EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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

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

Affiliations see next page

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Contents

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

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

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

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

Collectors

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

Frédéric Triponez, MD
Samira M Sadowski, MD
Department of Thoracic and Endocrine Surgery, University Hospitals of Geneva, Geneva, Switzerland

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

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

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

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

Compilation and Coordination

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

Preliminary

I hope this is not developing into a tradition that the last edition of the year takes so long for the release. Like last year the blame is on me, the start of the year tasks were a little bit overwhelming, leaving little time for the ESES collection.

Once again the list contains over 200 entries. This is clearly not the intention of the list. So please again, try to keep your literature suggestions short, if in any doubt, please omit the reference. I know many of the contributors do a nice job, but some still contribute over 100 references. Please get this down to 30-40.

The developer of Reference Manager stopped program support end of last year and my institution will no longer provide support starting April 1, 2017. Thus, this will be definitively the last time, the ESES list is distributed in the Reference Manager format. Starting 2017 the list will only be distributed in the Endnote, RTF and PDF format. If there is a damand for other (still supported) formats, please let me know, I will look into it.

We hope you enjoy the new edition and find it helpful,

Yours

Ulrich Beutner

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	1.448
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
Cancer	4.889	Langenbecks Arch Surg	2.191
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, †IF 2013, no IF for 2014

Thyroid

Meta-Analyses

Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: A systematic review.
Eur J Surg Oncol,
E. M. Gane, Z. A. Michaleff, M. A. Cottrell, S. M. McPhail, A. L. Hatton, B. J. Panizza and S. P. O'Leary. 2016.
INTRODUCTION: Shoulder pain and dysfunction may occur following neck dissection among people being treated for head and neck cancer. This systematic review aims to examine the prevalence and incidence of shoulder and neck dysfunction after neck dissection and identify risk factors for these post-operative complications. METHODS: Electronic databases (Pubmed, CINAHL, EMBASE, Cochrane) were searched for articles including adults undergoing neck dissection for head and neck cancer. Studies that reported prevalence, incidence or risk factors for an outcome of the shoulder or neck were eligible and assessed using the Critical Review Form - Quantitative Studies. RESULTS: Seventy-five articles were included in the final review. Prevalence rates for shoulder pain were slightly higher after RND (range, 10-100%) compared with MRND (range, 0-100%) and SND (range, 9-25%). The incidence of reduced shoulder active range of motion depended on surgery type (range, 5-20%). The prevalence of reduced neck active range of motion after neck dissection was 1-13%. Type of neck dissection was a risk factor for shoulder pain, reduced function and health-related quality of life. CONCLUSIONS: The prevalence and incidence of shoulder and neck dysfunction after neck dissection varies by type of surgery performed and measure of dysfunction used. Pre-operative education for patients undergoing neck dissection should acknowledge the potential for post-operative shoulder and neck problems to occur and inform patients that accessory nerve preservation lowers, but does not eliminate, the risk of developing musculoskeletal complications.
PubMed-ID: 27956321
http://dx.doi.org/10.1016/j.ejso.2016.10.026

Extralaryngeal branching of the recurrent laryngeal nerve: a meta-analysis of 28,387 nerves.
Langenbecks Arch Surg, 401(7):913-23.
B. M. Henry, J. Vikse, M. J. Graves, S. Sanna, B. Sanna, I. M. Tomaszewska, R. S. Tubbs and K. A. Tomaszewski. 2016.
INTRODUCTION: The recurrent laryngeal nerves (RLN) are branches of the vagus nerve that go on to innervate most of the intrinsic muscles of the larynx. Historically, the RLN has been considered to branch after it enters the larynx, but numerous studies have demonstrated that it often branches before. The wide variability of this extralaryngeal branching (ELB) has significant implications for the risk of iatrogenic injury. We aimed to assess the anatomical characteristics of ELB comprehensively. METHODS: Articles on the ELB of the RLN were identified by a comprehensive database search. Relevant data were extracted and pooled into a meta-analysis of the prevalence of branching, branching pattern, distance of ELB point from the larynx, and presence of positive motor signals in anterior and posterior ELB branches. RESULTS: A total of 69 articles (n = 28,387 nerves) from both intraoperative and cadaveric modalities were included in the meta-analysis. The overall pooled prevalence of ELB was 60.0 % (95 % CI 52.0-67.7). Cadaveric and intraoperative subgroups differed with prevalence rates of 73.3 % (95 % CI 61.0-84.0) and 39.2 % (95 % CI 29.0-49.9), respectively. Cadavers most often presented with a ELB pattern of bifurcation, with a prevalence of 61.1 %, followed by no branching at 23.4 %. Branching of the RLN occurred most often at a distance of 1-2 cm (74.8 % of cases) prior to entering the larynx. A positive motor signal was most often noted in anterior RLN branches (99.9 %) but only in 1.5 % of posterior branches. CONCLUSIONS: The anatomy of the RLN is highly variable, and ELB is likely to have been underreported in intraoperative studies. Because of its high likelihood, the possibility of ELB needs to be assessed in patients to prevent iatrogenic injury and long-term postoperative complications.
PubMed-ID: 27251487
http://dx.doi.org/10.1007/s00423-016-1455-7

Relation between therapy options for Graves' disease and the course of Graves' ophthalmopathy: a systematic review and meta-analysis.
J Endocrinol Invest, 39(11):1225-33.
H. X. Li, N. Xiang, W. K. Hu and X. L. Jiao. 2016.
BACKGROUND: The relation between therapy options for Graves' disease (GD) and the course of Graves' ophthalmopathy (GO) are still controversial. Our aim was to compare the occurrence of development or

worsening of GO in patients who were treated with antithyroid drugs (ATDs) or radioactive iodine (RAI) or thyroidectomy (TX). METHODS: We conducted a comprehensive search of the Embase and PubMed database. Odds ratio (OR) was used as a measure of the effect of therapy options for GD on the risk of development or worsening of GO. The analysis was further stratified by factors that could affect the treatment effects. RESULTS: Nine trials involving 1773 patients were included. RAI therapy showed a significant effect on the risk of development or worsening GO compared with ATD (OR 2.25; 95 % CI 1.61-3.14; P < 0.00001). Glucocorticoid prophylaxis was effective in preventing GO development or worsening (0.40; 0.23-0.68; P = 0.002); especially for patients with preexisting GO (0.41; 0.23-0.73; P = 0.002). At 3 months, showed GO to be improved in 17 TX and 21 total thyroid ablation (TTA) patients, with no significant difference between the two groups; between 6 and 12 months, TTA did show significant beneficial effect on the improvement of GO (6.02; 2.80-12.96; P < 0.00001); GO was found to be inactive in a significantly higher percentage of patients in the TTA (2.17; 1.04-4.52; P = 0.04). CONCLUSION: Radioiodine therapy is a significant risk factor for development or worsening of GO in GD. But GO progression can be prevented by prophylactic glucocorticoids in patients with preexisting GO. Compared with TX alone, TTA induces an earlier and steadier GO improvement in patients with mild to moderate-severe and active GO. Whether this is sufficient to offer TTA to patients needs further investigation.
PubMed-ID: 27220843
http://dx.doi.org/10.1007/s40618-016-0484-y

The Effect of Prophylactic Central Neck Dissection on Locoregional Recurrence in Papillary Thyroid Cancer After Total Thyroidectomy: A Systematic Review and Meta-Analysis : pCND for the Locoregional Recurrence of Papillary Thyroid Cancer.
Ann Surg Oncol,
W. Zhao, L. You, X. Hou, S. Chen, X. Ren, G. Chen and Y. Zhao. 2016.
BACKGROUND: The use of prophylactic central neck dissection (pCND) for papillary thyroid cancer (PTC) without clinical evidence of nodal metastasis (cN0) remains controversial. This study was designed to examine whether pCND for PTC affected locoregional recurrence (LRR). METHODS: A systematic review was performed to compare the LRR between patients with PTC who underwent total thyroidectomy (TT) and pCND and those who underwent TT alone. The primary outcome was LRR. Other outcomes, including postoperative radioiodine (RAI) ablation and surgically related complications, were evaluated. A meta-analysis was performed using the random-effects model. RESULTS: We included 17 studies, which comprised 4437 patients. Patients in the TT+pCND group had a significantly reduced risk of LRR (risk ratio [RR] = 0.66; 95% confidence interval [CI]: 0.49-0.90; P = 0.008). The LRR in the central neck compartment (RR = 0.35; 95% CI 0.18-0.68; P = 0.002) was significantly lower in the TT+pCND group, whereas the LRR in the lateral neck compartment was similar between the two groups. Compared with the TT alone group, patients in the TT+pCND group tended to receive higher RAI (74.6% vs. 59.9%) and experience temporary hypocalcemia (odds ratio [OR] = 2.37; 95% CI 1.89-2.96; P < 0.00001), permanent hypocalcemia (OR = 1.93; 95% CI 1.05-3.57; P = 0.03), and increased overall morbidity (OR = 2.56; 95% CI 1.75-3.74; P < 0.00001). CONCLUSIONS: This meta-analysis suggested that although pCND reduced the LRR in PTC-specifically in the central neck compartment-it was accompanied by an increased rate of postoperative hypocalcemia. However, the evidence is limited and randomized, controlled trials are needed to clarify this role further.
PubMed-ID: 27913945
http://dx.doi.org/10.1245/s10434-016-5691-4

Randomized controlled trials

Clinical Efficacy of Intravenous Lidocaine for Thyroidectomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial.
World J Surg, 40(12):2941-7.
G. J. Choi, H. Kang, E. J. Ahn, J. I. Oh, C. W. Baek, Y. H. Jung and J. Y. Kim. 2016.
BACKGROUND: Systemic lidocaine has analgesic and anti-inflammatory effects. The purpose of this prospective, randomized, double-blind study was to evaluate the effects of intravenous lidocaine on pain following thyroidectomy. METHODS: Fifty-eight adult patients scheduled for total thyroidectomy were randomly allocated to receive a 1.5 mg/kg lidocaine bolus followed by a 2 mg/kg/h infusion during surgery, or the same volume of normal saline (control). After thyroidectomy, we evaluated postoperative pain, nausea, fentanyl consumption, frequency of pushing the button (FPB) for patient-controlled analgesia (PCA), High-sensitivity C-reactive protein (hs-CRP) in serum, and patient satisfaction scores regarding the recovery process. RESULTS:

Postoperative pain and nausea scores were significantly lower in the lidocaine group for the first 4 h following thyroidectomy, compared to the control group. Fentanyl consumption and FPB for the PCA were also significantly reduced in the lidocaine group for 4 h following thyroidectomy, and hs-CRP was significantly less in the lidocaine group at postoperative days 1 and 3. Furthermore, satisfaction scores were significantly higher in the lidocaine group compared to the control group. CONCLUSIONS: Intravenous lidocaine effectively reduced postoperative pain and nausea following thyroidectomy as well as improved the quality of recovery. TRIAL REGISTRATION NUMBER: Clinicaltrials.gov NCT01608360.
PubMed-ID: 27379388
http://dx.doi.org/10.1007/s00268-016-3619-6

PTH(1-34) for the Primary Prevention of Postthyroidectomy Hypocalcemia: The THYPOS Trial.
J Clin Endocrinol Metab, 101(11):4039-45.
A. Palermo, G. Mangiameli, G. Tabacco, F. Longo, C. Pedone, S. I. Briganti, D. Maggi, F. Vescini, A. Naciu, A. Lauria Pantano, N. Napoli, S. Angeletti, P. Pozzilli, P. Crucitti and S. Manfrini. 2016.
CONTEXT: There are no studies evaluating teriparatide for prevention of post-thyroidectomy hypocalcemia. OBJECTIVE: Our objective was to evaluate whether teriparatide can prevent postsurgical hypocalcemia and shorten the hospitalization in subjects at high risk of hypocalcemia following thyroid surgery. DESIGN: This was a prospective phase II randomized open-label trial. SETTING: This trial was set on a surgical ward. PATIENTS: Twenty-six subjects (six males, 20 females) with intact PTH lower than10 pg/ml 4 hours after thyroidectomy were included. INTERVENTION: Subjects were randomized (1:1) to receive SC administration of 20 mcg of teriparatide every 12 hours until the discharge (treatment group) or to follow standard clinical care (control group). MAIN OUTCOME MEASURE: Adjusted serum calcium, duration of hospitalization, and calcium/calcitriol supplementation were measured. RESULTS: Overall, the incidence of hypocalcemia was 3/13 in treatment group and 11/13 in the control group (P = .006). Treated patients had a lower risk of hypocalcemia than controls (relative risk, 0.26 [95% confidence interval, 0.09-0.723)]). The median duration of hospitalization was 3 days (interquartile range, 1) in control subjects and 2 days (interquartile range, 0) in treated subjects (P = .012). One month after discharge, 10/13 subjects in the treatment group had stopped calcium carbonate supplements, while only 5/13 in the control group had discontinued calcium. The ANOVA for repeated measures showed a significant difference in calcium supplements between groups at 1-month visit (P = .04) as well as a significant difference between discharge and 1-month visit in the treatment group (P for interaction time group = .04) Conclusions: Teriparatide may prevent postsurgical hypocalcemia, shorten the duration of hospitalization, and reduce the need for calcium and vitamin D supplementation after discharge in high risk subjects after thyroid surgery.
PubMed-ID: 27525532
http://dx.doi.org/10.1210/jc.2016-2530

Contribution of intraoperative neural monitoring to preservation of the external branch of the superior laryngeal nerve: a randomized prospective clinical trial.
Langenbecks Arch Surg,
M. Uludag, N. Aygun, K. Kartal, B. Citgez, E. Besler, G. Yetkin, C. Kaya, H. Ozsahin, M. Mihmanli and A. Isgor. 2016.
PURPOSE: The purpose of this study was to evaluate the effect of intraoperative neuromonitoring (IONM) on the injury rate of the external branch of the superior laryngeal nerve (EBSLN) during thyroidectomy. METHODS: A total of 133 consenting patients (98 female, 35 male; mean age, 45.6 +/- 11.7 years) undergoing thyroidectomy were randomly assigned to 2 groups. In group 1 (n = 65 patients, 105 nerves), superior thyroid pole dissection was performed with no attempt to identify the EBSLN; in group 2 (n = 68 patients, 106 nerves), IONM was used to identify the EBSLN during surgery. EBSLN function was evaluated by intraoperative electromyography of the cricothyroid muscle. The EBSLN Voice Impairment Index-5 (VII-5) was conducted preoperatively and at 1, 3, and 6 months postoperatively. The primary outcome was the prevalence of EBSLN injury. The secondary outcomes were the identification rate of the EBSLN using IONM and changes in postoperative voice performance. RESULTS: EBSLN injury was detected in eight (12.3%) patients and nine (8.6%) nerves in group 1 and in one (1.5%) patient and one (0.9%) nerve in group 2 (patients, p = 0.015; nerves, p = 0.010). IONM contributed significantly to visual (p < 0.001) and functional (p < 0.001) nerve identification in group 2. The VII-5 indicated more voice changes in group 1 than 2 at 1, 3, and 6 months postoperatively (p = 0.012, p = 0.015, and p = 0.02, respectively). CONCLUSION: IONM contributes to visual and functional identification of the EBSLN and decreases the rate of EBSLN injury during superior pole dissection. Routine use of IONM to identify the EBSLN will minimize the risk of injury during thyroidectomy.
PubMed-ID: 28035477
http://dx.doi.org/10.1007/s00423-016-1544-7

Consensus Statements/Guidelines

- None -

Other Articles

The cause of brachial plexopathy in robot-assisted transaxillary thyroidectomy-A neurophysiological investigation.
Laryngoscope, 126(9):2187-93.
U. Alkan, O. Zarchi, N. Rabinovics, Y. Nachalon, R. Feinmesser and G. Bachar. 2016.
OBJECTIVES/HYPOTHESIS: During robot-assisted transaxillary thyroidectomy, the patient's arm is maintained in an overhead flexed position for a prolonged time, which poses a risk of postoperative brachial plexopathy. The aim of the study was to identify the causes of brachial plexopathy and to assess the benefit of intraoperative neurophysiological monitoring (IONM) in preventing positional brachial plexopathy in this setting. STUDY DESIGN: Retrospective case series. METHODS: The computerized database of a tertiary medical center was searched for all consecutive patients who underwent robot-assisted transaxillary thyroidectomy between 2012 and 2014. Clinical, operative, and outcome parameters were collected from the medical files. Findings were compared between patients operated with and without IONM. RESULTS: The cohort included 30 patients, 14 operated with IONM and 16 without. Three events of impending brachial plexopathy were detected in the monitored group. The monitored group had significantly better shoulder movement (P = .003), a lower rate of hypoesthesia (P = .011), less pain (P = .001) in the early postoperative period than the nonmonitored group and higher quality of life in the early postoperative period (P = .012). The monitored group was significantly younger than the nonmonitored one (P = .02) and had a significantly larger diameter of thyroid nodule than the nonmonitored group (P = .043). CONCLUSIONS: IONM during robot-assisted transaxillary thyroidectomy may improve short-term postoperative pain and shoulder movement and longer-term quality of life. LEVEL OF EVIDENCE: 4 Laryngoscope, 126:2187-2193, 2016.
PubMed-ID: 26774192
http://dx.doi.org/10.1002/lary.25850

Low postoperative nonstimulated thyroglobulin as a criterion for the indication of low radioiodine activity in patients with papillary thyroid cancer of intermediate risk 'with higher risk features'.
Clin Endocrinol (Oxf), 85(3):453-8.
P. W. Rosario, G. F. Mourao and M. R. Calsolari. 2016.
OBJECTIVE: This study evaluated low-activity (131) I therapy in patients with papillary thyroid carcinoma (PTC) of intermediate risk 'with higher risk features' who had low nonstimulated thyroglobulin (Tg) after thyroidectomy. DESIGN AND PATIENTS: This was a prospective study including 102 patients with tumours >1 cm and aggressive histology; and/or >3 positive lymph node (LN) or LN >1.5 cm or exhibiting macroscopic extracapsular extension, and clinically apparent (cN1); and/or a combination of a tumour >4 cm, microscopic extrathyroidal extension and LN metastases (cN1). After thyroidectomy, all patients had nonstimulated Tg < 0.3 ng/ml and negative antithyroglobulin antibodies (TgAb) and neck ultrasonography (US). The patients were treated with a low activity of (131) I (1110 or 1850 MBq). RESULTS: Post-therapy whole-body scanning (RxWBS) showed ectopic uptake in four patients. When evaluated 12 months after (131) I therapy, nonstimulated Tg </= 0.2 ng/ml with negative TgAb and US, defined as excellent response to initial therapy, was achieved in 101 patients (99%). Only one patient with positive initial RxWBS had structural disease. During follow-up, four patients (4%) relapsed, including LN metastases in two, pulmonary metastases in one, and elevated Tg in one. The other 98 patients remained with nonstimulated Tg </= 0.2 ng/ml and negative TgAb and US. There was no case of death due to the tumour. CONCLUSIONS: We conclude that in intermediate-risk patients 'with higher risk features', low nonstimulated Tg measured with a second-generation assay can be used as criterion for the administration of low (131) I activities (1850 MBq or less).
PubMed-ID: 26801644
http://dx.doi.org/10.1111/cen.13024

Recombinant human thyrotropin-stimulated thyroglobulin level at the time of radioactive iodine ablation is an independent prognostic marker of differentiated thyroid carcinoma in the setting of prophylactic

central neck dissection.
Clin Endocrinol (Oxf), 85(3):459-65.
J. H. Moon, J. Y. Choi, W. J. Jeong, S. H. Ahn, W. W. Lee, K. M. Kim, S. H. Choi, S. Lim, Y. J. Park, K. H. Yi, J. Park do and H. C. Jang. 2016.
OBJECTIVE: We investigated the value of the stimulated thyroglobulin (Tg) level at the time of recombinant human thyrotropin (rhTSH)-aided remnant ablation for predicting disease status 1 year later in patients with DTC who underwent total thyroidectomy with central neck dissection (CND). DESIGN, SETTING, AND PARTICIPANT: This was a prospective observational study of 253 consecutive patients with DTC who underwent rhTSH-aided RAI ablation after total thyroidectomy and prophylactic CND. Patients with evidence of initial distant metastasis or positive Tg antibodies were excluded. MAJOR OUTCOME MEASURE: We compared rhTSH-stimulated Tg level at RAI ablation according to the disease status at 1 year and evaluated optimal cut-off value of rhTSH-stimulated Tg. Binary logistic regression analysis was performed to investigate the independent predictive factors for disease status 1 year after ablation. RESULTS: Among study participants, 228 (90.1%) were considered disease free at 1 year after remnant ablation. Patients with persistent or recurrent disease were more likely to be aged >/=45 years, and to have N1b stage, TNM stage III or IV, and higher rhTSH-stimulated Tg level at RAI ablation. The optimal cut-off of rhTSH-stimulated Tg for predicting persistent or recurrent disease was 1.79 ng/ml, with a negative predictive value of 99.5%. A serum rhTSH-stimulated Tg level >/=1.79 at the time of ablation was independently associated with persistent or recurrent disease 1 year later. N1b stage tended to be associated with persistent or recurrent disease. CONCLUSION: A low stimulated serum Tg level at rhTSH-aided RAI ablation may be a favourable prognostic marker in the setting of prophylactic CND.
PubMed-ID: 26833982
http://dx.doi.org/10.1111/cen.13029

Predictors for papillary thyroid cancer persistence and recurrence: a retrospective analysis with a 10-year follow-up cohort study.
Clin Endocrinol (Oxf), 85(3):466-74.
T. P. de Castro, W. Waissmann, T. C. Simoes, R. C. de Mello and D. P. Carvalho. 2016.
OBJECTIVE: We aimed to determine outcome predictors of papillary thyroid cancer (PTC) persistence and recurrence, separately. CONTEXT: The factors contributing to either persistence or recurrence of PTC are poorly defined, as both outcomes are usually evaluated together. DESIGN AND PATIENTS: In this 10-year follow-up cohort study, 190 PTC patients were evaluated (18-85 years old; registered from 1 January 1990 to31 December 1999 at a Brazilian Cancer Care referral Hospital). After initial surgery, we examined persistence (disease detected up to 1 year), recurrence (disease detected after 1 year) and PTC-free status (disease absence during follow-up). MEASUREMENTS: Outcome predictors were modelled using multinomial logit regression analysis. RESULTS: The univariate analysis showed that persistence and recurrence were significantly associated with lymph node metastasis (OR = 12.33; OR = 2.84, respectively), local aggressiveness (OR = 5.22; OR = 3.35) and extrathyroidal extension (OR = 5.07; OR = 7.11). Persistence was associated with male sex (OR = 3.49), age above 45 years old at diagnosis (OR = 1.03), macroscopic lymph node metastasis (OR = 5.85), local aggressiveness (OR = 5.22), each 1-cm tumour size increase (OR = 1.34), a cancer care referral hospital as the place of initial surgery (OR = 2.3), thyroidectomy or near total thyroidectomy(OR = 3.03) and neck dissection (OR = 3.19). Recurrence was associated with the time of radioactive iodine ((131) I) therapy (OR = 3.71). After data modelling, persistence was associated with macroscopic lymph node metastasis (OR = 6.17), 1-cm increases in tumour size (OR = 1.30) and thyroidectomy or near total thyroidectomy (OR = 3.82), while recurrence was associated with surgery at referral hospital (OR = 3.79). CONCLUSIONS: The best predictors of persistence were tumour size and macroscopic lymph node metastasis; when the initial surgery is of quality, the recurrence depends more on tumour's biology aspects.
PubMed-ID: 26834009
http://dx.doi.org/10.1111/cen.13032

Can the follow-up of patients with papillary thyroid carcinoma of low and intermediate risk and excellent response to initial therapy be simplified using second-generation thyroglobulin assays?
Clin Endocrinol (Oxf), 85(4):596-601.
P. W. Rosario, G. F. Mourao and M. R. Calsolari. 2016.
OBJECTIVE: In view of the low probability of recurrence, the cost-effective follow-up of patients with papillary thyroid carcinoma (PTC) of low or intermediate risk and excellent response to initial therapy represents a challenge. This study evaluated the cases of structural recurrence among these patients. PATIENTS: The sample comprised 578 patients with PTC of low or intermediate risk, who were submitted to total thyroidectomy with or without (131) I therapy and exhibited an excellent response to initial therapy defined based on nonstimulated thyroglobulin (Tg) </=0.2 ng/ml and negative neck ultrasonography (US). RESULTS: Twelve

patients (2%) showed structural recurrence. At the time when recurrence was 'confirmed', Tg elevation had not occurred in only two patients, one with lymph node metastases <1 cm detected by US and the other with pulmonary metastases. Antithyroglobulin antibodies (TgAb) were undetectable in both patients. The first alteration observed in patients with recurrence was Tg elevation in six patients, Tg elevation associated with suspicious US in three, and suspicious US in two. An increase in TgAb was not the first alteration in any of the patients. Among the 560 patients who continued to have Tg </= 0.2 ng/ml, US permitted the detection of only one neck recurrence. Measurement of TgAb did not detect any recurrence. CONCLUSION: Our results confirm that in patients with PTC of low or intermediate risk an excellent response to initial therapy can be defined based on nonstimulated Tg </= 0.2 ng/ml. Follow-up consisting only of clinical examination and periodic measurement of Tg with a second-generation assay may be sufficient.
PubMed-ID: 26940991
http://dx.doi.org/10.1111/cen.13053

