomas?
Otolaryngol Head Neck Surg, 153(2):183-8.
T. E. Heineman, D. I. Kutler, M. A. Cohen and W. I. Kuhel. 2015.
OBJECTIVE: To analyze the utility of intraoperative parathyroid hormone (IOPTH) monitoring for patients with primary hyperparathyroidism who had evidence of single-gland disease on preoperative imaging with modified 4-dimensional computed tomography that was done in conjunction with ultrasonography (Mod 4D-CT/US). STUDY DESIGN: Case series with chart review. SETTING: Tertiary care university medical center. SUBJECTS AND METHODS: Patients were drawn from consecutive directed parathyroidectomies performed between December 2001 and June 2013 by the senior authors. All patients had primary hyperparathyroidism and underwent a Mod 4D-CT/US study that showed findings on both studies that were consistent with a single adenoma. The modified Miami criteria were used for IOPTH monitoring (parathyroid hormone decrease by >50% and into the normal range). RESULTS: Of 356 patients who underwent parathyroid surgery, 206 had a single gland localized on the Mod 4D-CT and the US studies. IOPTH monitoring was used in 172 cases, of which 169 had adequate clinical follow-up to assess the surgical outcome. Twenty-one patients (12.4%) had IOPTH values that did not meet modified Miami criteria after removal of one gland, of which 7 were found to have multigland disease (4.1%). Three patients (1.8%) had persistent primary hyperparathyroidism despite an IOPTH that met modified Miami criteria. CONCLUSIONS: Although IOPTH monitoring correctly identifies a small percentage of patients with

multigland disease, some patients will be subjected to unnecessary neck explorations that can result in difficult intraoperative decisions, such as whether to remove normal or equivocal-sized glands when they are encountered.
PubMed-ID: 26124265
http://dx.doi.org/10.1177/0194599815590597

Real-Time Localization of Parathyroid Adenoma during Parathyroidectomy.
N Engl J Med, 373(1):96-8.
J. Jayender, T. C. Lee and D. T. Ruan. 2015.
PubMed-ID: 26132962
http://dx.doi.org/10.1056/NEJMc1415448

Transient and permanent hypocalcemia after total thyroidectomy: Early predictive factors and long-term follow-up results.
Surgery,
S. T. Seo, J. W. Chang, J. Jin, Y. C. Lim, K. S. Rha and B. S. Koo. 2015.
BACKGROUND: Post-thyroidectomy hypocalcemia is among the most common complications of total thyroidectomy. The purpose of this study was to evaluate early predictive factors and long-term changes in intact parathyroid hormone (iPTH) levels in patients with transient and permanent hypocalcemia after total thyroidectomy. PATIENTS AND METHODS: A total of 349 consecutive patients who underwent total thyroidectomy with or without neck dissection between 2009 and 2011 were reviewed. PTH, total calcium (Ca), and ionized Ca (iCa) levels were evaluated at 1 hour, and 1, 3, 5, and 7 days, and 1, 3, 6, and 12 months postoperatively. Biochemical profiles at 1 hour after total thyroidectomy in patients with transient and permanent hypocalcemia were compared. Patients with postoperative hypocalcemia were followed for 12 months. RESULTS: Lesser preoperative serum levels of Ca and more extensive surgery were significantly associated with postoperative hypocalcemia ($P < .05$). The absolute level and relative decline (%) in iPTH at 1 hour were the most reliable predictors of postoperative hypocalcemia according to the receiver operating characteristics curve, with a threshold of 10.42 pg/mL and 70%. Sensitivity and specificity of the predictors were 83.4% (95% CI, 76.4-89.1), 100% (95% CI, 84.6-100.0), 84.1 (95% CI, 77.2-89.7), and 95.5% (95% CI, 77.2-99.9), respectively. Parathyroid function recovered in the first month after total thyroidectomy in 78 of 99 patients (79%) with transient hypocalcemia. However, 46 of 61 patients (74%) with a subnormal iPTH level at 3 months after surgery had permanent hypocalcemia. CONCLUSION: Mean postoperative PTH level and the mean relative decline in PTH measured 1 hour postoperatively were the most reliable predictors of postoperative or permanent hypocalcemia.
PubMed-ID: 26144879
http://dx.doi.org/10.1016/j.surg.2015.04.041

The clinical importance of parathyroid atypia: Is long-term surveillance necessary?
Surgery, 158(4):929-36.
K. L. McCoy, R. R. Seethala, M. J. Armstrong, M. N. Nikiforova, M. T. Stang, S. E. Carty and L. Yip. 2015.
BACKGROUND: The uncommon diagnosis of atypical parathyroid adenoma (APA) creates a clinical conundrum for surveillance. We evaluated a large series of APA to determine long-term outcomes. METHODS: Prospectively collected data were retrieved for patients with a diagnosis of histologic APA defined by presence of >/=2 criteria: clinical/intraoperative adherence, fibrotic bands, trabecular growth, or mitotic rate of >1/10 per high-power field without indisputable signs of malignancy. Follow-up was at 2 weeks, 6 months, and yearly thereafter. RESULTS: From 1970 to 2014, 51 patients (1.2%) with primary hyperparathyroidism had a diagnosed APA. Mean age was 56 years (range, 19-83), and 61% were women. Intraoperatively, 11 of 51 glands (22%) were adherent, requiring concurrent thyroid lobectomy. Common microscopic findings were fibrosis (78%), trabecular growth (37%), and increased mitotic count (24%); the mean APA weight was 3.14 g (range, 167 mg-38 g). Loss of heterozygosity occurred in 25 of 38 tested patients (66%) at the p21 locus in 9 cases, at CDC73 and PTEN in 6, and at RB1 in 4 cases, with mean fractional allelic loss of 24% (range, 6-79). With mean follow-up of 5 years (range, 0.5-18), no patient has developed recurrence. CONCLUSION: Over a mean follow-up of 5 years, we observed no recurrences after APA resection. Molecular features had no discernable impact, indicating that long-term follow-up may be unnecessary.
PubMed-ID: 26210223
http://dx.doi.org/10.1016/j.surg.2015.06.022

Parathyroid imaging and successful Parathyroidectomy.
Clin Endocrinol (Oxf),

S. Minisola, C. Cipriani and J. Pepe. 2015.
PubMed-ID: 26299903
http://dx.doi.org/10.1111/cen.12880

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline.
J Clin Endocrinol Metab, 100(8):2807-31.
L. K. Nieman, B. M. Biller, J. W. Findling, M. H. Murad, J. Newell-Price, M. O. Savage and A. Tabarin. 2015.
OBJECTIVE: The objective is to formulate clinical practice guidelines for treating Cushing's syndrome. PARTICIPANTS: Participants include an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. The European Society for Endocrinology co-sponsored the guideline. EVIDENCE: The Task Force used the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews and used the best available evidence from other published systematic reviews and individual studies. CONSENSUS PROCESS: The Task Force achieved consensus through one group meeting, several conference calls, and numerous e-mail communications. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. CONCLUSIONS: Treatment of Cushing's syndrome is essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of comorbidities via directly treating the cause of Cushing's syndrome and by adjunctive treatments (eg, antihypertensives). Surgical resection of the causal lesion(s) is generally the first-line approach. The choice of second-line treatments, including medication, bilateral adrenalectomy, and radiation therapy (for corticotrope tumors), must be individualized to each patient.
PubMed-ID: 26222757
http://dx.doi.org/10.1210/jc.2015-1818

Other Articles

A two-decade experience of head and neck paragangliomas in a whole population-based single centre cohort.
Eur Arch Otorhinolaryngol, 272(8):2045-53.
T. Anttila, V. Hayry, T. Nicoli, J. Hagstrom, K. Aittomaki, P. Vikatmaa, M. Niemela, K. Saarilahti, A. Makitie and L. J. Back. 2015.
Paragangliomas are rare neuroendocrine tumours arising from neural crest-derived tissue. In the head and neck region typical locations are the carotid bifurcation, vagal nerve or jugulotympanic region. Paragangliomas are normally benign, and malignant transformation is rare. During the past decade the understanding of the genetic and molecular aetiology has had an important clinical impact on the management of PGs. This is a retrospective review of all histologically verified paragangliomas diagnosed and managed at an academic tertiary care referral centre between 1990 and 2010. Data on age, sex, symptoms, tumour location, management and follow-up were recorded. There were 64 patients with 74 tumours. Thirty-six per cent of the tumours were located in the carotid body region, 48 % in the jugulotympanic region and 15 % in the vagal nerve. One tumour was located in the dorsal neck. Most (95 %) of the patients were treated primarily with surgery and with curative intent. Definitive radiation therapy was primarily given to two patients. Recurrent or residual tumours were treated with surgery in three patients and with radiation therapy in nine patients. The typical long-term post-operative sequel was vocal

cord paralysis. Local recurrence was found in 6 % of patients. Symptoms and findings related to paragangliomas are variable and management should be individualized. Surgery remains the primary choice of the current treatment options, but often is challenging and warrants a multidisciplinary approach. We present an algorithm on the management of head and neck paragangliomas based on current knowledge.
PubMed-ID: 24973967
http://dx.doi.org/10.1007/s00405-014-3161-9

Posterior retroperitoneoscopic versus laparoscopic adrenalectomy in sporadic and MENIIA pheochromocytomas.
Surg Endosc, 29(8):2164-70.
A. Kiriakopoulos, A. Petralias and D. Linos. 2015.
INTRODUCTION: Retroperitoneal adrenalectomy (PRA) comprises an alternative approach in the management of adrenal tumors that has been set as the treatment of choice in our Institution. We assess the impact of PRA the management of hereditary and sporadic pheochromocytomas comparing its outcomes to the laparoscopic technique, in a case-controlled setting. PATIENTS AND METHODS: From May 2008 to January 2013, 17 patients [5 males and 12 females, mean age: 51 yrs (range 26-73)] with pheochromocytomas underwent PRA. Demographics, tumor characteristics, operative time, complications, hospital stay, and postoperative pain (based on VAS score at days 1 and 3) were compared to 17 selected laparoscopic patient controls [7 males and 10 females, mean age 49 yrs (range 25-64)]. RESULTS: 17 patients, 11 with the sporadic form and 6 with MENIIA associated pheochromocytomas, comprised the retroperitoneoscopic group. 19 pheochromocytomas with a mean size 3.7 cm (range 1.7-7.0) at a mean operative time: 105.6 min (range 60-180) were accordingly excised. In the laparoscopic group, 13 patients had sporadic pheochromocytomas, whereas 4 patients had MENIIA syndrome. Mean tumor size of the laparoscopic series was 5.1 cm (range 1.7-8.5) at a mean operative time of 137 min (range 75-195). No mortality or conversions were encountered in both groups. No blood transfusions were needed. Mean visual analog scale pain scores were significantly lower for the retroperitoneoscopic group both on days 1 and 3 [0.94 (0-3) vs 4.15 (3-6), $p < 0.001$ and 0.06 (0-1) vs 3.5 (2-6) $p < 0.001$] respectively. Mean hospital stay for the patients of the retroperitoneoscopic group was significantly better than the laparoscopic group [(2.1 +/- 0.24 days vs 40 +/- 0.70 days) $p < 0.001$]. CONCLUSIONS: Retroperitoneoscopic adrenalectomy is associated with excellent clinical results in the management of sporadic and hereditary pheochromocytomas. Moreover, it appears to be superior to the laparoscopic approach, because it is faster and affords the patient with less pain and shorter hospital stay.
PubMed-ID: 25303922
http://dx.doi.org/10.1007/s00464-014-3912-0

Primary aldosteronism: functional histopathology and long-term follow-up after unilateral adrenalectomy.
Clin Endocrinol (Oxf), 82(5):639-47.
C. Volpe, B. Hamberger, A. Hoog, K. Mukai, J. Calissendorff, H. Wahrenberg, J. Zedenius and M. Thoren. 2015.
OBJECTIVES: To investigate the long-term outcome after unilateral adrenalectomy in patients with primary aldosteronism (PA) and to establish the role of functional pathology for the final diagnosis of aldosterone-producing adenoma (APA) or hyperplasia. DESIGN: A single-centre, retrospective cohort study in a hospital setting. PATIENTS: Consecutive patients with PA, n = 120, who underwent unilateral adrenalectomy between 1985 and 2010. Preoperative and postoperative data were analysed. To indicate the site of aldosterone secretion in the resected adrenal, we added functional methods to routine histopathology, using in situ hybridization and immunohistochemistry to detect the presence of enzymes needed for aldosterone (CYP11B2) and cortisol (CYP11B1, CYP17A1) synthesis. RESULTS: The median follow-up was 5 years and the cure rate of PA 91%. Hypertension was improved in 97% and normalized in 38%. Functional histopathology changed the final diagnosis from APA to hyperplasia in 6 cases (7%). Five of these had no expression of or staining for aldosterone synthase in the adenoma, but only in nodules in the adjacent cortex. All except one APA patient were cured of PA. They had lower preoperative serum potassium and higher 24-h urinary aldosterone than patients with hyperplasia. Among patients with hyperplasia 16 of 26 were cured. CONCLUSIONS: Most patients were cured of PA by unilateral adrenalectomy. Almost all noncured benefitted from the operation as the blood pressure improved. Functional histopathology proved helpful in the distinction between APA and hyperplasia, and we recommend that functional histopathology should be added to routine histopathology to improve the diagnostic evaluation and aid in tailoring the follow-up.
PubMed-ID: 25347939
http://dx.doi.org/10.1111/cen.12645

Supine or sitting plasma metanephrine screening? A unifying solution for patients and doctors.
Clin Endocrinol (Oxf), 82(5):776-7.
V. Chortis, I. Bancos, R. K. Crowley and W. Arlt. 2015.
PubMed-ID: 25376196
http://dx.doi.org/10.1111/cen.12659

Diagnostic value of ACTH stimulation test in determining the subtypes of primary aldosteronism.
J Clin Endocrinol Metab, 100(5):1837-44.
Y. Jiang, C. Zhang, W. Wang, T. Su, W. Zhou, L. Jiang, W. Zhu, J. Xie and G. Ning. 2015.
BACKGROUND: Adrenal venous sampling is recommended as the golden standard for subtyping primary aldosteronism (PA). However, it is invasive and inconvenient, and seeking a better way to make differential diagnosis of PA is necessary. OBJECTIVE: The objective of the study was to evaluate the diagnostic value of ACTH stimulation test under 1 mg dexamethasone suppression test (DST) in determining the subtypes of PA. METHODS: Ninety-five patients with PA confirmed by saline infusion test were included in this study. According to adrenal venous sampling and histopathology, 39 patients were diagnosed as bilateral adrenal hyperplasia (BAH), 37 as aldosterone-producing adenoma (APA), and 19 as unilateral adrenal hyperplasia (UAH). An ACTH stimulation test under 1 mg DST was performed in all patients. Plasma aldosterone and cortisol levels were measured every 30 minutes until 120 minutes after the iv injection of 50 IU ACTH. RESULTS: During the ACTH stimulation test, aldosterone levels in APA and UAH were similar ($P > .05$) but higher than those in BAH ($P < .001$). Furthermore, stimulated aldosterone levels of unilateral PA (APA and UAH) were significantly higher than bilateral PA (BAH) ($P < .001$). Receiver-operated characteristics curve analyses showed the aldosterone after ACTH stimulation was effective for distinguishing between unilateral PA and bilateral PA. The diagnostic accuracy was highest at 120 minutes after ACTH stimulation, and the optimal cutoff value of the aldosterone was 77.90 ng/dL, with a sensitivity of 76.8%, a specificity of 87.2%, a positive predictive value of 89.6%, and a negative predictive value of 72.3%. CONCLUSIONS: The ACTH stimulation test under 1 mg DST is useful to determine the subtypes of PA, especially in unilateral and bilateral PA, and may guide further treatment in PA patients.
PubMed-ID: 25695882
http://dx.doi.org/10.1210/jc.2014-3551

An analysis of different therapeutic options in patients with Cushing's syndrome due to bilateral macronodular adrenal hyperplasia: a single-centre experience.
Clin Endocrinol (Oxf), 82(6):808-15.
N. M. Albiger, F. Ceccato, M. Zilio, M. Barbot, G. Occhi, S. Rizzati, A. Fassina, F. Mantero, M. Boscaro, M. Iacobone and C. Scaroni. 2015.
CONTEXT: Bilateral macronodular adrenal hyperplasia (BMAH) is a rare form of Cushing's syndrome (CS). A variety of in vivo tests to identify aberrant receptor expression have been proposed to guide medical treatment. Unilateral adrenalectomy (UA) may be effective in selected patients, but little is known about recurrence during follow-up. OBJECTIVE: To describe a series of patients with BMAH and CS treated by different approaches, with a particular focus on the benefit of UA. DESIGN AND PATIENTS: We retrospectively assessed 16 patients with BMAH and CS (11 females, five males), analysing the in vivo cortisol response to different provocative tests. Twelve of the 16 patients underwent UA and were monitored over the long term. RESULTS: Based on in vivo test results, octreotide LAR or propranolol was administered in one case of food-dependent CS and two patients with a positive postural test. A significant improvement in biochemical values was seen in all patients but with limited clinical response. UA was performed in 12 patients, producing long-term remission in three (106 +/- 28 months; range: 80-135), recurrence in eight (after 54 +/- 56 months; range 12-180) and persistence in one other. Four patients subsequently underwent contralateral adrenalectomy for overt CS, one received ketoconazole, and four other patients remain under observation for subclinical CS. CONCLUSIONS: Medical treatment based on cortisol response to provocative tests had a limited role in our patients, whereas UA was useful in some of them. Although recurrence is likely, the timing of onset is variable and close follow-up is mandatory to identify it.
PubMed-ID: 25727927
http://dx.doi.org/10.1111/cen.12763