Intra-Operative Indocyanine Green Angiography of the Parathyroid Gland.
World J Surg, 40(10):2378-81.
J. Vidal Fortuny, W. Karenovics, F. Triponez and S. M. Sadowski. 2016.
Major complications of thyroid and parathyroid surgery are recurrent laryngeal nerve injuries and definitive hypoparathyroidism. The use of intra-operative Indocyanine Green Angiography for confirmation of vascular status of the parathyroid gland is reported here.
PubMed-ID: 26944954
http://dx.doi.org/10.1007/s00268-016-3493-2

Recurrence in patients with clinically early-stage papillary thyroid carcinoma according to tumor size and surgical extent.
Am J Surg, 212(3):419-25 e1.
J. W. Kim, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim. 2016.
BACKGROUND: To investigate whether post-treatment recurrence differs by tumor size or surgical extent in clinically early-stage papillary thyroid carcinoma (PTC) patients. METHODS: A total of 1,041 surgical patients with PTC 4 cm or less and no clinical evidence of metastases to regional or distant sites were included. Cox proportional hazard models were used to identify the clinicopathological variables predictive of post-treatment recurrence. RESULTS: Central nodal involvement was found in 313 (34.1%) of 918 patients who underwent prophylactic central lymph node dissection. For the median follow-up of 83 months, 25 (2.4%) of 1,041 patients had a regional recurrence and 12 (1.2%) patients died of other causes. Male gender, tumor size, extranodal extension, and positive resection margin remained independent variables predictive of recurrence by multivariate analysis (P < .05 each). There was no significant impact of age (<45 vs >/=45 years, P = .944) or surgical extent (unilateral vs bilateral thyroidectomy, P = .776) on recurrence. CONCLUSIONS: Tumor size in patients with PTC of 4 cm or less is an important predictive factor for post-treatment recurrence.
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http://dx.doi.org/10.1016/j.amjsurg.2015.12.015

68Ga-DOTATOC PET/CT in Patients with Iodine- and 18F-FDG-Negative Differentiated Thyroid Carcinoma and Elevated Serum Thyroglobulin.
J Nucl Med, 57(10):1512-7.
I. Binse, T. D. Poeppel, M. Ruhlmann, S. Ezziddin, R. Gorges, A. Sabet, K. Beiderwellen, A. Bockisch and S. J. Rosenbaum-Krumme. 2016.
This study evaluated the impact of 68Ga-DOTATOC PET/CT in detecting recurrence or metastases in differentiated thyroid carcinoma (DTC) patients with elevated serum thyroglobulin and both negative radioiodine imaging and negative 18F-FDG PET/CT. METHODS: 68Ga-DOTATOC PET/CT (CT without contrast, low-dose) was performed on average 6 wk after negative 18F-FDG PET/CT (CT contrast-enhanced, full-dose) in 15 consecutive radioiodine-negative DTC patients with elevated and rising thyroglobulin. Visual assessment of 68Ga-DOTATOC PET/CT images used a 4-point scale for classification of lesions (0, no pathologic findings; 1, benign; 2, equivocal; 3, malignant). PET findings were correlated with the histologic subtype of tumor, levels of serum thyroglobulin, and morphologic findings on full-dose CT and neck ultrasound. Histology or clinical and imaging follow-up served as a reference standard. Analysis was performed on a patient and lesion basis. RESULTS: 68Ga-DOTATOC PET/CT was true-positive in 5 patients (10 tumor lesions) and was false-positive in 1 patient. The rate of positive 68Ga-DOTATOC PET/CT was significantly higher in poorly differentiated/oxyphilic carcinomas (4/4 patients) than in papillary (1/5) or follicular (0/6) tumors. Thyroglobulin levels tended to be higher in patients with tumor localization on 68Ga-DOTATOC PET/CT, but differences were not significant. In 2 of 5 patients with true-positive findings on 68Ga-DOTATOC PET/CT, CT alone but not ultrasound identified 2 of

10 tumor lesions, but in both patients 68Ga-DOTATOC-PET/CT revealed further tumor lesions not detected on CT alone. CONCLUSION: 68Ga-DOTATOC PET/CT should be considered in the case of negative 18F-FDG PET/CT in radioiodine-negative DTC patients with elevated and rising thyroglobulin. Imaging with 68Ga-DOTATOC appears promising especially in poorly differentiated and oxyphilic subtypes of DTC.
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http://dx.doi.org/10.2967/jnumed.115.171942

Prognostic role of the Bethesda System for conventional papillary thyroid carcinoma.
Head Neck, 38(10):1509-14.
H. M. Gweon, H. R. Koo, E. J. Son, J. A. Kim, J. H. Youk, S. W. Hong and B. J. Lim. 2016.
BACKGROUND: The purpose of this study was to investigate the role of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) as a prognostic marker in conventional papillary thyroid carcinoma (PTC). METHODS: A total of 397 patients who underwent ultrasound-guided fine-needle aspiration biopsy (FNAB) and surgery for conventional PTCs were enrolled. The association between the Bethesda category and histopathologic result was evaluated. RESULTS: Among the Bethesda categories, a significant difference was found in the presence of extrathyroidal extension (Bethesda category III, 3.2% [7 of 220]; category V, 19.1% [42 of 220]; and category VI, 77.7% [171 of 220]; $p < .001$) and lymph node metastasis (Bethesda category III, 3.8% [6 of 156]; category V, 16.7% [26 of 156]; and category VI, 79.5% [124 of 156]; $p < .001$). Multivariate analysis showed that the Bethesda category was independently predictive of extrathyroidal extension ($p = .013$) and lymph node metastasis ($p = .035$). CONCLUSION: Conventional PTC with a higher Bethesda category at the time of cytology diagnosis would be poor prognosis. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: First-1514, 2016.
PubMed-ID: 27062195
http://dx.doi.org/10.1002/hed.24466

Successful intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve, a multidisciplinary approach: The Massachusetts Eye and Ear Infirmary monitoring collaborative protocol with experience in over 3000 cases.
Head Neck, 38(10):1487-94.
A. A. Macias, S. Eappen, I. Malikin, J. Goldfarb, S. Kujawa, P. M. Konowitz, D. Kamani and G. W. Randolph. 2016.
BACKGROUND: Although intraoperative nerve monitoring (IONM) is utilized increasingly, the information on the related anesthesia technique is limited. This study presents an up-to-date clinical algorithm, including setup and troubleshooting of an IONM system, endotracheal tube placement, and anesthetic parameters. To our knowledge, this is the first interdisciplinary collaborative protocol for monitored neck surgery based on the published evidence and clinical experience. METHODS: The Departments of Otolaryngology Head and Neck Surgery, Anesthesiology, and Audiology collaboratively developed a protocol for IONM of the recurrent laryngeal nerve (RLN) based on published evidence and our experience with 3000 patients over a 16-year period. RESULTS: No complications related to monitoring or endotracheal tube placement were noted when the IONM protocol was implemented at Massachusetts Eye and Ear Infirmary (MEEI). The IONM protocol has proven to be vital in standardizing care and in avoiding intraoperative errors. CONCLUSION: An IONM system entails an anesthesiologist who understands the challenges posed by this technique; muscle relaxation must be minimized/eliminated to optimize IONM. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: First-1494, 2016.
PubMed-ID: 27062311
http://dx.doi.org/10.1002/hed.24468

Clinical outcomes of patients with hypercalcitoninemia after initial treatment for medullary thyroid cancer and postoperative serum calcitonin cutoffs for predicting structural recurrence.
Head Neck, 38(10):1501-8.
Y. Y. Cho, H. W. Jang, J. Y. Jang, T. H. Kim, J. H. Choe, J. H. Kim, J. S. Kim, S. W. Kim and J. H. Chung. 2016.
BACKGROUND: Persistent hypercalcitoninemia is reported in 40% to 60% of patients with medullary thyroid cancer (MTC) after initial therapy, but their clinical outcomes have not been clearly studied. We evaluated the outcomes of MTC with hypercalcitoninemia and assessed the cutoffs of postoperative serum calcitonin for predicting structural recurrence. METHODS: A dynamic risk assessment system was used to categorize clinical outcomes in this retrospective study. Receiver operating characteristic (ROC) curve analysis was used to calculate the calcitonin cutoffs for predicting structural recurrence. RESULTS: Among 120 patients operated on, 30 (25%) had persistent hypercalcitoninemia. Of that group, 18 (60%) had biochemical persistent disease and 11 (37%) developed structural identified disease, including 1 death (3%). Postoperative calcitonin <29 pg/mL predicted structural disease with 100% sensitivity, 90.5% specificity, and 100% negative predictive value.

CONCLUSION: One third of the patients with MTC with hypercalcitoninemia experienced structural recurrence, and postoperative basal serum calcitonin might be a simple tumor marker to predict structural recurrence. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: First-1508, 2016.
PubMed-ID: 27062421
http://dx.doi.org/10.1002/hed.24469

Incidence of permanent hypocalcaemia after total thyroidectomy with or without central neck dissection for thyroid carcinoma: a nationwide claim study.
Clin Endocrinol (Oxf), 85(3):483-7.
G. H. Seo, Y. J. Chai, H. J. Choi and K. E. Lee. 2016.
OBJECTIVE: Permanent hypocalcaemia is the most common and serious complication after total thyroidectomy (TT). This study examined the impact of central neck dissection (CND) and institutional volume on rates of permanent hypocalcaemia by analysing data held in the nationwide claim database of South Korea. DESIGN: Data from patients who underwent TT due to thyroid carcinoma from 2007-2013 were obtained from the Health Insurance Review and Assessment Service database. Of these, patients prescribed more than 1000 mg of elemental calcium for more than 288 days during the first 360 days postsurgery were defined as having permanent hypocalcaemia. RESULTS: In total, 192 333 patients (32 988 male and 159 345 female) were eligible for analysis. Of these, 52 707 (27.4%) underwent TT alone and 139 626 (72.6%) underwent TT plus CND. The incidence of permanent hypocalcaemia was greater in the TT plus CND group than in the TT alone group (5.4% vs 4.6%, P < 0.001). The age- and sex-adjusted risk for permanent hypocalcaemia in the TT plus CND group was 1.20 (P < 0.001). CND did not raise the rates of permanent hypocalcaemia in institutes with a low volume of annual cases (<200), whereas permanent hypocalcaemia was more common in the TT plus CND group than in the TT alone group (3.5% vs 2.9%, P = 0.002) in institutes with a large volume of annual cases (>/=800). CONCLUSIONS: TT plus CND was associated with a greater risk of permanent hypocalcaemia than TT alone. Surgeons should consider the risk of permanent hypocalcaemia when deciding whether to perform CND.
PubMed-ID: 27063793
http://dx.doi.org/10.1111/cen.13082

Improving the adoption of thyroid cancer clinical practice guidelines.
Laryngoscope, 126(11):2640-5.
I. Likhterov, R. M. Tuttle, G. C. Haser, H. K. Su, D. Bergman, E. E. Alon, V. Bernet, E. Brett, R. Cobin, E. H. Dewey, G. Doherty, L. L. Dos Reis, J. Klopper, S. L. Lee, M. A. Lupo, J. Machac, J. I. Mechanick, M. Milas, L. Orloff, G. Randolph, D. S. Ross, M. E. Rowe, R. Smallridge, D. Terris, R. P. Tufano and M. L. Urken. 2016.
OBJECTIVES/HYPOTHESIS: To present an overview of the barriers to the implementation of clinical practice guidelines (CPGs) in thyroid cancer management and to introduce a computer-based clinical support system. DATA SOURCES: PubMed. REVIEW METHODS: A review of studies on adherence to CPGs was conducted. RESULTS: Awareness and adoption of CPGs is low in thyroid cancer management. Barriers to implementation include unfamiliarity with the CPGs and financial concerns. Effective interventions to improve adherence are possible, especially when they are readily accessible at the point of care delivery. Computerized clinical support systems show particular promise. The authors introduce the clinical decision making modules (CDMMs) of the Thyroid Cancer Care Collaborative, a thyroid cancer-specific electronic health record. These computer-based modules can assist clinicians with implementation of these recommendations in clinical practice. CONCLUSION: Computer-based support systems can help clinicians understand and adopt the thyroid cancer CPGs. By integrating patient characteristics and guidelines at the point of care delivery, the CDMMs can improve adherence to the guidelines and help clinicians provide high-quality, evidence-based, and individualized patient care in the management of differentiated thyroid cancer. Laryngoscope, 126:2640-2645, 2016.
PubMed-ID: 27074952
http://dx.doi.org/10.1002/lary.25986

Supramaximal neurostimulation with laryngeal palpation to predict postoperative vocal fold mobility.
Laryngoscope, 126(12):2863-8.
W. Cha, I. Cho, J. Y. Jang, J. K. Cho, S. G. Wang and J. H. Park. 2016.
OBJECTIVES/HYPOTHESIS: Recurrent laryngeal nerve (RLN) injury during thyroidectomy or parathyroidectomy is a challenging issue and causes significant morbidity. We adopted the supramaximal stimulation protocol for neurostimulation with laryngeal palpation (NSLP) and tried to evaluate the predictive values of supramaximal NSLP for immediate postoperative vocal fold (VF) mobility. STUDY DESIGN: Prospective cohort study. METHODS: Prospectively, 293 patients who underwent thyroid and parathyroid surgery and 542 RLNs at risk were enrolled in this study. During NSLP, the current was escalated to 3 mA until definite laryngeal twitch was observed. Immediate postoperative VF mobility was evaluated using flexible laryngoscopy. RESULTS:

Diagnostic accuracy of NSLP is calculated according to cutoff values of minimal current intensity (1 mA, 1.5 mA, and 2 mA). At 2mA, sensitivity was 81.82%, specificity 100%, positive predictive value 100%, and negative predictive value 99.62%. CONCLUSIONS: Supramaximal NSLP might be a simple and reliable method to predict immediate postoperative VF mobility in open thyroid and parathyroid surgeries when intraoperative neuromonitoring is unavailable. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:2863-2868, 2016.
PubMed-ID: 27074966
http://dx.doi.org/10.1002/lary.26011

Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma.
Ann Surg Oncol, 23(9):2866-73.
S. K. Kim, I. Park, J. W. Woo, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
BACKGROUND: Because lymph node (LN) metastasis has been proven to be a predictor for locoregional recurrence (LRR) in papillary thyroid microcarcinoma (PTMC), better knowledge about the predictors for LN metastasis in PTMC is required. METHODS: We retrospectively reviewed 5656 PTMC patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection between January 1997 and June 2015. RESULTS: Male gender (adjusted odds ratio [OR] 2.332), conventional variant (adjusted OR 4.266), tumor size >0.5 cm (adjusted OR 1.753), multiplicity (adjusted OR 1.168), bilaterality (adjusted OR 1.177), and extrathyroidal extension (ETE) (adjusted OR 1.448) were independent predictors for high prevalence of central LN metastasis (CLNM), whereas per 10-year age increment (adjusted OR 0.760) and chronic lymphocytic thyroiditis (adjusted OR 0.791) were independent predictors for low prevalence of CLNM. In addition, male gender (adjusted OR 1.489), tumor size >0.5 cm (adjusted OR 1.295), multiplicity (adjusted OR 1.801), ETE (adjusted OR 1.659), and CLNM (adjusted OR 4.359) were independent predictors for high prevalence of lateral LN metastasis (LLNM), whereas per 10-year age increment (adjusted OR 0.838) was an independent predictor for low prevalence of LLNM. There was a statistically significant difference in LRR with regard to nodal stage ($p < 0.001$). CONCLUSIONS: Meticulous perioperative evaluation of LN metastasis is required for PTMC patients with the above predictors.
PubMed-ID: 27075321
http://dx.doi.org/10.1245/s10434-016-5225-0

Neural Monitoring in Thyroid Surgery: Is it Evidence-Based? Is it Cost-Effective?
World J Surg, 40(11):2829-30.
A. Anuwong, H. Y. Kim and G. Dionigi. 2016.
PubMed-ID: 27091204
http://dx.doi.org/10.1007/s00268-016-3513-2

The Long-Term Prognosis of Voice Pitch Change in Female Patients After Thyroid Surgery.
World J Surg, 40(10):2382-90.
J. O. Park, J. S. Bae, S. H. Lee, M. R. Shim, Y. S. Hwang, Y. H. Joo, Y. H. Park and D. I. Sun. 2016.
BACKGROUND: Relatively large numbers of patients complain of lower-pitched voices after thyroidectomy. However, little is known about the risk factors for, prognosis of, or progression over time of, such changes, in female patients. METHODS: We analyzed the data of 217 patients who underwent thyroid surgery and postoperative (2 weeks, and 3, 6, and 12 months after surgery) voice work-ups. To identify patients with lower-pitched voices, speaking fundamental frequencies (SFFs) were compared before and after surgery. The change was calculated for all patients (postoperative change in SFF, DeltaSFF). RESULTS: The mean DeltaSFF was 8.35 +/- 17.06 Hz and significant changes in voice pitch (DeltaSFF >/=12 Hz) were evident in 93 (42.85 %) patients after surgery, mostly within 6 months, and only 18.4 % of patients had lower-pitched voices 1 year after surgery. On multivariate analysis, age (>/=52 vs. <52 years) and extent of surgery remained significant predictors of lower-pitched voice after surgery. The DeltaSFFs of older patients (>/=52) were significantly greater than those of younger patients (<52) at the 2-week follow-up, but not at the 3-, 6-, or 12-month follow-ups. The DeltaSFFs of patients who underwent total thyroidectomy were significantly higher than those who underwent lobectomy at the postoperative 2-week follow-up, but did not differ at the 3-, 6-, and 12-month follow-ups. CONCLUSIONS: Patients frequently experience a lower-pitched voice after thyroid surgery. Such problems develop more frequently in the early postoperative period, in aged patients, and in those who had undergone total thyroidectomy. However, over time, the changes usually decrease to levels similar to those of patients without these risk factors.
PubMed-ID: 27094557
http://dx.doi.org/10.1007/s00268-016-3511-4

Response to Treatment is Highly Predictable in cN0 Patients with Papillary Thyroid Carcinoma.
World J Surg, 40(9):2123-30.
A. Gorshtein, C. Benbassat, E. Robenshtok, I. Shimon and D. Hirsch. 2016.
BACKGROUND: While involvement of macrometastatic lymph nodes is a recognized independent predictor of an adverse course in papillary thyroid cancer (PTC) patients, the clinicopathological variables associated with disease persistence/recurrence in clinically node-negative (cN0) disease are not well defined. The indications for prophylactic central neck dissection (pCND) in this patient group remain unclear as well. We aim to investigate the risk factors associated with short- and long-term persistence/recurrence of PTC in patients with cN0 disease at presentation compared to patients with PTC and cervical lymph node involvement (N1) and the response to initial treatment in these subgroups of patients. METHODS: Data were collected retrospectively for 392 consecutive patients with PTC, 223 with cN0 disease and 169 with N1 disease, who were treated and followed at a single tertiary medical center in which pCND is not routinely performed for PTC. RESULTS: Compared to patients with N1 disease, patients with cN0 disease had significantly smaller tumors, lower rates of multifocality, and less extrathyroidal extension. Persistency rates at 1 year were 6.7 % in the cN0 group and 47 % in the N1 group, and at last follow-up, 3.6 and 33.5 %, respectively (p = 0.001 for both time points). Within the cN0 group, those with persistent disease at 1 year (n = 15) had significantly larger tumors and higher stimulated thyroglobulin. Only six had structural residual disease, four of them lymph node metastases. All patients with persistent disease were initially treated with total thyroidectomy and radioiodine. Recurrence occurred in only three patients. After 8.3 +/- 3.8 years of follow-up, eight patients with cN0 had persistent disease, three of them biochemical. Higher American Joint Committee of Cancer stage and extrathyroidal extension were the only factors that predicted disease persistence at the last follow-up in this group. CONCLUSIONS: Patients with cN0 PTC and no distant metastases are usually disease free after thyroidectomy with/without radioactive iodine and do not need further interventions. The initial staging in these patients is a valid prognostic factor for disease outcomes.
PubMed-ID: 27094559
http://dx.doi.org/10.1007/s00268-016-3507-0

Clinicopathologic characteristics and pattern of central lymph node metastasis in papillary thyroid cancer located in the isthmus.
Laryngoscope, 126(10):2419-21.
Y. C. Lee, S. Y. Na, H. Chung, S. I. Kim and Y. G. Eun. 2016.
OBJECTIVES/HYPOTHESIS: The aim of this study was to evaluate the clinicopathologic characteristics and pattern of lymph node (LN) metastasis in papillary thyroid cancer (PTC) located in the isthmus. STUDY DESIGN: Retrospective cohort study. METHODS: One hundred ninety consecutive patients with PTC who underwent total thyroidectomy and bilateral central neck dissection were analyzed. Preoperative ultrasonography was reviewed to identify PTC located in the isthmus. Clinicopathologic factors including age, sex, tumor size, extrathyroidal extension (ETE), margin, angiolymphatic invasion, and nodal metastasis were evaluated. RESULTS: Of 190 PTC patients, 14 patients (7.3%) had a tumor located in the isthmus. The PTCs located in the isthmus were more likely to have ETE and central LN involvement. Furthermore, PTCs located in the isthmus had a higher frequency of metastasis to pretracheal and prelaryngeal LNs than those located in the lobes. CONCLUSION: PTCs located in the isthmus were associated with ETE and more likely to involve the pretracheal and prelaryngeal LNs. LEVEL OF EVIDENCE: 4 Laryngoscope, 126:2419-2421, 2016.
PubMed-ID: 27098428
http://dx.doi.org/10.1002/lary.25926

Thyroid lobectomy is an effective option for unilateral benign nodular disease.
Clin Endocrinol (Oxf), 85(4):602-8.
M. Lytrivi, A. Kyrilli, A. Burniat, M. Ruiz Patino, Y. Sokolow and B. Corvilain. 2016.
OBJECTIVE: The use of thyroid lobectomy in the treatment of unilateral, benign nodules is limited by the potential of nodular recurrence in the remaining lobe. This study aimed to assess the rate and clinical impact of nodular recurrence in the contralateral lobe after thyroid lobectomy and to identify predictive factors of recurrence. DESIGN: Single-centre retrospective study. PATIENTS: Records of patients that underwent lobectomy for unilateral thyroid nodules between 1991 and 2010 were reviewed and 270 patients were included. Exclusion criteria were: presence of contralateral nodule(s) >/=5 mm on preoperative ultrasound, diagnosis of cancer necessitating completion thyroidectomy or pseudonodules. Recurrence was defined as the occurrence of nodule(s) >/=5 mm in the remaining lobe on at least one postoperative ultrasound. A set of clinical, imaging, histological and biochemical parameters was tested as predictors of recurrence using logistic regression. RESULTS: After a median follow-up of 78 months (range, 12-277 months), the global recurrence rate was 42% and recurrence of nodules of a size >/=1 cm occurred in 19%. Reoperation rate was 1.1%. 90% of patients were

treated postoperatively by levothyroxine. Median time to nodular recurrence was 4 years. Preoperative contralateral lobe volume and resected thyroid weight were identified as significant predictors of recurrence (P = 0.045 and P = 0.03 respectively). CONCLUSIONS: Thyroid lobectomy is an effective therapeutic strategy for unilateral, benign nodules, resulting in a low rate of clinically relevant nodular relapse in a mildly iodine-deficient area. Patients with uninodular disease and a contralateral lobe of normal size are particularly good candidates for lobectomy.
PubMed-ID: 27106627
http://dx.doi.org/10.1111/cen.13088

What is the best treatment of incidental papillary thyroid microcarcinoma?
Laryngoscope, 126(10):2203-4.
R. L. Witt. 2016.
PubMed-ID: 27107211
http://dx.doi.org/10.1002/lary.26049

Association between Magnesium Disorders and Hypocalcemia following Thyroidectomy.
Otolaryngol Head Neck Surg, 155(3):402-10.
J. C. Nellis, R. P. Tufano and C. G. Gourin. 2016.
OBJECTIVE: To identify factors associated with postoperative hypocalcemia after thyroid surgery and to understand the relationship among hypocalcemia, length of hospitalization, and costs of care. STUDY DESIGN: Retrospective database analysis. METHODS: Discharge data from the Nationwide Inpatient Sample for 620,744 patients who underwent thyroid surgery from 2001 to 2010 were analyzed through cross-tabulations and multivariate regression modeling. Hypocalcemia, length of stay, and costs were examined as dependent variables. Secondary independent variables included magnesium and phosphate metabolism disorders, vitamin D deficiency, menopause, sex, extent of surgery, malignancy, and surgeon volume. RESULTS: Hypocalcemia was reported in 6% of patients and was significantly more common for the following variables: women, age <65 years, patients from the Northeast, total thyroidectomy +/- neck dissection patients, low-volume surgical care, malignancy, recurrent laryngeal nerve injury, and patients with disorders of magnesium or phosphate metabolism (P < .001). Magnesium and phosphate disorders were present in <1% of patients. Magnesium disorders were significantly more likely for patients with hypocalcemia (7%; P < .001), and hypocalcemia was present in 52% of patients with magnesium disorders (P < .001). On multiple logistic regression analysis, the odds of hypocalcemia were greatest for patients with magnesium disorders (odds ratio, 12.71; 95% confidence interval, 8.59-18.82). This relationship was not attenuated by high-volume surgical care. Hypocalcemia and magnesium disorders were both associated with increased length of stay and costs, with a greater effect for magnesium disorders than for hypocalcemia (P < .001). CONCLUSIONS: Disorders of magnesium metabolism are an independent risk factor for postthyroidectomy hypocalcemia and are associated with significantly increased costs and length of stay.
PubMed-ID: 27118818
http://dx.doi.org/10.1177/0194599816644594

Antiplatelet and Anticoagulant Medications Significantly Increase the Risk of Postoperative Hematoma: Review of over 4500 Thyroid and Parathyroid Procedures.
Ann Surg Oncol, 23(9):2874-82.
S. C. Oltmann, A. Y. Alhefdhi, M. H. Rajaei, D. F. Schneider, R. S. Sippel and H. Chen. 2016.
PURPOSE: Antiplatelet and/or anticoagulant medication use is common. Abstinence a week before surgery may still result in altered hemostasis. The study aim was to report on perioperative antiplatelet and anticoagulant use in thyroidectomy and parathyroidectomy patients, and to determine the association with postoperative hematoma (POH) rates. METHODS: Retrospective review of a prospective endocrine surgery database was performed. Procedure extent was defined as unilateral, bilateral, or extensive. Antiplatelets were categorized as none, 325 mg aspirin (ASA), <325 mg ASA, clopidogrel, or other. Anticoagulants were categorized as none, oral, or injectable. RESULTS: A total of 4514 patients were identified. POH developed in 22 patients (0.5 %). Rates were similar between age, gender, and reoperative status. POH were seven times more common after thyroidectomy (0.8 vs. 0.1 %, p < 0.01). Unilateral procedures had lower POH rates than bilateral or extensive (0.1 vs. 0.9 vs. 0.8 %, p < 0.01). POH rates in patients receiving 325 mg ASA (0.8 %) or clopidogrel (2.2 %) were much higher than patients not receiving antiplatelets (0.5 %) or receiving <325 mg ASA (0.1 %, p = 0.04). Oral anticoagulants (2.2 %) and injectable anticoagulants (10.7 %) had much higher POH rates than patients not receiving anticoagulants (0.4 %, p < 0.01). Target organ, patient gender, procedure extent, antiplatelet use, and anticoagulant use were included on logistic regression to determine association with POH. Bilateral procedures, thyroidectomy, clopidogrel, oral, and injectable anticoagulants were all independently associated with POH.

CONCLUSIONS: POH occur more frequently after thyroidectomy and during bilateral procedures. Patients requiring clopidogrel or any anticoagulant coverage are at much higher risk for POH. These higher-risk patients should be considered for observation to ensure prompt POH recognition and intervention.
PubMed-ID: 27138383
http://dx.doi.org/10.1245/s10434-016-5241-0

Outcomes in thyroid surgery are affected by racial, economic, and healthcare system demographics.
Laryngoscope, 126(9):2194-9.
Z. Al-Qurayshi, G. W. Randolph, S. Srivastav, R. Aslam, P. Friedlander and E. Kandil. 2016.
OBJECTIVES/HYPOTHESIS: Disparities in economic and social parameters have been identified as underlying factors that influence diseases outcomes. We aim to examine the influence of community-specific measures on outcomes related to thyroid surgery. STUDY DESIGN: A cross-sectional study utilizing the State Inpatient databases and State Ambulatory Surgery and Services databases, 2010 to 2011. Those databases were merged with the County Health Ranking database. METHODS: The study population included adult (>/=18 years) inpatients and outpatients who underwent thyroidectomy. Access and outcomes of thyroidectomy was assessed in relation to demographics and health-risk status of the patient's community. RESULTS: A total of 14,220 inpatient and 7,215 outpatient thyroidectomies were included. Low-volume surgeons were more likely to operate on patients living in high-risk communities (P < .05). Patients from these communities of high health risk were more likely to be women, and African Americans (P < .05 each). Compared to low-risk communities, patients from high-risk settings had a higher risk of postoperative complications (odds ratio: 1.58, 95% confidence interval: 1.23, 2.04, P < .001). They also experienced longer hospitalization (P = .003) and higher readmission risk (3.0% vs. 1.5%, P = .03). Interestingly, despite divergent and lower outcome parameters, hospital charges for patients of high-risk communities were in the highest quartile (>$34,535.55) compared to low-health-risk communities (P < .001). CONCLUSIONS: Patients from high-health-risk communities and who are undergoing thyroidectomies are more likely to be women and African Americans. Management of those patients is more likely to be performed by low-volume surgeons and more likely to be associated with unfavorable outcomes. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:2194-2199, 2016.
PubMed-ID: 27139800
http://dx.doi.org/10.1002/lary.25871

Metadherin Expression is Associated with Extrathyroidal Extension in Papillary Thyroid Cancer Patients.
Ann Surg Oncol, 23(9):2883-8.
R. F. Moore, A. B. Sholl, L. Kidd, Z. Al-Qurayshi, K. Tsumagari, O. M. Emejulu, R. Kholmatov, P. Friedlander, Z. Y. Abd Elmageed and E. Kandil. 2016.
BACKGROUND: Metadherin (MTDH) is widely recognized as a promising molecular marker for tumor recurrence and poor survival in many cancers. By multiple pathways, MTDH promotes oncogenesis, metastasis, and chemoresistance. This study investigated the role of MTDH in papillary thyroid carcinoma (PTC) to determine its potential association with aggressive clinical and pathologic features, including its relation in tumors harboring a BRAF (V600E) mutation. METHODS: Expression of MTDH was assessed by immunohistochemistry in 96 cases of PTC, including primary thyroid malignancies and lymph node metastases. The status of BRAF (V600E) mutation was determined by real-time polymerase chain reaction. RESULTS: Overexpression of MTDH was observed in 26 % (23/88) of primary PTC cases. High-intensity staining was observed in 75 % (6/8) of lymph nodes with metastatic PTC and moderate staining in 25 % (2/8) of cases. Normal adjacent thyroid tissue and benign thyroid controls were found to have significantly lower MTDH expression than cancer tissue ($p < 0.05$). Apical staining of MTDH was observed in 19 % of thyroid tumors and not observed in normal thyroid tissue. Interestingly, MTDH expression was associated with extrathyroidal extension ($p < 0.05$) and not associated with age, gender, overall tumor stage, or BRAF (V600E) mutation status. CONCLUSION: In a subset of PTC patients, MTDH was overexpressed and associated with extrathyroidal extension. Further studies are warranted to explore the utility of MTDH to improve risk stratification of current molecular panels for PTC.
PubMed-ID: 27146414
http://dx.doi.org/10.1245/s10434-016-5245-9

High Level of Agreement Between Pretherapeutic 124I PET and Intratherapeutic 131I Imaging in Detecting Iodine-Positive Thyroid Cancer Metastases.
J Nucl Med, 57(9):1339-42.
M. Ruhlmann, W. Jentzen, V. Ruhlmann, C. Pettinato, G. Rossi, I. Binse, A. Bockisch and S. Rosenbaum-Krumme. 2016.
UNLABELLED: The aim of this retrospective study was to assess the level of agreement between PET and

scintigraphy using diagnostic amounts of (124)I and therapeutic amounts of (131)I, respectively, in detecting iodine-positive metastases in patients with differentiated thyroid carcinoma. METHODS: The study included patients who underwent PET /: CT 24 and 120 h after administration of approximately 25 MBq of (124)I and subsequently underwent imaging 5-10 d after administration of 1-10 GBq of (131)I. For each patient, the intratherapeutic (131)I imaging comprised a whole-body scintigraphy scan and a SPECT/CT scan of the neck to distinguish between metastatic and thyroid remnant tissues. Iodine uptake was rated as a metastatic focus if located outside the thyroid bed. Lesion- and patient-based analyses were performed. RESULTS: The study included 137 patients with 227 metastases iodine-positive on both functional imaging modalities. In the lesion-based analysis, (124)I PET and (131)I imaging detected 98% (223/227) and 99% (225/227) of the iodine-positive metastases, respectively; the level of agreement between (124)I PET and (131)I imaging was 97% (221/227). Four metastases (3 lymph node and 1 bone) in 4 patients were (124)I-negative but (131)I-positive, and 2 lymph node metastases in 2 patients were (131)I-negative but (124)I-positive. In the patient-based analysis, 61 of the 137 patients presented with iodine-positive metastases. (124)I PET and (131)I imaging detected at least one iodine-positive metastasis in 97% (59/61) and 98% (60/61) of the patients, respectively. The level of agreement was 95% (58/61). Both imaging modalities concordantly identified 76 of 137 patients without pathologic iodine uptake. CONCLUSION: Because of the high level of agreement, pretherapeutic (124)I PET/CT is an adequate methodology in the detection of iodine-positive metastases and can be used as a reliable tool for staging of thyroid cancer patients and individualized treatment planning.
PubMed-ID: 27151981
http://dx.doi.org/10.2967/jnumed.115.169649

Utility and cost-effectiveness of molecular testing in thyroid nodules with indeterminate cytology.
Clin Endocrinol (Oxf), 85(4):624-31.
E. Labourier. 2016.
CONTEXT: Molecular testing on biopsies from thyroid nodules with indeterminate cytology can improve patient management by preventing unnecessary surgeries on benign nodules. OBJECTIVE: The aim of the study was to determine the health outcome benefits and cost-effectiveness of molecular testing in nodules with AUS/FLUS or FN/SFN cytology. DESIGN: The initial diagnosis and treatment of a hypothetical cohort of adult U.S. patients with solitary thyroid nodules >/=1 cm was simulated by decision analytic modelling using Medicare cost estimates for three management strategies, standard of care without molecular testing (StC), gene expression classifier (GEC) and mutation and miRNA testing (MMT). RESULTS: Gene expression classifier decreased the rate of unnecessary surgeries by 32% relative to StC, yielding incremental costs of $1008 per patient or $5070 per unnecessary surgery avoided. MMT decreased the surgery rate by 67%, yielding incremental savings of -$1384 per patient or -$3170 per unnecessary surgery avoided. Results remained robust in deterministic sensitivity analyses; MMT was dominant for every variable tested. Independent of cancer prevalence, MMT yielded 52% fewer unnecessary surgeries relative to GEC #bib70% fewer two-stage thyroidectomies and correctly identified 70% more benign nodules. Test specificity had to be >68% for molecular testing to be cost-effective and decrease by >50% the rate of unnecessary surgeries performed on benign nodules. CONCLUSIONS: Molecular testing with high benign diagnostic yield can generate both positive health outcomes (less surgeries) and positive economic outputs (cost savings). These results are consistent with previously reported cost-utility data and provide valuable insights for informed decision-making by patients, physicians and payers.
PubMed-ID: 27155136
http://dx.doi.org/10.1111/cen.13096

Graves' disease in children: long-term outcomes of medical therapy.
Clin Endocrinol (Oxf), 85(4):632-5.
S. Rabon, A. M. Burton and P. C. White. 2016.
BACKGROUND AND OBJECTIVES: Management options are limited for the treatment of Graves' disease, and there is controversy regarding optimal treatment. We describe the demographic and biochemical characteristics of children with Graves' disease and the outcomes of its management. METHODS: This is a retrospective study reviewing medical records from 2001 to 2011 at a tertiary-care paediatric hospital. Diagnostic criteria included elevated free T4 and total T3, suppressed TSH, and either positive thyroid-stimulating immunoglobulin or thyroid receptor antibodies or clinical signs suggestive of Graves' disease, for example exophthalmos. Patients were treated with antithyroid drugs (ATD), radioactive iodine, or thyroidectomy. The main outcome measures were remission after medical therapy for at least 6 months and subsequent relapse. RESULTS: A total of 291 children met diagnostic criteria. A total of 62 were male (21%); 117 (40%) were Hispanic, 90 (31%) Caucasian, and 59 (20%) African American. Mean age (+/-standard deviation) at diagnosis was 12.3 +/- 3.8 (range 3-18.5) years. At diagnosis, 268 patients were started on an antithyroid drug and 23 underwent thyroid ablation or thyroidectomy.

Fifty-seven (21%) children achieved remission and 16 (28%) of these patients relapsed, almost all within 16 months. Gender and ethnicity did not affect rates of remission or relapse. Of 251 patients treated with methimazole, 53 (21%) had an adverse reaction, including rash, arthralgias, elevated transaminases, or neutropenia. CONCLUSIONS: Most children with Graves' disease treated with ATD do not experience remission, but most remissions do not end in relapse. Adverse reactions to methimazole are common but generally mild.
PubMed-ID: 27169644
http://dx.doi.org/10.1111/cen.13099

Thyroid hormone and its metabolites in relation to quality of life in patients treated for differentiated thyroid cancer.
Clin Endocrinol (Oxf), 85(5):781-8.
E. T. Massolt, M. van der Windt, T. I. Korevaar, B. L. Kam, J. W. Burger, G. J. Franssen, I. Lehmphul, J. Kohrle, W. E. Visser and R. P. Peeters. 2016.
BACKGROUND: Levothyroxine (LT4) is the standard of care in patients with hypothyroidism. Despite this replacement therapy, quality of life (QoL) remains impaired in a substantial amount of patients. The reasons for this are still a matter of debate. Suggested causes include lack of endogenous T3 secretion by the thyroid, changes in other thyroid hormone metabolites and interference by autoimmune processes. OBJECTIVE: To investigate the association between thyroid function tests (TFTs) and QoL in patients with a history of differentiated thyroid cancer on LT4 monotherapy. These patients lack endogenous thyroidal T3 secretion in the absence of autoimmune disease. MATERIALS AND METHODS: This is a cross-sectional study in 143 patients (69.2% female). Initial therapy consisted of total thyroidectomy followed by radioiodine ablation minimally one year before inclusion. We assessed health-related QoL (RAND-36), thyroid-specific QoL (ThyPRO) and fatigue with the Multidimensional Fatigue Inventory. Extensive TFTs were assessed, including 3,5-diiodo-L-thyronine (3,5-T2). RESULTS: Mean age was 50.2 years and mean time since diagnosis was 8.4 years. Median TSH was 0.042 mU/l, total T4 145.0 nmol/l, free T4 25.6 pmol/l, total T3 1.93 nmol/l, reverse T3 0.53 nmol/l and 3,5-T2 0.86 nmol/l. Multiple linear regression analyses did not show any association between QoL and the different TFTs, including T4/T3 and 3,5-T2/T3 ratios reflecting peripheral metabolism. CONCLUSION: We did not find any association between TFTs and QoL in athyreotic patients on LT4 monotherapy. Our data do not provide evidence that a slight increase in dose improves fatigue or well-being in hypothyroid patients on LT4 therapy.
PubMed-ID: 27175823
http://dx.doi.org/10.1111/cen.13101

Incidence and Risk Factors for Occult Level 3 Lymph Node Metastases in Papillary Thyroid Cancer.
Ann Surg Oncol, 23(11):3587-92.
S. Fraser, N. Zaidi, O. Norlen, A. Glover, S. Kruijff, M. Sywak, L. Delbridge and S. B. Sidhu. 2016.
BACKGROUND: Papillary thyroid cancer (PTC) frequently disseminates into cervical lymph nodes. Lateral node involvement is described in up to 50 % patients undergoing prophylactic lateral neck dissection. This study aimed to assess this finding and identify which factors predict for occult lateral node disease. METHODS: Patients with fine needle aspiration-confirmed PTC (Bethesda V or VI), without evidence of cervical lymph node metastases, underwent a total thyroidectomy with prophylactic ipsilateral central and level 3 dissection. Level 3 nodes were removed by compartmental dissection or by sampling the sentinel nodes overlying the jugular vein, according to surgeon preference. Data were collected prospectively from January 2011 to August 2014. Statistical analysis was performed by SPSS software. RESULTS: A total of 137 patients underwent total thyroidectomy with prophylactic ipsilateral central and level 3 dissection for PTC. The incidence of occult level 3 disease was 30 % (41/137 patients). A total of 48 % of patients (66/137) harbored occult central neck disease. A total of 80.5 % of patients with pN1b disease had macrometastases (>/=2 mm), and 15 % exhibited skip metastases with central compartment sparing. In patients with pN1b disease, a median of 6 level 3 nodes were retrieved, with an average involved nodal ratio of 0.29. Multivariate regression demonstrated risk factors for occult lateral neck metastasis include tumor size (odds ratio 1.1), upper pole tumors (odds ratio 6.6), and vascular invasion (odds ratio 3.2) ($p < 0.05$). CONCLUSIONS: PTC is associated with a significant incidence of occult central and lateral nodal metastases. In patients undergoing prophylactic central neck dissection, inclusion of level 3 dissection should be considered in patients with large upper lobe cancers.
PubMed-ID: 27188295
http://dx.doi.org/10.1245/s10434-016-5254-8

124I PET Assessment of Response of Bone Metastases to Initial Radioiodine Treatment of Differentiated Thyroid Cancer.
J Nucl Med, 57(10):1499-504.
W. Jentzen, F. Verschure, A. van Zon, R. van de Kolk, R. Wierts, J. Schmitz, A. Bockisch and I. Binse. 2016.
Iodine-positive bone metastases (BMs) are often resistant after initial radioiodine therapy applying the standard-activity approach. A comprehensive lesion-based response study for BMs has not, to our knowledge, yet been performed. In this study, pretherapy and follow-up 124I PET/CT data on BMs from differentiated thyroid cancer patients were retrospectively analyzed to assess the relationship between absorbed dose (AD) of radiation and response after initial radioiodine treatment. METHODS: Before and after initial radioiodine therapy, patients underwent serial PET/CT scanning after administration of 20-40 MBq of 124I. The pretherapy PET data were used to segment BM volumes and to predict the average ADs after administration of dosimetry-guided 131I activity. The lower volume limit of determinability of the applied segmentation method was a sphere volume of 0.16 mL. This volume limit classified the BMs into known-volume and fixed-volume groups with their respective average and minimum ADs. Follow-up 124I and 18F-FDG PET/CT data after treatment were analyzed to assess lesion-based therapy response. Response rates at different AD thresholds were calculated and were expressed as the percentage of completely responding BMs above the respective AD threshold. BMs with a maximum extent greater than twice the PET spatial resolution were visually scored for nonuniformity. RESULTS: In total, 61 BMs in 10 patients were included, of which 46 and 15 comprised the known-volume group and the fixed-volume group, respectively. The median follow-up time was 5.6 mo (range, 3.7-23.2 mo). The median average and median minimum ADs in therapy were 183 Gy (range, 39-3,600 Gy) and 270 Gy (range, 63-1,300 Gy), respectively. A range of response rate of 70%-80% was achieved at an AD threshold range of 350-650 Gy. There were 26 BMs that were amenable to visual assessment of nonuniformity, of which two thirds (17/26) were scored as clearly nonuniform, and the majority (11/17) of these nonuniform BMs responded incompletely. CONCLUSION: Both the high AD threshold associated with high response rates and the low median AD per unit of 131I activity elucidate the difficulty in achieving therapeutic efficacy for BMs when a single standard activity is administered. The relatively high AD threshold range is possibly a result of distinct levels of spatial nonuniformity in ADs.
PubMed-ID: 27199362
http://dx.doi.org/10.2967/jnumed.115.170571

The weepy nerve-different sensitivity of left and right recurrent laryngeal nerves under tensile stress in a porcine model.
Langenbecks Arch Surg, 401(7):983-90.
W. Lamade, M. Bechu, E. Lauzana, P. Kohler, S. Klein, T. Tuncer, N. I. Rashid, E. Kahle, B. Erdmann and U. Meyding-Lamade. 2016.
PURPOSE: Recurrent laryngeal nerve palsy in thyroid surgery is still a threatening complication. Our aim was to analyze the impact of prolonged tensile stress on the recurrent laryngeal nerve (RLN) in an animal model using continuous intraoperative neuromonitoring (C-IONM). METHODS: Constant tensile stress was applied to left and right RLNs in 20 pigs (40 RLN). In a pilot study, five animals were subjected to a tensile force of 0.34 +/- 0.07 N for 10 min and changes in amplitude were documented using C-IONM. In the main study, a force of 1.2 N was applied until the signal amplitude was reduced by 85 %, in 15 pigs. Nerve conductivity was analyzed by threshold current measurements. RESULTS: Good correlation was found between stress and amplitude decrease in the pilot study as well as between signal decrease and duration of trauma in the main study. Great variations were found inter- and intra-individually. These variations were most prominent at 85 % signal reduction (median 36 min, range 0.3-171 min). There was no side specificity (left 0.3-171 min, right 0.3-168 min, respectively, p = 0.19). However, in each individual animal, there was a sensitive (0.3-98.9 min) and less sensitive nerve (26.8-171 min). These differences became highly significant at 85 % of signal reduction (p = 0.008), where the vulnerability is 1.4 to 146.4 times higher on one side (mean 4.3). CONCLUSIONS: Our study demonstrates the presence of a sensitive RLN that was 4.3 times more vulnerable than the contralateral nerve (range 1.4-146.4 times, p = 0.008). Thus, the right and the left nerves cannot be assumed to be of equal sensitivity to trauma. In our data, the more sensitive nerve does not occur predominantly on one side and was named the "weepy nerve.".
PubMed-ID: 27209314
http://dx.doi.org/10.1007/s00423-016-1439-7

Commentary on the use of thyroglobulin as a biomarker for iodine status in adults.
Clin Endocrinol (Oxf), 85(3):344-6.
M. L. Mitchell and H. W. Hsu. 2016.
PubMed-ID: 27213699
http://dx.doi.org/10.1111/cen.13109

Lobectomy is a more Cost-Effective Option than Total Thyroidectomy for 1 to 4 cm Papillary Thyroid Carcinoma that do not Possess Clinically Recognizable High-Risk Features.
Ann Surg Oncol, 23(11):3641-52.
B. H. Lang and C. K. Wong. 2016.
BACKGROUND: Although lobectomy is a viable alternative to total thyroidectomy (TT) in low-risk 1 to 4 cm papillary thyroid carcinoma (PTC), lobectomy is associated with higher locoregional recurrence risk and need for completion TT upon discovery of a previously unrecognized histologic high-risk feature (HRF). The present study evaluated long-term cost-effectiveness between lobectomy and TT. METHODS: Our base case was a hypothetical female cohort aged 40 years with a low-risk 2.5 cm PTC. A Markov decision tree model was constructed to compare cost-effectiveness between lobectomy and TT after 25 years. Patients with an unrecognized HRF (including aggressive histology, microscopic extrathyroidal extension, lymphovascular invasion, positive resection margin, nodal metastasis >5 mm, and multifocality) underwent completion TT after lobectomy. Outcome probabilities, utilities, and costs were estimated from the literature. The threshold for cost-effectiveness was set at US$50,000/quality-adjusted life-year (QALY). Sensitivity and threshold analyses were used to examine model uncertainty. RESULTS: After 25 years, each patient who underwent lobectomy instead of TT cost an extra US$772.08 but gained an additional 0.300 QALY. The incremental cost-effectiveness ratio was US$2577.65/QALY. In the sensitivity analysis, the lobectomy arm began to become cost-effective only after 3 years. Despite varying the reported prevalence of clinically unrecognized HRFs, complication from surgical procedures, annualized recurrence rates, unit cost of surgical procedure or complication, and utility score, lobectomy remained more cost-effective than TT. CONCLUSIONS: Despite the higher locoregional recurrence risk and having almost half of the patients undergoing completion TT after lobectomy upon discovery of a previously unrecognized HRF, initial lobectomy was a more cost-effective long-term option than initial TT for 1 to 4 cm PTCs without clinically recognized HRFs.
PubMed-ID: 27221359
http://dx.doi.org/10.1245/s10434-016-5280-6