High False Positivity in Positron Emission Tomography is a Potential Diagnostic Pitfall in Patients with Suspected Adrenal Metastasis.
World J Surg, 39(8):1902-8.
B. H. Lang, B. J. Cowling, J. Y. Li, K. P. Wong and K. Y. Wan. 2015.
BACKGROUND: Although 18F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) is a potentially powerful, non-invasive imaging tool in differentiating adrenal

metastasis from benign disease, some adenomas also exhibit high FDG uptake, therefore mimicking metastasis (i.e., false positives). We aimed to evaluate the accuracy of FDG-PET/CT based exclusively on histology and to identify risk factors for adrenal metastasis. METHODS: Among the 289 consecutive patients who underwent adrenalectomy, 39 (78.0%) patients had suspected solitary adrenal metastasis and had a positive preoperative FDG-PET/CT. The FDG-PET/CT findings were correlated with the histology of the excised adrenal gland. To identify risk factors for adrenal metastasis, characteristics were compared between patients with histologically proven adrenal metastasis and those without. Youden's index was used to calculate the optimal cut-off value for predicting adrenal metastasis. RESULTS: Histology of the excised adrenal tumor confirmed adrenal metastasis in 28/39 (71.8%) patients while non-metastatic lesions comprised mostly benign adrenal cortical adenoma (n=10) and one non-functional pheochromocytoma. Therefore, the overall false-positive rate of FDG-PET/CT was 28.2%. History of primary lung malignancy [odds ratio (OR) (95% CI) 20.00 (1.01-333.3), p=0.049] and SUVmax>2.65 [OR (95% CI) 31.606 (2.46-405.71), p=0.008] were independent risk factors for adrenal metastasis. CONCLUSIONS: Single adrenal uptake on FDG-PET/CT in suspected solitary adrenal metastasis was associated with a high false-positive rate (28.2%). Risk factors associated with adrenal metastasis included a history of known primary lung malignancy and a SUVmax>2.65 at the adrenal lesion of interest on FDG-PET/CT. Based on these findings, a new algorithm was constructed.
PubMed-ID: 25809060
http://dx.doi.org/10.1007/s00268-015-3035-3

Patterns of Use and Short-Term Outcomes of Minimally Invasive Surgery for Malignant Pheochromocytoma: A Population-Level Study.
World J Surg, 39(8):1966-73.
P. Goffredo, M. A. Adam, S. M. Thomas, R. P. Scheri, J. A. Sosa and S. A. Roman. 2015.
BACKGROUND: Malignant pheochromocytoma is rare, and there is a scarcity of data on the use of minimally invasive surgery (MIS) for treatment. The aims of this study were to analyze patterns of use of MIS for malignant pheochromocytoma in the U.S. and compare short-term outcomes to those of open adrenalectomy. METHODS: Patients with malignant pheochromocytoma undergoing MIS, including laparoscopy, robotic assisted, laparoscopy converted to open, or open adrenalectomy, were culled from the National Cancer Database, from 1998 to 2011. Data were examined using simple summary statistics, Chi2 and student's t tests, Mann-Whitney test, and logistic regression. RESULTS: A total of 36 MIS and 67 open adrenalectomies were identified in 2010-2011. No significant differences were observed between the two treatment groups in demographic characteristics or comorbidities. Preoperative diagnosis of malignancy was made in 52.8% of MIS and 48.5% of open patients (p=NS). MIS and open adrenalectomies did not differ with respect to lymph node metastases, vascular invasion, extra-adrenal-extension, and distant metastases (all p=NS). MIS tended to more often be used to perform partial adrenalectomy (38.9 vs. 20.4% open, p=0.061); surgical margins, 30-day readmission and mortality rates were similar to open adrenalectomy (all p=NS). Tumors removed via MIS were smaller (48.7 vs. 73.3 mm open, p=0.003) and associated with a shorter length of stay. CONCLUSIONS: A significant proportion of patients with malignant pheochromocytomas underwent MIS, with short-term outcomes which are comparable to those of open surgery. Further studies focused on long-term survival and recurrence are needed to assess the role of MIS in the management of these rare tumors.
PubMed-ID: 25821949
http://dx.doi.org/10.1007/s00268-015-3040-6

Semiquantitative 123I-Metaiodobenzylguanidine Scintigraphy to Distinguish Pheochromocytoma and Paraganglioma from Physiologic Adrenal Uptake and Its Correlation with Genotype-Dependent Expression of Catecholamine Transporters.
J Nucl Med, 56(6):839-46.
A. van Berkel, J. U. Rao, J. W. Lenders, N. S. Pellegata, B. Kusters, I. Piscaer, A. R. Hermus, T. S. Plantinga, J. F. Langenhuijsen, D. Vriens, M. J. Janssen, M. Gotthardt and H. J. Timmers. 2015.
(123)I-metaiodobenzylguanidine ((123)I-MIBG) scintigraphy plays an important role in the diagnostic evaluation of patients with pheochromocytoma and paraganglioma (PPGL). (123)I-MIBG targets cell membrane and vesicular catecholamine transporters of chromaffin cells and facilitates localization of the primary tumor and metastatic lesions. Its specificity for the diagnosis of adrenomedullary chromaffin cell tumors can be jeopardized by physiologic uptake by the normal adrenal medulla. The aim of this study was to distinguish between PPGLs and normal adrenal glands by evaluating semiquantitative (123)I-MIBG uptake and to examine genotype-specific differences in correlation with expression of catecholamine transporter systems. METHODS: Sixty-two PPGLs collected from 57 patients with hereditary mutations in SDHA (n = 1), SDHB (n = 2), and SDHD (n = 4) (SDH is succinate dehydrogenase); von Hippel-Lindau (VHL; n = 2); RET (n = 12); neurofibromin 1 (NF1; n = 2); and MYC-associated factor X (MAX; n = 1), and with sporadic PPGLs (n = 33) were investigated. Preoperative planar

and SPECT images were semiquantitatively analyzed using uptake measurements. Tumor-to-liver and normal adrenal-to-liver ratios were calculated and correlated with clinical characteristics including genotype, tumor size, and plasma metanephrines concentrations. The expression of norepinephrine transporter (NET) and vesicular monoamine transporter (VMAT-1) was evaluated immunohistochemically in paraffin-embedded tumor tissues. RESULTS: Mean tumor-to-liver ratios of PPGL lesions were significantly higher than normal adrenal-to-liver ratios ($P < 0.001$). Cutoff values to distinguish between physiologic and pathologic adrenal uptake were established at 0.7 (100% sensitivity, 10.3% specificity) and 4.3 (100% specificity, 66.1% sensitivity). No statistically significant differences in (123)I-MIBG uptake were found across PPGLs of different genotypes. Mean NET expression in hereditary cluster 2 (RET, NF1, MAX) and apparently sporadic tumors was significantly higher than for hereditary cluster 1 (SDHx, VHL) PPGLs ($P = 0.011$ and 0.006, respectively). Mean VMAT-1 expression in hereditary cluster 1 PPGLs was significantly higher than for cluster 2 tumors ($P = 0.010$). (123)I-MIBG uptake significantly correlated with maximum tumor diameter ($P = 0.002$). (123)I-MIBG uptake, however, did not correlate with either NET or VMAT-1 expression. CONCLUSION: Liver-normalized semiquantitative (123)I-MIBG uptake may be helpful to distinguish between pheochromocytoma and physiologic adrenal uptake. Genotype-specific differences in the expression of NET and VMAT-1 do not translate into differences in (123)I-MIBG uptake.
PubMed-ID: 25883126
http://dx.doi.org/10.2967/jnumed.115.154815

Primary Aldosteronism: the spectre of cure.
Clin Endocrinol (Oxf), 82(6):785-8.
M. J. Brown. 2015.
PubMed-ID: 25891888
http://dx.doi.org/10.1111/cen.12796

Primary Aldosteronism: unnecessary complexity in definition and diagnosis as a barrier to wider clinical care.
Clin Endocrinol (Oxf), 82(6):779-84.
G. A. Kline. 2015.
PubMed-ID: 25891981
http://dx.doi.org/10.1111/cen.12798

Risk of catecholaminergic crisis following glucocorticoid administration in patients with an adrenal mass: a literature review.
Clin Endocrinol (Oxf),
C. Barrett, S. H. van Uum and J. W. Lenders. 2015.
BACKGROUND: Glucocorticoids as diagnostic or therapeutic agents have been reported to carry an increased risk of catecholaminergic crisis (CC) in patients with pheochromocytoma or paraganglioma (PPGL). METHODS: We searched literature databases using the following terms: pheochromocytoma, paraganglioma, adrenal incidentaloma, steroids, glucocorticoids, dexamethasone suppression test (DST), hypertensive crisis, cosyntropin and CRH. From all published case reports (1962-2013), we reviewed medical history, presenting symptoms, dose and route of steroid administration, location and size of adrenal mass, biochemical phenotype and outcome. RESULTS: Twenty-five case reports describing a CC were identified. Three patients with an adrenal incidentaloma suffered a CC following high-dose DST, and in one case, this was fatal. In two of these patients, biochemical testing missed the diagnosis, and in the third, a DST was done despite elevated urinary metanephrines. No CC has been reported for patients undergoing a low-dose DST. Three of 16 patients who received therapeutic glucocorticoids and four of six patients following cosyntropin testing died. No specific biochemical phenotype was related to adverse events. CONCLUSIONS: Although a causal relationship cannot be established from this review, it seems prudent to exclude a PPGL in patients with a large incidentaloma or when high-dose DST is considered in a patient with an incidentaloma of any size. Our literature review does not support the need for biochemical testing for PPGL prior to a low-dose (1 mg) DST. Finally, before starting therapeutic glucocorticoids, any clinical signs or symptoms of a potential PPGL should prompt reliable biochemical testing to rule out a PPGL.
PubMed-ID: 25940577
http://dx.doi.org/10.1111/cen.12813

Effectiveness and safety of laparoscopic adrenalectomy of large pheochromocytoma: a prospective, nonrandomized, controlled study.
Am J Surg, 210(2):230-5.

W. Wang, P. Li, Y. Wang, Y. Wang, Z. Ma, G. Wang, J. Gao and H. Zhou. 2015.
BACKGROUND: Laparoscopic adrenalectomy (LA) is normally used to treat small-sized (<6 cm) pheochromocytoma (PCC). This study evaluated the effectiveness and safety of LA for treating large (>/=6 cm) PCC. METHODS: Fifty-one patients with resectable, large-sized (>/=6 cm) PCC were prospectively enrolled for elective LA (n = 23) or open adrenalectomy (n = 28). RESULTS: LA was converted into open adrenalectomy in 2 patients (2/23, 8.7%); LA was associated with relatively longer operative time (P = .033) but less intraoperative bleeding (P < .001), faster resumption of ambulatory status (P < .001), and shorter duration of postoperative hospitalization (P < .001). Frequency of PCC recurrence was similar between the 2 groups (P = 1.000). CONCLUSIONS: LA is a feasible, effective, and safe treatment modality for large-sized (>/=6 cm) PCC. LA is associated with minimal invasiveness and faster postoperative recovery.
PubMed-ID: 25952614
http://dx.doi.org/10.1016/j.amjsurg.2014.11.012

Long-Term Outcome of Bilateral Laparoscopic Adrenalectomy Measured by Disease-Specific Questionnaire in a Unique Group of Patients with Cushing's Syndrome.
Ann Surg Oncol,
V. Neychev, S. M. Steinberg, L. Yang, A. Mehta, N. Nilubol, M. F. Keil, L. Nieman, C. A. Stratakis and E. Kebebew. 2015.
BACKGROUND: Laparoscopic bilateral adrenalectomy (LBA) is recommended for patients with bilateral adrenal disease and occult or unresectable ectopic Cushing's syndrome (CS). There are limited data on long-term outcomes after LBA, partly due to the lack of disease-specific tools for the measurement of impact on patients' health and quality of life. METHODS: We used a disease-specific questionnaire covering all major clinicopathologic characteristics of CS. We compared the outcome from LBA to a control group of 60 patients who had thyroidectomy (matched for age, gender, and time of surgery, 2:1 control-to-CS). RESULTS: Twenty-eight patients (20 women and 8 men) underwent LBA for CS. Of them, 24 patients (86 %) provided responses to our questionnaire. Ninety-two percent of patients' responses indicated a significant improvement of general Cushing's physical features with complete resolution reported in 59 % of responses. Significant improvement of associated biochemical abnormalities and comorbidities was reported in 83 % of patients' responses including complete reversal in 58 %. Significant improvement in emotional-behavioral symptoms was reported in 84 % of patients' responses with complete recovery in 53 %. All patients expressed satisfaction with LBA and significant improvement in their general health and self-reported quality of life. All of the improvements after LBA were statistically significant compared with the control group. CONCLUSIONS: Our disease-specific questionnaire enables a clearer understanding of the association between the clinical, metabolic, and emotional-behavioral features of CS, its treatment with LBA, and long-term impact on patient-reported quality of life. This disease-specific questionnaire may be useful for future studies in patients with CS.
PubMed-ID: 25968622
http://dx.doi.org/10.1245/s10434-015-4605-1

Notch1 pathway in adrenocortical carcinomas: correlations with clinical outcome.
Endocr Relat Cancer, 22(4):531-43.
C. L. Ronchi, S. Sbiera, B. Altieri, S. Steinhauer, V. Wild, M. Bekteshi, M. Kroiss, M. Fassnacht and B. Allolio. 2015.
Previous SNP array analyses have revealed genomic alterations of the Notch pathway as being the most frequent abnormality in adrenocortical tumors (ACTs). The aim of the present study was to evaluate the expression of components of Notch signaling in ACTs and to correlate them with clinical outcome. The mRNA expression of JAG1, NOTCH1, and selected target genes of NOTCH1 (HES1, HES5, and HEY2) was evaluated in 80 fresh frozen samples (28 normal adrenal glands (NAGs), 24 adenomas (ACAs), and 28 carcinomas (ACCs)) by quantitative RT-PCR. Immunohistochemistry was performed in 221 tissues on paraffin slides (16 NAGs, 27 ACAs, and 178 ACCs) for JAG1, activated NOTCH1 (aNOTCH1), and HEY2. An independent ACC validation cohort (n=77) was then also investigated. HEY2 mRNA expression was higher in ACCs than it was in ACAs (P<0.05). The protein expression of all of the factors was high (H-score 2-3) in a larger proportion of ACCs as compared to ACAs and NAGs (JAG1 in 27, 15, and 10%; aNOTCH1 in 13, 8, and 0%; HEY2 in 66, 61, and 33% respectively, all P<0.001). High JAG1 expression was associated with earlier tumor stages and lower numbers of metastases in ACCs (both P=0.08) and favorably impacted overall and progression-free survival (PFS) (131 vs 30 months, hazard ratio (HR) 0.45, and 37 vs 9 months, HR 0.51, both P<0.005). This impact on overall survival (OS) was confirmed in the validation cohort. No such association was observed for aNOTCH1 or HEY2. In conclusion, different components of the Notch1 signaling pathway are overexpressed in ACCs, which suggests a role for the pathway in malignant transformation. However, JAG1 is overexpressed in a subgroup of ACCs with a better clinical outcome.