Comparison of the harmonic focus and the thunderbeat for open thyroidectomy.
Langenbecks Arch Surg, 401(6):851-9.
S. Van Slycke, J. P. Gillardin, K. Van Den Heede, J. Minguet, H. Vermeersch and N. Brusselaers. 2016.
PURPOSE: An effective method for controlling haemostasis during open thyroidectomy procedures is crucial because of the high risks of haemorrhage and neck haematoma. This study aimed to demonstrate the efficacy of the integrated ultrasonic/bipolar Thunderbeat for this procedure. METHODS: This retrospective non-inferiority study compared the Thunderbeat and the ultrasonic Harmonic Focus(R) devices in 761 consecutive patients receiving a partial or total open thyroidectomy (with or without neck dissection). The main outcomes were duration of surgery, blood loss, and length of hospitalisation. Secondary outcomes were occurrence of hypocalcaemia, recurrent nerve paralysis, or other post-operative complications. A non-inferiority logistic regression approach was used to evaluate primary outcomes, adjusting for age, gender, body mass index, type of surgery, anaesthesiology score, and indication (benign or malign). RESULTS: The data demonstrated that the Thunderbeat was non-inferior to the Focus in terms of duration of surgery, blood loss, and length of hospital stay. Furthermore, subgroup analyses showed non-inferiority of the Thunderbeat for partial thyroidectomy (all three outcomes), total thyroidectomy (duration of surgery and length of hospitalisation), and total thyroidectomy with neck dissection (length of hospitalisation). In terms of recurrent nerve paralysis and post-operative complications, the Thunderbeat performed at least as well as the Focus; however, no conclusions could be drawn regarding the occurrence of post-operative hypocalcaemia. CONCLUSION: In a cohort of patients that underwent partial or total thyroidectomy, the Thunderbeat appeared to be at least as good as the Harmonic Focus.
PubMed-ID: 27222244
http://dx.doi.org/10.1007/s00423-016-1448-6

Charting a course through the CEAs: diagnosis and management of medullary thyroid cancer.
Clin Endocrinol (Oxf), 85(3):340-3.
C. W. Rowe, C. Bendinelli and S. McGrath. 2016.
Medullary thyroid cancer (MTC) is an uncommon thyroid cancer that requires a high index of suspicion to

facilitate diagnosis of early-stage disease amenable to surgical cure. The challenges of diagnosis, as well as management in the setting of persistent disease, are explored in the context of a case presenting with the incidental finding of elevated carcinoembryonic antigen (CEA) and an (18) F-fluorodeoxyglucose positron emission tomography ((18) F-FDG-PET)-positive thyroid incidentaloma detected following treatment of colorectal cancer. Strategies to individualize prognosis, and emerging PET-based imaging modalities, particularly the potential role of (18) F-DOPA-PET in staging, are reviewed.
PubMed-ID: 27230389
http://dx.doi.org/10.1111/cen.13114

Implications of oncocytic change in papillary thyroid cancer.
Clin Endocrinol (Oxf), 85(5):797-804.
J. H. Hong, H. S. Yi, S. Yi, H. W. Kim, J. Lee and K. S. Kim. 2016.
OBJECTIVE: Although the presence of oncocytic change in less than 75% of a tumour is not considered to indicate oncocytic variants of papillary thyroid carcinoma (PTC), we frequently observe partial oncocytic change, especially in obese PTC patients. Thus, we sought to investigate the relationship between the presence of oncocytic change of PTC and its prognosis. DESIGN, SETTING AND PARTICIPANTS: We retrospectively studied 142 patients with PTC who had undergone surgery between 2000 and 2005, and re-evaluated their PTC slides to record the proportion of oncocytic change in 10% increments from 0% to 100%. MAJOR OUTCOME MEASURE: We analysed the relationship between the proportion of oncocytic change and clinicopathological prognostic factors. RESULTS: Oncocytic change was found in 45.8% (65/142) of PTC patients. The proportion of patients with oncocytic change was higher in obese patients than in lean patients and showed a significant correlation with the BMI (r = 0.195, P = 0.020). The PTC patients with oncocytic change showed a higher recurrence rate than PTC patients without oncocytic change (30.8% vs 11.7%, respectively; P = 0.005). The presence of oncocytic change in PTC patients was associated with a shorter disease-free survival in a Kaplan-Meier analysis after a mean follow-up of 8.9 years. CONCLUSION: The patients with PTC with oncocytic change presented with a higher recurrence rate and were more likely to be obese. These findings suggest that presence of oncocytic change is a poor prognostic factor in PTC patients, even if the oncocytic change involves less than 75% of a tumour.
PubMed-ID: 27234487
http://dx.doi.org/10.1111/cen.13115

Comparative proteomic analysis of tear fluid in Graves' disease with and without orbitopathy.
Clin Endocrinol (Oxf), 85(5):805-12.
C. Aass, I. Norheim, E. F. Eriksen, E. C. Bornick, P. M. Thorsby and M. Pepaj. 2016.
BACKGROUND: Graves' orbitopathy (GO) is a severe organ-specific autoimmune inflammatory ocular complication most often associated with Graves' disease (GD). Besides the cosmetic problems these patients develop, GO may also cause severe, sight-threatening complications. Additionally, GO complicates the treatment of patients with GD, making the identification of Graves patients at risk for eye disease before they develop symptoms a critical step in the clinical management and quality of life of these patients. The high concentration of proteins in tear fluid makes it an important source for studying potential protein biomarkers for GO. PATIENTS AND METHODS: The aim of this study was to quantitatively compare tear fluid from GD patients with moderate/severe GO (GO) and patients with GD without GO (controls) using untargeted quantitative proteomics based on dimethyl labelling in combination with two-dimensional liquid chromatography-mass spectrometry. RESULTS: Among the 1212 proteins identified, 16 showed significant alterations in abundance between the two groups. Thus, in this study, we reveal a number of novel dysregulated proteins in GO which may contribute to a better understanding of the disease. In particular, upregulation of lacrimal gland proteins such as lysozyme C, lacritin, antileukoproteinase and zinc-alpha-2-glycoprotein 1 suggests involvement of the lacrimal gland in the pathogenesis of GO. CONCLUSIONS: It remains to be elucidated whether some of these proteins can be used as markers for patients at risk for developing GO as well as useful indicators for disease activity.
PubMed-ID: 27256639
http://dx.doi.org/10.1111/cen.13122

Patients with high-risk differentiated thyroid cancer have a lower I-131 ablation success rate than low-risk ones in spite of a high ablation activity.
Clin Endocrinol (Oxf), 85(6):926-31.
J. Winter, M. Winter, T. Krohn, A. Heinzel, F. F. Behrendt, R. M. Tuttle, F. M. Mottaghy and F. A. Verburg. 2016.
OBJECTIVE: To examine success rates in strictly defined high-risk differentiated thyroid cancer (DTC) patients who received a high-activity (>/=5550 MBq) adjuvant postoperative I-131 therapy and compare these to the

rates found in highest risk and low-risk patients. DESIGN: Retrospective database study. PATIENTS: We examined 377 patients with DTC who received I-131 ablation. Patients with distant metastases were classified as very high risk. Patients with primary tumours >4 cm, extensive extrathyroidal invasion (pT4a or pT4b in accordance with the 7th edition of the TNM system), and patients with >/=5 lymph node metastases or any lateral compartment lymph node metastases were considered high risk. All other patients were considered low risk. MEASUREMENTS: Ablation success rate at first TSH-stimulated follow-up. RESULTS: The ablation success rate was 72.6% in low-risk patients, 51.7% in high-risk patients and 13.8% in highest risk patients (all differences P < 0.001). In none of the groups, a significant difference in the initial I-131 activity was found between patients with successful and unsuccessful ablation (low risk: P = 0.16, high risk: P = 0.91 and highest risk: P = 0.48). Furthermore, there was no difference in ablation success between patients who received <5550 MBq and those who received >/=5550 Mbq (low risk: P = 0.31, high risk: P = 0.69 and highest risk: P = 0.22). CONCLUSIONS: Patients with high-risk DTC have a significantly reduced I-131 ablation success rate compared to low-risk ones in spite of high initial I-131 activities. As successful ablation is prognostically important, efforts should be made to improve outcome in these patients.
PubMed-ID: 27256714
http://dx.doi.org/10.1111/cen.13123

Ultrasonographic risk factors of malignancy in thyroid nodules.
Langenbecks Arch Surg, 401(6):839-49.
A. Rios, B. Torregrosa, J. M. Rodriguez, D. Rodriguez, A. Cepero, M. D. Abellan, N. M. Torregrosa, A. M. Hernandez and P. Parrilla. 2016.
INTRODUCTION: Between 40 and 50 % of the population will have at least one thyroid nodule, although only 5-8 % will have a malignant one. OBJECTIVE: The objective of this study was to establish the ultrasonographic characteristics which allow us to distinguish benignity from malignancy in thyroid nodules. METHODS: In the study population, inclusion criteria are (1) a single thyroid nodule and (2) multinodular goiter and exclusion criteria are (1) previous thyroid surgery and (2) fine needle aspiration (FNA) in the past month. This study is a double-blind prospective study. The study protocol is as follows: (1) clinical study; (2) ultrasound examination; (3) FNA; and (4) surgery-follow-up. The variables analysed are as follows: a multinodular nodule or goitre; colloid degeneration; morphology; margins; hyperechoic rim; rim thickness; rim morphology; size; angle between the major axis and the skin; echostructure; posterior acoustic findings; calcifications; thick colloid; localization of the intrathyroid nodular tissue; and characteristics in the Doppler scan. RESULTS: A total of 221 thyroid nodules were analysed. The following ultrasound findings were associated with malignancy (p < 0.05): a nodule with posterior acoustic shadowing; the echotexture of the nodule; intranodular colloid degeneration; nodule margins; nodular morphology; the presence of thick colloid; the angle between the major axis and the skin; characteristics of the intranodular vessels using color Doppler and Doppler energy; and calcifications. In the multivariate analysis, the following factors persisted as predictors of malignancy: the echotexture of the nodule (odds ratio 12.81), microcalcifications (OR 9.05), and chaotic vascularisation in the Doppler energy (OR 43.47). CONCLUSIONS: The high-resolution ultrasound allowed for a more reliable diagnosis of malignancy. The main findings of malignancy were the hypoechogenicity echotexture, microcalcifications, and chaotic intranodular vessels using Doppler energy.
PubMed-ID: 27263038
http://dx.doi.org/10.1007/s00423-016-1451-y

Comparing a thyroid prognostic nomogram to the existing staging systems for prediction risk of death from thyroid cancers.
Eur J Surg Oncol, 42(10):1491-6.
K. A. Pathak, P. Lambert, R. W. Nason and T. Klonisch. 2016.
OBJECTIVE: Thyroid prognostic nomogram can be applied across different histological types for predicting the individualized risk of death from thyroid cancer. The objective of this study was to compare the strength of our recently published thyroid prognostic nomogram with 12 existing staging systems to predict the risk of death from thyroid cancer. METHOD: This study included 1900 thyroid cancer patients, from a population based cohort of 2296 patients, on whom adequate staging information was available. Competing risk sub-hazard models were used to compare 12 pre-existing prognostic models with the nomogram model. Their relative strengths for prediction of patients' individualized risks of death from thyroid cancer were compared using Akaike information criterion (AIC), delta AIC, and concordance index. R version 3.2.2 was used to analyze the data. RESULTS: Our cohort of 450 males and 1450 females included 1796 (93.4%) differentiated thyroid cancers. Amongst the compared models, thyroid prognostic nomogram model appeared to be better than other models for predicting the risk of death from all non-anaplastic thyroid cancer (concordance index = 94.4), differentiated thyroid cancer (concordance index = 94.1) and papillary thyroid cancer (concordance index = 94.7). The difference from next

best staging systems was most pronounced in non-anaplastic thyroid cancer (delta AIC = 114.8), followed by differentiated thyroid cancer (delta AIC = 35.6) and papillary thyroid cancer (delta AIC = 8.4). CONCLUSIONS: Thyroid prognostic nomogram model was found to be better than the other models compared for predicting risk of death from thyroid cancer.
PubMed-ID: 27265038
http://dx.doi.org/10.1016/j.ejso.2016.05.016

Recurrent laryngeal nerve injury in thyroid surgery: Clinical pathways and resources consumption.
Head Neck, 38(11):1657-65.
C. C. Ferrari, S. Rausei, F. Amico, L. Boni, F. Y. Chiang, C. W. Wu, H. Y. Kim and G. Dionigi. 2016.
BACKGROUND: The impact of recurrent laryngeal nerve (RLN) injury management in thyroid surgery seems to be relevant to patients, National Healthcare System (NHS), and society. METHODS: We studied resource consumption in the management of patients with RLN injury versus noninjured patients investigating 3 perspectives (patients, NHS, and society) in 5 clinical pathways. RESULTS: Direct medical costs supported by the NHS range from a minimum of euro (euro) 79.46 to a maximum of euro 3261.95. From the patient's perspective, the direct medical costs supported by the patient increased from a minimum of euro 3.60 to a maximum of euro 499.45. Productivity losses were accounted in euro 156 per day per patient. From the NHS perspective, the percentage increase ranged from 43.25% to 98.14%. From the patient's perspective, it ranged from 51.52% to 80.60%. CONCLUSION: The analysis shows a significant economic impact of RLN injury management, which varies depending on the damage, duration, and severity. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 1708-1716, 2016.
PubMed-ID: 27265888
http://dx.doi.org/10.1002/hed.24489

Intraoperative Frozen Section in "Suspicious for Papillary Thyroid Carcinoma" after Adoption of the Bethesda System.
Otolaryngol Head Neck Surg, 155(5):779-86.
S. Abu-Ghanem, O. Cohen, T. Raz Yarkoni, D. M. Fliss and M. Yehuda. 2016.
OBJECTIVE: To evaluate the accuracy and utility of intraoperative frozen section examination (iFSE) in patients with a preoperative fine-needle aspiration (FNA) cytology of "suspicious for malignancy" (SFM)-Bethesda V, after the adoption of the Bethesda System for Reporting Thyroid Cytopathology. STUDY DESIGN: Case series with chart review. SETTING: Tertiary medical center. SUBJECTS AND METHODS: All patients with SFM-Bethesda V who underwent thyroid surgery with iFSE between 2010 and 2015 were included. In cases where the iFSE was reported to be malignant, a total thyroidectomy was performed; otherwise, thyroid lobectomy (hemithyroidectomy) was performed. RESULTS: The current series included 47 patients diagnosed preoperatively with FNA cytology of SFM-Bethesda V. The malignancy rate was 74.5% (35 of 47). Twenty-four patients with nonmalignant iFSE results underwent lobectomy during their initial surgery: 12 were subsequently found with benign final histology and did not undergo completion thyroidectomy; the other 12 patients had malignant results on final histology, but only 4 of them underwent completion thyroidectomy. iFSE resulted in a sensitivity and specificity of 65.7% and 100%, respectively, with a positive predictive value of 100% (23 of 23) and a negative predictive value of 50% (12 of 24). Accuracy of the iFSE methodology was 74.5% (35 of 47). CONCLUSIONS: With no significant preoperative clinical or sonographic predictors for thyroid malignancy and given the high specificity of iFSE, our results support the use of iFSE for patients with preoperative FNA cytology of SFM-Bethesda V who are undergoing thyroid surgery, to determine the extent of required surgery.
PubMed-ID: 27271266
http://dx.doi.org/10.1177/0194599816653114

Can We Predict the Lateral Compartment Lymph Node Involvement in RET-Negative Patients with Medullary Thyroid Carcinoma?
Ann Surg Oncol, 23(11):3653-9.
M. M. Chandeze, S. Noullet, M. Faron, C. Tresallet, G. Godiris-Petit, F. Tissier, C. Buffet, L. Leenhardt, N. Chereau and F. Menegaux. 2016.
BACKGROUND: Lateral lymph node dissection (LND) in the absence of macroscopic nodal metastasis remains controversial in sporadic medullary thyroid carcinoma (MTC). OBJECTIVES: The aims of our study were to determine the risk of lateral lymph node (LN) metastases with a focus on lateral contralateral N1, and to define a risk-adapted surgical treatment for these patients. METHODS: All patients who underwent surgery from 1980 to 2012 for previously untreated RET-negative MTC were reviewed. We focused on the lateral compartments of LN metastases and identified three groups: no lateral LN metastases, ipsilateral lateral (ILL)-LN metastases with no contralateral LN involvement, and contralateral lateral (CLL)-LN metastases. RESULTS: Overall, 131 patients

underwent surgery for RET-negative MTC. A total thyroidectomy with LND was performed in 112 patients (85 %), including 97 patients who had an ILL-LND and 92 patients who had a CLL-LND. Lateral LN metastases (N1) occurred in 40 patients (37 %): 31 patients (32 %) had ILL-LN metastases with no contralateral LN involvement, and 9 patients (10 %) had CLL-LN metastases. The preoperative cut-offs for LN metastases in the ILL compartment were very low, with a smallest tumor size of 5 mm, and lowest serum calcitonin level of 38 pg/ml. Disease-free survival rates decreased from 92 % for patients with no lateral LN metastases to 41 % for patients with ILL-LN metastases and 0 % for patients with CLL-LN metastases. CONCLUSIONS: ILL-LND should be performed in every patient and only a minority of MTC patients with small micro-MTC, and low serum calcitonin levels should not have a CLL-LND.
PubMed-ID: 27271930
http://dx.doi.org/10.1245/s10434-016-5292-2

Prognostic markers and response to vandetanib therapy in sporadic medullary thyroid cancer patients.
Eur J Endocrinol, 175(3):173-80.
V. Tiedje, S. Ting, R. F. Walter, T. Herold, K. Worm, J. Badziong, D. Zwanziger, K. W. Schmid and D. Fuhrer. 2016.
OBJECTIVE: Medullary thyroid carcinoma (MTC) occurs sporadically in 75% of patients. Metastatic disease is associated with significantly poorer survival. The aim of this study was to identify prognostic markers for progressive MTC and oncogenic factors associated with response to vandetanib therapy. DESIGN AND METHODS: Clinical courses of 32 patients with sporadic MTC (n=10 pN0cM0, n=8 pN1cM0, n=14 pN1cM1) were compared with genetic profiles of the patients' primary tumour tissue. Analysis for RET proto-oncogene mutations was performed by Sanger sequencing and next-generation sequencing (NGS). The mRNA expression (mRNA count) of 33 targets was measured by nCounter NanoString analysis. RESULTS: Somatic RET mutations occurred in 21/32 patients. The RET918 mutation was found in 8/14 pN1cM1 patients. BRAF (P=0.019), FGFR2 (P=0.007), FGFR3 (P=0.044) and VEGFC (P=0.042) mRNA expression was significantly lower in pN1cM0/pN1cM1 compared with pN0cM0 patients, whereas PDGFRA (P=0.026) mRNA expression was significantly higher in pN1cM0/pN1cM1 when compared with pN0cM0 patients. Among the 10/32 vandetanib-treated patients, 5 showed partial response (PR), all harbouring the RET918 mutation. mRNA expression of FLT1 (P=0.039), FLT4 (P=0.025) and VEGFB (P=0.042) was significantly higher in therapy responders. CONCLUSIONS: In this study, we identified molecular markers in primary tumour tissue of sporadic MTC associated with the development of metastasis (both lymph node and organ metastasis) as well as response to vandetanib therapy.
PubMed-ID: 27283290
http://dx.doi.org/10.1530/EJE-16-0252

Relevance of BRAF and NRAS mutations in the primary tumor and metastases of papillary thyroid carcinomas.
Head Neck, 38(12):1772-9.
M. Canadas-Garre, P. Becerra-Massare, A. Moreno Casares, M. A. Calleja-Hernandez and J. M. Llamas-Elvira. 2016.
BACKGROUND: Multifocality of papillary thyroid carcinoma (PTC) is common. BRAF and NRAS mutations are the most frequent genetic alterations in PTC. The purpose of this study was to determine the distribution and relevance of BRAFT1799A and NRAS mutations in PTC. METHODS: BRAFT1799A and NRAS mutations were evaluated in 195 intrathyroid or metastatic foci from 29 patients with multifocal PTC. RESULTS: BRAFT1799A mutation was positive in 46.7% of the 59 intrathyroid and 136 metastatic foci (91/195 foci). Heterogeneous BRAF pattern was observed in 51.7% patients (15/29 patients). Irrespective of BRAF status at diagnosis (thyroid or nodes), all patients with recurrent PTC presented BRAF-mutated metastases during follow-up. All foci were negative for NRAS mutations. CONCLUSION: BRAF but not NRAS mutations were heterogeneously distributed among primary tumor, nodal sites, and recurrent disease. The BRAF status of metastases generated during the follow-up can differ from the status of foci at diagnosis. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 1772-1779, 2016.
PubMed-ID: 27299298
http://dx.doi.org/10.1002/hed.24517

Characteristics of young adults of Belarus with post-Chernobyl papillary thyroid carcinoma: a long-term follow-up of patients with early exposure to radiation at the 30th anniversary of the accident.
Clin Endocrinol (Oxf), 85(6):971-8.
M. Fridman, A. K. Lam and O. Krasko. 2016.
OBJECTIVES: Studies of thyroid cancer related to the Chernobyl accident have focused on children as they are

the most vulnerable group with the highest risk of developing radiation-associated cancer. In contrast, our research aimed to look at the clinical and pathological features of patients with post-Chernobyl papillary thyroid carcinoma that were 2 years old or less at the time of the Chernobyl accident. DESIGN: The study subjects were patients (n = 359) aged 0 to 2 at the time of the Chernobyl accident and aged >/=19 years at presentation/surgery who were treated in Belarus for papillary thyroid carcinoma during the period 2003-2013. RESULTS: In conventional or oncocytic variant of papillary thyroid carcinoma, the prevalence of extra-thyroidal extension, nodal disease, infiltrative growth or lymphatic vessel invasion was above 50%. These features were less pronounced when compared to tall cell or diffuse sclerosing variants of papillary thyroid carcinoma. The highest frequency of central lymph node metastases was found in patients aged 1-2 years at exposure (P = 0.004). Subjects exposed in utero were characterized by absent/insignificant lymphocytic infiltration around the carcinoma (P = 0.025), predominance of conventional papillary architecture and an association with lymphocytic thyroiditis. CONCLUSIONS: A number of features were associated with this group of patients that were very young at the time of radiation exposure. In addition, the incidence and basic characteristics of adult papillary thyroid carcinoma varied depending on the types of exposure conditions.
PubMed-ID: 27314225
http://dx.doi.org/10.1111/cen.13137

Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology.
Am J Surg, 212(5):946-52.
T. Karatzas, I. Vasileiadis, E. Zapanti, G. Charitoudis, E. Karakostas and G. Boutzios. 2016.
BACKROUND: We investigated the efficacy of thyroglobulin antibodies (TgAb) in detecting malignancy in indeterminate thyroid nodules and evaluated the possible association between TgAb and autoimmunity in papillary thyroid carcinoma (PTC). METHODS: This retrospective, nonrandomized study included 1,646 patients who had undergone preoperative fine-needle aspiration biopsy to evaluate their thyroid nodules, and then standard total thyroidectomy. Of 194 patients (11.8%) with indeterminate nodules, 61 (31.4%) had PTC and 133 (68.6%) had benign nodules at the final histologic examination. RESULTS: Univariate analysis showed that multifocality (P = .002), bilaterality (P = .003), lymph-node metastasis (P = .030), and capsule penetration (P = .003) were significantly associated with positive TgAb in patients with indeterminate cytology and histopathologic diagnosis of PTC. The multivariate analysis showed that TgAb positivity (P < .001) and preoperative thyroid-stimulating hormone levels (P = .022) were independent predictive factor for PTC diagnosis in patients with indeterminate cytology. CONCLUSIONS: Preoperative TgAb could be a marker for PTC in patients with indeterminate thyroid nodules, increasing diagnostic accuracy. TgAb positivity could also influence the clinical assessment and subsequent selection of total thyroidectomy.
PubMed-ID: 27324384
http://dx.doi.org/10.1016/j.amjsurg.2015.12.030