PubMed-ID: 25979380
http://dx.doi.org/10.1530/ERC-15-0163

A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome.
Eur J Endocrinol, 173(4):M23-32.
M. Reincke, K. Ritzel, A. Osswald, C. Berr, G. Stalla, K. Hallfeldt, N. Reisch, J. Schopohl and F. Beuschlein. 2015.
OBJECTIVE: Our aim was to review short- and long-term outcomes of patients treated with bilateral adrenalectomy (BADx) in ACTH-dependent Cushing's syndrome. METHODS: We reviewed the literature and analysed our experience with 53 patients treated with BADx since 1990 in our institution. RESULTS: BADx is considered if ACTH-dependent Cushing's syndrome is refractory to other treatment modalities. In Cushing's disease (CD), BADx is mainly used as an ultima ratio after transsphenoidal surgery and medical therapies have failed. In these cases, the time span between the first diagnosis of CD and treatment with BADx is relatively long (median 44 months). In ectopic Cushing's syndrome, the time from diagnosis to BADx is shorter (median 2 months), and BADx is often performed as an emergency procedure because of life-threatening complications of severe hypercortisolism. In both situations, BADx is relatively safe (median surgical morbidity 15%; median surgical mortality 3%) and provides excellent control of hypercortisolism; Cushing's-associated signs and symptoms are rapidly corrected, and co-morbidities are stabilised. In CD, the quality of life following BADx is rapidly improving, and long-term mortality is low. Specific long-term complications include the development of adrenal crisis and Nelson's syndrome. In ectopic Cushing's syndrome, long-term mortality is high but is mostly dependent on the prognosis of the underlying malignant neuroendocrine tumour. CONCLUSION: BADx is a relatively safe and highly effective treatment, and it provides adequate control of long-term co-morbidities associated with hypercortisolism.
PubMed-ID: 25994948
http://dx.doi.org/10.1530/EJE-15-0265

Cushing's syndrome.
Lancet, 386(9996):913-27.
A. Lacroix, R. A. Feelders, C. A. Stratakis and L. K. Nieman. 2015.
Chronic exposure to excess glucorticoids results in diverse manifestations of Cushing's syndrome, including debilitating morbidities and increased mortality. Genetic and molecular mechanisms responsible for excess cortisol secretion by primary adrenal lesions and adrenocorticotropic hormone (ACTH) secretion from corticotroph or ectopic tumours have been identified. New biochemical and imaging diagnostic approaches and progress in surgical and radiotherapy techniques have improved the management of patients. The therapeutic goal is to normalise tissue exposure to cortisol to reverse increased morbidity and mortality. Optimum treatment consisting of selective and complete resection of the causative tumour is necessay to allow eventual normalisation of the hypothalamic-pituitary-adrenal axis, maintenance of pituitary function, and avoidance of tumour recurrence. The development of new drugs offers clinicians several choices to treat patients with residual cortisol excess. However, for patients affected by this challenging syndrome, the long-term effects and comorbidities associated with hypercortisolism need ongoing care.
PubMed-ID: 26004339
http://dx.doi.org/10.1016/S0140-6736(14)61375-1

The clinical course of patients with adrenal incidentaloma: is it time to reconsider the current recommendations?
Eur J Endocrinol, 173(2):275-82.
D. Kastelan, I. Kraljevic, T. Dusek, N. Knezevic, M. Solak, B. Gardijan, M. Kralik, T. Poljicanin, T. Skoric-Polovina and Z. Kastelan. 2015.
OBJECTIVE: The current guidelines for the management of adrenal incidentaloma advise hormonal and radiological follow-up of patients for 2-5 years after the initial diagnosis. However, the vast majority of adrenal incidentaloma are non-functional benign cortical adenomas that require no treatment, so the routine application of the current strategies often results in a number of unnecessary biochemical and radiological investigations. The aim of this study was to analyse the clinical course of patients with adrenal incidentaloma and to provide a critical review of the current management strategy of the disease. DESIGN AND METHODS: This was a retrospective study performed in the Croatian Referral Center for adrenal gland disorders. The study included 319 consecutive patients with adrenal incidentaloma, 174 of which were followed for at least 24 months. RESULTS: The vast majority of patients were diagnosed with benign adrenal masses, whereas in about 5% of them adrenal tumor corresponded to adrenal carcinoma or metastasis. Tumor density was found to be superior to tumor size in distinguishing benign adrenal masses from malignant tumors and pheochromocytomas. During

the follow-up, no patient demonstrated a clinically significant increase in tumor size. In addition, no changes, either in metanephrines and normetanephrines or in the activity of renin-aldosterone axis, were observed during the follow-up. Six patients developed subclinical Cushing's syndrome (SCS) whereas eight patients with SCS showed biochemical remission during follow-up. CONCLUSION: The study suggests that the risk of an adrenal mass initially diagnosed as benign and non-functional becoming malignant or hormonally active is extremely low. Therefore, the clinical management of those patients should be tailored on an individual basis in order to avoid unnecessary procedures.
PubMed-ID: 26024670
http://dx.doi.org/10.1530/EJE-15-0199

15 YEARS OF PARAGANGLIOMA: Imaging and imaging-based treatment of pheochromocytoma and paraganglioma.
Endocr Relat Cancer, 22(4):T135-45.
F. Castinetti, A. Kroiss, R. Kumar, K. Pacak and D. Taieb. 2015.
Although anatomic imaging to assess the precise localization of pheochromocytomas/paragangliomas (PHEOs/PGLs) is unavoidable before any surgical intervention on these tumors, functional imaging is becoming an inseparable portion of the imaging algorithm for these tumors. This review article presents applications of the most up-to-date functional imaging modalities and image-based treatment to PHEOs/PGLs patients. Functional imaging techniques provide whole-body localization (number of tumors present along with metastatic deposits) together with genetic-specific imaging approaches to PHEOs/PGLs, thus enabling highly specific and sensitive PHEO/PGL detection and delineation that now greatly impact the management of patients. Radionuclide imaging techniques also play a crucial role in the prediction of possible radioactive treatment options for PHEO/PGL. In contrast to previous imaging algorithms used for either assessement of these patients or their follow-up, endocrinologists, surgeons, oncologists, pediatricians, and other specialists require functional imaging before any therapeutic plan is outlined to the patient, and follow-up, especially in patients with metastatic disease, is based on the periodic use of functional imaging, often reducing or substituting for anatomical imaging. In similar specific indications, this will be further powered by using PET/MR in the assessment of these tumors. In the near future, it is expected that PHEO/PGL patients will benefit even more from an assessement of the functional characteristics of these tumors and new imaging-based treatment options. Finally, due to the use of new targeting moieties, gene-targeted radiotherapeutics and nanobodies-based theranostic approaches are expected to become a reality in the near future.
PubMed-ID: 26045470
http://dx.doi.org/10.1530/ERC-15-0175

The Treatment of Cushing's Disease.
Endocr Rev, 36(4):385-486.
R. Pivonello, M. De Leo, A. Cozzolino and A. Colao. 2015.
Cushing's disease (CD), or pituitary-dependent Cushing's syndrome, is a severe endocrine disease caused by a corticotroph pituitary tumor and associated with increased morbidity and mortality. The first-line treatment for CD is pituitary surgery, which is followed by disease remission in around 78% and relapse in around 13% of patients during the 10-year period after surgery, so that nearly one third of patients experience in the long-term a failure of surgery and require an additional second-line treatment. Patients with persistent or recurrent CD require additional treatments, including pituitary radiotherapy, adrenal surgery, and/or medical therapy. Pituitary radiotherapy is effective in controlling cortisol excess in a large percentage of patients, but it is associated with a considerable risk of hypopituitarism. Adrenal surgery is followed by a rapid and definitive control of cortisol excess in nearly all patients, but it induces adrenal insufficiency. Medical therapy has recently acquired a more important role compared to the past, due to the recent employment of novel compounds able to control cortisol secretion or action. Currently, medical therapy is used as a presurgical treatment, particularly for severe disease; or as postsurgical treatment, in cases of failure or incomplete surgical tumor resection; or as bridging therapy before, during, and after radiotherapy while waiting for disease control; or, in selected cases, as primary therapy, mainly when surgery is not an option. The adrenal-directed drug ketoconazole is the most commonly used drug, mainly because of its rapid action, whereas the glucocorticoid receptor antagonist, mifepristone, is highly effective in controlling clinical comorbidities, mainly glucose intolerance, thus being a useful treatment for CD when it is associated with diabetes mellitus. Pituitary-directed drugs have the advantage of acting at the site responsible for CD, the pituitary tumor. Among this group of drugs, the dopamine agonist cabergoline and the somatostatin analog pasireotide result in disease remission in a consistent subgroup of patients with CD. Recently, pasireotide has been approved for the treatment of CD when surgery has failed or when surgery is not an option, and mifepristone has been approved for the treatment of Cushing's syndrome when associated with impairment of glucose metabolism in case of the lack of a surgical indication. Recent experience suggests that

the combination of different drugs may be able to control cortisol excess in a great majority of patients with CD.
PubMed-ID: 26067718
http://dx.doi.org/10.1210/er.2013-1048

Robotic posterior retroperitoneal adrenalectomy.
J Surg Oncol,
A. K. Okoh, H. Yigitbas and E. Berber. 2015.
Since its initial description by Mercan et al. laparoscopic posterior retroperitoneal (PR) adrenalectomy has served as an alternaltive to the transabdominal (TL) approach for the treatment of adrenal pathologies. Robotic adrenal surgery has been reported to improve surgeon ergonomics and facilitate dissection. In patients with bilateral adrenal masses, PR adrenalectomy may be the approach of choice. We herein describe the technique, discuss its limitations and present a critical review of the current literature. J. Surg. Oncol. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26073649
http://dx.doi.org/10.1002/jso.23909

Adrenal Imaging Features Predict Malignancy Better than Tumor Size.
Ann Surg Oncol,
J. Y. Yoo, K. L. McCoy, S. E. Carty, M. T. Stang, M. J. Armstrong, G. M. Howell, D. L. Bartlett, M. E. Tublin and L. Yip. 2015.
INTRODUCTION: In adrenal tumors, size >/=4 cm has been an indication for adrenalectomy due to concern for malignancy. We compared mass size to imaging features (ImF) for accuracy in diagnosing adrenal malignancy. METHODS: Data were retrieved for 112 consecutive patients who had adrenalectomy from January 2011 to August 2014. ImF was classified as nonbenign if HU > 10 on unenhanced CT scan or if loss of signal on out-of-phase imaging was absent on chemical-shift MRI. Indications for resection included hormonal hypersecretion, nonbenign ImF, and/or size >/=4 cm. RESULTS: Of 113 resected adrenals, 37 % were functional. Histologic malignancy occurred in 18 % (20/113) and included 3 adrenocortical carcinomas (ACC), 1 epithelioid liposarcoma, 1 lymphoma, 1 malignant nerve sheath tumor, and 14 adrenal metastases. Patients with malignancies were older (mean age, 60 +/- 13 vs. 51 +/- 14 years, p = 0.01). Malignant tumors were larger on preoperative imaging (mean 5.3 +/- 3.2 vs. 3.9 +/- 2.4 cm, p = 0.03). All 20 malignant masses had nonbenign ImF. In predicting malignancy, the sensitivity, specificity, NPV, and PPV of nonbenign ImF was 100, 57, 100, and 33 %, respectively. Size >/=4 cm was less predictive with sensitivity, specificity, NPV, and PPV of 55, 61, 86, and 23 %, respectively. If size >/=4 cm had been used as the sole criterion for surgery, 45 % of malignancies (9/20) would have been missed including 8 metastases and an ACC. CONCLUSIONS: In resected adrenal tumors, the presence of nonbenign ImF is more sensitive for malignancy than mass size (100 vs. 55 %) with equivalent specificity. Regardless of mass size, adrenalectomy should be strongly considered when non-benign ImF are present.
PubMed-ID: 26088650
http://dx.doi.org/10.1245/s10434-015-4684-z

15 YEARS OF PARAGANGLIOMA: The association of pituitary adenomas and phaeochromocytomas or paragangliomas.
Endocr Relat Cancer, 22(4):T105-22.
S. M. O'Toole, J. Denes, M. Robledo, C. A. Stratakis and M. Korbonits. 2015.
The combination of pituitary adenomas (PA) and phaeochromocytomas (phaeo) or paragangliomas (PGL) is a rare event. Although these endocrine tumours may occur together by coincidence, there is mounting evidence that, in at least some cases, classical phaeo/PGL-predisposing genes may also play a role in pituitary tumorigenesis. A new condition that we termed '3Pas' for the association of PA with phaeo and/or PGL was recently described in patients with succinate dehydrogenase mutations and PAs. It should also be noted that the classical tumour suppressor gene, MEN1 that is the archetype of the PA-predisposing genes, is also rarely associated with phaeos in both mice and humans with MEN1 defects. In this report, we review the data leading to the discovery of 3PAs, other associations linking PAs with phaeos and/or PGLs, and the corresponding clinical and molecular genetics.
PubMed-ID: 26113600
http://dx.doi.org/10.1530/ERC-15-0241

15 YEARS OF PARAGANGLIOMA: Metabolism and pheochromocytoma/paraganglioma.
Endocr Relat Cancer, 22(4):T83-90.
M. Mannelli, E. Rapizzi, R. Fucci, L. Canu, T. Ercolino, M. Luconi and W. F. Young, Jr. 2015.

The discovery of SDHD as a pheochromocytoma/paraganglioma susceptibility gene was the prismatic event that led to all of the subsequent work highlighting the key roles played by mitochondria in the pathogenesis of these tumors and other solid cancers. Alterations in the function of tricarboxylic acid cycle enzymes can cause accumulation of intermediate substrates and subsequent changes in cell metabolism, activation of the angiogenic pathway, increased reactive oxygen species production, DNA hypermethylation, and modification of the tumor microenvironment favoring tumor growth and aggressiveness. The elucidation of these tumorigenic mechanisms should lead to novel therapeutic targets for the treatment of the most aggressive forms of pheochromocytoma/paraganglioma.
PubMed-ID: 26113605
http://dx.doi.org/10.1530/ERC-15-0215

15 YEARS OF PARAGANGLIOMA: Genetics and mechanism of pheochromocytoma-paraganglioma syndromes characterized by germline SDHB and SDHD mutations.
Endocr Relat Cancer, 22(4):T71-82.
B. E. Baysal and E. R. Maher. 2015.
Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine neoplasms that derive from small paraganglionic tissues which are located from skull base to the pelvic floor. Genetic predisposition plays an important role in development of PPGLs. Since the discovery of first mutations in the succinate dehydrogenase D (SDHD) gene, which encodes the smallest subunit of mitochondrial complex II (SDH), genetic studies have revealed a major role for mutations in SDH subunit genes, primarily in SDHB and SDHD, in predisposition to both familial and non-familial PPGLs. SDH-mutated PPGLs show robust expression of hypoxia induced genes, and genomic and histone hypermethylation. These effects occur in part through succinate-mediated inhibition of alpha-ketoglutarate-dependent dioxygenases. However, details of mechanisms by which SDH mutations activate hypoxic pathways and trigger subsequent neoplastic transformation remain poorly understood. Here, we present a brief review of the genetic and mechanistic aspects of SDH-mutated PPGLs.
PubMed-ID: 26113606
http://dx.doi.org/10.1530/ERC-15-0226

Magnetic resonance spectroscopy of paragangliomas: new insights into in vivo metabolomics.
Endocr Relat Cancer, 22(4):M1-8.
A. Varoquaux, Y. le Fur, A. Imperiale, A. Reyre, M. Montava, N. Fakhry, I. J. Namer, G. Moulin, K. Pacak, M. Guye and D. Taieb. 2015.
Paragangliomas (PGLs) can be associated with mutations in genes of the tricarboxylic acid (TCA) cycle. Succinate dehydrogenase (SDHx) mutations are the prime examples of genetically determined TCA cycle defects with accumulation of succinate. Succinate, which acts as an oncometabolite, can be detected by ex vivo metabolomics approaches. The aim of this study was to evaluate the potential role of proton magnetic resonance (MR) spectroscopy ((1)H-MRS) for identifying SDHx-related PGLs in vivo and noninvasively. Eight patients were prospectively evaluated with single voxel (1)H-MRS. MR spectra from eight tumors (four SDHx-related PGLs, two sporadic PGLs, one cervical schwannoma, and one cervical neurofibroma) were acquired and interpreted qualitatively. Compared to other tumors, a succinate resonance peak was detected only in SDHx-related tumor patients. Spectra quality was considered good in three cases, medium in two cases, poor in two cases, and uninterpretable in the latter case. Smaller lesions had lower spectra quality compared to larger lesions. Jugular PGLs also exhibited a poorer spectra quality compared to other locations. (1)H-MRS has always been challenging in terms of its technical requisites. This is even more true for the evaluation of head and neck tumors. However, (1)H-MRS might be added to the classical MR sequences for metabolomic characterization of PGLs. In vivo detection of succinate might guide genetic testing, characterize SDHx variants of unknown significance (in the absence of available tumor sample), and even optimize a selection of appropriate therapies.
PubMed-ID: 26115958
http://dx.doi.org/10.1530/ERC-15-0246

Optimum position of left adrenal vein sampling for subtype diagnosis in primary aldosteronism.
Clin Endocrinol (Oxf),
H. Umakoshi, N. Wada, T. Ichijo, K. Kamemura, Y. Matsuda, Y. Fuji, T. Kai, T. Fukuoka, R. Sakamoto, A. Ogo, T. Suzuki, M. Tsuiki and M. Naruse. 2015.
CONTEXT: Although adrenal vein sampling (AVS) is the standard method for subtype diagnosis in primary aldosteronism (PA), protocol details including the sampling position in the adrenal vein are not standardized. OBJECTIVE: To establish the optimum sampling position in the left adrenal vein based on postoperative outcome in PA patients. DESIGN AND SETTING: Retrospective study in nine referral centres. PARTICIPANTS: Of 496 consecutive PA patients who underwent AVS between 2006 and 2013, 217 with successful AVS under

cosyntropin stimulation, and with concomitant data from two positions: proximal (common trunk) and distal (central vein) to the junction with the inferior phrenic vein, were included. MAIN OUTCOME MEASURES: Discordant rate of subtype diagnosis between common trunk and central vein, and postoperative outcomes in patients with discordant results. RESULTS: Subtype diagnosis using common trunk and central vein was discordant in 10 (4.6%) of the 217 patients (kappa = 0.87, P < 0.05). Of these 10 patients, eight with left unilateral subtype and two with bilateral subtype using common trunk data showed bilateral subtype and unilateral subtype, respectively, using central vein data. Five patients with left unilateral subtype and one with bilateral subtype by common trunk data underwent unilateral adrenalectomy. All six patients were cured of PA after adrenalectomy, resulting in false-negative rates of 17% (1/6) by common trunk data, and 83% (5/6) by central vein data. CONCLUSION: In view of its better potential diagnostic accuracy, technical ease, lower cost and lower risk of vein rupture, blood sampling from the common trunk of the left adrenal vein may be preferable as the standard method of AVS in patients with PA, although additional studies in a larger number of cases are required.
PubMed-ID: 26123796
http://dx.doi.org/10.1111/cen.12847