Hypermetabolism on (18)F-Fluorodeoxyglucose Positron Emission Tomography Scan Does Not Influence the Interpretation of Thyroid Cytopathology, and Nodules with a SUVmax <2.5 Are Not at Increased Risk for Malignancy.
Thyroid, 26(9):1300-7.
P. Valderrabano, J. Montilla-Soler, M. Mifsud, M. Leon, B. Centeno, L. Khazai, T. Padhya, T. McCaffrey, J. Russell, B. McIver and K. Otto. 2016.
BACKGROUND: Hypermetabolism of thyroid nodules on (18)F-fluorodeoxyglucose positron emission tomography (PET) is associated with a higher prevalence of malignancy. However, the definition of hypermetabolism and its impact on cytological interpretation are unclear. METHODS: Medical records of all patients with thyroid nodules who had undergone cytological evaluation at the Moffitt Cancer Center between October 2008 and May 2014 were retrospectively reviewed. Those with a PET scan performed within one year of the cytology composed the study group, and the rest were used as controls. The distribution of the cytological categories, percentage of resection, and prevalence of malignancy among each Bethesda category was compared between both groups. RESULTS: Fifteen percent (436) of all thyroid nodules with cytological evaluation were in the study group. Maximum standardized uptake values (SUVmax) were directly associated with the probability of having a malignant or a follicular neoplasm cytological diagnosis; and inversely associated with the probability of having a benign cytological diagnosis. However, the prevalence of cancer within each Bethesda category was not associated with SUVmax values. It was found that the prevalence of malignant cytology increased to >5% with SUVmax values >/=2.5. SUVmax values were significantly higher in malignant than in benign nodules on histology (mean values 10.8 vs. 5) but with significant overlap between both groups for either the whole cohort or nodules with indeterminate cytology only limiting its use for differential diagnosis. CONCLUSIONS: The prevalence of malignancy in thyroid nodules with a SUVmax <2.5 is similar to the general

population, and management should not be modified in those patients. The increased prevalence of malignancy among hypermetabolic thyroid nodules (SUVmax >/=2.5) is well characterized by cytology and does not impact the interpretation of cytological categories. Therefore, SUVmax value does not add relevant information once cytology is available.
PubMed-ID: 27324615
http://dx.doi.org/10.1089/thy.2015.0654

Nonthyroid Metastasis to the Thyroid Gland: Case Series and Review with Observations by Primary Pathology.
Otolaryngol Head Neck Surg, 155(6):961-8.
J. O. Russell, K. Yan, B. Burkey and J. Scharpf. 2016.
OBJECTIVE: Nonthyroid metastases to the thyroid gland can cause morbidity, including dysphagia, dysphonia, and airway compromise. Because metastatic malignancies portend a poor prognosis, obtaining equipoise between treatment morbidity and local disease progression is paramount. We reviewed cases of nonthyroid metastases to determine treatment and prognostic recommendations. STUDY DESIGN: Case series with chart review. SETTING: Tertiary care hospital. SUBJECTS AND METHODS: We searched PubMed for reported cases between 1994 and September 2013 using search terms as follows: any combination of primary tumor locations and thyroid, as well as the terms thyroid and metastasis. Only unique cases of nonthyroid metastases were included. Combined with 17 additional tumors at our own institution, we found 818 unique nonthyroid metastases, of which 384 had management and survival data available. RESULTS: Renal cell carcinoma was most common, presenting in 293 (35.8%) patients, followed by lung and gastrointestinal malignancies. Patients were treated with total thyroidectomy (34.0%), subtotal thyroidectomy including lobectomy (32.6%), and no surgery (33.5%). Surgical management was associated with improved survival duration (P < .01). Locoregional recurrence was less likely in patients treated with total versus partial thyroidectomy (4.8% vs 13%). Extent of surgical management did not have a significant effect on patient survival. Delayed presentation was associated with improved survival duration (P = .01). CONCLUSIONS: Nonthyroid metastases to the thyroid gland are unusual tumors. Surgical intervention is associated with improved survival, but expected morbidity of untreated tumors is difficult to assess. Site of origin, time to diagnosis, and surgical approach are related to survival and recurrence rates.
PubMed-ID: 27329421
http://dx.doi.org/10.1177/0194599816655783

Surgeon volume in thyroid surgery: Surgical efficiency, outcomes, and utilization.
Laryngoscope, 126(11):2630-9.
C. Meltzer, M. Klau, D. Gurushanthaiah, J. Tsai, D. Meng, L. Radler and A. Sundang. 2016.
OBJECTIVES/HYPOTHESIS: To test our hypothesis that high-surgeon volume is associated with improved surgical efficiency and 30-day outcomes, and lower hospital utilization. STUDY DESIGN: Retrospective observational cohort, 2008-2013. METHODS: A total of 3,135 patients with hemithyroidectomy or total thyroidectomy performed by a high-volume surgeon, propensity score-matched to 3,135 patients with the same procedure performed by a low-volume surgeon. All-cause 30-day complication, mortality, readmission, and emergency department visit rates, proportion of outpatient procedures, cut-to-close time, and length of stay were assessed. RESULTS: Hemithyroidectomies: Compared to low-volume surgeons, high-volume surgeons had fewer readmitted patients (2.7% vs. 7.0%, P < .05), more outpatient procedures (46% vs. 29%, P < .05), and shorter lengths of stay (mean [standard deviation] 16.6 [22.1] vs. 21.7 [27.5] hours, P < .05) and surgical (cut-to-close) times (1.7 [0.7] vs. 2.0 [1.1] hours, P < .05). Total thyroidectomies: High-volume surgeons had lower rates of all surgery-related complications (5.7% vs. 7.5%, P < .05), hypocalcemia (4.9% vs. 7.0%, P < .05), surgical site infections (0.3% vs. 1.0%, P < .05), more outpatient procedures (13% vs. 3%, P < .05), shorter lengths of stay (29.9 [32.8] vs. 39.8 [36.2] hours, P < .05), and cut-to-close times (2.4 [1.1] vs. 3.0 [1.7] hours, P < .05). CONCLUSION: High-volume surgeons improve patient safety and have the potential to contribute to organizational efficiency that may be underutilized in some settings. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:2630-2639, 2016.
PubMed-ID: 27334930
http://dx.doi.org/10.1002/lary.26119

Effects of Radioiodine Treatment on Salivary Gland Function in Patients with Differentiated Thyroid Carcinoma: A Prospective Study.
J Nucl Med, 57(11):1685-91.
E. N. Klein Hesselink, A. H. Brouwers, J. R. de Jong, A. N. van der Horst-Schrivers, R. P. Coppes, J. D. Lefrandt, P. L. Jager, A. Vissink and T. P. Links. 2016.
Complaints of a dry mouth (xerostomia) and sialoadenitis are frequent side effects of radioiodine treatment in differentiated thyroid cancer (DTC) patients. However, detailed prospective data on alterations in salivary gland functioning after radioiodine treatment (131I) are scarce. Therefore, the primary aim of this study was to prospectively assess the effect of high-activity radioiodine treatment on stimulated whole saliva flow rate. Secondary aims were to study unstimulated whole and stimulated glandular (i.e., parotid and submandibular) saliva flow rate and composition alterations, development of xerostomia, characteristics of patients at risk for salivary gland dysfunction, and whether radioiodine uptake in salivary glands on diagnostic scans correlates to flow rate alterations. METHODS: In a multicenter prospective study, whole and glandular saliva were collected both before and 5 mo after radioiodine treatment. Furthermore, patients completed the validated xerostomia inventory. Alterations in salivary flow rate, composition, and xerostomia inventory score were analyzed. Salivary gland radioiodine uptake on diagnostic scans was correlated with saliva flow rate changes after radioiodine treatment. RESULTS: Sixty-seven patients (mean age +/- SD, 48 +/- 17 y; 63% women, 84% underwent ablation therapy) completed both study visits. Stimulated whole saliva flow rate decreased after ablation therapy (from 0.92 [interquartile range, 0.74-1.25] to 0.80 [interquartile range, 0.58-1.18] mL/min, P = 0.003), as well as unstimulated whole- and stimulated glandular flow rates (P < 0.05). The concentration of salivary electrolytes was similar at both study visits, whereas the output of proteins, especially amylase (P < 0.05), was decreased. The subjective feeling of dry mouth increased (P = 0.001). Alterations in saliva flow rate were not associated with semiquantitatively assessed radioiodine uptake in salivary glands on diagnostic scans. For the small cohort of patients undergoing repeated radioiodine therapy, we could not demonstrate alterations in salivary parameters. CONCLUSION: We prospectively showed that salivary gland function is affected after high-activity radioiodine ablation therapy in patients with DTC. Therefore, more emphasis should be placed on salivary gland dysfunction during follow-up for DTC patients receiving high-activity radioiodine treatment.
PubMed-ID: 27339871
http://dx.doi.org/10.2967/jnumed.115.169888

Interaction of Age at Diagnosis with Transcriptional Profiling in Papillary Thyroid Cancer.
World J Surg, 40(12):2922-9.
Y. C. Hsu, C. L. Liu, P. S. Yang, C. H. Tsai, J. J. Lee and S. P. Cheng. 2016.
BACKGROUND: Age is an important prognostic factor for papillary thyroid cancer (PTC). However, little is known about why advanced age is associated with poor prognosis. The study investigated the changes in transcriptional profiling related to age. METHODS: RNA sequencing data of PTC samples were retrieved from The Cancer Genome Atlas data portal. Spearman's correlation was used to test the association between age and gene expression. Correlation in the same direction to disease severity was considered functionally relevant. Functional enrichment analysis and pathway annotations were performed. RESULTS: There was no correlation between age and thyroid-specific genes, except for a weak, negative association between age and TSHR expression. Among 272 genes with a positive association between gene expression and age, the most prominent alteration was metabolic pathways, particularly glycolysis. Among 482 genes with a negative association between gene expression and age, the most enriched biological process was immune-related functions, particularly natural killer cell-mediated cytotoxicity. CONCLUSIONS: Our analysis characterized the age-associated molecular landscape in PTC. Metabolic alterations and immune dysregulation are probable mechanisms involving in worse prognosis in older patients with PTC.
PubMed-ID: 27384173
http://dx.doi.org/10.1007/s00268-016-3625-8

Prophylactic "First-Step" Central Neck Dissection (Level 6) Does Not Increase Morbidity After (Total) Thyroidectomy.
Ann Surg Oncol, 23(12):4016-22.
A. Selberherr, P. Riss, C. Scheuba and B. Niederle. 2016.
BACKGROUND: In terms of morbidity, prophylactic central neck dissection (CND; level 6) in potentially malignant thyroid disease is discussed controversially. The rates of (transient and permanent) hypoparathyroidism and palsy of the recurrent laryngeal nerve (RLN) after "first-step" (FS-)CND are analyzed in this study. METHODS: Bilateral and unilateral FSCND, i.e., lymph node dissection along the RLN before (total) thyroidectomy, was performed bilaterally in 68 (group 1) and unilaterally in 44 patients (group 2), respectively. The rates of hypoparathyroidism and palsy of the RLN were documented prospectively and were compared to

237 patients of group 3 (controls) who underwent (total) thyroidectomy only. RESULTS: Fifteen of 68 patients (22 %) of group 1 developed transient and one patient had permanent hypoparathyroidism. Transient unilateral palsy of the RLN was observed in ten patients (15 %); none were permanent. Transient hypoparathyroidism was monitored in 10 of 44 patients (23 %) of group 2 and permanent hypoparathyroidism in 1 (2 %). Six patients (14 %) developed temporary palsy of the RLN; one remained permanent. Palsy was seen in 3 patients on the contralateral side of unilateral FSCND. Transient and permanent hypoparathyroidism was observed in 50 (21 %) and 2 (1 %) of 237 controls. Transient palsy of the RLN was documented in 22 (9 %) of 237 controls and permanent palsy of the RLN in 4 (2 %). CONCLUSIONS: In this single-center series, the overall permanent morbidity was low (1 %). Therefore, FSCND may be recommended (even prophylactically) for experienced high-volume surgeons in patients with thyroid nodules suspicious for malignancy.
PubMed-ID: 27393573
http://dx.doi.org/10.1245/s10434-016-5338-5

Surgery in MEN 2A Patients Older Than 5 Years with Micro-MTC: Outcome at Long-term Follow-up.
Otolaryngol Head Neck Surg, 155(5):787-9.
F. Tonelli, F. Giudici, T. Marcucci, T. Cavalli, S. Spini, R. G. Gheri and M. L. Brandi. 2016.
In multiple endocrine neoplasia syndrome type 2A (MEN 2A), early total thyroidectomy (TT; performed before the age of 5 years) is the best option to prevent medullary thyroid carcinoma (MTC) development, but the management of MEN 2A patients diagnosed after childhood is still under debate. Seventeen consecutive patients diagnosed with MEN 2A after the age of 5 years (mean age, 23.3 years) with a pathologic diagnosis of micro-MTC without nodal involvement were enrolled. All patients underwent TT with thymectomy and central compartment lymph node dissection. During surgery, parathyroid tissue removal occurred in 14 patients. No major postoperative complications nor persistent hypoparathyroidism was observed. After a mean follow-up of 16.6 years, no patient developed primary hyperparathyroidism or disease recurrence. Even if TT is recommended before the age of 5, when MEN 2A diagnosis is performed after this age in micro-MTC without nodal involvement, TT with thymectomy and central compartment lymphadenectomy can provide good oncologic and functional results.
PubMed-ID: 27406704
http://dx.doi.org/10.1177/0194599816654856

Multifocal Versus Solitary Papillary Thyroid Carcinoma.
World J Surg, 40(9):2139-43.
A. Kiriakopoulos, A. Petralias and D. Linos. 2016.
BACKGROUND: Papillary Thyroid Carcinoma (PTC) which accounts for >85 % of all thyroid cancers in iodine-rich areas, appears either as a single tumor or as two or more, neoplastic foci within the thyroid gland (Multifocal PTC). We present the comparative results between solitary and MFC PTC. MATERIALS AND METHODS: Demographics, tumor characteristics (size, laterality, foci number, histologic subtype) and TNM staging were compared between solitary and MFPTC patients. The presence of lymphocytic or Hashimoto's thyroditis was also recorded. RESULTS: From January 2008 to December 2012, among 647 PTC patients, 241(37.2 %) had MFPTC 177 females (73.4 %) and 64 males (26.6 %), mean age 48.5 years (range 12-87). Mean number of tumor foci was 3.3 (range 2-26). MFPTC patients presented with more advanced T stage (28.2 vs. 18.7 %, $p = 0.01$) and more LN metastases (28.6 vs. 15.5 %, $p < 0.001$). Foci number correlates with male gender and LN metastases ($p = 0.014$ and $p = 0.019$, respectively). Central (N1a) or lateral (N1b) LN involvement correlates strongly with male gender ($p = 0.024$) and younger age ($p < 0.001$). The follicular variant was the next most frequent histologic subtype associated with extremely rare LN metastases. CONCLUSION: MFPTC comprises a more aggressive form of papillary thyroid cancer since it is associated with more frequent N1a/ N1b disease and occurs more frequently in T3/T4 patients. MFPTC foci number correlates with male gender and LN metastases.
PubMed-ID: 27412628
http://dx.doi.org/10.1007/s00268-016-3628-5

The changing incidence of thyroid cancer.
Nat Rev Endocrinol, 12(11):646-53.
C. M. Kitahara and J. A. Sosa. 2016.
During the past few decades, the incidence of thyroid cancer has increased substantially in many countries, including the USA. The rise in incidence seems to be attributable both to the growing use of diagnostic imaging and fine-needle aspiration biopsy, which has led to enhanced detection and diagnosis of subclinical thyroid cancers, and environmental factors. The latest American Thyroid Association (ATA) practice guidelines for the management of adult patients with thyroid nodules and differentiated thyroid cancer differ substantially from the previous ATA guidelines published in 2009. Specifically, the problems of overdiagnosis and overtreatment of a

disease that is typically indolent, where treatment-related morbidity might not be justified by a survival benefit, now seem to be acknowledged. As few modifiable risk factors for thyroid cancer have been established, the specific environmental factors that have contributed to the rising incidence of thyroid cancer remain speculative. However, the findings of several large, well-designed epidemiological studies have provided new information about exposures (such as obesity) that might influence the development of thyroid cancer. In this Review, we describe the changing incidence of thyroid cancer, suggest potential explanations for these trends, emphasize the implications for patients and highlight ongoing and potential strategies to combat this growing clinical and public health issue.
PubMed-ID: 27418023
http://dx.doi.org/10.1038/nrendo.2016.110

Surgical Methods and Experiences of Surgeons did not Significantly Affect the Recovery in Phonation Following Reconstruction of the Recurrent Laryngeal Nerve.
World J Surg, 40(12):2948-55.
K. Yoshioka, A. Miyauchi, M. Fukushima, K. Kobayashi, M. Kihara and A. Miya. 2016.
BACKGROUND: We reported phonatory recovery in the majority of 88 patients after recurrent laryngeal nerve (RLN) reconstruction. Here we analyzed factors that might influence the recovery, in a larger patient series. METHODS: At Kuma Hospital, 449 patients (354 females and 95 males) underwent RLN reconstruction with direct anastomosis, ansa cervicalis-to-RLN anastomosis, free nerve grafting, or vagus-to-RLN anastomosis; 47.4 % had vocal cord paralysis (VCP) preoperatively. Maximum phonation time (MPT) and mean airflow rate during phonation (MFR) were measured 1 year post surgery. Forty patients whose unilateral RLNs were resected and not reconstructed and 1257 normal subjects served as controls. RESULTS: Compared to the VCP patients, the RLN reconstruction patients had significantly longer MPTs 1 year after surgery, nearing the normal values. The MFR results were similar but less clear. Detailed analyses of 228 female patients with reconstruction for whom data were available revealed that none of the following factors significantly affected phonatory recovery: age, preoperative VCP, method of reconstruction, site of distal anastomosis, use of magnifier, thickness of suture thread, and experience of surgeon. Of these 228 patients, 24 (10.5 %) had MPTs <9 s 1 year after surgery, indicating insufficient recovery in phonation. This insufficiency was also not associated with the factors mentioned above. CONCLUSIONS: Approximately 90 % of patients who needed resection of the RLN achieved phonatory recovery following RLN reconstruction. The recovery was not associated with gender, age, preoperative VCP, surgical method of reconstruction, or experience of the surgeon. Performing reconstruction during thyroid surgery is essential whenever the RLN is resected.
PubMed-ID: 27431320
http://dx.doi.org/10.1007/s00268-016-3634-7

National Trends in the Surgical Treatment of Non-advanced Medullary Thyroid Cancer (MTC): An Evaluation of Adherence with the 2009 American Thyroid Association Guidelines.
World J Surg, 40(12):2930-40.
E. H. Chang, W. Lutfi, J. Feinglass, A. E. Reiher, T. Moo-Young and M. K. Bhayani. 2016.
BACKGROUND: Medullary thyroid cancer (MTC) represents the third most common type of thyroid cancer, and the prognosis depends on the stage of the disease at diagnosis and completeness of tumor resection. In 2009, the American Thyroid Association (ATA) published guidelines with evidence-based recommendations for the treatment of MTC. This study aimed to determine national adherence rates of the treatment according to the ATA guidelines specific for MTC. METHODS: Patients diagnosed with MTC from 2004 to 2013 were identified from the National Cancer Database. Guideline adherence rates for the treatment of MTC before and after the publication of ATA guidelines were analyzed and compared to determine patient and clinical variables that affected treatment. RESULTS: A total of 3693 patients diagnosed with MTC were identified. We found 60.3 % of the patients had localized MTC and 39.7 % had regional metastases. Older age, female sex and having Medicaid or being uninsured were directly correlated with more advanced disease upon diagnosis ($p < 0.001$). Overall, a greater proportion of patients received care in accordance with the recommendations following the ATA guidelines' publication in 2009: 61.4 % of patients treated between 2004 and 2008 versus 66.8 % of patients treated between 2009 and 2013 received care in accordance with the recommendations ($p < 0.01$). Factors such as older age, African American race, localized disease at diagnosis, lower estimated median zip code household income and being treated in a community versus an academic hospital were associated with a lower likelihood of receiving care in accordance with the guidelines. CONCLUSION: Adherence rates to the ATA recommendations for the treatment of MTC increased modestly following the publication of guidelines in 2009 with the largest increase seen in community hospitals. Being older, African American, diagnosed with localized disease and treated in a community hospital rather than in an academic institution was correlated with a lower likelihood of receiving treatment in accordance with the guidelines. Efforts should be made to continuously

increase the adherence rates to the MTC ATA guidelines and to decrease socioeconomic disparities that continue to exist in the treatment of MTC.
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http://dx.doi.org/10.1007/s00268-016-3643-6

Preoperative Cytologic Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: A Prospective Analysis.
Thyroid, 26(10):1466-71.
K. C. Strickland, M. Vivero, V. Y. Jo, A. C. Lowe, M. Hollowell, X. Qian, T. J. Wieczorek, C. A. French, L. A. Teot, P. M. Sadow, E. K. Alexander, E. S. Cibas, J. A. Barletta and J. F. Krane. 2016.
BACKGROUND: The term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been proposed to replace noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) in recognition of the indolent behavior of this tumor. The ability to differentiate NIFTP from classical papillary thyroid carcinoma (cPTC) by fine-needle aspiration (FNA) would facilitate conservative management for NIFTP. The aim of this study was to determine if NIFTP can be distinguished prospectively from cPTC. METHODS: From June 2015 to January 2016, thyroid FNAs with a diagnosis of "malignant" or "suspicious for malignancy" were prospectively scored for features associated with NIFTP/FVPTC (microfollicular architecture) or cPTC (papillae, psammomatous calcifications, sheet-like architecture, and nuclear pseudoinclusions) and categorized as NIFTP/FVPTC, cPTC, or indeterminate. Results were correlated with subsequent histologic diagnoses. RESULTS: The study included 52 patients with 56 resected nodules with a cytologic diagnosis of "malignant" (43/56) or "suspicious for malignancy" (13/56). Forty-nine patients (94%) underwent initial total thyroidectomy. Histopathologic diagnoses included 42 cPTC, 8 NIFTP, 3 invasive FVPTC, 2 follicular adenomas, and 1 poorly differentiated carcinoma. Excluding 7 indeterminate cases, 89% (8/9) of nodules classified as NIFTP/FVPTC on FNA demonstrated follicular-patterned lesions on histology (5 NIFTP, 1 invasive FVPTC, 2 follicular adenomas). Cytopathologists prospectively identified cPTC in 95% (38/40) of cases. CONCLUSIONS: In thyroid FNAs with cytologic features concerning for PTC, NIFTP/FVPTC can be distinguished from cPTC in most cases by assessing a limited number of features. Therefore, it is both feasible and appropriate to attempt to separate NIFTP/FVPTC from cPTC on FNA to promote appropriate clinical management.
PubMed-ID: 27457786
http://dx.doi.org/10.1089/thy.2016.0280

Risk factors for lymph node metastasis in papillary thyroid microcarcinoma: Older patients with fewer lymph node metastases.
Eur J Surg Oncol, 42(10):1478-82.
L. Zhang, J. Yang, Q. Sun, Y. Liu, F. Liang, Z. Liu, G. Chen, S. Chen, Z. Shang, Y. Li and X. Li. 2016.
BACKGROUND: Lymph node metastasis (LNM) is an important consideration in treatment strategy selection for papillary thyroid microcarcinoma (PTMC). The aim of this study was to investigate the risk factors for LNM and high-volume LNM (hvLNM, >5 metastatic lymph nodes). METHODS: A consecutive series of 1226 PTMC (947 female, 279 male) patients was reviewed. All patients underwent at least central neck dissection. Clinical-pathological features were assessed. All patients were allocated into Group A (</=39 yrs), Group B (40-59 yrs), or Group C (>/=60 yrs) for risk factor analysis. RESULTS: Among all patients, 438 LNM and 73 hvLNM were detected. Older patients had significantly fewer LNM (A: 51.45% of 346, B: 30.15% of 786, and C: 24.47% of 94) and fewer hvLNM (A: 11.85%, B: 3.94%, and C: 1.06%). Male, multifocality, and tumor diameter >0.5 cm were also correlated with LNM and hvLNM. In multivariate analysis, older patients had lower risk of LNM (odds ratio [OR] 0.389 in B, 0.305 in C), and chronic thyroiditis was protective factor for LNM (OR 0.524). Male (OR 1.651), tumor diameter >0.5 cm (OR 1.850), and multifocality (OR 1.928) were risk factors for LNM. Similarly, older patients had lower risk of hvLNM (OR 0.313 in B, OR 0.085 in C). Male (OR 2.590), tumor diameter >0.5 cm (OR 2.180), and multifocality (OR 1.980) were also risk factors for hvLNM. CONCLUSION: Older PTMC patients may have fewer LNM and lower risk of hvLNM. For patients >/=60 years old, dynamic observation may be an option for clinical management.
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http://dx.doi.org/10.1016/j.ejso.2016.07.002

The Ethical Implications of the Reclassification of Noninvasive Follicular Variant Papillary Thyroid Carcinoma.
Thyroid, 26(9):1167-72.
I. Likhterov, M. Osorio, S. P. Moubayed, J. C. Hernandez-Prera, R. Rhodes and M. L. Urken. 2016.
BACKGROUND: Several studies have highlighted the lack of consensus in the diagnosis of follicular variant of papillary thyroid carcinoma (FVPTC). An international multidisciplinary panel to address the controversy was

assembled at the annual meeting of the Endocrine Pathology Society in March of 2015, leading to the recent publication reclassifying encapsulated (or noninvasive) FVPTC (EFVPTC) as a benign neoplasm. Does this change in histologic taxonomy warrant a change in clinical practice, and how should it affect those who have been given this diagnosis in the past? We consider the financial and psychological impact of this reclassification and discuss the ethical, legal, and practical issues involved with sharing this information with the patients who are affected. SUMMARY: The total direct and indirect cost of thyroid cancer surveillance in patients is significant. High levels of clinically relevant distress affect up to 43% of patients with papillary thyroid carcinoma, as estimated by the Distress Thermometer developed by the National Comprehensive Cancer Network for detecting distress in cancer patients. Although there are currently no legal opinions that establish a precedent for recontacting patients whose clinical status is altered by a change in nomenclature, the prudent course would be to attend to the requirements of medical ethics. CONCLUSION: Informing patients with a previous diagnosis of EFVPTC that the disease has been reclassified as benign is expected to have a dramatic effect on their surveillance needs and to alleviate the psychological impact of living with a diagnosis of cancer. It is important to re-evaluate the pathologic slides of those patients at risk to ensure that the invasive nature of the tumor is comprehensively evaluated before notifying a patient of a change in diagnosis. The availability of the entire tumor for evaluation of the capsule may prove to be a challenge for a portion of the population at risk. We believe that it is the clinician's professional duty to make a sincere and reasonable effort to convey the information to the affected patients. We also believe that the cost savings with respect to the need for additional surgery, radioactive iodine, and rigorous surveillance associated with a misinterpretation of the biology of the diagnosis of EFVPTC in less experienced hands will likely more than offset the cost incurred in histologic review and patient notification.
PubMed-ID: 27480127
http://dx.doi.org/10.1089/thy.2016.0212

The Safety and Efficacy of Weekly Paclitaxel Administration for Anaplastic Thyroid Cancer Patients: A Nationwide Prospective Study.
Thyroid, 26(9):1293-9.
N. Onoda, K. Sugino, T. Higashiyama, M. Kammori, K. Toda, K. Ito, A. Yoshida, N. Suganuma, N. Nakashima, S. Suzuki, K. Tsukahara, H. Noguchi, M. Koizumi, T. Nemoto, H. Hara, A. Miyauchi and I. Sugitani. 2016.
BACKGROUND: Anaplastic thyroid cancer (ATC) is a rare and extremely aggressive malignancy, with a median survival of less than 6 months due to rapid progression and resistance to multimodal therapies. Effective treatment strategies have not been identified. A prospective clinical study was performed to objectively evaluate outcomes of treatment with paclitaxel. METHODS: An investigator-initiated, multicenter, nonrandomized, open-label, single-arm study to evaluate the feasibility and efficacy of weekly paclitaxel (80 mg/m(2)) administration for patients with pathologically confirmed ATC was conducted in a nationwide organization. RESULTS: Feasibility was analyzed in 56 patients. More than one course of treatment was performed in 52 (93%) patients retaining sufficient dose intensity (>84%). No patient had to terminate the treatment because of an adverse event. The median overall survival was 6.7 months [confidence interval 4.4-9.0]. The 6-month survival was 54%. Among the 42 patients with an evaluable lesion, none demonstrated complete remission, 9 (21%) showed partial remission, 22 (52%) achieved stable disease, and 8 (19%) exhibited progressive disease; 3 did not complete the initial treatment course. The objective response rate was 21%, and the clinical benefit rate was 73%. The median time to progression was 1.6 months. Statistically, no additional effect of concomitant radiation was demonstrated in 6 patients receiving combined therapy. Eight patients, in whom a complete post-treatment surgical removal of the tumor was feasible, survived significantly longer (median 7.6 months [CI 8.1-23.0]) than the other 34 patients in whom the tumor could not be completely removed after chemotherapy (5.4 months [CI 3.0-7.8], p = 0.018). SUMMARY: The study demonstrates objective and accurate information concerning the feasibility and efficacy of a standardized treatment with weekly paclitaxel administration for ATC patients. CONCLUSIONS: Weekly paclitaxel administration for ATC patients can be of clinical benefit in a neo-adjuvant setting.
PubMed-ID: 27484330
http://dx.doi.org/10.1089/thy.2016.0072

Features and Outcome of Autonomous Thyroid Nodules in Children: 31 Consecutive Patients Seen at a Single Center.
J Clin Endocrinol Metab, 101(10):3856-62.
S. Ly, M. C. Frates, C. B. Benson, H. E. Peters, F. D. Grant, L. A. Drubach, S. D. Voss, H. A. Feldman, J. R. Smith, J. Barletta, M. Hollowell, E. S. Cibas, F. D. Moore, Jr., B. Modi, R. C. Shamberger and S. A. Huang. 2016.
CONTEXT: Most thyroid nodules are benign and their accurate identification can avoid unnecessary procedures. In adult patients, documentation of nodule autonomy is accepted as reassurance of benign histology and as justification to forgo biopsy or thyroidectomy. In contrast, the negative predictive value of nodule autonomy in

children is uncertain. Some recent publications recommend surgical resection as initial management, but few address the degree of TSH suppression or the specific scintigraphic criteria used to diagnose autonomy. OBJECTIVE: The objective of the study was to study the presenting features and cancer risk of children with autonomous nodules. DESIGN AND SETTING: Medical records of all 31 children diagnosed with autonomous nodules at our center from 2003 to 2014 were retrospectively reviewed. PATIENTS AND RESULTS: All children met full diagnostic criteria for autonomous nodules, defined by both autonomous 123I uptake into the nodule and the suppression of uptake in the normal thyroid parenchyma on scintigraphy performed during hypothyrotropinemia. The median age of presentation was 15 years (range 3-18 y) with a female to male ratio of 15:1. Fifty-eight percent of patients had solitary nodules and 42% had multiple nodules. The median size of each patient's largest autonomous nodule was 39 mm (range 18-67 mm). Most of the children in this series (68%) had diagnostic biopsies and/or operative pathology of their largest autonomous nodule, which showed benign cytology or histology in all cases. CONCLUSIONS: In this pediatric series, the cancer rate observed in biopsied or resected autonomous nodules was 0%. Whereas larger studies are needed to confirm our findings, these results agree with earlier reports suggesting that thyroid cancer is rare in rigorously defined autonomous nodules and support that conservative management may be offered to selected children who meet strict diagnostic criteria for autonomous nodules, deferring definitive therapies until adulthood when the risks of thyroidectomy and 131I ablation are lower.
PubMed-ID: 27501280
http://dx.doi.org/10.1210/jc.2016-1779

TERT promoter mutations and long-term survival in patients with thyroid cancer.
Endocr Relat Cancer, 23(10):813-23.
T. H. Kim, Y. E. Kim, S. Ahn, J. Y. Kim, C. S. Ki, Y. L. Oh, K. Kim, J. W. Yun, W. Y. Park, J. H. Choe, J. H. Kim, J. S. Kim, S. W. Kim and J. H. Chung. 2016.
TERT promoter mutations are emerging prognostic biomarkers in multiple cancers and are found in highly aggressive thyroid cancer. Our aim is to investigate the prognostic value of these mutations for the outcome of thyroid cancer-related mortality in a large cohort of thyroid cancer patients. This was a retrospective study of 409 patients (393 with differentiated thyroid cancer) with a median age of 44 years (range 16-81 years) and median follow-up of 13 years (interquartile range 11-16 years). Analyses of associations between mutational status and various clinicopathological variables were performed. TERT promoter mutations were identified in 32 (9.8%) papillary, 11 (16.7%) follicular and seven (43.8%) poorly differentiated/anaplastic thyroid cancer patients. The presence of TERT promoter mutations was associated with factors such as increased age ($P < 0.001$), extrathyroidal invasion ($P = 0.01$), increased stage at diagnosis ($P < 0.001$) and dedifferentiated histological type ($P = 0.001$). A TERT promoter mutation was independently associated with poorer overall survival in patients with differentiated thyroid cancer (10-year survival rate, 66.2% vs 98.3% for wild type; adjusted HR, 7.18; 95% CI: 2.77-18.59) and in patients with papillary cancer (74.2% vs 99.3%; 14.20; 3.03-66.68). Concomitant TERT and BRAF mutations worsened the survival rate of patients with papillary cancer (82.6% vs 99.4% for exclusively BRAF mutation alone; 5.62; 1.85-17.09). In conclusion, the presence of TERT promoter mutations is independently associated with increased mortality in patients with differentiated thyroid cancer. The results suggest that inclusion of TERT promoter mutation analysis with conventional clinicopathological evaluation can lead to better prognostication and management for individual patients.
PubMed-ID: 27528624
http://dx.doi.org/10.1530/ERC-16-0219

Risk Factors of 131I-Induced Salivary Gland Damage in Thyroid Cancer Patients.
J Clin Endocrinol Metab, 101(11):4085-93.
B. Hollingsworth, L. Senter, X. Zhang, G. N. Brock, W. Jarjour, R. Nagy, P. Brock, K. R. Coombes, R. T. Kloos, M. D. Ringel, J. Sipos, I. Lattimer, R. Carrau and S. M. Jhiang. 2016.
CONTEXT: Sialadenitis and xerostomia are major adverse effects of 131I therapy in thyroid cancer patients. The risk factors for these adverse effects, other than administered activity of 131I, have not been investigated. OBJECTIVE: The aim of this study is to identify risk factors for 131I-induced salivary gland damage among follicular cell-derived thyroid cancer patients. DESIGN: We enrolled 216 thyroid cancer patients who visited The Ohio State University Wexner Medical Center between April 2013 and April 2014. Symptoms of xerostomia and sialadenitis were identified via questionnaire and medical record search. To validate the findings in a large cohort, we retrospectively searched for ICD-9/10 codes for sialadenitis, xerostomia, and autoimmune disease associated with Sjogren's syndrome (AID-SS) in our existing database (n = 1507). Demographic and clinical information was extracted from medical records. Multivariate analyses were performed to identify independent predictors for salivary gland damage. RESULTS: 131I treatment associated with higher incidence of xerostomia and sialadenitis. Patients with xerostomia had 46 mCi higher mean cumulative 131I activity and 21 mCi higher

mean first-administered 131I activity than patients without xerostomia. Increased age associated with higher incidence of xerostomia, and females had a higher incidence of sialadenitis. Patients who experienced sialadenitis before 131I therapy had higher sialadenitis incidence after 131I therapy. 131I-treated patients diagnosed with AID-SS, whether before or after 131I treatment, had a higher incidence of xerostomia and sialadenitis among 131I-treated patients. CONCLUSION: Risk factors for 131I-induced salivary gland damage include administered 131I activity, age, gender, history of sialadenitis before 131I treatment, and AID-SS diagnosis.
PubMed-ID: 27533304
http://dx.doi.org/10.1210/jc.2016-1605

IRAK1, a Target of miR-146b, Reduces Cell Aggressiveness of Human Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 101(11):4357-66.
C. K. Chou, S. Y. Chi, C. H. Huang, F. F. Chou, C. C. Huang, R. T. Liu and H. Y. Kang. 2016.
CONTEXT: MicroRNA (miR)-146b is overexpressed in papillary thyroid carcinoma (PTC) and is associated with extrathyroidal invasion, advanced tumor stage, and poor prognosis. However, the underlying mechanism of miR-146b in relation to its oncogenic behavior in PTC and its putative targets remain unknown. OBJECTIVE: The purpose was to investigate IL-1 receptor-associated kinase 1 (IRAK1) as the potential miR-146b target gene and its involvement in PTC. DESIGN: We used genome-wide microarray, computational analysis, and 3' UTR reporter gene assays to identify IRAK1 as a miR-146b target gene. In vitro gain/loss-of-function experiments were further performed to determine the effects of IRAK1 on proliferation, colony formation, and wound-healing in PTC cancer cell lines. Expression levels of miR-146b and IRAK1 of 50 cases of PTC and its adjacent normal thyroid specimens were assessed via qRT-PCR. RESULTS: Microarray expression profile revealed that the mRNA level of IRAK1 gene was down-regulated by miR-146b. The 3' UTR of IRAK1 mRNA was found to be a molecular target of miR-146b posttranscriptional repression in BCPAP cells by reporter gene assays. MiR-146b promoted the migration and proliferation of PTC cells by down-regulating IRAK1 expression, whereas restoration of IRAK1 expression reversed this effect. In addition, the expression of IRAK1 mRNA was significantly lower in PTC clinical tissue samples than normal adjacent thyroid specimens and showed a strong inverse correlation with the expression of miR-146b in PTC specimens. CONCLUSION: Our results demonstrated that IRAK1 is a direct target of miR-146b and has functional roles to inhibit various aggressive PTC cell activities. In conjunction with current therapeutic regimens, targeting the miR-146b-IRAK1 axis may provide a potential approach for PTC management.
PubMed-ID: 27533309
http://dx.doi.org/10.1210/jc.2016-2276

Incidence, Risk Factors, and Clinical Outcomes of Incidental Parathyroidectomy During Thyroid Surgery.
Ann Surg Oncol, 23(13):4310-5.
M. K. Applewhite, M. G. White, M. Xiong, J. D. Pasternak, L. Abdulrasool, L. Ogawa, I. Suh, J. E. Gosnell, E. L. Kaplan, Q. Y. Duh, P. Angelos, W. T. Shen and R. H. Grogan. 2016.
BACKGROUND: The reported rate of incidental parathyroidectomy (IP) during thyroid surgery is between 5.2 and 21.6 %. Current literature reports wide discrepancy in incidence, risk factors, and outcomes. Thus study was designed to address definitively the topic of IP and identify associated risk factors and clinical outcomes with this multi-institutional study. METHODS: This retrospective cohort study included 1767 total thyroidectomies that occurred between 1995 and 2014 at two academic centers. Pathologic reports were reviewed for the presence of unintentionally removed parathyroid glands. Demographics, potential risk factors, and postoperative calcium levels were compared with matched control group. Logistic regression, t tests, and Chi squared tests were used when appropriate. RESULTS: IP occurred in 286 (16.2 %) of thyroidectomies. Risk factors for IP were: malignancy, neck dissection, and lymph node metastases ($p = 0.005$, <0.001, and <0.001). Fifty-three (19.2 %) of IPs were intrathyroidal. Those with IP were more likely to have postoperative biochemical (65.6 vs. 42.0 %; $p < 0.001$) and symptomatic (13.4 vs. 8.1 %; $p = 0.044$) hypocalcemia than controls. The number of parathyroids identified intraoperatively was inversely correlated with the number of parathyroid glands in the specimen ($p < 0.001$). CONCLUSIONS: Our findings indicate that malignancy, lymph node dissection, and metastatic nodal disease are risk factors for IP. Patients with IP were more likely to have postoperative biochemical and symptomatic hypocalcemia than controls, showing that there is a physiologic consequence to IP. Additionally, intraoperative surgeon identification of parathyroid glands results in a lower incidence of IP, highlighting the importance of awareness of parathyroid anatomy during thyroid surgery.
PubMed-ID: 27541813
http://dx.doi.org/10.1245/s10434-016-5439-1

The Learning Curve of Transareola Single-site Laparoendoscopic Thyroidectomy: CUSUM Analysis of a Single Surgeon's Experience.
Surg Laparosc Endosc Percutan Tech, 26(5):364-7.
G. Zhu, X. Zhang, Z. Tang, Z. Tan, J. Chen and Y. Shan. 2016.
BACKGROUND: Transareola single-site laparoendoscopic thyroidectomy (TASSET) is a rapidly advancing minimally invasive procedure. The purpose of this study was to evaluate the learning curve for TASSET. SUBJECTS AND METHODS: Forty-five consecutive patients were prospectively divided into group 1 (initial phase), group 2 (intermediate phase), and group 3 (advanced phase) according to their surgical order (15 patients in each group). The operative time, operative blood loss, duration of hospital stay, postoperative pain, and postoperative complications were compared using phases. RESULTS: Statistically significant differences were observed in the different learning phases, among operative time ($P<0.05$), operative blood loss ($P<0.05$), hospital stay ($P<0.05$), and postoperative pain ($P<0.05$). The postoperative complication rate was low (3/45). CONCLUSIONS: Learning curve of the TASSET are improved synchronized at different phases and technical indicators. The establishment of operative space take longer time to skilled master.
PubMed-ID: 27552376
http://dx.doi.org/10.1097/SLE.0000000000000309

The impact of family history on non-medullary thyroid cancer.
Eur J Surg Oncol, 42(10):1455-63.
I. J. Nixon, C. Suarez, R. Simo, A. Sanabria, P. Angelos, A. Rinaldo, J. P. Rodrigo, L. P. Kowalski, D. M. Hartl, M. L. Hinni, J. P. Shah and A. Ferlito. 2016.
INTRODUCTION: Around 10% of patients with non-medullary thyroid cancer (NMTC) will have a positive family history for the disease. Although many will be sporadic, families where 3 first-degree relatives are affected can be considered to represent true familial non-medullary thyroid cancer (FNMTC). The genetic basis, impact on clinical and pathological features, and overall effect on prognosis are poorly understood. METHODS: A literature review identified articles which report on genetic, clinical, therapeutic and screening aspects of FNMTC. The results are presented to allow an understanding of the genetic basis and the impact on clinical-pathological features and prognosis in order to inform clinical decision making. RESULTS: The genetic basis of FNMTC is unknown. Despite this, significant progress has been made in identifying potential susceptibility genes. The lack of a test for FNMTC has led to a clinical definition requiring a minimum of 3 first-degree relatives to be diagnosed with NMTC. Although some have shown an association with multi-centric disease, younger age and increased rates of extra-thyroidal extension and nodal metastases, these findings are not supported by all. The impact of FNMTC is unclear with all groups reporting good outcome, and some finding an association with more aggressive disease. The role of screening remains controversial. CONCLUSION: FNMTC is rare but can be diagnosed clinically. Its impact on prognostic factors and the subsequent role in influencing management is debated. For those patients who present with otherwise low-risk differentiated thyroid cancer, FNMTC should be included in risk assessment when discussing therapeutic options.
PubMed-ID: 27561845
http://dx.doi.org/10.1016/j.ejso.2016.08.006

Robot-assisted transaxillary thyroid surgery-retrospective analysis of anthropometric features.
Langenbecks Arch Surg, 401(7):975-81.
D. D. Axente and N. A. Constantea. 2016.
PURPOSE: The vast majority of studies published on robot-assisted thyroid surgery are South Korean. This study aims to assess the impact of certain anthropometric parameters on performing robot-assisted thyroid surgery on Caucasian patients. MATERIALS AND METHODS: A total of 91 patients underwent robot-assisted surgery by the axillary approach in the Fifth Surgical Clinic, City Hospital Cluj-Napoca, between 2010 and 2015. Besides the specific clinical and pathological parameters, a series of anthropometric parameters and the postoperative occurrence of skin disorders in the cervical or subclavicular region were determined for each patient. RESULTS: There was an increase in dissection time and console time, which was directly proportional to the patients' body mass index. There were no statistically significant differences in the incidence of postoperative complications in patients with different body mass indices. The postoperative drainage volume was significantly higher in overweight or obese patients. The time needed to visualize the thyroid lodge was longer in patients with wider shoulders, and there was a negative correlation between neck length and console time. A statistically significant direct correlation was found between the clavicle length-neck length ratio and the duration of the entire intervention. There was no significant influence of any of these parameters on the duration of hospitalization or the occurrence of other postoperative complications. CONCLUSIONS: The nutritional status of the patients and the other anthropometric parameters influenced the duration and difficulty of the intervention, without affecting its safety in terms of intra- and postoperative- complications.

PubMed-ID: 27566161
http://dx.doi.org/10.1007/s00423-016-1505-1

Papillary Thyroid Carcinoma With Rare Exon 15 BRAF Mutation Has Indolent Behavior: A Single-Institution Experience.
J Clin Endocrinol Metab, 101(11):4413-20.
L. Torregrossa, D. Viola, E. Sensi, M. Giordano, P. Piaggi, C. Romei, G. Materazzi, P. Miccoli, R. Elisei and F. Basolo. 2016.
CONTEXT: Approximately 40% of papillary thyroid carcinomas (PTCs) harbor the BRAF V600E mutation, which is significantly associated with the advanced clinicopathological features of PTC at diagnosis, a higher recurrence rate, and disease-related mortality. BRAF alterations other than V600E are less common in PTC, and their clinical significance remains to be established. OBJECTIVE: The aim of the study was to describe a large cohort of rare exon 15 BRAF alterations (r-BRAF) and the clinicopathological features of PTC harboring these alterations and to clarify their clinical significance. METHODS: A total of 2961 PTCs were collected from 2006 to 2013 and screened for exon 15 BRAF alterations. RESULTS: Exon 15 BRAF alterations were found in 1186 of 2961 PTC cases (40.0%). In particular, we found the BRAF V600E mutation in 95.3% (1131 of 1186) and r-BRAF in 4.7% (55 of 1186) of the cases. r-BRAF were found in 18 microcarcinomas, 33 follicular variants, one classic variant, and one trabecular/solid variant. The most frequent r-BRAF was BRAF K601E (35 of 55; 63.6%), followed by BRAF V600_K601delinsE (seven of 55; 12.7%) and BRAF T599I-V600_R603del (two of 55; 3.6%). The remaining 11 alterations were found in one case only. The large majority of these tumors were unifocal (34 of 55; 61.8%), completely encapsulated (46 of 55; 83.6%), and intrathyroidal (53 of 55; 96.4%) with a low prevalence of lymph node metastases (one of 55; 1.8%) and a less advanced tumor stage at diagnosis (American Joint Commission on Cancer stage I/II, 51 of 55; 92.7%). CONCLUSIONS: r-BRAF are very uncommon in PTC and are found almost exclusively in PTC with low-risk clinicopathological features.
PubMed-ID: 27571181
http://dx.doi.org/10.1210/jc.2016-1775

Detection and Prognostic Significance of Circulating Tumor Cells in Patients With Metastatic Thyroid Cancer.
J Clin Endocrinol Metab, 101(11):4461-7.
J. Y. Xu, B. Handy, C. L. Michaelis, S. G. Waguespack, M. I. Hu, N. Busaidy, C. Jimenez, M. E. Cabanillas, H. A. Fritsche, Jr., G. J. Cote and S. I. Sherman. 2016.
CONTEXT: Individual patient prognostication for advanced thyroid cancer (TC) is challenging. Circulating tumor cells (CTCs) have been shown to be a valuable prognostic marker for other solid cancers. OBJECTIVE: We hypothesized that CTCs are present in the blood of patients with advanced TC and their number can predict overall survival (OS). SETTING: This is a prospective study at a tertiary cancer hospital. Patients, Interventions, and Main Outcome Measures: Initial studies were performed with TC cell lines to determine the feasibility of detection using the Veridex CellSearch. CTC enumeration was performed in blood samples from 18 patients with distantly metastatic medullary TC (metMTC), 14 with distantly metastatic differentiated TC (metDTC), and 10 controls with a history of TC but no evidence of disease. The prognostic value of CTC levels to predict OS in metMTC patients was assessed. RESULTS: CellSearch detected cells from MTC and DTC but not anaplastic TC cell lines. Six metMTC patients but no metDTC or control patients had more than or equal to 5 CTCs detected by the CellSearch assay. Median survival in metMTC patients with more than or equal to 5 CTCs was 13 months vs 51.5 months for those with less than 5 CTCs (P = .0116). The hazard ratio for mortality of patients with more than or equal to 5 CTCs compared with those with less than 5 CTCs was 3.95 (1.20-13.0, P = .0245). CONCLUSIONS: The presence of more than or equal to 5 CTCs in patients with metMTC is associated with worse OS. Larger cohorts are required to validate the prognostic value of CTC enumeration.
PubMed-ID: 27575943
http://dx.doi.org/10.1210/jc.2016-2567

Application of molecular biology of differentiated thyroid cancer for clinical prognostication.
Endocr Relat Cancer, 23(11):R499-R515.
V. Marotta, C. Sciammarella, A. Colao and A. Faggiano. 2016.
Although cancer outcome results from the interplay between genetics and environment, researchers are making a great effort for applying molecular biology in the prognostication of differentiated thyroid cancer (DTC). Nevertheless, role of molecular characterisation in the prognostic setting of DTC is still nebulous. Among the most common and well-characterised genetic alterations related to DTC, including mutations of BRAF and RAS and RET rearrangements, BRAFV600E is the only mutation showing unequivocal association with clinical outcome. Unfortunately, its accuracy is strongly limited by low specificity. Recently, the introduction of next-

generation sequencing techniques led to the identification of TERT promoter and TP53 mutations in DTC. These genetic abnormalities may identify a small subgroup of tumours with highly aggressive behaviour, thus improving specificity of molecular prognostication. Although knowledge of prognostic significance of TP53 mutations is still anecdotal, mutations of the TERT promoter have showed clear association with clinical outcome. Nevertheless, this genetic marker needs to be analysed according to a multigenetic model, as its prognostic effect becomes negligible when present in isolation. Given that any genetic alteration has demonstrated, taken alone, enough specificity, the co-occurrence of driving mutations is emerging as an independent genetic signature of aggressiveness, with possible future application in clinical practice. DTC prognostication may be empowered in the near future by non-tissue molecular prognosticators, including circulating BRAFV600E and miRNAs. Although promising, use of these markers needs to be refined by the technical sight, and the actual prognostic value is still yet to be validated.
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http://dx.doi.org/10.1530/ERC-16-0372