15 YEARS OF PARAGANGLIOMA: Pathology of pheochromocytoma and paraganglioma.
Endocr Relat Cancer, 22(4):T123-33.
A. S. Tischler and R. R. deKrijger. 2015.
Pathologists using their routine diagnostic tools can contribute both to the care of patients with pheochromocytoma/paraganglioma and to understanding the pathobiology of the tumors. They can document details of tissue organization and cytology that are accessible only by microscopy and can characterize admixtures of cell types that are morphologically distinct or show differential expression of immunohistochemical markers. Current roles and challenges for pathologists include differential diagnosis, identifying clues to the presence of hereditary disease, and effective communication of pathology information for clinical and research purposes. Future roles will increasingly involve risk stratification, identification of actionable targets for personalized therapies, and aiding the interpretation of molecular tests by helping characterize genetic variants of unknown significance. It remains to be determined to what extent the need for pathology input will be overshadowed by the availability of genetic testing and other molecular analyses at ever-decreasing cost, together with very effective clinical paradigms for risk stratification and patient care.
PubMed-ID: 26136457
http://dx.doi.org/10.1530/ERC-15-0261

Robotic lateral transabdominal adrenalectomy.
J Surg Oncol,
C. Nomine-Criqui, L. Brunaud, A. Germain, M. Klein, T. Cuny, A. Ayav and L. Bresler. 2015.
Laparoscopic transabdominal adrenalectomy is considered to be the standard of care for adrnalectomy. Widespread adoption of robotic technology has positioned robotic adrenalectomy as an option in some medical centers. Many studies have compared laparoscopic versus robotic approaches to perform adrenalectomy and evaluated potential advantages to balance higher costs. This review summarizes current available data regarding the use of the robotic system to perform adrenalectomy (RA) and its comparison with laparoscopic adrenalectomy (LA). J. Surg. Oncol. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26179549
http://dx.doi.org/10.1002/jso.23960

Reversing the established order: Should adrenal venous sampling precede cross-sectional imaging in the evaluation of primary aldosteronism?
J Surg Oncol,
M. Asmar, H. Wachtel, Y. Yan, D. L. Fraker, D. Cohen and S. O. Trerotola. 2015.
BACKGROUND: Adrenal venous sampling (AVS) is the definitive evaluation for primary aldosteronism (PA). Pre-AVS cross-sectional imaging does not reduce the need for AVS. The goal of this study was to examine whether performing AVS prior to imaging could decrease the use of imaging in the evaluation of PA at a high volume, experienced center. METHODS: We performed a retrospective analysis of all AVS procedures (n = 337) done for PA from 2001-2013. Patients whose cross-sectional imaging reports were unavailable (n = 90) or AVS was non-diagnostic (n = 12) were excluded. AVS was performed using modified Mayo technique. Univariate analysis utilized the chi2 test and fisher's exact test. RESULTS: Of the 235 patients analyzed, 63% (n = 148) were male. The mean age was 55 +/- 11 years. AVS was non-lateralizing in 43% (n = 101); these patients might have avoided imaging with an AVS-first approach. Imaging and AVS were concordant in 52% (n = 123). In patients </=40yo (n = 23), 35% (n = 8) had no lateralization on AVS, and might have avoided imaging in an AVS-

first approach. Imaging and AVS were concordant in 52% (n = 12) of patients </=40yo, versus 52% (n = 111) of patients >40yo (P = 0.987). CONCLUSION: An AVS-first, imaging-second approach could have avoided CT/MRI in 43% of patients. At a high volume, experienced center, performing AVS first on patients with PA may reduce unnecessary cross-sectional imaging studies. J. Surg. Oncol. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26185950
http://dx.doi.org/10.1002/jso.23963

Incidental and Intentional Medicine Achieve Similar Results in Primary Hyperaldosteronism.
Ann Surg Oncol,
L. E. Kuo, H. Wachtel, R. E. Roses, D. L. Fraker and R. R. Kelz. 2015.
BACKGROUND: Primary hyperaldosteronism is a common cause of hypertension, with significant cardiovascular, renal, and metabolic sequelae. Delayed diagnosis of primary hyperaldosteronism can lead to severe disease and lower cure rates after adrenalectomy. This study investigated the presentation and outcomes of patients who had primary hyperaldosteronism diagnosed after incidental discovery of an adrenal mass. METHODS: A retrospective cohort study investigated patients receiving adrenalectomy for primary hyperaldosteronism at the authors' institution from 2001 to 2014. Patients were classified as nonincidental if the aldosteronoma was identified on imaging performed for a hypertension or hypokalemia workup or after a biochemical diagnosis or as incidental if the aldosteronoma was identified on imaging performed for any other reason. Nonincidental and incidental patients were compared in terms of patient demographics, clinical history, preoperative test results, surgical pathology findings, and postoperative course. RESULTS: The study included 210 patients, 17 (8.1 %) of whom were incidental. At the time of surgical evaluation, 88 % of the incidental patients met the criteria for primary hyperaldosteronism screening based on hypokalemia or the degree of hypertension. The incidental patients were younger than the nonincidental patients, but the two groups were otherwise demographically and clinically similar. The incidental patients had larger aldosteronomas than the nonincidental patients. The nonincidental and incidental patients had similar rates of postoperative cure and failure. CONCLUSIONS: Nonincidental and incidental patients have comparable disease severity before surgical evaluation and similar rates of postoperative cure. Increased adherence to guidelines for screening of primary hyperaldosteronism will lead to a more timely diagnosis for all patients and a higher potential for surgical cure.
PubMed-ID: 26193964
http://dx.doi.org/10.1245/s10434-015-4729-3

Is there a role for segmental adrenal venous sampling and adrenal sparing surgery in patients with primary aldosteronism?
Eur J Endocrinol, 173(4):465-77.
F. Satoh, R. Morimoto, K. Seiji, N. Satani, H. Ota, Y. Iwakura, Y. Ono, M. Kudo, M. Nezu, K. Omata, Y. Tezuka, Y. Kawasaki, S. Ishidoya, Y. Arai, K. Takase, Y. Nakamura, K. McNamara, H. Sasano and S. Ito. 2015.
OBJECTIVE AND DESIGN: Adrenal venous sampling (AVS) is critical to determine the subtype of primary aldosteronism (PA). Central AVS (C-AVS) - that is, the collection of effluents from bilateral adrenal central veins (CV) - sometimes does not allow differentiation between bilateral aldosterone-producing adenomas (APA) and idiopathic hyperaldosteronism. To establish the best treatment course, we have developed segmental AVS (S-AVS); that is, we collect effluents from the tributaries of CV to determine the intra-adrenal sources of aldosterone overproduction. We then evaluated the clinical utility of this novel approach in the diagnosis and treatment of PA. METHODS: We performed C-AVS and/or S-AVS in 297 PA patients and assessed the accuracy of diagnosis based on the results of C-AVS (n=138, 46.5%) and S-AVS (n=159, 53.5%) by comparison with those of clinicopathological evaluation of resected specimens. RESULTS: S-AVS demonstrated both elevated and attenuated secretion of aldosterone from APA and non-tumorous segments, respectively, in patients with bilateral APA and recurrent APA. These findings were completely confirmed by detailed histopathological examination after surgery. S-AVS, but not C-AVS, also served to identify APA located distal from the CV. CONCLUSIONS: Compared to C-AVS, S-AVS served to identify APA in some patients, and its use should expand the pool of patients eligible for adrenal sparing surgery through the identification of unaffected segments, despite the fact that S-AVS requires more expertise and time. Especially, this new technique could enormously benefit patients with bilateral or recurrent APA because of the preservation of non-tumorous glandular tissue.
PubMed-ID: 26194502
http://dx.doi.org/10.1530/EJE-14-1161

Incidence of adrenal crisis in patients with adrenal insufficiency.
Clin Endocrinol (Oxf),
L. C. Smans, E. S. Van der Valk, A. R. Hermus and P. M. Zelissen. 2015.
BACKGROUND: An adrenal crisis (AC) is a potential life-threatening event in patients with adrenal insufficiency

(AI). This study aims to determine the incidence, causes, and risk factors of AC in AI. METHODS: Patients with AI diagnosed and treated at the University Medical Center Utrecht for the past 30 years were identified, and all medical records were assessed by two independent investigators. The observed frequency of AC was determined as incidence rate, calculated as the number of AC divided by person-years (PY). In addition, precipitating factors and risk factors were assessed. RESULTS: We observed an incidence rate of 5.2 AC (95% CI 4.3-6.3) per 100 PY in primary adrenal insufficiency (PAI, a total of 111 patients), and 3.6 AC (95% CI 3.1-4.1) per 100 PY in secondary adrenal insufficiency (SAI a total of 319 patients). Patients with an established diagnosis of tertiary (glucocorticoid-induced) adrenal insufficiency (a total of 28 patients) had 15.1 AC (95% CI 11.0-19.9) per 100 PY. The most important risk factor was the existence of comorbidity. Gastro-enteritis and other infections were the most common precipitating factors for AC. CONCLUSION: AC still occurs relatively frequent in patients with AI, mostly precipitated by infections and particularly in patients with high comorbidity. This should be taken into account in the education and follow-up of patients with AI.
PubMed-ID: 26208266
http://dx.doi.org/10.1111/cen.12865

Do additional imaging studies change operative management in patients undergoing adrenalectomy?
Surgery, 158(4):1003-11.
I. Lou, D. F. Schneider, G. E. Leverson, R. S. Sippel and H. Chen. 2015.
BACKGROUND: The purpose of this study is to determine the incidence of a secondary imaging modality (SIM) in the workup of adrenal masses and the usefulness of this additional imaging in changing surgical management. METHODS: A retrospective analysis of our adrenalectomy database was performed on adult patients who underwent >/=1 imaging study before surgery. A multivariate logistic regression model was then constructed to identify patient factors that predisposed SIM. RESULTS: From February 2001 to August 2014, 264 cases met inclusion criteria, of which 98 (37%) were identified to have SIM. Patients with cancer (P = .001), incidentaloma (P = .002), and pheochromocytoma (P < .0001) were more likely to undergo additional imaging. MRI was the most commonly obtained SIM. In addition, 90 of the 98 cases (92%) met indications for adrenalectomy with primary imaging study and biochemical screening alone. Of the remaining 8 cases, in only 4 instances (4%) did SIM modify surgical decision making. CONCLUSION: The high incidence of unnecessary additional imaging performed in patients undergoing adrenalectomy is counterproductive to efforts toward cost-conscious, high-quality health care. Patients with adrenal tumors would benefit from early surgical referral to allow the surgeon to help guide clinical decision making and to avoid the use of excessive imaging.
PubMed-ID: 26233809
http://dx.doi.org/10.1016/j.surg.2015.05.031

Primary Aldosteronism: Seismic Shifts.
J Clin Endocrinol Metab, 100(8):2853-5.
J. W. Funder. 2015.
PubMed-ID: 26247594
http://dx.doi.org/10.1210/jc.2015-2800

Novel Somatic Mutations in Primary Hyperaldosteronism are related to the Clinical, Radiological and Pathological Phenotype.
Clin Endocrinol (Oxf),
U. I. Scholl, J. M. Healy, A. Thiel, A. L. Fonseca, T. C. Brown, J. W. Kunstman, M. J. Horne, D. Dietrich, J. Riemer, S. Kucukkoylu, E. N. Reimer, A. C. Reis, G. Goh, G. Kristiansen, A. Mahajan, R. Korah, R. P. Lifton, M. L. Prasad and T. Carling. 2015.
Aldosterone-producing adenomas (APAs) and bilateral adrenal hyperplasia are important causes of secondary hypertension. Somatic mutations in KCNJ5, CACNA1D, ATP1A1, ATP2B3 and CTNNB1 have been described in APAs. OBJECTIVE: To characterize clinical-pathological features in APAs and unilateral adrenal hyperplasia, and correlate them with genotypes. DESIGN: Retrospective study. SUBJECTS AND MEASUREMENTS: Clinical and pathological characteristics of 90 APAs and 7 diffusely or focally hyperplastic adrenal glands were reviewed, and samples were examined for mutations in known disease genes by Sanger or exome sequencing. RESULTS: Mutation frequencies were: KCNJ5, 37.1%; CACNA1D, 10.3%; ATP1A1, 8.2%; ATP2B3, 3.1%; CTNNB1, 2.1%. Previously unidentified mutations included I157K, F154C and 2 insertions (I150_G151insM and I144_E145insAI) in KCNJ5, all close to the selectivity filter, V426G_V427E_A428_L433del in ATP2B3, and A39Efs*3 in CTNNB1. Mutations in KCNJ5 were associated with female, and other mutations with male gender (p=0.007). On computed tomography, KCNJ5-mutant tumors displayed significantly greater diameter (p=0.023), calculated area (p=0.002) and lower pre-contrast Hounsfield Units (p=0.0002) vs. tumors with mutations in other genes. Accordingly, KCNJ5-mutant tumors were predominantly comprised of lipid-rich fasciculata-like clear cells,

whereas other tumors were heterogeneous (p=5x10-6 vs. non-KCNJ5 mutant and p=0.0003 vs. wild type tumors, respectively). CACNA1D mutations were present in two samples with hyperplasia without adenoma. CONCLUSIONS: KCNJ5 mutant tumors appear to be associated with fasciculata-like clear cell predominant histology and tend to be larger with a characteristic imaging phenotype. Novel somatic KCNJ5 variants likely cause adenomas by loss of potassium selectivity, similar to previously described mutations. This article is protected by copyright. All rights reserved.
PubMed-ID: 26252618
http://dx.doi.org/10.1111/cen.12873

15 YEARS OF PARAGANGLIOMA: Pheochromocytoma, paraganglioma and genetic syndromes: a historical perspective.
Endocr Relat Cancer, 22(4):T147-59.
T. Else. 2015.
The last decades have elucidated the genetic basis of pheochromocytoma (PC) and paraganglioma (PGL) (PCPGL)-associated hereditary syndromes. However, the history of these syndromes dates back at least another 150 years. Detailed descriptions by clinicians and pathologists in the 19th and 20th centuries led to the recognition of the PCPGL-associated syndromes von Hippel-Lindau disease, neurofibromatosis type 1, and multiple endocrine neoplasia type 2. In the beginning of the current millennium the molecular basis of the hereditary PGL syndrome was elucidated by the discovery of mutations in genes encoding enzymes of the Krebs cycle, such as succinate dehydrogenase genes (SDHx) and other mutations, causing 'pseudo-hypoxia' signaling. These recent developments also marked a paradigm shift. It reversed the traditional order of genetic research that historically aimed to define the genetic basis of a known hereditary syndrome but now is challenged with defining the full clinical phenotype associated with a newly defined genetic basis. This challenge underscores the importance to learn from medical history, continue providing support for clinical research, and train physicians with regards to their skills to identify patients with PCPGL-associated syndromes to extend our knowledge of the associated phenotype. This historical overview provides details on the history of the paraganglial system and PCPGL-associated syndromes. As such, it hopefully will not only be an interesting reading for the physician with a historical interest but also emphasize the necessity of ongoing astute individual clinical observations and clinical registries to increase our knowledge regarding the full phenotypic spectrum of these conditions.
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http://dx.doi.org/10.1530/ERC-15-0221

15 YEARS OF PARAGANGLIOMA: Clinical manifestations of paraganglioma syndromes types 1-5.
Endocr Relat Cancer, 22(4):T91-103.
D. E. Benn, B. G. Robinson and R. J. Clifton-Bligh. 2015.
The paraganglioma (PGL) syndromes types 1-5 are autosomal dominant disorders characterized by familial predisposition to PGLs, phaeochromocytomas (PCs), renal cell cancers, gastrointestinal stromal tumours and, rarely, pituitary adenomas. Each syndrome is associated with mutation in a gene encoding a particular subunit (or assembly factor) of succinate dehydrogenase (SDHx). The clinical manifestations of these syndromes are protean: patients may present with features of catecholamine excess (including the classic triad of headache, sweating and palpitations), or with symptoms from local tumour mass, or increasingly as an incidental finding on imaging performed for some other purpose. As genetic testing for these syndromes becomes more widespread, presymptomatic diagnosis is also possible, although penetrance of disease in these syndromes is highly variable and tumour development does not clearly follow a predetermined pattern. PGL1 syndrome (SDHD) and PGL2 syndrome (SDHAF2) are notable for high frequency of multifocal tumour development and for parent-of-origin inheritance: disease is almost only ever manifest in subjects inheriting the defective allele from their father. PGL4 syndrome (SDHB) is notable for an increased risk of malignant PGL or PC. PGL3 syndrome (SDHC) and PGL5 syndrome (SDHA) are less common and appear to be associated with lower penetrance of tumour development. Although these syndromes are all associated with SDH deficiency, few genotype-phenotype relationships have yet been established, and indeed it is remarkable that such divergent phenotypes can arise from disruption of a common molecular pathway. This article reviews the clinical presentations of these syndromes, including their component tumours and underlying genetic basis.
PubMed-ID: 26273102
http://dx.doi.org/10.1530/ERC-15-0268

Curative Resection of Adrenocortical Carcinoma: Rates and Patterns of Postoperative Recurrence.
Ann Surg Oncol,
N. Amini, G. A. Margonis, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I.

Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2015.
BACKGROUND: Adrenocortical carcinoma (ACC) is a rare malignancy. The aim of this study was to determine the incidence and patterns of recurrence after curative-intent surgery for ACC. METHODS: Patients who underwent curative-intent resection for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the United States ACC study group. Patients with metastasis or an R2 margin were excluded. Patterns and rates of recurrence were determined and classified as locoregional and distant recurrence. RESULTS: A total of 180 patients with a median age of 52 years (interquartile range 43-61) were identified. Most patients underwent open surgery (n = 111, 64.5 %) and had an R0 resection margin (n = 117, 75.0 %). At last follow-up, 116 patients (64.4 %) had experienced recurrence (locoregional only, n = 41, 36.3 %; distant only, n = 51, 45.1 %; locoregional and distant, n = 21, 18.6 %). Median time to recurrence was 18.8 months. Several factors were associated with locoregional recurrence, including left-sided ACC location (odds ratio [OR] 2.71, 95 % confidence interval [CI] 1.06-6.89) and T3/T4 disease (reference T1/T2, OR 3.04, 95 % CI 1.19-7.80) (both $p < 0.05$). Distant recurrence was associated with larger tumor size (OR 1.11, 95 % CI 1.01-1.24) and T3/T4 disease (reference T1/T2, OR 5.23, 95 % CI 1.70-16.10) (both $p < 0.05$). Patients with combined locoregional and distant recurrence had worse survival (3- and 5-year survival: 39.5, 19.7 %) versus patients with distant-only (3- and 5-year survival 55.1, 43.3 %) or locoregional-only recurrence (3- and 5-year survival 81.4, 64.1 %) ($p = 0.01$). CONCLUSIONS: Nearly two-thirds of patients experienced disease recurrence after resection of ACC. Although a subset of patients experienced recurrence with locoregional disease only, many patients experienced recurrence with distant disease as a component of recurrence and had a poor prognosis.
PubMed-ID: 26282907
http://dx.doi.org/10.1245/s10434-015-4810-y

Whole Body Metabolic Tumor Volume and Total Lesion Glycolysis Predict Survival in Patients with Adrenocortical Carcinoma.
Ann Surg Oncol,
K. Satoh, D. Patel, W. Dieckmann, N. Nilubol and E. Kebebew. 2015.
BACKGROUND: Adrenocortical carcinoma (ACC) is a rare but lethal malignancy with few reliable prognostic markers. FDG-PET metabolic parameters have been shown to predict survival in several cancers. The objective was to determine if metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax) could serve as prognostic markers in patients with ACC. METHODS: A total of 30 patients with ACC prospectively underwent 18F-FDG PET/CT prior to treatment. Whole body MTV, TLG, and SUVmax were measured by a semiautomatic method. A median cutoff was used to determine an association with overall survival (OS) from the time of 18F-FDG PET/CT by the Kaplan-Meier method. RESULTS: Patients with high whole body MTV (>87.0 mL),TLG (>229.4 SUVlbm*mL), or SUVmax (>8.9 SUV) had a worse OS compared with those with low whole body MTV (median OS, 24 vs 45.1 months, $p < .01$), TLG (median OS, 24 vs 40.3 months, $p < .005$), or SUVmax (median OS, 23.7 vs 35.5 months, $p < .02$). In patients who had operable disease (n = 23), high whole body MTV (>87.0 mL) and TLG (>229.4 SUVlbm*mL) had a worse OS compared with those with low whole body MTV (median OS, 25.1 vs 45.1 months, $p < .05$) and TLG (median OS, 25.1 vs 40.3 months, $p < .05$), but a high SUVmax (>8.9 SUV) was not associated with worse OS ($p = .11$). CONCLUSIONS: Patients with ACC and a high whole body MTV, TLG, and SUVmax have a worse prognosis and OS. Measurement of whole body MTV and TLG may be helpful for guiding therapy for patients with ACC.
PubMed-ID: 26282908
http://dx.doi.org/10.1245/s10434-015-4813-8

Adrenocortical Carcinoma: Impact of Surgical Margin Status on Long-Term Outcomes.
Ann Surg Oncol,
G. A. Margonis, Y. Kim, J. D. Prescott, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2015.
BACKGROUND: The influence of surgical margin status on long-term outcomes of patients undergoing adrenal resection for ACC remains not well defined. We studied the impact of surgical tumor margin status on recurrence-free survival (RFS) and overall survival (OS) of patients undergoing resection for ACC. METHODS: A total of 165 patients who underwent adrenal resection for ACC and met inclusion criteria were identified form a multi-institutional database. Clinicopathological data, pathologic margin status, and long-term outcomes were assessed. Patients were stratified into two groups based on margin status: R0 (margin >1 mm) versus R1.

RESULTS: R0 resection was achieved in 126 patients (76.4 %), whereas 39 patients (23.6 %) had an R1 resection. Median and 5-year OS for patients undergoing R0 resection were 96.3 months and 64.8 % versus 25.1 months and 33.8 % for patients undergoing an R1 resection (both $p < 0.001$). On multivariable analysis, surgical margin status was an independent predictor of worse OS (hazard ratio [HR] 2.22, 95 % confidence interval [CI] 1.03-4.77; $p = 0.04$). The incidence of recurrence also differed between the two groups; 5-year RFS was 30.3 % among patients with an R0 resection versus 13.8 % among patients who had an R1 resection ($p = 0.03$). Lymph node metastasis (N1) was an independent predictor of RFS (HR 2.70, 95 % CI 1.04-6.99; $p = 0.04$). CONCLUSIONS: A positive margin after ACC resection was associated with worse long-term survival. Patient selection and an emphasis on surgical technique to achieve R0 margins are pivotal to optimizing the best chance for long-term outcome among patients with ACC.
PubMed-ID: 26286195
http://dx.doi.org/10.1245/s10434-015-4803-x

MANAGEMENT OF ENDOCRINE DISEASE: Outcome of adrenal sparing surgery in heritable pheochromocytoma.
Eur J Endocrinol,
F. Castinetti, D. Taieb, J. F. Henry, M. K. Walz, C. Guerin, T. Brue, B. Conte-Devolx, H. Neumann and F. Sebag. 2015.
The management of hereditary pheochromocytoma has drastically evolved in the last 20 years. Bilateral pheochromocytoma does not increase mortality in multiple endocrine neoplasia type 2 (MEN 2) or von Hippel-Lindau (VHL) mutation carriers who are followed regularly, but these mutations induce major morbidities if total bilateral adrenalectomy is performed. Cortical sparing adrenal surgery may be proposed to avoid definitive adrenal insufficiency. The surgical goal is to leave sufficient cortical tissue to avoid glucocorticoid replacement therapy. This approach was achieved by the progressive experience of minimally invasive surgery via the transperitoneal or retroperitoneal route. Cortical sparing adrenal surgery exhibits less than 5% significant recurrence after 10 years of follow-up and normal glucocorticoid function in more than 50% of cases. Therefore, cortical sparing adrenal surgery should be systematically considered in the management of all patients with MEN 2 or VHL hereditary pheochromocytoma. Hereditary pheochromocytoma is a rare disease, and a randomized trial comparing cortical sparing vs. classical adrenalectomy is probably not possible. This lack of data most likely explains why cortical sparing surgery has not been adopted in most expert centers that perform at least 20 procedures per year for the treatment of this disease. This review examined recent data to provide insight into the technique, its indications, and results and subsequent follow-up in the management of patients with hereditary pheochromocytoma with a special emphasis on MEN 2.
PubMed-ID: 26297495
http://dx.doi.org/10.1530/EJE-15-0549

Robotic adrenalectomy: the jury is still out.
Gland Surg, 4(4):277-8.
M. W. Ball and M. E. Allaf. 2015.
A minimally-invasive approach is the gold standard for surgical management of the majority of adrenal masses. While laparoscopy has traditionally been used, robotic adrenalectomy is becoming increasingly utilized. This article discusses a recent systematic review and meta-analysis from European Urology that analyzed evidence comparing laparoscopic and robotic adrenalectomy. Robotic adrenalectomy is associated with lower blood loss, length of stay and fewer complications compared to laparoscopic adrenalectomy; however information on efficacy and cost are not addressed. Ultimately, well-done randomized controlled trials (RCTs) are necessary to determine the benefits and cost of robotics in adrenal surgery.
PubMed-ID: 26311226
http://dx.doi.org/10.3978/j.issn.2227-684X.2015.04.16

NET

Meta-Analyses

Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms.
Br J Surg, 102(9):1026-36.
F. J. Huttner, J. Koessler-Ebs, T. Hackert, A. Ulrich, M. W. Buchler and M. K. Diener. 2015.
BACKGROUND: Pancreatic enucleation is a tissue-sparing approach to pancreatic neoplasms and may result in better postoperative pancreatic function than standard pancreatic resection. The objective of this review was to compare the postoperative outcome after pancreatic enucleation versus standard resection. METHODS: MEDLINE, Embase and the Cochrane Library were searched systematically until February 2015 to identify studies comparing the outcome of enucleation versus standard resection for pancreatic neoplasms. After critical appraisal, meta-analysis was performed and the findings were presented as odds ratios or weighted mean differences with corresponding 95 per cent c.i. RESULTS: Twenty-two observational studies (1148 patients) were included. Duration of surgery (P < 0.001), blood loss (P < 0.001), length of hospital stay (P = 0.04), and postoperative endocrine (P < 0.001) and exocrine (P = 0.01) insufficiency were lower after enucleation than after standard resection. Mortality (P = 0.44), overall complications (P = 0.74), reoperation rate (P = 0.93) and delayed gastric emptying (P = 0.15) were not significantly different between the two approaches. The overall rate of postoperative pancreatic fistula (POPF) was higher after enucleation than after standard resection (P < 0.001). However, the raised POPF rate did not result in higher mortality or overall morbidity. Sensitivity analysis of high-volume studies (total of more than 20 enucleations and more than 4 per year) showed that, in specialized centres, enucleation can be performed with no increased risk of POPF (P = 0.12). CONCLUSION: Compared with standard resection, pancreatic enucleation can be performed effectively and with comparable safety in high-volume institutions. Enucleation should be considered instead of standard resection for selected pancreatic neoplasms.
PubMed-ID: 26041666
http://dx.doi.org/10.1002/bjs.9819

Randomized controlled trials

- None -

Consensus Statements/Guidelines

Consensus Recommendations for the Diagnosis and Management of Pancreatic Neuroendocrine Tumors: Guidelines from a Canadian National Expert Group.
Ann Surg Oncol, 22(8):2685-99.
S. Singh, C. Dey, H. Kennecke, W. Kocha, J. Maroun, P. Metrakos, T. Mukhtar, J. Pasieka, D. Rayson, C. Rowsell, L. Sideris, R. Wong and C. Law. 2015.
Pancreatic neuroendocrine tumors (pNETs) are rare heterogeneous tumors that have been steadily increasing in both incidence and prevalence during the past few decades. Pancreatic NETs are categorized as functional (F) or nonfunctional (NF) based on their ability to secrete hormones that elicit clinically relevant symptoms. Specialized diagnostic tests are required for diagnosis. Treatment options are diverse and include surgical resection, intraarterial hepatic therapy, and peptide receptor radionuclide therapy (PRRT). Systemic therapy options include targeted agents as well as chemotherapy when indicated. Diagnosis and management should occur through a collaborative team of health care practitioners well-experienced in managing pNETs. Recent advances in pNET treatment options have led to the development of the Canadian consensus document described in this report. The discussion includes the epidemiology, classification, pathology, clinical presentation and prognosis, imaging and laboratory testing, medical and surgical management, and recommended treatment algorithms for pancreatic neuroendocrine cancers.
PubMed-ID: 25366583
http://dx.doi.org/10.1245/s10434-014-4145-0

Other Articles

Long-term Prognosis of Resected Pancreatic Neuroendocrine Tumors in von Hippel-Lindau Disease Is Favorable and Not Influenced by Small Tumors Left in Place.
Ann Surg, 262(2):384-8.
L. de Mestier, S. Gaujoux, J. Cros, O. Hentic, M. P. Vullierme, A. Couvelard, G. Cadiot, A. Sauvanet, P. Ruszniewski, S. Richard and P. Hammel. 2015.
BACKGROUND: Management of pancreatic neuroendocrine tumors (PNETs) associated with von Hippel-Lindau disease (VHL) is challenging because of the malignant potential and difficulty in predicting prognosis. OBJECTIVE: Compare the long-term outcome of resected VHL-PNET and sporadic PNET. METHODS: Data of all patients with VHL (n = 23) operated on for nonmetastatic PNET were reviewed. Patient characteristics and recurrence-free survival rates were compared with those in patients operated on for sporadic PNET, matched for tumor size, stage, and Ki-67 index. RESULTS: Patients in both groups had similar demographic characteristics, except that patients with VHL were younger (36 vs 56 years, P < 0.0001). Median tumor size was 30 mm. Median Ki-67 index was 3% and 4% in the VHL and sporadic groups (P = 0.95), respectively, and lymph node metastases were present in 43% and 30% of cases, respectively (P = 0.45). Sixteen (70%) patients with VHL had multiple PNET; lesions less than 15 mm were left in place in 11 patients. Median postoperative follow-up was 107 months (interquartile range, 57-124 months) and 71 months (interquartile range, 58-131 months) in the VHL and control groups, respectively. Median recurrence-free survival could not have been estimated in the VHL group due to the low number of events (hazard ratio, 5.6; 95% confidence interval, 1.4-22.6; P = 0.013). Five patients with VHL died (3 from VHL-related tumors including 1 from PNET), whereas only one control patient died due to unrelated causes. CONCLUSIONS: The long-term outcome of resected VHL-PNET is better than that of sporadic PNET. PNET less than 15 mm left in place did not progress. A parenchyma-sparing surgical strategy seems appropriate in patients with VHL-PNET, who may develop more life-threatening tumors of other organs.
PubMed-ID: 25185468
http://dx.doi.org/10.1097/SLA.0000000000000856

Frequency and clinical correlates of somatic Ying Yang 1 mutations in sporadic insulinomas.
J Clin Endocrinol Metab, 100(5):E776-82.
U. D. Lichtenauer, G. Di Dalmazi, E. P. Slater, T. Wieland, A. Kuebart, A. Schmittfull, T. Schwarzmayr, S. Diener, D. Wiese, W. E. Thasler, M. Reincke, T. Meitinger, M. Schott, M. Fassnacht, D. K. Bartsch, T. M. Strom and F. Beuschlein. 2015.
CONTEXT: Insulinomas represent pancreatic neuroendocrine neoplasms that cause severe morbidity attributed to their often pronounced endocrine activity. Apart from hereditary forms such as multiple endocrine neoplasia type 1 (MEN-1), genetic causes for sporadic insulinoma development had remained obscure until recently. Applying next-generation sequencing methods, disease-causing genetic alterations have been identified in various endocrine tumors. OBJECTIVE AND DESIGN: Paired tumor and blood DNA from eight patients with sporadic insulinomas (five females and two malignant tumors) were analyzed by whole-exome sequencing. After this initial analysis, Ying Yang 1 (YY1) mutation status was assessed in a larger cohort of 39 additional insulinomas (including eight malignant and one liver metastasis) from three German hospitals by targeted sequencing. The mutation status was correlated with various clinical parameters. RESULTS: A range of one to 12 somatic genetic variants were identified by exome sequencing. A recurrent somatic Thr372Arg YY1 point mutation was detected in two patients of the initial cohort and four patients of the second cohort (total, six of 47; 13%). The presence of the mutation was associated with a trend toward higher age (63.5 y; IQR, 48.0-74.0 vs 45.0 y; IQR, 33.0-63.0; P = .05), and all affected patients were females (six of six; P = .04). All other clinical parameters, including the presence of malignancy and metastatic spread, tumor localization, and hypoglycemic episodes were not different between YY1-mutated and nonmutated tumor carriers. CONCLUSIONS: The somatic Thr372Arg YY1 mutation is a relevant finding in female patients with sporadic insulinomas. The prevalence of this mutation in this Caucasian population is considerably lower compared to that of a recently described Asian cohort.
PubMed-ID: 25763608
http://dx.doi.org/10.1210/jc.2015-1100

Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma.
Endocr Relat Cancer, 22(3):289-98.
J. Hadoux, D. Malka, D. Planchard, J. Y. Scoazec, C. Caramella, J. Guigay, V. Boige, S. Leboulleux, P. Burtin, A. Berdelou, Y. Loriot, P. Duvillard, C. N. Chougnet, D. Deandreis, M. Schlumberger, I. Borget, M. Ducreux and E. Baudin. 2015.
There is no standard for second-line chemotherapy in poorly differentiated grade 3 neuroendocrine carcinoma (G3-NEC) patients. We analyzed the antitumor efficacy of 5-fluorouracil and oxaliplatin (FOLFOX) chemotherapy in this population. A single-center retrospective analysis of consecutive G3-NEC patients treated with FOLFOX chemotherapy after failure of a cisplatinum-based regimen between December 2003 and June 2012 was performed. Progression-free survival (PFS), overall survival (OS), response rate, and safety were assessed according to RECIST 1.1 and NCI.CTC v4 criteria. Twenty consecutive patients were included (seven males and 13 females; median age 55; range 23-87 years) with a performance status of 0-1 in 75% of them. Primary location was gastroenteropancreatic in 12, thoracic in four, other in two, and unknown in two patients. There were 12 (65%) large-cell and 7 (30%) small-cell G3-NEC tumors, and 1 (5%) unknown. All patients had distant metastases. Twelve (60%) patients received FOLFOX as second-line treatment and 8 (40%) as third-line treatment or later and the median number of administered cycles was 6 (range 3-14). The median follow-up was 19 months. Median PFS was 4.5 months. Among the 17 evaluable patients, five partial responses (29%), six stable diseases (35%), and six progressive diseases (35%) were observed. Median OS was 9.9 months. Main Grade 3-4 toxicities were neutropenia (35%), thrombopenia (20%), nausea/vomiting (10%), anemia (10%), and elevated liver transaminases (10%). Our results indicate that the FOLFOX regimen could be considered as a second-line option in poorly differentiated G3-NEC patients after cisplatinum-based first-line treatment but warrant further confirmation in future larger prospective studies.
PubMed-ID: 25770151
http://dx.doi.org/10.1530/ERC-15-0075

The Supporting Role of (18)FDG-PET in Patients with Neuroendocrine Tumors.
Ann Surg Oncol, 22(7):2107-9.
J. R. Howe. 2015.
PubMed-ID: 25777088
http://dx.doi.org/10.1245/s10434-015-4484-5

Octreoscan Versus FDG-PET for Neuroendocrine Tumor Staging: A Biological Approach.
Ann Surg Oncol, 22(7):2295-301.
M. H. Squires, 3rd, N. Volkan Adsay, D. M. Schuster, M. C. Russell, K. Cardona, K. A. Delman, J. H. Winer, D. Altinel, J. M. Sarmiento, B. El-Rayes, N. Hawk, C. A. Staley, 3rd, S. K. Maithel and D. A. Kooby. 2015.
BACKGROUND: Clinicians may order Octreoscan or positron emission tomography (PET) scan for staging patients with neuroendocrine tumors (NETs). (111)In-Octreoscan (Octreoscan) identifies tumors by radiolabeled targeting of somatostatin receptors, while 18F-fluorodeoxyglucose-positron emission tomography ((18)FDG-PET) measures differential tissue glucose transport. We assessed the sensitivity of both nuclear imaging modalities with pathologic correlation to define the best initial choice for NET staging after standard cross-sectional imaging. METHODS: We identified all patients diagnosed with NETs of gastrointestinal or pancreatic origin who underwent nuclear imaging staging by Octreoscan and/or PET from 2000 to 2013. Imaging results were correlated with tumor differentiation and grade of pathology specimens. RESULTS: Imaging and pathology results were identified for 153 patients. Of these, 131 underwent Octreoscan, 43 underwent PET, and 21 patients had both performed. Overall sensitivity of Octreoscan and PET for NET detection was similar (77 vs. 72 %; p = not significant). For well-differentiated NETs, Octreoscan (n = 124) demonstrated sensitivity of 80 vs. 60 % (p = 0.28) for PET (n = 30). For poorly-differentiated NETs, Octreoscan (n = 7) proved significantly less sensitive than PET (n = 13) (57 vs. 100 %; p = 0.02). The sensitivity of Octreoscan versus PET varied similarly when analyzed by WHO tumor grade: Grade 1 (79 vs. 52 %; p = 0.16), Grade 2 (85 vs. 86 %; p = not significant), and Grade 3 (57 vs. 100 %; p = 0.02). CONCLUSIONS: Tumor differentiation can be used to guide selection of nuclear imaging modalities for staging gastrointestinal and pancreatic NETs. Octreoscan appears more sensitive than (18)FDG-PET for well-differentiated NETs, whereas (18)FDG-PET demonstrates superior sensitivity for poorly-differentiated NETs.
PubMed-ID: 25786743
http://dx.doi.org/10.1245/s10434-015-4471-x

Therapeutic Strategies for Advanced Pancreatic Neuroendocrine Tumors with Segmental Portal Hypertension.
World J Surg, 39(8):1974-80.
F. Dumont, Y. Goudard, C. Caramella, D. Goere, E. Baudin and D. Elias. 2015.
BACKGROUND: Pancreatic neuroendocrine tumors (PNET) locally advanced may lead to significant local symptoms especially segmental portal hypertension (SPH) with risk of bleeding. The aim of our study was to evaluate the role of SPH on the PNET management in an expert center. METHODS: Forty-two patients treated for locally advanced PNET with SPH between January 1984 and December 2012 were retrospectively analyzed. RESULTS: The median age was 55 years (25-75). The median tumor size was 7.5 cm (3-20). Thirty four (80.9%) patients were metastatic mainly in the liver (n=33, 79%) with a frequent (n=16, 38.1%) involvement>20%. The surgery was impossible because of SPH in 7 (16.6%) cases. Pancreatic resection was performed in 28 (66.7%) cases by distal pancreatectomy. Neoadjuvant chemotherapy (n=24, 57%) had no impact on SPH with no modification of collateral circulation. Among operated on patients, complete macroscopic resection was obtained in 19 (67.8%) patients. The mortality and severe morbidity rate was respectively 3.6 and 18%. Five year overall survival (OS) was similar in operated and no operated patients. (61%; p=0.64). The 5-year OS was 77.9 or 55.4% in patients who underwent a complete or incomplete macroscopic resection of primary and metastases, respectively. CONCLUSION: PNET resection associated with SPH is feasible with a low morbimortality. SPH was not improved by chemotherapy. Prolonged survival was observed after complete macroscopic resection.
PubMed-ID: 25804547
http://dx.doi.org/10.1007/s00268-015-3030-8

Impact of variant pancreatic arterial anatomy and overlap in regional perfusion on the interpretation of selective arterial calcium stimulation with hepatic venous sampling for preoperative localization of occult insulinoma.
Surgery, 158(1):162-72.
S. M. Thompson, A. Vella, F. J. Service, C. S. Grant, G. B. Thompson and J. C. Andrews. 2015.
BACKGROUND: To determine the impact of variant pancreatic arterial anatomy and overlap in regional perfusion on the interpretation of selective arterial calcium stimulation (SACST) with hepatic venous sampling for preoperative localization of occult insulinoma. METHODS: An institutional review board-approved retrospective review was undertaken of 42 patients with surgically confirmed, occult insulinoma who underwent SACST from January 1996 to March 2014. Location of the insulinoma was predicted initially based on the biochemical results of SACST alone according to Doppman's criteria. Pancreatic arteriograms were reviewed blinded to the biochemical results and the regional perfusion of each artery assessed. The anatomic and perfusion data were combined with the biochemical results to make a second prediction and compared with the surgical findings. RESULTS: The biochemical results were positive in 1, 2, and 3 arterial distributions in 73.8%, 21.4%, and 4.8% of patients, respectively. The celiac trunk and superior mesenteric artery (SMA) anatomy were aberrant in 38.1% and 35.7% of patients, respectively. Clinically significant variations included dorsal pancreatic artery replaced to SMA (21.4%) and celiac stenosis (4.8%). Significant variation and overlap in regional pancreatic perfusion was observed, particularly for the SMA. Sensitivity for insulinoma localization was 54.8% (diagnostic arteriography), 73.8% (biochemical data), 88.1% (biochemical, anatomic, perfusion data), and 92.8% (arteriographic, biochemical, anatomic, perfusion data). CONCLUSION: Careful review of the pancreatic arterial anatomy and regional perfusion is critical for correct interpretation of the biochemical results of SACST and improves the sensitivity of localization for occult insulinoma, particularly in the presence of pancreatic arterial variants or overlap in regional perfusion.
PubMed-ID: 25873534
http://dx.doi.org/10.1016/j.surg.2015.03.004

Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors.
Endocr Relat Cancer, 22(3):431-41.
A. Dasari, A. Phan, S. Gupta, A. Rashid, S. C. Yeung, K. Hess, H. Chen, E. Tarco, H. Chen, C. Wei, K. Anh-Do, D. Halperin, F. Meric-Bernstam and J. Yao. 2015.
Preclinical data suggest multiple roles for the IGF1 receptor (IGF1R) in neuroendocrine tumors (NETs), including mediating resistance to mammalian target of rapamycin (mTOR) inhibitors. Everolimus, an oral mTOR inhibitor, and octreotide long-acting repeatable (LAR) are approved for subgroups of well-differentiated NET. The primary objective of the present study was to establish the safety and recommended phase II dose (RP2D) of cixutumumab, a monoclonal antibody (MAB) against IGF1R, with everolimus and octreotide LAR. Patients with well-differentiated NET were treated with 10 mg everolimus p.o. daily, 20 mg octreotide LAR i.m. every 21 days,

and escalating doses of cixutumumab. An expansion cohort was enrolled at RP2D. Correlative studies included the evaluation of mTOR pathway inhibition in paired tumor biopsies and the effects of this combination on metabolism via indirect calorimetry. Nineteen patients with progressive disease were enrolled, including nine to the expansion portion. Two patients had dose-limiting toxicities of grade 3 mucositis at 15 mg/kg cixutumumab. Long-term tolerance at RP2D was problematic, and the most common >/=grade 3 adverse event was fatigue. One patient with metastatic insulinoma had a confirmed partial response, whereas 17 had stable disease. The median progression-free survival was 43.6 weeks, and the median overall survival was 25.5 months. The RP2D of this combination per the predefined study protocol of 10 mg/kg cixutumumab i.v., 20 mg octreotide LAR i.m. every 21 days plus 10 mg everolimus p.o. daily is associated with non-dose-limiting toxicities that limit long-term tolerance. Although a signal of activity was noted in the present study, this will need to be reconciled with limited tolerance of the combination and data from larger studies of anti-IGF1R MABs in NET that have been disappointing.
PubMed-ID: 25900182
http://dx.doi.org/10.1530/ERC-15-0002

Carcinoid and neuroendocrine tumors: building on success.
J Clin Oncol, 33(16):1855-63.
P. L. Kunz. 2015.
We have come a long way in our understanding and treatment of neuroendocrine tumors since the term "karzinoide" was coined in 1907. Neuroendocrine tumors are a group of biologically and clinically heterogeneous neoplasms that most commonly originate in the lungs, GI tract, and pancreas. The selection of initial and subsequent therapies requires careful consideration of both tumor and treatment characteristics. With recent advances, we now have more tools for the diagnosis and treatment of our patients. This comprehensive review article summarizes recent advances in the field of neuroendocrine tumors and places them into context for best management practices.
PubMed-ID: 25918282
http://dx.doi.org/10.1200/JCO.2014.60.2532

Reappraisal of pancreatic enucleations: A single-center experience of 126 procedures.
Surgery, 158(1):201-10.
F. Faitot, S. Gaujoux, L. Barbier, M. Novaes, S. Dokmak, B. Aussilhou, A. Couvelard, V. Rebours, P. Ruszniewski, J. Belghiti and A. Sauvanet. 2015.
BACKGROUND: Parenchyma-sparing pancreatectomies, especially enucleations, could avoid disappointing functional results associated with standard resections for benign/low-grade pancreatic neoplasms. This study aimed to assess short- and long-term outcomes in a large, single-center series of enucleations. METHODS: All 126 patients who underwent enucleation for benign/low-grade neoplasms between 1996 and 2011 were included retrospectively. RESULTS: Lesions were mainly incidentally diagnosed (71%), most often located in the head (46%), and with a median size of 20 mm. Enucleations were mainly performed for branch-duct intraductal papillary mucinous neoplasm (30%), nonfunctioning pancreatic neuroendocrine tumors (29%), and mucinous cystadenoma (21%). Overall mortality was 0.8% and morbidity 63%, mainly owing to pancreatic fistula (57%). Most were significant clinically, that is, grade B or C (41%), but managed conservatively (85%). Reoperation rate was 3%, mainly owing to hemorrhage. Postoperative de novo diabetes was 0.8%, and exocrine insufficiency never observed. The 1-, 3-, and 5-year recurrence-free survival were 100%, 98%, and 93%, respectively. CONCLUSION: Enucleation is associated with substantial morbidity, especially pancreatic fistula. Enucleations as an alternative to standard resection are best indicated for small, benign, and low-grade lesions located far from the main pancreatic duct. Enucleations should be proposed to young and fit patients able to tolerate postoperative morbidity and who could benefit from the excellent long-term results.
PubMed-ID: 25956743
http://dx.doi.org/10.1016/j.surg.2015.03.023

Surgical Management of Small Bowel Neuroendocrine Tumors: Specific Requirements and Their Impact on Staging and Prognosis.
Ann Surg Oncol,
A. Pasquer, T. Walter, V. Hervieu, J. Forestier, J. Y. Scoazec, C. Lombard-Bohas and G. Poncet. 2015.
BACKGROUND: Small bowel neuroendocrine tumors (SB-NETs) are characterized by two main features: they usually are metastatic at diagnosis and multiple in 30 % of cases. As such, SB-NETs require specific surgical management. This retrospective study examined local recurrence, survival, and prognosis of SB-NETs after adapted surgery. METHODS: All consecutive patients with SB-NETs who underwent resection of at least one primary tumor between 1 January 2000 and 1 January 2013 were analyzed. The preoperative morphologic

workup, histologic classification, and metastatic lymph node (LN) ratio (LNs involved/removed) were recorded. RESULTS: The study enrolled 107 patients, 35 (33 %) of whom had multiple SB-NETs (range 1-44; mean 3.1). Preoperative imaging and perioperative surgical examination missed 61 and 33 % of SB-NETs, respectively, in contrast to pathologic examination. Of the 107 patients, 43 % had carcinoid syndrome, 70 % had metastatic disease, and 90 % had LN involvement. The median number of LNs retrieved was 12 (range 1-69). The LN ratio (LNs involved/removed) was 0.25. The highest tumoral grades were G1 (in 61 % of patients) and G2 (in 37 % of patients). Of the 107 patients, 13 (12 %) had local LN recurrence. The rate of LN recurrence-free survival at 5 years was 88 %. The median overall survival (OS) time was 128 months (range 91-165 months). In the multivariate analysis, high chromogranin A (CgA) levels and peritoneal carcinomatosis were significantly associated with shorter OS. CONCLUSIONS: Systematic palpation of the entire small bowel detects more multiple NETs than preoperative imaging. Systematic surgery with extensive LN resection is associated with low local recurrence. High CgA levels and carcinomatosis are linked with shorter survival.
PubMed-ID: 26014153
http://dx.doi.org/10.1245/s10434-015-4620-2

Long-Term Survival with Long-Acting Somatostatin Analogues Plus Aggressive Cytoreductive Surgery in Patients with Metastatic Neuroendocrine Carcinoma.
J Am Coll Surg, 221(1):26-36.
G. B. Deutsch, J. H. Lee and A. J. Bilchik. 2015.
BACKGROUND: Long-acting somatostatin analogues (S-LAR) improve recurrence-free survival in patients with metastatic neuroendocrine tumor (NET) from gastrointestinal (GI) primary, but their impact on overall survival when combined with aggressive cytoreductive surgery is unclear. STUDY DESIGN: We reviewed our institutional cancer database to identify patients who underwent cytoreductive surgery for metastatic NET from GI primary between December 1997 and June 2013. Additionally, a cohort selected from 3,384 metastatic neuroendocrine cases in the SEER-Medicare database (January 2003 to December 2009) was used to verify and expand on our results. RESULTS: Most of the 49 patients from our institution had primary lesions in the small intestine (22 of 49 [44.9%]) or pancreas (14 of 49 [28.6%]); 37 patients (75.5%) had metastatic disease at initial diagnosis. These patients underwent 1 (32 of 49 [65.3%]), 2 (11 of 49 [22.4%]), or at least 3 (6 of 49 [12.3%]) surgical procedures; 33 patients (67.3%) underwent resection plus ablation, 19 (38.7%) underwent major hepatectomy, and 34 (69.4%) received S-LAR (29.4% administered preoperatively). Median follow-up was 112 months. Rates of 1-, 5-, 10-, and 15-year disease-specific survival (DSS) were 94%, 78%, 64%, and 31%, respectively, in the 34 patients undergoing aggressive cytoreductive surgery plus S-LAR. Of the SEER-Medicare population, 1,741 patients met inclusion criteria. The DSS for the 104 patients treated with combination therapy was 68.3% at 5 years and 60.6% at 10 years, as compared with 54.7% and 51.8%, respectively, for the 202 patients receiving surgery alone, and 50.0% and 36.0%, respectively, for the 342 patients receiving S-LAR alone ($p < 0.0001$). The group receiving neither treatment ($n = 1,093$) had 5-year and 10-year DSS of 34.3% and 26.3%, respectively. CONCLUSIONS: Long-acting somatostatin analogues combined with aggressive cytoreductive surgery improves the long-term survival of select patients with metastatic NET from GI primary.
PubMed-ID: 26027502
http://dx.doi.org/10.1016/j.jamcollsurg.2015.03.055