Investigation of brain GABA+ in primary hypothyroidism using edited proton MR spectroscopy.
Clin Endocrinol (Oxf), 86(2):256-62.
B. Liu, H. Yang, F. Gao, Q. Wang, B. Zhao, T. Gong, Z. Wang, W. Chen, G. Wang and R. A. Edden. 2017.
OBJECTIVE: Evidence indicates that thyroid hormones have effects on the inhibitory GABAergic system. The aim of this study was to investigate whether brain GABA levels are altered in patients with hypothyroidism compared with healthy controls. DESIGN/METHODS: Fifteen patients with primary hypothyroidism and 15 matched healthy controls underwent single-voxel MEGA-PRESS magnetic resonance spectroscopy at 3T, to quantify GABA levels in the median prefrontal cortex (mPFC) and posterior cingulate cortex (PCC). All participants underwent thyroid function test. Neuropsychological performances were evaluated by administration of the Montreal Cognitive Assessment (MoCA) and the 21-item Beck Depression Inventory-II (BDI-II). RESULTS: The patients with hypothyroidism had significantly lower GABA+ levels in the mPFC compared with healthy controls (P = 0.016), whereas no significant difference (P = 0.214) was observed in the PCC. Exploratory analyses revealed that mPFC GABA+ levels were negatively correlated with the BDI-II scores in patient group (r = -0.60, P = 0.018). No correlations were found between GABA+ levels and TSH or fT3 or fT4 levels in either region (all P > 0.05). CONCLUSION: This study suggests that alteration of GABAergic neurotransmission may play an important role in the pathophysiology of primary hypothyroidism, providing intriguing neurochemical clues to understand thyroid-brain interactions.
PubMed-ID: 27581339
http://dx.doi.org/10.1111/cen.13177

Is TSH necessary for initial assessment of thyroid nodules?
Clin Endocrinol (Oxf), 86(2):263-9.
H. Cai, Y. Qiao, H. Xi, Q. Luo, X. Yuan, Y. Yang and Z. Lv. 2017.
OBJECTIVE: The use of thyrotropin (TSH) in the initial assessment of thyroid nodules is inefficient and leads to unnecessary assessment costs. We compared the total costs of thyroid nodule assessment with or without the use of TSH in the initial assessment. METHODS: A total of 1808 patients with thyroid nodules received TSH, fine-needle aspiration (FNA) and thyroid scintigraphy (TS) assessment, including 83 autonomously functioning thyroid nodule (AFTN) cases and 1725 non-AFTN cases. The total costs of the TSH strategy and non-TSH strategies were compared. The ratio of single-use costs of FNA to TS (CFNA/TS) was used as the main outcome measure. RESULTS: Only when 6.03 </= CFNA/TS </= 27.17, the lowest total costs were associated with using the conventional TSH strategy. When CFNA/TS <6.03 or CFNA/TS >27.17, the lowest costs were found with FNA and TS, respectively. CONCLUSION: From the perspective of cost economics, in iodine-sufficient areas, we recommend that the decision on the use of TSH for the initial assessment of thyroid nodules should be based on the testing costs of FNA and TS in that medical unit.
PubMed-ID: 27581500
http://dx.doi.org/10.1111/cen.13178

Additional value of a high sensitive thyroglobulin assay in the follow-up of patients with differentiated thyroid carcinoma.
Clin Endocrinol (Oxf), 86(3):419-24.
A. H. Groen, M. S. Klein Hesselink, J. T. Plukker, W. J. Sluiter, A. N. van der Horst-Schrivers, A. H. Brouwers, E. G. Lentjes, A. C. Muller Kobold and T. P. Links. 2017.
OBJECTIVE: Thyroglobulin (Tg) is an excellent tumour marker, as detectable or increasing Tg levels are highly indicative of persistent or recurrent differentiated thyroid carcinoma (DTC). The clinical value of a highly sensitive (hs)-Tg assay in patients with DTC has not yet been established. The aim of this study was to investigate the

additional value of unstimulated hs-Tg measurements (Tg-on) compared to stimulated IRMA-Tg measurements (Tg-off) in the follow-up of patients with DTC. DESIGN, PATIENTS, MEASUREMENTS: We retrospectively studied patients treated for DTC between 2006 and 2013 and compared hs-Tg and IRMA-Tg measurements. The study group consisted of 99 DTC patients in remission; Tg-on was measured 3 months after remnant ablation and Tg-off 6 months after ablation. RESULTS: In the study group, 44 patients showed a hs-Tg-on <0.15 mug/l (functional sensitivity); of these, 43 had an IRMA-Tg-off measurement <1.0 mug/l, resulting in a negative predictive value of 97.7% and a positive predictive value of 56.4%. CONCLUSIONS: The hs-Tg-on measurement is able to predict patients with an IRMA-Tg-off <1.0 mug/l, and therefore decreases the need for Tg stimulation after ablation.
PubMed-ID: 27588675
http://dx.doi.org/10.1111/cen.13180

Total thyroidectomy versus lobectomy in conventional papillary thyroid microcarcinoma: Analysis of 8,676 patients at a single institution.
Surgery, 161(2):485-92.
S. K. Kim, I. Park, J. W. Woo, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2017.
BACKGROUND: Because there is a controversy regarding the management of papillary thyroid microcarcinoma, the purpose of this study was to compare lobectomy with total thyroidectomy as a primary operative treatment for papillary thyroid microcarcinoma. Loco-regional recurrence in the contralateral remnant lobe can be managed safely by completion thyroidectomy via the previous scar. However, reoperation for operation bed (thyroidectomy site) or regional lymph node (central or lateral) recurrence generally is associated with morbidity. Therefore, we analyzed overall loco-regional recurrence and loco-regional recurrence outside of the contralateral remnant lobe separately. METHODS: We retrospectively reviewed 8,676 conventional patients with papillary thyroid microcarcinoma who underwent thyroidectomy. RESULTS: Lobectomy was performed in 3,289 (37.9%) patients, and total thyroidectomy was performed in 5,387 (62.1%) patients. Total thyroidectomy significantly decreased the risk of overall loco-regional recurrence (adjusted hazard ratio 0.398, P < .001). However, total thyroidectomy did not significantly decrease the risk of loco-regional recurrence outside of the contralateral remnant lobe (adjusted hazard ratio 0.880, P = .640). Particularly in conventional papillary thyroid microcarcinoma patients with multifocality, total thyroidectomy significantly decreased the risk of overall loco-regional recurrence (adjusted hazard ratio 0.284, P = .002) and loco-regional recurrence outside of the contralateral remnant lobe (adjusted hazard ratio 0.342, P = .020). CONCLUSION: Although lobectomy is associated with contralateral remnant lobe recurrence, lobectomy did not increase the risk of loco-regional recurrence outside of the contralateral remnant lobe in patients with papillary thyroid microcarcinoma, except in those with multifocality. Because recurrence in the contralateral remnant lobe can be managed safely by completion thyroidectomy, lobectomy may be a safe operative option for select patients with papillary thyroid microcarcinoma without multifocality.
PubMed-ID: 27593085
http://dx.doi.org/10.1016/j.surg.2016.07.037

Multifocality in Sporadic Medullary Thyroid Carcinoma: An International Multicenter Study.
Thyroid, 26(11):1563-72.
G. F. Essig, Jr., K. Porter, D. Schneider, D. Arpaia, S. C. Lindsey, G. Busonero, D. Fineberg, B. Fruci, K. Boelaert, J. W. Smit, J. A. Meijer, L. H. Duntas, N. Sharma, G. Costante, S. Filetti, R. S. Sippel, B. Biondi, D. J. Topliss, F. Pacini, R. M. Maciel, P. C. Walz and R. T. Kloos. 2016.
BACKGROUND: Current surgical standard of care in sporadic medullary thyroid carcinoma (sMTC) consists of a minimum of total thyroidectomy with central neck dissection. Some have suggested thyroid lobectomy with isthmusectomy and central neck dissection for patients with sMTC, given their lower frequency of bilateral disease, although this topic has not been thoroughly studied. This study assessed the prevalence of multifocality in sMTC via a large international multi-institutional retrospective review to quantify this prevalence, including the impact of geography, to assess more accurately the risks associated with alternative surgical approaches. METHODS: A retrospective chart review of sMTC patients from 11 institutions over 29 years (1983-2011) was undertaken. Data regarding focality, extent of disease, RET germline analysis plus family and clinical history for multiple endocrine neoplasia type 2 (MEN2), and demographic data were collected and analyzed. RESULTS: Patients from four continents and seven countries were included in the sample. Data for 313 patients with documented sMTC were collected. Of these, 81.2% were confirmed with negative RET germline testing, while the remaining 18.8% demonstrated a negative family history and no manifestations of MEN2 syndromes other than MTC. Bilateral disease was identified in 17/306 (5.6%) patients, while multifocal disease was noted in 50/312 (16.0%) sMTC patients. When only accounting for germline negative patients, these rates were not significantly different (5.6% and 17%, respectively). Among them, when disease was unifocal in the ipsilateral

lobe and isthmus, bilateral disease was present in 6/212 (2.8%) cases. When disease was multifocal in the ipsilateral lobe or isthmus, then bilateral disease was present in 8/37 (21.6%) cases ($p < 0.001$). No geographic differences in focality were identified. CONCLUSIONS: The 5.6% prevalence of bilateral foci in sMTC suggests that total thyroidectomy should remain the standard of care for initial surgery, as less complete thyroid surgery may fail to address fully the primary site of disease. Whether ipsilateral tumor focality should be an independent factor determining the need for completion thyroidectomy when sMTC is diagnosed after hemithyroidectomy remains to be determined.
PubMed-ID: 27604949
http://dx.doi.org/10.1089/thy.2016.0255

Computed Tomography-Detected Central Lymph Node Metastasis in Ultrasonography Node-Negative Papillary Thyroid Carcinoma: Is It Really Significant?
Ann Surg Oncol, 24(2):442-9.
S. K. Kim, J. W. Woo, I. Park, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2017.
BACKGROUND: Because of the limitations in ultrasonography (US), the advantages of computed tomography (CT) for detecting central lymph node (LN) metastasis have been suggested in papillary thyroid carcinoma (PTC). METHODS: First, we compared the diagnostic accuracy of US and CT for detecting central LN metastasis in 6577 central neck levels from 3668 PTC patients. Second, to examine the clinical impact of CT-detected central LN metastasis (CT cN1a) in PTC patients with clinically node negative in US (US cN0), we selected two groups: group I comprised 1245 US cN0 PTC patients who did not have CT scans and did not undergo central neck dissection (CND), while group II comprised 348 US cN0 and CT cN1a PTC patients who underwent CND. After propensity score matching, 254 matched pairs were yielded. RESULTS: For detecting central LN metastasis, CT showed significantly higher sensitivity (38.9 vs. 27.5 %; $p < 0.001$) and accuracy (66.1 vs. 63.2 %; $p < 0.001$) than US. Furthermore, US + CT showed significantly higher sensitivity (47.8 vs. 27.5 %; $p < 0.001$) and accuracy (69.0 vs. 63.2 %; $p < 0.001$) than US. After matching, radioactive iodine ablation (81.5 vs. 85.8 %; $p = 0.235$) and locoregional recurrence ($p = 0.663$) were not significantly different between groups I and II. CONCLUSIONS: Despite the diagnostic advantages of preoperative CT, 'CT-based CND' in US cN0 PTC patients did not significantly influence postoperative management and locoregional recurrence. The strategy for the management of central neck in PTC patients can be sufficiently determined by US only.
PubMed-ID: 27624581
http://dx.doi.org/10.1245/s10434-016-5552-1

WOMEN IN CANCER THEMATIC REVIEW: Thyroid-stimulating hormone in thyroid cancer: does it matter?
Endocr Relat Cancer, 23(11):T109-T21.
H. Nieto and K. Boelaert. 2016.
Differentiated thyroid cancer is the most common endocrine malignancy and the incidence is increasing rapidly worldwide. Appropriate diagnosis and post-treatment monitoring of patients with thyroid tumours are critical. Fine needle aspiration cytology remains the gold standard for diagnosing thyroid cancer, and although there have been significant refinements to this technique, diagnostic surgery is often required for patients suspected to have malignancy. Serum thyroid-stimulating hormone (TSH) is higher in patients with malignant thyroid nodules than in those with benign disease, and TSH is proportionally increased in more aggressive tumours. Importantly, we have shown that the pre-operative serum TSH concentration independently predicts the presence of malignancy in subjects presenting with thyroid nodules. Establishing the use of TSH measurements in algorithms identifying high-risk thyroid nodules in routine clinical practice represents an exciting, cost-efficient and non-invasive approach to optimise thyroid cancer diagnosis. Binding of TSH to receptors on thyrocytes stimulates a number of growth promoting pathways both in normal and malignant thyroid cells, and TSH suppression with high doses of levothyroxine is routinely used after thyroidectomy to prevent cancer recurrence, especially in high-risk tumours. This review examines the relationship between serum TSH and thyroid cancer and reflects on the clinical potential of TSH measurements in diagnosis and disease monitoring.
PubMed-ID: 27633516
http://dx.doi.org/10.1530/ERC-16-0328

Riedel's thyroiditis association with IgG4-related disease.
Clin Endocrinol (Oxf), 86(3):425-30.
M. N. Stan, V. Sonawane, T. J. Sebo, P. Thapa and R. S. Bahn. 2017.
CONTEXT: IgG4-positive (+) plasma cells have been reported in both Riedel's thyroiditis (RT) and Hashimoto's thyroiditis (HT). These cells are the hallmark of IgG4-related disease (IgG4-RD). OBJECTIVE: We sought to determine whether RT is part of IgG4-RD spectrum. DESIGN, SETTING AND PATIENTS: This was a case-

control study performed at a tertiary medical centre. We included RT cases from the period 1958 to 2008 that had sufficient paraffin-embedded tissue for IgG4 immunostaining. Controls were patients with HT, age and gender matched, with similar pathology criteria. MAIN OUTCOME MEASURE: The main outcome measures were the intensity of the IgG4 staining and the clinical and histological correlates with IgG4-RD. RESULTS: Six pairs of RT and HT were analysed. The mean age was 44.7 years. In both groups, 5/6 cases had positive IgG4 staining. The mean number of IgG4 + cells/ HPF, normalized to the degree of inflammation, was 3.2 +/- 3.0 SD (RT) vs 0.9 +/- 0.7 (HT), P = 0.15, for fibrotic areas and 2.1 +/- 2.3 SD vs 1.0 +/- 0.8 (P = 0.39) for areas with lymphoid aggregates. We found the number of IgG4 + cells in RT to be inversely correlated with the duration of disease (P = 0.046). Three RT cases had associated comorbidities from the IgG4-RD spectrum while none of the HT cases had such conditions. CONCLUSIONS: Riedel's thyroiditis is a component of IgG4-RD with the density of the IgG4 + lymphocytic infiltrate being time dependent. In this small study, we did not identify differences in IgG4 infiltration between RT and HT, minimizing the utility of this marker in RT diagnosis.
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http://dx.doi.org/10.1111/cen.13238

Total thyroidectomy: a clue to understanding the metabolic changes induced by subclinical hyperthyroidism?
Clin Endocrinol (Oxf), 86(2):270-7.
P. Bel Lassen, A. Kyrilli, M. Lytrivi, M. Ruiz Patino and B. Corvilain. 2017.
OBJECTIVE: The effects of endogenous subclinical hyperthyroidism (eSCH) on heart and bone have been well documented. There are only limited data available regarding the impact of eSCH on weight regulation and lipid metabolism. Our aim was to evaluate the changes in body weight and metabolic parameters after total thyroidectomy in patients with pre-operative eSCH compared with pre-operative patients with euthyroid (EUT). DESIGN: A retrospective study of 505 patients who underwent total thyroidectomy for benign multinodular goitre in an academic hospital in Brussels (Belgium) was performed. PATIENT'S MEASUREMENTS: Two hundred and 25 patients were included (eSCH group: n = 74; EUT group: n = 151). The mean follow-up time was 26.1 +/- 0.8 months and was similar in both groups. RESULTS: Absolute BMI gain was significantly greater in the eSCH group than in the EUT group (1.11 +/- 0.17 vs 0.33 +/- 0.13 kg/m2 ; P = 0.003). A significant increase in LDL cholesterol was observed in the eSCH group (16.1 +/- 3.8 mg/dl; P < 0.001) but not in the EUT group (0.0 +/- 3.0 mg/dl; P = 0.88). In a multivariate model, pre-operative TSH levels were the main factor significantly associated with increases in BMI or LDL cholesterol. Post-operative median TSH levels and L-thyroxine substitution were similar in both groups. CONCLUSION: After total thyroidectomy, increases in weight and serum cholesterol were observed in the eSCH group. Given that post-operative TSH levels were similar in the two groups, these observations are probably due to the correction of eSCH, suggesting a direct effect of eSCH on body weight regulation and lipid metabolism.
PubMed-ID: 27651121
http://dx.doi.org/10.1111/cen.13237

Extent of Extrathyroidal Extension as a Significant Predictor of Nodal Metastasis and Extranodal Extension in Patients with Papillary Thyroid Carcinoma.
Ann Surg Oncol, 24(2):460-8.
J. W. Kim, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim. 2017.
BACKGROUND: Extrathyroidal extension (ETE) and extranodal extension (ENE) indicate poor prognosis for patients with papillary thyroid carcinoma (PTC). The relationships among ETE, ENE, and nodal metastasis (N1) have not been thoroughly studied. In this study, we examined the relationships among the extent of ETE, N1, ENE, and posttreatment recurrence in patients with PTC. METHODS: This study enrolled 1693 consecutive patients with previously untreated PTC who underwent thyroidectomy between 2006 and 2009. The extent of ETE was graded based on intraoperative and pathological findings, and central and lateral neck (N1b) nodal metastases and ENE were pathologically determined. Univariate and multivariate analyses were used to identify the association of clinicopathological factors with recurrence-free survival (RFS) and to define the relationships among the extent of ETE, N1, and ENE. RESULTS: Of 1693 patients, 1087 (64.2 %) had ETE and 201 (11.9 %) had ENE. Pathologically positive lymph nodes were found in 783 patients (46.2 %), of whom 236 (30.1 %) had N1b. During the median follow-up of 86 months, 90 (5.3 %) patients had recurrences. Multivariate analyses showed that multifocality, ETE, T and N classification, the risk of structural recurrence proposed by the American Thyroid Association, and ENE were independent variables for RFS (P < .05). Patients with macroscopic ETE had a 13-fold increased risk of recurrence, and ETE had significant relationships with N1, N1b, and ENE (all P < .001). CONCLUSIONS: Local extension, nodal involvement, and ENE contribute to posttreatment recurrence of PTC. Macroscopic ETE predicts nodal metastasis and ENE, which are adverse pathologic features.

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http://dx.doi.org/10.1245/s10434-016-5594-4

Shear-Wave Elastography for Papillary Thyroid Carcinoma can Improve Prediction of Cervical Lymph Node Metastasis.
Ann Surg Oncol, 23(Suppl 5):722-9.
A. Y. Park, J. A. Kim, E. J. Son and J. H. Youk. 2016.
BACKGROUND: This study aimed to investigate whether the elasticity index of shear-wave elastography (SWE) can predict cervical lymph node (LN) metastasis of papillary thyroid carcinoma (PTC). METHODS: This retrospective study included 363 patients with a surgical diagnosis of PTC who underwent preoperative SWE evaluation. The elasticity indices of PTC (E mean, E max, E min, E ratio-p, and E ratio-m) and gray-scale ultrasound (US) parameters (extrathyroidal extension, multifocality, and cervical LN metastasis) were correlated with the pathologic staging parameters. The optimal cutoff values for the elasticity indices were determined for the prediction of cervical LN metastasis, and diagnostic performance was compared between gray-scale US and the combined application of gray-scale US and SWE. RESULTS: The findings showed E mean and E max to be associated with central LN metastasis (P = 0.037) and E min to be associated with lateral LN metastasis (P = 0.015). An E mean value higher than 124 kPa or an E max value higher than 138 kPa with suspicious gray-scale US findings improved the sensitivity and area under the curve (AUC) for predicting central LN metastasis (sensitivity, 45.4 and 44.6 % vs. 28 %, P < 0.001; AUC, 0.659 and 0.667 vs. 0.615, P = 0.011 and 0.019), whereas an E min value higher than 63 kPa with suspicious gray-scale US findings improved the sensitivity and AUC for predicting lateral LN metastasis (sensitivity, 95.8 vs. 75 %, P = 0.025; AUC, 0.924 vs. 0.871, P = 0.047). CONCLUSION: The quantitative elasticity index of PTC on preoperative SWE could be useful for predicting cervical LN metastasis.
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http://dx.doi.org/10.1245/s10434-016-5572-x

Routine Level 2b Dissection may be Recommended Only in N1b Papillary Thyroid Carcinoma with Three- or Four-Level Lateral Lymph Node Metastasis.
Ann Surg Oncol, 23(Suppl 5):694-700.
S. K. Kim, I. Park, N. Hur, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
BACKGROUND: Due to the low incidence of level 2b metastasis and the risk of spinal accessory nerve injury, previous studies have argued against routine level 2b dissection for N1b papillary thyroid carcinoma (PTC). However, other studies have suggested the importance of including level 2b during lateral neck dissection. Therefore, this study aimed to determine the necessity of routine level 2b dissection. METHODS: The study retrospectively reviewed 327 N1b PTC patients who underwent unilateral modified radical neck dissection between January 1997 and May 2016. RESULTS: The incidence of level 2b metastasis was 10.4 %, compared with 53.5 % for level 2a metastasis. The univariate analysis showed that large tumor size (p = 0.027) and simultaneous lateral lymph node metastasis (LLNM) (p = 0.002) were significantly associated with level 2b metastasis. The multivariate analysis showed that three-level (adjusted odds ratio [OR] 6.032; p = 0.020) and four-level (adjusted OR 9.398; p = 0.012) simultaneous LLNM were independent predictors for level 2b metastasis. CONCLUSIONS: Due to the low incidence of level 2b metastasis, routine level 2b dissection may not be necessary for N1b PTC patients. Level 2b dissection may be reserved for patients with more than three-level simultaneous LLNM or clinical/radiological evidence of level 2b metastasis.
PubMed-ID: 27654111
http://dx.doi.org/10.1245/s10434-016-5521-8

Bone Metastases and Skeletal-Related Events in Medullary Thyroid Carcinoma.
J Clin Endocrinol Metab, 101(12):4871-7.
J. Y. Xu, W. A. Murphy, Jr., D. R. Milton, C. Jimenez, S. N. Rao, M. A. Habra, S. G. Waguespack, R. Dadu, R. F. Gagel, A. K. Ying, M. E. Cabanillas, S. P. Weitzman, N. L. Busaidy, R. V. Sellin, E. Grubbs, S. I. Sherman and M. I. Hu. 2016.
CONTEXT: Bone metastases (BM) can lead to devastating skeletal-related events (SREs) in cancer patients. Data regarding medullary thyroid carcinoma (MTC) with BM are lacking. OBJECTIVE: We evaluated the natural history of BM and SREs in MTC patients identified by a cancer center tumor registry. SETTING: The study was conducted at a tertiary cancer center. PATIENTS AND MAIN OUTCOME MEASURES: We retrospectively reviewed the charts of MTC patients with BM who received care from 1991 to 2014 to characterize BM and SREs. RESULTS: Of 1008 MTC patients treated, 188 were confirmed to have BM (19%), of whom 89% (168 of 188) had nonosseous distant metastases. Median time from MTC to BM diagnosis was 30.9 months (range 0-533 mo); 25% (45 of 180) had BM identified within 3 months of MTC diagnosis. Median follow-up after detecting

BM was 1.6 years (range 0-23.2 y). Most patients (77%) had six or more BM lesions, most often affecting the spine (92%) and pelvis (69%). Many patients (90 of 188, 48%) experienced one or more SREs, most commonly radiotherapy (67 of 90, 74%) followed by pathological fracture (21 of 90, 23%). Only three patients had spinal cord compression. Patients with more than 10 BM lesions were more likely to experience SREs (odds ratio 2.4; P = .007), with no difference in 5-year mortality after MTC diagnosis between patients with (31%) and without SREs (23%) (P = .11). CONCLUSIONS: In this large retrospective series, BM in MTC was multifocal, primarily involving the spine and pelvis, supporting screening these regions for metastases in at-risk patients. SREs were common but spinal cord compression was rare. Antiresorptive therapies in this population should be investigated further with prospective trials.
PubMed-ID: 27662441
http://dx.doi.org/10.1210/jc.2016-2815