The expanding role of somatostatin analogues in the treatment of neuroendocrine tumours: the CLARINET study.
Clin Endocrinol (Oxf),
G. Kaltsas and A. B. Grossman. 2015.
PubMed-ID: 26052840
http://dx.doi.org/10.1111/cen.12831

Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: Do size and symptoms matter?
Surgery,
V. Sallinen, C. Haglund and H. Seppanen. 2015.
BACKGROUND: Nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) are rare tumors with highly variable outcome. Current guidelines recommend surveillance for small tumors (</=2 cm), but a scientific basis for such recommendation is scarce. METHODS: Patients who underwent surgery for NF-PNET during 2001-2013 were identified from a prospectively maintained database and reviewed retrospectively. RESULTS: Fifty-eight patients that had undergone an operative procedure for NF-PNET were identified. Forty-one patients (71%) were symptomatic. Median size of the tumor was 2.5 cm (range 0.9-12.0 cm). WHO 2010 grade was predictive of both overall- and disease-free survival ($P < .001$), whereas size alone was not. Twenty-four patients had a small NF-PNET (</=2 cm), of whom 16 were symptomatic and 8 asymptomatic. Seven patients with small

symptomatic NF-PNETs showed signs of malignant behavior: 4 had lymph node metastases, 1 had liver metastases before surgery, 3 developed liver metastases, and 3 died of the disease. All 7 patients had either bile duct or pancreatic duct obstruction or both on preoperative imaging. On the contrary, patients with small asymptomatic NF-PNETs did not develop distant metastases nor died of disease. CONCLUSION: The 2010 grading system from the World Health Organization can be used to predict survival. Symptomatic small NF-PNETs that caused bile and/or pancreatic duct obstruction had poor outcome. In contrast, asymptomatic small NF-PNETs seem to have benign course, and are candidates for surveillance.
PubMed-ID: 26070847
http://dx.doi.org/10.1016/j.surg.2015.04.035

[In Process Citation].
Chirurg, 86(7):707.
H. Dralle and I. Satiroglu. 2015.
PubMed-ID: 26092260
http://dx.doi.org/10.1007/s00104-015-0036-6

Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms.
Endocr Relat Cancer, 22(4):657-64.
M. Heetfeld, C. N. Chougnet, I. H. Olsen, A. Rinke, I. Borbath, G. Crespo, J. Barriuso, M. Pavel, D. O'Toole and T. Walter. 2015.
Data on gastroenteropancreatic neuroendocrine neoplasms (NEN) G3 (well-differentiated neuroendocrine tumors (NET G3) and neuroendocrine carcinoma (NEC)) are limited. We retrospectively study patients with NET G3 and NEC from eight European centers. Data examined included clinical and pathological characteristics at diagnosis, therapies and outcomes. Two hundred and four patients were analyzed (37 NET G3 and 167 NEC). Median age was 64 (21-89) years. Tumor origin included pancreas (32%) and colon-rectum (27%). The primary tumor was resected in 82 (40%) patients. Metastatic disease was evident at diagnosis in 88% (liver metastases: 67%). Median Ki-67 index was 70% (30% in NET G3 and 80% in NEC; P<0.001). Median overall survival (OS) for all patients was 23 (95% CI: 18-28) months and significantly higher in NET G3 (99 vs 17 months in NEC; HR=8.3; P<0.001). Platinum-etoposide first line chemotherapy was administered in 113 (68%) NEC and 12 (32%) NET G3 patients. Disease control rate and progression free survival (PFS) were significantly higher in NEC compared to NET G3 (P<0.05), whereas OS was significantly longer in NET G3 (P=0.003). Second- and third-line therapies (mainly FOLFIRI and FOLFOX) were given in 79 and 39 of NEC patients; median PFS and OS were 3.0 and 7.6 months respectively after second-line and 2.5 and 6.2 months after third-line chemotherapy. In conclusion, NET G3 and NEC are characterized by significant differences in Ki-67 index and outcomes. While platinum-based chemotherapy is effective in NEC, it seems to have limited value in NET G3.
PubMed-ID: 26113608
http://dx.doi.org/10.1530/ERC-15-0119

Liver transplantation for metastatic neuroendocrine tumors: Outcomes and prognostic variables.
J Surg Oncol,
L. S. Sher, D. M. Levi, J. S. Wecsler, M. Lo, L. M. Petrovic, S. Groshen, L. Ji, T. D. Uso, A. J. Tector, A. S. Hamilton, J. W. Marsh and M. E. Schwartz. 2015.
BACKGROUND: Patient selection for liver transplantation for metastatic neuroendocrine tumors remains a topic of debate. There is no established MELD exception, making it difficult to obtain donor organs. METHODS: A multicenter database was created assessing outcomes for liver and multivisceral transplantation for metastatic neuroendocrine tumors and identifying prognostic factors for survival. Demographic, transplant, primary tumor site and management, pathology, recurrent disease and survival data were collected and analyzed. Survival probabilities were calculated using the Kaplan-Meier method. RESULTS: Analysis included 85 patients who underwent liver transplantation November 1988-January 2012 at 28 centers. One, three, and five-year patient survival rates were 83%, 60%, and 52%, respectively; 40 of 85 patients died, with 20 of 40 deaths due to recurrent disease. In univariate analyses, the following were predictors of poor prognosis: large vessel invasion (P < 0.001), extent of extrahepatic resection at liver transplant (P = 0.007), and tumor differentiation (P = 0.003). In multivariable analysis, predictors of poor overall survival included large vessel invasion (P = 0.001), and extent of extrahepatic resection at liver transplant (P = 0.015). CONCLUSION: In the absence of poor prognostic factors, metastatic neuroendocrine tumor is an acceptable indication for liver transplantation. Identification of favorable prognostic factors should allow assignment of a MELD exception similar to hepatocellular carcinoma. J. Surg. Oncol. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26171686
http://dx.doi.org/10.1002/jso.23973

Management and outcomes of appendicular neuroendocrine tumours: Retrospective review with 5-year follow-up.
Eur J Surg Oncol, 41(9):1243-6.
B. Amr, F. Froghi, M. Edmond, K. Haq and R. Thengungal Kochupapy. 2015.
BACKGROUND: Neuroendocrine (NEN) tumours are the commonest type of tumours affecting the appendix. The majority of cases are diagnosed incidentally on post-operative histopathological examination of the resected appendicectomy specimen. Preoperative diagnosis remains a challenge, unless the patient presents with obvious features of carcinoid syndrome or signs of metastatic disease. Hence, the authors present our five-year experience in diagnosing and managing NEN tumours of the appendix. METHODS: Retrospective review of all patients underwent an emergency appendicectomy with intention to treat clinically suspected appendicitis at Derriford Hospital (Plymouth, Devon, UK) was undertaken. Patients with diagnoses other than NEN of the appendix were excluded. For patients with appendicular NEN, demographic data, pre-operative inflammatory markers, post-operative histology results as well as follow-up investigations were obtained using patients' electronic records. Case notes were reviewed for clinical presentation, operative details and follow-up information. RESULTS: 2724 patients underwent emergency appendicectomy between January 2009 and May 2014. Carcinoid tumours were identified in 17 histologically examined appendicectomy specimens. Clinically, all patients presented with acute appendicitis with raised inflammatory markers in 58.5% of patients. Median tumour size was 5 (1-20) mm. Median postoperative follow up was 2.9 (0.92-5.8) years. All patients remained tumour free with no evidence of metastasis or recurrence during the entire study period. CONCLUSION: Appendicular NEN are rare and usually diagnosed incidentally; hence precise examination of routine appendicectomy specimens is fundamental in the diagnosis. Simple appendicectomy is sufficient for tumours less than 1 cm for adequate clearance, whilst right hemi-colectomy is recommended for larger tumours.
PubMed-ID: 26188371
http://dx.doi.org/10.1016/j.ejso.2015.06.010

Discordance of Histologic Grade Between Primary and Metastatic Neuroendocrine Carcinomas.
Ann Surg Oncol,
T. Adesoye, M. A. Daleo, A. G. Loeffler, E. R. Winslow, S. M. Weber and C. S. Cho. 2015.
BACKGROUND: The prognosis and management of neuroendocrine carcinoma are largely driven by histologic grade as assessed by mitotic activity. The authors reviewed their institutional experience to determine whether the histologic grade of neuroendocrine carcinoma can differ between primary and metastatic tumors. METHODS: This study examined patients who underwent operative resection of both primary and metastatic foci of neuroendocrine carcinoma. Resected tumors were independently reviewed and categorized as low, intermediate, or high grade as determined by mitotic count. RESULTS: The authors identified 20 patients with metastatic neuroendocrine carcinoma treated at their institution between 1997 and 2013 for whom complete pathologic review of primary and metastatic tumors was possible. Primary lesions were found in the small intestine (n = 12), pancreas (n = 7), ampulla (n = 1), stomach (n = 1), and rectum (n = 1). The timing of hepatic metastasis was synchronous in 15 cases and metachronous in 5 cases. The histologic grade was concordant between primary and metastatic tumors in 9 cases and discordant in 11 cases. Among the discordant cases, 7 had a higher metastatic grade than primary grade, and 4 had a lower metastatic grade than primary grade. Metachronous presentation was associated with a higher likelihood of grade discordance ($p = 0.03$). The histologic grade of all metachronous metastases differed from that of the primary tumors. CONCLUSION: There is a high prevalence of histologic grade discordance between primary and metastatic foci of neuroendocrine carcinoma, particularly among patients with a metachronous metastatic presentation. Given the importance of histologic grade in disease prognostication and treatment planning, this finding may be informative for the management of patients with metastatic neuroendocrine carcinoma.
PubMed-ID: 26193965
http://dx.doi.org/10.1245/s10434-015-4733-7

Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis.
Langenbecks Arch Surg, 400(6):715-23.
F. J. Huttner, L. Schneider, I. Tarantino, R. Warschkow, B. M. Schmied, T. Hackert, M. K. Diener, M. W. Buchler and A. Ulrich. 2015.
PURPOSE: There is an ongoing debate on whether palliative removal of the primary tumor may result in a survival benefit for patients with incurable stage IV pancreatic neuroendocrine tumors (P-NET). The objective of this study was to assess whether palliative resection of the primary tumor in patients with incurable stage IV P-NET has an impact on survival. METHODS: Patients with stage IV P-NET registered in the Surveillance,

Epidemiology, and End Results database between 2004 and 2011 were identified. Those undergoing resection of metastases were excluded. Overall and cancer-specific survival of patients who did and did not undergo resection of their primary tumor were compared by means of risk-adjusted Cox proportional hazard regression analysis and propensity score-matched analysis. RESULTS: A total of 442 stage IV P-NET patients were identified, of whom 75 (17.0 %) underwent palliative primary tumor resection. The latter showed a significant benefit in both overall survival (hazard ratio [HR] of death = 0.41, 95 % confidence interval [CI] 0.25-0.66, p < 0.001) and cancer-specific survival (HR of death = 0.41, 95 % CI 0.25-0.67, p < 0.001) in unadjusted multivariate Cox regression analysis; the benefit persisted after propensity score adjustment. CONCLUSIONS: This population-based analysis of stage IV P-NET patients provides compelling evidence that palliative resection of the primary tumor is associated with significant survival benefit. Thus, the recent recommendations judging resection of the primary as inadvisable and the accompanying trend towards fewer palliative resections of the primary tumor have to be contested.
PubMed-ID: 26198970
http://dx.doi.org/10.1007/s00423-015-1323-x

Succinate Dehydrogenase (SDH)-deficient pancreatic neuroendocrine tumor expands the SDH-related tumor spectrum.
J Clin Endocrinol Metab:jc20152689.
N. D. Niemeijer, T. G. Papathomas, E. Korpershoek, R. R. de Krijger, L. Oudijk, H. Morreau, J. P. Bayley, F. J. Hes, J. C. Jansen, W. N. Dinjens and E. P. Corssmit. 2015.
CONTEXT: Mutations in genes encoding the subunits of succinate dehydrogenase (SDH) can lead to pheochromocytoma (PCC)/paraganglioma (PGL) formation. However, SDH mutations have also been linked to non-paraganglionic tumors. OBJECTIVE: Investigate which non-paraganglionic tumors belong to the SDH-associated tumor spectrum. DESIGN: Retrospective cohort study Setting: Tertiary referral center Patients: All consecutive SDHA/SDHB/SDHC and SDHD mutation carriers followed at the Department of Endocrinology of the Leiden University Medical Center who were affected by non-PCC/PGL solid tumors. INTERVENTION: N/A Main Outcome Measures: SDHA/SDHB immunohistochemistry (IHC), mutation analysis, and loss of heterozygosity (LOH) analysis of the involved SDH-encoding genes. RESULTS: Twenty-five of 35 tumors (from 26 patients) showed positive staining on SDHB and SDHA immunohistochemistry. Eight tumors showed negative staining for SDHB and positive staining for SDHA: a pancreatic neuroendocrine tumor (NET), a macroprolactinoma, two gastric gastrointestinal stromal tumors (GIST), an abdominal ganglioneuroma and three renal cell carcinomas. With the exception of the abdominal ganglioneuroma, LOH was detected in all tumors. A prolactinoma in a patient with a germline SDHA mutation was the only tumor immunonegative for both SDHA and SDHB. Sanger sequencing of this tumor revealed a somatic mutation (p.D38V) as a likely second hit leading to biallelic inactivation of SDHA. One tumor (breast cancer) showed heterogeneous SDHB staining, positive SDHA staining and retention of heterozygosity. CONCLUSIONS: This study strengthens the etiological association of SDH genes with pituitary neoplasia, renal tumorigenesis and gastric GISTs. Furthermore, our results indicate that pancreatic NET also falls within the SDH-related tumor spectrum.
PubMed-ID: 26259135
http://dx.doi.org/10.1210/jc.2015-2689

Better Survival But Changing Causes of Death in Patients With Multiple Endocrine Neoplasia Type 1.
Ann Surg, 261(6):e147-8.
J. A. Norton, G. Krampitz, A. Zemek, T. Longacre and R. T. Jensen. 2015.
PubMed-ID: 26291955
http://dx.doi.org/10.1097/SLA.0000000000001211

General

Meta-Analyses

- None -

Randomized controlled trials

Localization of Hidden Insulinomas with (6)(8)Ga-DOTA-Exendin-4 PET/CT: A Pilot Study.
J Nucl Med, 56(7):1075-8.
K. Antwi, M. Fani, G. Nicolas, C. Rottenburger, T. Heye, J. C. Reubi, B. Gloor, E. Christ and D. Wild. 2015.
(111)In-DOTA-exendin-4 SPECT/CT has been shown to be highly efficient in the detection of insulinomas. We aimed at determining whether novel PET/CT imaging with [Nle(14),Lys(40)(Ahx-DOTA-(68)Ga)NH2]exendin-4 ((68)Ga-DOTA-exendin-4) is feasible and sensitive in detecting benign insulinomas. METHODS: (68)Ga-DOTA-exendin-4 PET/CT and (111)In-DOTA-exendin-4 SPECT/CT were performed in a randomized cross-over order on 5 patients with endogenous hyperinsulinemic hypoglycemia. The gold standard for comparison was the histologic diagnosis after surgery. RESULTS: In 4 patients histologic diagnosis confirmed a benign insulinoma, whereas one patient refused surgery despite a positive (68)Ga-DOTA-exendin-4 PET/CT scan. In 4 of 5 patients, previously performed conventional imaging (CT or MR imaging) was not able to localize the insulinoma. (68)Ga-DOTA-exendin-4 PET/CT correctly identified the insulinoma in 4 of 4 patients, whereas (111)In-DOTA-exendin-4 SPECT/CT correctly identified the insulinoma in only 2 of 4 patients. CONCLUSION: These preliminary data suggest that the use of (68)Ga-DOTA-exendin-4 PET/CT in detecting hidden insulinomas is feasible.
PubMed-ID: 25999434
http://dx.doi.org/10.2967/jnumed.115.157768

Consensus Statements/Guidelines

- None -

Other Articles

Management of 1- to 2-cm Carcinoid Tumors of the Appendix: Using the National Cancer Data Base to Address Controversies in General Surgery.
J Am Coll Surg, 220(5):894-903.
D. P. Nussbaum, P. J. Speicher, B. C. Gulack, J. E. Keenan, A. M. Ganapathi, B. R. Englum, D. S. Tyler and D. G. Blazer, 3rd. 2015.
BACKGROUND: The management of 1- to 2-cm appendiceal carcinoid tumors remains controversial. Here we use the National Cancer Data Base (NCDB) to compare long-term outcomes for patients treated via resection of the primary tumor alone vs right hemicolectomy (RHC). STUDY DESIGN: The 1998 to 2011 NCDB User File was queried to identify patients with 1- to 2-cm appendiceal carcinoids. Patients were stratified by surgical technique: resection of the primary tumor alone vs RHC with regional lymphadenectomy. Multivariable logistic regression was used to compare short-term outcomes. Survival was estimated using the Kaplan-Meier method with comparisons based on the log-rank test. RESULTS: A total of 916 patients were identified, including 42% managed with primary resection and 58% with RHC. Patients who underwent RHC had slightly larger tumors and higher-stage tumors; otherwise, there were no baseline differences between groups. The rates of positive margins were similar (5.5% vs 4.5%; p = 0.60). Among all patients, 1- and 5-year survival were 98.1% and 88.7% vs 96.7% and 87.4% (p = 0.52) for those managed via primary resection vs RHC, respectively. Among patients with moderate/high-grade/anaplastic carcinoids, 1- and 5-year survival were 93.3% and 72.0% vs 92.3% and 71.9%, respectively (p = 0.78). After adjustment with Cox proportional hazards modeling, we confirmed that there was no survival benefit for patients undergoing RHC (hazard ratio = 1.14; p = 0.72).

CONCLUSIONS: For 1- to 2-cm appendiceal carcinoids, formal resection of the right colon does not appear to improve survival, even for higher-grade tumors. Our findings suggest that resection of the primary tumor alone is adequate for all carcinoids <2 cm.
PubMed-ID: 25840530
http://dx.doi.org/10.1016/j.jamcollsurg.2015.01.005

Therapeutic Effectiveness of Screening for Multiple Endocrine Neoplasia Type 2A.
J Clin Endocrinol Metab, 100(7):2539-45.
A. Machens and H. Dralle. 2015.
CONTEXT: Although technological progress revolutionized detection of genetic predisposition to medullary thyroid cancer (MTC), carriers of mutations of disparate risks may not have benefitted alike from screening. OBJECTIVE: This investigation aimed at assessing the achievements of screening for multiple endocrine neoplasia type 2A (MEN 2A) in Germany and identifying current challenges. DESIGN: This was a retrospective analysis comprising 455 carriers at risk of MEN 2A screened and operated between 1963 and 2014. SETTING: The setting was tertiary surgical referral centers. PATIENTS: Included were 175 carriers of American Thyroid Association (ATA) level C mutations (codon 634); 116 carriers of ATA level B mutations (codons 609, 611, 618, 620 and 630); and 164 carriers of ATA level A mutations (codons 768, 790, 791, 804 and 891). INTERVENTIONS: The intervention was thyroidectomy. MAIN OUTCOME MEASURES: Main outcome measures were percentage of index patients among all carriers and percentage of MTC, node-positive MTC, and biochemical cure among non-index patients. RESULTS: The percentage of index patients among all carriers fell from 50% (ATA level C) and 100% (ATA levels B and A) to 16, 29, and 31%, respectively. Among non-index patients, the percentage of MTC fell for ATA levels C and B but not for ATA level A mutations. The corresponding percentage of node-positive MTC declined since 1963 from 100 to 0% (ATA level C) and since 1995 from 67 to 33% (ATA level B) and from 11 to 10% (ATA level A), whereas biochemical cure increased from 0 to 100% since 1963 (ATA level C), and since 1995 from 71 to 78% (ATA level B) and from 95 to 100% (ATA level A). CONCLUSIONS: Screening efforts need to focus on sporadic-appearing MTC to deplete the pool of unrecognized carriers of ATA level B and A mutations and enable earlier pre-emptive thyroidectomy in their offspring.
PubMed-ID: 25946031
http://dx.doi.org/10.1210/jc.2015-1689

Increasing incidence of duodenal neuroendocrine tumors: Incidental discovery of indolent disease?
Surgery, 158(2):466-71.
T. L. Fitzgerald, S. O. Dennis, S. D. Kachare, N. A. Vohra and E. E. Zervos. 2015.
BACKGROUND: There has been a marked increase in the recognized incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Studies have often combined duodenal neuroendocrine tumors (D-NETs) with other small bowel GEP-NETs. As a result, the natural history and clinical ramifications of these D-NETs is poorly understood. METHODS: Patients diagnosed with duodenal "carcinoid" tumors from 1983 to 2010 were identified in the Surveillance Epidemiology and End Results tumor registry. RESULTS: A total of 1,258 patients were identified. The mean age was 64 years. The majority of patients were male (55.6%), white (55.6%), and had stage I disease (66.2%). Patients meeting inclusion criteria were divided into 2 cohorts: (i) era 1 patients diagnosed with GEP-NETs from 1983 to 2005, and (ii) era 2 those diagnosed from 2005 to 2010. There was a clear increase in the incidence rate of D-NETs from 0.27 per 100,000 in 1983 to 1.1 per 100,000 in 2010 ($P < .001$). Comparison of patients from the different eras revealed that those in era 2 were more likely than era 1 to present with stage I disease (69.9 vs 57.5%; $P < .01$) and less likely to present with late-stage disease. The 5-year, disease-specific survival improved for era 2 patients compared with era 1 (89.3 vs 85.2%; $P = .05$); however, multivariate analysis demonstrated that stage but not era was associated with disease-specific survival. CONCLUSION: Prognosis for D-NETs, in contrast with other small bowel NETs, is excellent. There has been a steady increase in the recognized incidence of D-NETs, coincident with the migration to earlier disease stage and improved disease-specific survival.
PubMed-ID: 26013986
http://dx.doi.org/10.1016/j.surg.2015.03.042

My, How Things Have Changed in Multiple Endocrine Neoplasia Type 2A!
J Clin Endocrinol Metab, 100(7):2532-5.
E. G. Grubbs and R. F. Gagel. 2015.
PubMed-ID: 26151398
http://dx.doi.org/10.1210/jc.2015-2516

PTH(1-34) for Surgical Hypoparathyroidism: A Prospective, Open-Label Investigation of Efficacy and Quality of Life.
J Clin Endocrinol Metab, 100(9):3590-7.
A. Santonati, A. Palermo, E. Maddaloni, D. Bosco, A. Spada, F. Grimaldi, B. Raggiunti, R. Volpe, S. Manfrini and F. Vescini. 2015.
CONTEXT: Conventional therapy for hypoparathyroidism consists of calcium and calcitriol, but sometimes normal serum calcium cannot be maintained, and/or this approach might lead to nephrocalcinosis, nephrolithiasis, or renal insufficiency. OBJECTIVE: The objective of the study was to investigate the effects of 6 months of PTH(1-34) treatment in adult subjects with postoperative hypoparathyroidism and to evaluate quality-of-life changes. DESIGN: This was a 2-year prospective, open-label study. At baseline and after 6 months of PTH(1-34) treatment, calcium and vitamin D supplementation requirements, serum calcium, phosphate, creatinine, alkaline phosphatase, uric acid, and 24-hour urinary calcium excretion were evaluated. Quality of life was evaluated by the Rand 36-Item Short Form Health Survey covering eight domains of physical and mental health. SETTING: This was an Italian multicentric study. PARTICIPANTS: Participants included 42 subjects with surgical hypoparathyroidism (90% females, age range 34-77 y). INTERVENTION: The intervention included a twice-daily PTH(1-34) 20 mug sc injection. RESULTS: The mean serum calcium levels significantly increased from baseline to 15 days (7.6 +/- 0.6 vs 9.1 +/- 0.9 mg/dL, P < .001) and remained stable until the end of the observational period, despite a significant reduction in calcium and vitamin D supplementation. Phosphate levels gradually decreased from baseline to the sixth month (P = .005 for the trend), whereas the alkaline phosphatase increased (P < .001). Data from the Rand 36-Item Short Form Health Survey showed a significant improvement in the mean scores of all eight domains (P < .001). CONCLUSION: This is the largest study that demonstrates the effectiveness of PTH(1-34) in the treatment of adult patients with postsurgical hypoparathyroidism, and it shows that PTH(1-34) may improve the mental and physical health in hypoparathyroid subjects.
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Results of (68)Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1.
J Am Coll Surg, 221(2):509-17.
S. M. Sadowski, C. Millo, C. Cottle-Delisle, R. Merkel, L. A. Yang, P. Herscovitch, K. Pacak, W. F. Simonds, S. J. Marx and E. Kebebew. 2015.
BACKGROUND: Screening for neuroendocrine tumors (NETs) in patients with multiple endocrine neoplasia type 1 (MEN1) is recommended to detect primary and metastatic tumors, which can result in significant morbidity and mortality. The utility of somatostatin receptor imaging (68)Gallium-DOTATATE PET/CT in patients with MEN1 is not known. The aim of this study was to prospectively determine the accuracy of (68)Gallium-DOTATATE PET/CT vs (111)In- pentetreotide single-photon emission CT (SPECT)/CT and anatomic imaging in patients with MEN1. STUDY DESIGN: We performed a prospective study comparing (68)Gallium-DOTATATE PET/CT, (111)In-pentetreotide SPECT/CT, and triphasic CT scan to clinical, biochemical, and pathologic data in 26 patients with MEN1. RESULTS: (68)Gallium-DOTATATE PET/CT detected 107 lesions; (111)In-pentetreotide SPECT/CT detected 33 lesions; and CT scan detected 48 lesions. Lesions detected on (68)Gallium-DOTATATE PET/CT had high standard uptake value (SUV)max (median SUVmax = 72.8 [range 19 to 191]). In 7 of the 26 patients (27%), (68)Gallium-DOTATATE PET/CT was positive, with a negative (111)In-pentetreotide SPECT/CT, and in 10 patients (38.5%), additional metastases were detected (range 0.3 cm to 1.5 cm). In 8 of the 26 patients (31%), there was a change in management recommendations as a result of the findings on (68)Gallium-DOTATATE PET/CT that were not seen on (111)In-pentetreotide SPECT/CT and CT scan. CONCLUSIONS: (68)Gallium-DOTATATE PET/CT is more sensitive for detecting NETs than (111)In-pentetreotide SPECT/CT and CT scan in patients with MEN1. This imaging technique should be integrated into radiologic screening and surveillance of patients with MEN1 because it can significantly alter management recommendations.
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Current management of gastrointestinal stromal tumors: Surgery, current biomarkers, mutations, and therapy.
Surgery,
N. Valsangkar, A. Sehdev, S. Misra, T. A. Zimmers, B. H. O'Neil and L. G. Koniaris. 2015.
In the past decade, the addition of molecular diagnosis of mutations and use of tyrosine kinase inhibitors (TKIs), either as neoadjuvant/adjuvant therapy with surgery or as primary therapy in nonresectable gastrointestinal stromal tumors (GIST), has improved patient outcomes markedly. Additional therapeutics also are on the horizon. The goal of this review is to identify the current incidence, diagnostic modalities, and trends in

personalizing the medical and operative management for patients with GIST. Medline, PubMed, and Google scholar were queried for recently published literature regarding new molecular mechanisms, targeted therapies, and clinical trials investigating the treatment of GIST. The objective of this review is to highlight the biomarkers under development, newly discovered mutations, and newer therapies targeting specific mutational phenotypes which are continually improving the outlook for patients with this disease.
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http://dx.doi.org/10.1016/j.surg.2015.06.027

No Association of Blood Type O with Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1.
J Clin Endocrinol Metab:jc20152615.
S. Nell, R. S. van Leeuwaarde, C. R. Pieterman, J. M. de Laat, A. R. Hermus, O. M. Dekkers, W. W. de Herder, A. N. van der Horst-Schrivers, M. L, P. H. Bisschop, B. Havekes, I. H. Borel Rinkes, M. R. Vriens and G. D. Valk. 2015.
CONTEXT: An association between ABO blood type and the development of cancer, in particular, pancreatic cancer, has been reported in the literature. An association between blood type O and neuroendocrine tumors in multiple endocrine neoplasia type 1 (MEN1) patients was recently suggested. Therefore, blood type O was proposed as an additional factor to personalize screening criteria for neuroendocrine tumors in MEN1 patients. OBJECTIVE: The aim of this study was to assess the association between blood type O and the occurrence of neuroendocrine tumors in the national Dutch MEN1 cohort. DESIGN: Cohort study using the Dutch National MEN1 database, which includes >90% of the Dutch MEN1 population. Demographic and clinical data were analyzed by blood type. Chi-square tests and Fisher exact tests were used to determine the association between blood type O and occurrence of neuroendocrine tumors. A cumulative incidence analysis (Gray's test) was performed to assess the equality of cumulative incidence of neuroendocrine tumors in blood type groups, taking death as a competing risk into account. RESULTS: ABO blood type of 200 of 322 MEN1 patients was known. Demographic and clinical characteristics were similar amongst blood type O and non-O type cohorts. The occurrence of neuroendocrine tumors of the lung, thymus, pancreas and the gastrointestinal tract was equally distributed across the blood type O and non-O type cohorts (Grays's test for equality; P = 0.72). Furthermore, we found no association between blood type O and the occurrence of metastatic disease or survival. CONCLUSIONS: An association between blood type O and the occurrence of neuroendocrine tumors in MEN1 patients was not confirmed. Addition of the blood type to screening and surveillance practice seems for this reason not of additional value for identifying MEN1 patients at risk for the development of neuroendocrine tumors, metastatic disease or a shortened survival.
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Factors Predictive of Emergency Department Visits and Hospitalization Following Thyroidectomy and Parathyroidectomy.
Ann Surg Oncol,
R. A. FitzGerald, A. R. Sehgal, J. A. Nichols and C. R. McHenry. 2015.
BACKGROUND: This study aimed to determine the incidence and risk factors for emergency department (ED) visits and unplanned hospitalization after thyroid and parathyroid surgery. METHODS: A retrospective study of all patients who underwent thyroidectomy or parathyroidectomy from 2007 to 2014 was conducted to assess for ED visits or unplanned hospitalization within 30 days after surgery. Uni- and multivariate analyses were used to identify risk factors for ED visits and hospitalization. RESULTS: Of 864 patients who underwent thyroidectomy (n = 673) or parathyroidectomy (n = 191), 96 (11.1 %) had an ED visit and 41 (4.7 %) were hospitalized within 30 days after surgery. Univariate analysis showed hypocalcemia (p = 0.001), younger age (p = 0.02), total thyroidectomy (p = 0.01), and lack of private health insurance (p = 0.005) to be predictive of an ED visit and hypocalcemia (p = 0.0001), Hashimoto's thyroiditis (p = 0.049), total thyroidectomy (p = 0.005), and African American race (p = 0.03) were predictive of hospitalization after thyroidectomy. Multivariate analysis showed younger age (odds ratio [OR] 1.5 per 10-year decrease in age; p = 0.002; 95 % confidence interval [CI] 1.1-1.8) and Medicare insurance (OR 2.7; p = 0.01; 95 % CI 1.3-5.7) to be independently associated with an ED visit, and hypocalcemia (OR 4.7; p < 0.001; 95 % CI 2.2-11.0) was the only independent factor associated with hospitalization after thyroidectomy. Univariate analysis showed hypocalcemia, renal hyperparathyroidism, and multiglandular disease to be predictive of an ED visit and hospitalization after parathyroidectomy. The sample size for parathyroidectomy was too small for multivariate analysis. CONCLUSIONS: Targeted strategies for transitions of care for patients with postoperative hypocalcemia may help to reduce ED visits and hospitalization after thyroidectomy and parathyroidectomy.
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Chyle Fistula After Neck Dissection: An 8-Year, Single-Center, Prospective Study of Incidence, Clinical Features, and Treatment.
Ann Surg Oncol,
D. Ahn, J. H. Sohn and J. Y. Jeong. 2015.
BACKGROUND: Chyle fistula is a relatively rare complication of neck dissection, and there is a lack of consensus regarding its incidence, risk factors, and management. METHODS: Between 2007 and 2014, a total of 472 cases of neck dissection involving the level IV compartment were included in the study. The incidence, risk factors, and clinical course of chyle fistula were investigated, as well as the outcomes of conventional management and the use of octreotide injection in high-output chyle fistula. RESULTS: The overall incidence of chyle fistula was 4.7 % (22/472), with an incidence of 3.0 % and 6.2 % after right and left neck dissection, respectively. The presence of a metastatic lesion around the junction of the internal jugular vein and subclavian vein was the only factor significantly associated with the development of chyle fistula (approximately fourfold higher risk) in univariate and multivariate analyses. In 22 cases of chyle fistula, the mean total drainage volume was 3226 mL during a mean 15.4 days of drain placement. Total parental nutrition for the management of chyle fistula was required in 16 cases. Nine (40.9 %) of 22 cases experienced additional complications related to chyle fistula. Of the six high-output cases, four were managed with conservative methods plus octreotide injection, and three did not require surgery. CONCLUSIONS: The incidence of chyle fistula after neck dissection was higher than expected, especially on the right side. Surgeons should pay greater attention to chyle fistula from preoperative evaluation to postoperative management.
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