Clinical, Sonographic, and Pathological Characteristics of RAS-Positive Versus BRAF-Positive Thyroid Carcinoma.
J Clin Endocrinol Metab, 101(12):4938-44.
S. Kakarmath, H. T. Heller, C. A. Alexander, E. S. Cibas, J. F. Krane, J. A. Barletta, N. I. Lindeman, M. C. Frates, C. B. Benson, A. A. Gawande, N. L. Cho, M. Nehs, F. D. Moore, E. Marqusee, M. I. Kim, P. R. Larsen, N. Kwong, T. E. Angell and E. K. Alexander. 2016.
CONTEXT: Mutations in the BRAF and RAS oncogenes are responsible for most well-differentiated thyroid cancer. Yet, our clinical understanding of how BRAF-positive and RAS-positive thyroid cancers differ is incomplete. OBJECTIVE: We correlated clinical, radiographic, and pathological findings from patients with thyroid cancer harboring a BRAF or RAS mutation. DESIGN: Prospective cohort study. SETTING: Academic, tertiary care hospital. PATIENTS: A total of 101 consecutive patients with well-differentiated thyroid cancer. MAIN OUTCOME MEASURE: We compared the clinical, sonographic, and pathological characteristics of patients with BRAF-positive cancer to those with RAS-positive cancer. RESULTS: Of 101 patients harboring these mutations, 71 were BRAF-positive, whereas 30 were RAS-positive. Upon sonographic evaluation, RAS-positive nodules were significantly larger (P = .04), although BRAF-positive nodules were more likely to harbor concerning sonographic characteristics (hypoechogenicity [P < .001]; irregular margins [P = .04]). Cytologically, 70% of BRAF-positive nodules were classified positive for PTC, whereas 87% of RAS-positive nodules were indeterminate (P < .001). Histologically, 96% of RAS-positive PTC malignancies were follicular variants of PTC, whereas 70% of BRAF-positive malignancies were classical variants of PTC. BRAF-positive malignancies were more likely to demonstrate extrathyroidal extension (P = .003), lymphovascular invasion (P = .02), and lymph node metastasis (P < .001). CONCLUSIONS: BRAF-positive malignant nodules most often demonstrate worrisome sonographic features and are frequently associated with positive or suspicious Bethesda cytology. In contrast, RAS-positive malignancy most often demonstrates indolent sonographic features and more commonly associates with lower risk, "indeterminate" cytology. Because BRAF and RAS mutations are the most common molecular perturbations associated with well-differentiated thyroid cancer, these findings may assist with improved preoperative risk assessment by suggesting the likely molecular profile of a thyroid cancer, even when postsurgical molecular analysis is unavailable.
PubMed-ID: 27689252
http://dx.doi.org/10.1210/jc.2016-2620

Comprehensive management of recurrent thyroid cancer: An American Head and Neck Society consensus statement: AHNS consensus statement.
Head Neck, 38(12):1862-9.
J. Scharpf, M. Tuttle, R. Wong, D. Ridge, R. Smith, D. Hartl, R. Levine and G. Randolph. 2016.
This American Head and Neck Society (AHNS) consensus statement focuses on the detection and management of recurrent thyroid cancer. This document describes the radiologic approach to defining structural recurrent disease and the operative and nonoperative rationale in addressing identified structural disease to create equipoise in the personalized treatment strategy for the patient. The recommendations of this AHNS multidisciplinary consensus panel of the American Head and Neck Society are intended to help guide all multidisciplinary clinicians who diagnose or manage adult patients with thyroid cancer. The consensus panel is comprised of members of the American Head and Neck Society and its Endocrine Surgical Committee, and there is representation from medical endocrinology and both national and international surgical representation drawn from general/endocrine surgery and otolaryngology/head and neck surgery. Authors provided expertise for their respective sections, and consensus recommendations were made regarding the evaluation and treatment of recurrent thyroid cancer. Evidence-based literature support is drawn from thyroid cancer studies, recurrent thyroid cancer studies, and American Thyroid Association (ATA) guidelines. The manuscript was then distributed to members of the American Head and Neck Society Endocrine Committee and governing counsel for

further feedback. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 1862-1869, 2016.
PubMed-ID: 27717219
http://dx.doi.org/10.1002/hed.24513

Cancer Registries: Can We Improve the Quality of Thyroid Cancer Data?
Ann Surg Oncol,
C. M. Kiernan, M. A. Whiteside and C. C. Solorzano. 2016.
BACKGROUND: Cancer registries are used to report cancer care trends and outcomes. Information from these data sets is utilized to craft practice guidelines and management recommendations. Limited knowledge is available regarding the quality of the data contained within registries. We sought to determine the accuracy of a single variable, 'surgery of the primary site', in the Tennessee Cancer Registry (TCR). METHODS: A retrospective review of the TCR thyroid database was performed. Hospital facilities were classified as either Commission on Cancer (CoC) or non-CoC accredited. Certified Tumor Registrars at the TCR reviewed the abstracted text and/or telephoned the reporting facility staff to confirm the definitive thyroid procedure. RESULTS: A total of 921 thyroid cancer cases, diagnosed/treated at TN facilities during 2004-2011, were coded with thyroid lobectomy (TL). Overall, 369 (40 %) were incorrectly coded, of which 247(67 %) were changed to total thyroidectomy. The majority of cases (80 %) were reported by CoC facilities. When compared by facility type, 42 % of records submitted from CoC facilities contained incorrect codes for the variable 'surgery of the primary site' TL compared with 34 % of records submitted by non-CoC facilities (p = 0.047). CONCLUSION: In this study of the TCR, 40 % of records contained inaccurate coding of the variable 'surgery of the primary site'. Upon validation, 27 % of all records were changed from TL to total thyroidectomy. The rate of incorrect coding was higher in CoC reporting facilities than in non-CoC facilities. Using text-to-code re-abstraction audits and facility contact these discrepancies can be validated and corrected to improve data quality.
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http://dx.doi.org/10.1245/s10434-016-5612-6

Optimal cut-off age in the TNM Staging system of differentiated thyroid cancer: is 55 years better than 45 years?
Clin Endocrinol (Oxf), 86(3):438-43.
M. Kim, Y. N. Kim, W. G. Kim, S. Park, H. Kwon, M. J. Jeon, H. S. Ahn, S. H. Jung, S. W. Kim, W. B. Kim, J. H. Chung, Y. K. Shong, T. H. Kim and T. Y. Kim. 2017.
OBJECTIVE: Age >45 years is included as a variable in the tumor, node, metastases (TNM) staging of differentiated thyroid cancer (DTC), but a higher cut-off value has been suggested to be more clinically relevant and prevent over-staging. We evaluated the optimal age cut-off to predict disease-specific survival (DSS) in patients with DTC. DESIGN AND PATIENTS: This cohort study included 6333 patients with DTC who underwent thyroid surgery at two tertiary referral centres between 1996 and 2005. The optimal age cut-off value between 45 and 65 years for prediction of DSS was assessed. The proportion of variation explained (PVE) and Harrell's c-index was calculated to compare the predictability of each model. RESULTS: The median age of patients was 46.0 years (IQR 37.8-54.6), and 5498 (87%) were female. Median follow-up period was 10.0 years, and 10-year DSS rate was 98%. Using TNM staging with 45 years as the cut-off (TNM45), 10-year DSS rates of stage I-IV were 99.4%, 96.1%, 97.7% and 85.9%, respectively (PVE = 3.0%, Harrell's c-index = 0.693); and using 55 years as the cut-off (TNM55), 99.4%, 92.2%, 95.3% and 79.7%, respectively (PVE = 4.3%, Harrell's c-index = 0.776). On receiver operating characteristic curve analysis, the optimal age cut-off for prediction of DSS was 55.4 years (area under the curve = 0.837, P < 0.001). About 20% of patients were down-staged to stage I using TNM55 compared to that using TNM45. CONCLUSIONS: The cut-off age of 55 years was more appropriate for TNM staging to achieve better predictability for DSS in patients with DTC. This change would prevent over-staging in low-risk patients and prevent over-aggressive treatment.
PubMed-ID: 27731521
http://dx.doi.org/10.1111/cen.13254

Long-term Recurrence of Small Papillary Thyroid Cancer and Its Risk Factors in a Korean Multicenter Study.
J Clin Endocrinol Metab:jc20162287.
Y. Hwangbo, J. M. Kim, Y. J. Park, E. K. Lee, Y. J. Lee, D. J. Park, Y. S. Choi, K. D. Lee, S. Y. Sohn, S. W. Kim, J. H. Chung, D. J. Lim, M. H. Kim, M. J. Kim, Y. S. Jo, M. H. Shong, S. S. Koong, J. R. Hahm, J. H. Jung and K. H. Yi. 2016.
CONTEXT: Small papillary thyroid cancer (PTC) generally has excellent prognosis. However, the long-term recurrence is not uncommon, which sometimes leads to morbidity or mortality. OBJECTIVE: To identify the high-risk factors for long-term recurrence in patients with small PTC by stratifying their pathologic characteristics.

DESIGN, SETTING, AND PATIENTS: We conducted a nationwide, retrospective, multicenter study including 3,282 patients with PTC size </=2 cm from 9 high volume hospitals in Korea. MAIN OUTCOME MEASURES: The maximally selected chi-square method was used to find the best cutoff points of tumor size, number of metastatic lymph nodes (LN), and the ratio of metastatic to examined LNs (LNR) to predict recurrence. The Kaplan-Meier analysis and Cox proportional hazards regression model were used to analyze recurrence and risk factors. RESULTS: The optimal tumor size cutoff was 1.8 cm (10-year recurrence rates for tumors sized 0.1-1.7cm and 1.8-2.0cm; 7.7% vs. 17.2%, respectively). Metastatic LNs </=1 and >/=2 provided optimal estimates of recurrence (10-year recurrence rates; 4.0% vs. 16.8%, respectively). The LNR of 0.19 was the optimal cutoff point for predicting the risk of recurrence (10-year recurrence rates for LNR of 0-0.18 and 0.19-1; 2.7% vs. 16.2%, respectively). LN metastasis, lobectomy, tumor size >/=1.8 cm and bilateral tumors were independent risk factors for recurrence. CONCLUSIONS: Long-term recurrence was increased in patients who underwent lobectomy, or with tumor sized >/=1.8cm, 2 or more metastatic lymph nodes, or bilateral tumors. For the patients with these high risk features, total thyroidectomy could be considered to avoid reoperation.
PubMed-ID: 27732329
http://dx.doi.org/10.1210/jc.2016-2287

The History of the Follicular Variant of Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab:jc20162976.
G. Tallini, R. M. Tuttle and R. A. Ghossein. 2016.
CONTEXT: The purpose of this review is to provide the historical context to recent developments in the classification of the follicular variant of papillary thyroid carcinoma (FVPTC), an entity that has long created significant controversy. The scope is to illustrate the evolution of the diagnostic criteria for papillary thyroid carcinoma, clarifying the role of molecular analysis, and the impact on patient management. EVIDENCE ACQUISITION: A PubMed search using the terms "follicular variant" and "papillary thyroid carcinoma" covering the years 1960-2016 was performed. Additional references were identified through review of the citations of the retrieved articles. EVIDENCE SYNTHESIS: The encapsulated/well demarcated non-invasive form of FVPTC that occurs annually in 45,000 patients worldwide was thought for 30 years to be a carcinoma. Many studies have now shown almost no recurrence in these non-invasive tumors, even in patients treated by surgery alone without radioactive iodine therapy. The categorization of the tumor as outright cancer has led to aggressive forms of treatment, with their side effects, financial costs, and the psychological and social impact of a cancer diagnosis. Recently, the encapsulated/well demarcated non-invasive, FVPTC was renamed as "Non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) by an international group of experts. The new terminology lacks the carcinoma label enabling clinicians to avoid aggressive therapy. By taking the reader through the history of FVPTC, this article explains how diagnostic criteria for thyroid carcinoma of follicular cells have evolved over the last 60 years. It discusses the steps that led to the labeling of FVPTC as cancer and highlights the various studies that helped reclassify and rename this tumor. CONCLUSIONS: The encapsulated/well demarcated non-invasive form of FVPTC was thought to be a carcinoma for 30 years. By understanding the history of FVPTC, future classification of tumors will be greatly improved.
PubMed-ID: 27732333
http://dx.doi.org/10.1210/jc.2016-2976

Thyroglobulin Liquid Chromatography-Tandem Mass Spectrometry Has a Low Sensitivity for Detecting Structural Disease in Patients with Antithyroglobulin Antibodies.
Thyroid, 27(1):74-80.
U. Azmat, K. Porter, L. Senter, M. D. Ringel and F. Nabhan. 2017.
BACKGROUND: Thyroglobulin (Tg) measurement in patients with positive antithyroglobulin antibodies (anti-TgAbs) is not reliable. Tg measurement using liquid chromatography-tandem mass spectrometry (LC/MS) may be useful in this setting. METHODS: This is a retrospective study with the objective of determining the accuracy of Tg-LC/MS in patients with thyroid cancer with anti-TgAbs. All patients with follicular cell-derived thyroid cancer (TC) who had thyroglobulin measured using LC/MS assay from November 1, 2013, to November 7, 2014, were evaluated. The frequency of detectable Tg-LC/MS was evaluated, with a functional sensitivity (FS) of 0.5 ng/mL in patients with structural disease. Then performance of Tg-LC/MS versus Tg immunometric assay (IMA) was compared using either Immulite assay (Tg-1) with a FS of 0.9 ng/mL or Beckman assay (Tg-B) with a FS of 0.1 ng/mL in detecting structural disease in patients with positive anti-TgAbs. RESULTS: A total of 154 consecutive patients were included in this evaluation. Of these, 116 (75%) patients were positive for anti-TgAbs. In patients with structural disease and positive anti-TgAbs, Tg-LC/MS was undetectable in 43.7% of patients. Then the diagnostic accuracy for structural disease of Tg-LC/MS was compared with each Tg-IMA assay separately. In the 26 patients with positive anti-TgAbs where a Tg-I assay was used, the sensitivity and specificity for detecting structural disease were 33.3% and 88.2%, respectively, for the Tg-I assay, and 44.4% and 94.1%, respectively,

for the Tg-LC/MS assay. In the 74 patients with positive anti-TgAbs where Tg-B was used, the sensitivity and specificity for detection of structural disease were 72.7% and 71.4%, respectively, for the Tg-B assay, and 62.6% and 93.7%, respectively, for the Tg-LC/MS assay. CONCLUSION: In patients with thyroid cancer with positive anti-TgAbs, Tg-LC/MS was frequently undetectable and was less sensitive for detecting disease than a Tg assay was with a functional sensitivity of 0.1 ng/mL. For patients with detectable Tg-LC/MS and anti-TgAbs, use of the assay for monitoring requires further prospective studies.
PubMed-ID: 27736322
http://dx.doi.org/10.1089/thy.2016.0210

Thyroglobulin Measurement in Fine-Needle Aspiration Improves the Diagnosis of Cervical Lymph Node Metastases in Papillary Thyroid Carcinoma.
Ann Surg Oncol, 24(3):739-44.
Z. Al-Hilli, V. Strajina, T. J. McKenzie, G. B. Thompson, D. R. Farley, M. Regina Castro, A. Algeciras-Schimnich and M. L. Richards. 2017.
BACKGROUND: Papillary thyroid carcinoma (PTC) is frequently associated with cervical lymph node metastases. Guidelines recommend performing ultrasound-guided fine-needle aspiration cytology (FNAC) for suspicious nodes to guide management. No specific recommendations are available for the use of FNA thyroglobulin assay (FNA-Tg). This study investigated the diagnostic value of performing FNAC and FNA-Tg. METHODS: Patient demographics, preoperative investigations, surgery, and lymph node pathology were collected for patients with PTC who underwent lateral neck lymphadenectomy and central compartment reexploration from January 2000 to July 2015. Sensitivities and accuracies were obtained. Patients with both diagnostic studies performed were compared using McNemar's test of paired proportion. Patient, imaging, and lymph node characteristics were correlated with test accuracy. RESULTS: The 480 patients in this study underwent 706 lateral neck dissections or central compartment reexploration. All the patients underwent preoperative neck ultrasound. Among these patients, FNAC alone was performed before 426 operations (60 %), FNAC with FNA-Tg before 105 operations (15 %), and surgery without biopsy for 175 patients (25 %). The sensitivity, positive predictive value, and accuracy were respectively 96, 95, 100 % for FNAC, 99, 97, and 97 % for FNA-Tg, and 95, 92, and 97 % for FNAC in combination with FNA-Tg. In the subgroup of patients who had both tests performed, the sensitivity of FNA-Tg was superior to that of FNAC (95 vs 87 %; p = 0.04). The addition of FNA-Tg to FNAC increased the detection of metastatic PTC by 13 %. CONCLUSIONS: For diagnosing cervical lymph node metastases in PTC, FNA-Tg is a valuable adjunct to FNAC. Its use should be considered to avoid missing metastatic disease in patients who may benefit from lymphadenectomy.
PubMed-ID: 27738849
http://dx.doi.org/10.1245/s10434-016-5625-1

Initial Size of Metastatic Lesions Is Best Prognostic Factor in Patients with Metastatic Differentiated Thyroid Carcinoma Confined to the Lung.
Thyroid, 27(1):49-58.
M. Kim, W. G. Kim, S. Park, H. Kwon, M. J. Jeon, J. J. Lee, J. S. Ryu, T. Y. Kim, Y. K. Shong and W. B. Kim. 2017.
BACKGROUND: For patients with lung metastases of differentiated thyroid carcinoma (DTC), there is no consensus on the maximal size of metastatic lesions to use when determining the intensity of follow-up and additional therapeutic options. This study evaluated the clinical outcomes and survival of patients with metastatic DTC confined to the lung, using the maximal diameter of lung lesions in the initial computed tomography. METHODS: This retrospective cohort study included 112 DTC patients with metastases confined to the lung. The clinical responses were evaluated according to changes in the serum levels of stimulated thyroglobulin or antithyroglobulin antibody, disease status was evaluated according to radiological findings, progression-free survival (PFS), and cancer-specific survival (CSS). RESULTS: Macronodular lung metastases (>/=1 cm) were observed in 27 (24%) patients, and these patients had significantly poor biochemical responses and disease status (p < 0.001, and p < 0.001, respectively), irrespective of radioactive iodine (RAI) avidity. After adjusting for age, sex, primary tumor size, extrathyroidal invasion, cervical lymph node metastasis, time of lung metastasis, and RAI avidity, the macronodular group also had shorter PFS and CSS (p = 0.009 and p = 0.03, respectively) than the micronodular group. From the multivariate analyses, RAI avidity was not an independent prognostic factor predicting PFS and CSS. In the subgroup analyses, RAI avidity was a significant prognostic factor associated with better PFS and CSS (p = 0.013 and p = 0.021, respectively) in the micronodular group only. CONCLUSIONS: The initial largest diameter of metastatic lesions is the most important prognostic factor for predicting poor clinical outcomes and survival in patients with metastatic DTC confined to the lung.
PubMed-ID: 27750021
http://dx.doi.org/10.1089/thy.2016.0347

Targeting autophagy sensitizes BRAF-mutant thyroid cancer to vemurafenib.
J Clin Endocrinol Metab:jc20161999.
W. Wang, H. Kang, Y. Zhao, I. Min, B. Wyrwas, M. Moore, L. Teng, R. Zarnegar, X. Jiang and T. J. Fahey, 3rd. 2016.
CONTEXT: The RAF inhibitor vemurafenib has provided a major advance for the treatment of patients with BRAF-mutant metastatic melanoma. However, BRAF-mutant thyroid cancer is relatively resistant to vemurafenib, and the reason for this disparity remains unclear. Anti-cancer therapy induced autophagy can trigger adaptive drug resistance in a variety of cancer types and treatments. To date, role of autophagy during BRAF inhibition in thyroid cancer remains unknown. OBJECTIVE: In this study, we investigate if autophagy is activated in vemurafenib treated BRAF-mutant thyroid cancer cells, and whether autophagy inhibition improves or impairs the treatment efficacy of vemurafenib. DESIGN: Autophagy level was determined by western blot assay and transmission electron microscopy. The combined effects of autophagy inhibitor and vemurafenib were assessed in terms of cell viability in vitro and tumor growth rate in vivo. Whether the endoplasmic reticulum (ER) stress was in response to vemurafenib-induced autophagy was also analyzed. RESULTS: Vemurafenib induced a high level of autophagy in BRAF-mutant thyroid cancer cells. Inhibition of autophagy by either a pharmacological inhibitor or interfering RNA knockdown of essential autophagy genes augmented vemurafenib-induced cell death. Vemurafenib-induced autophagy was independent of MAPK signaling pathway and was mediated through the ER stress response. Finally, administration of vemurafenib with the autophagy inhibitor hydroxychloroquine promoted more pronounced tumor suppression in vivo. CONCLUSIONS: Our data demonstrate that vemurafenib induces ER stress response-mediated autophagy in thyroid cancer and autophagy inhibition may be a beneficial strategy to sensitize BRAF-mutant thyroid cancer to vemurafenib.
PubMed-ID: 27754804
http://dx.doi.org/10.1210/jc.2016-1999

Preoperative differentiation between noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and non-NIFTP.
Clin Endocrinol (Oxf), 86(3):444-50.
S. Y. Hahn, J. H. Shin, H. K. Lim, S. L. Jung, Y. L. Oh, I. H. Choi and C. K. Jung. 2017.
BACKGROUND: A recent concept was proposed that the noninvasive encapsulated follicular variant of papillary thyroid carcinoma reclassified as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" is benign. Our aim was to identify the differences between NIFTP and non-NIFTP preoperatively. METHODS: This retrospective study included a total of 208 patients with 208 follicular variant of papillary thyroid carcinomas (FVPTC) that were surgically confirmed at three university hospitals from 2008 to 2014. Clinical factors, the biopsy techniques and ultrasonography (US) imaging characteristics were compared between the NIFTP and non-NIFTP groups. RESULTS: A total of 34 NIFTP (16.3%) and 174 non-NIFTP (83.7%) were observed. For NIFTPs, the need for surgery was indicated by ultrasonography-guided fine needle aspiration (US-FNA) in 54.3% and by ultrasonography-guided core needle biopsy (US-CNB) in 100% (P = 0.008). For non-NIFTP, no significant difference was noted in the rates of surgical indication between US-FNA and US-CNB (62.6% vs 78.9%, P = 0.054). The most common biopsy diagnosis of NIFTP was Bethesda category V (28.6%) in the US-FNA group and category IV (45.5%) in the US-CNB group. US diagnosis of NIFTP had a significantly lower rate of the high suspicion of malignancy than that of non-NIFTP (14.7% vs 37.9%, P = 0.024). Central nodal metastasis was found in only one case (2.9%) of NIFTP patients, but none had distance metastasis or recurrence. CONCLUSION: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features lacks malignant US features and is better triaged using US-CNB than using US-FNA to facilitate the surgical management. US evaluation is pivotal in determining the next step of FVPTC management.
PubMed-ID: 27761926
http://dx.doi.org/10.1111/cen.13263

Examining the Role of Preoperative Positron Emission Tomography/Computerized Tomography in Combination with Ultrasonography in Discriminating Benign from Malignant Cytologically Indeterminate Thyroid Nodules.
Thyroid, 27(1):95-102.
M. M. Merten, M. R. Castro, J. Zhang, J. Durski and M. Ryder. 2017.
BACKGROUND: Cytologically defined indeterminate thyroid nodules are a diagnostic challenge. Surgical lobectomy remains the gold standard for definitive diagnosis. However, 70-85% of nodules are ultimately benign. The primary objective of this study was to evaluate the negative predictive value (NPV) of F18-fluorodeoxyglucose (FDG) positron emission computed tomography (PET/CT) in excluding cancer among cytologically indeterminate thyroid nodules within the authors' institution using surgical pathology as the gold-

standard reference. In addition, a systematic review was performed of published prospective studies on the NPV of PET/CT in evaluating indeterminate thyroid nodules. METHODS: A retrospective review was performed of all patients aged >/=18 years seen at the Mayo Clinic between January 1, 2000, and December 31, 2014, with cytologically defined indeterminate thyroid nodules (suspicious for Hurthle cell neoplasm or follicular neoplasm; N = 858), who had a PET/CT within one year of fine-needle aspiration (n = 80) and underwent definitive diagnostic lobectomy (n = 51). Nodules were considered PET negative if they had a standardized uptake value (SUV) <5. Additionally, a systematic review was performed of published prospective studies on the NPV of PET/CT across multiple sites. RESULTS: Fifty-one patients met the eligibility criteria. The retrospective review combined with a systematic review of eight prospective studies suggests that indeterminate nodules with a negative PET (SUV <5) have a low risk of malignancy (NPV 94%). The cancer prevalence in the institution is 14% and 27% in the combined prospective studies. CONCLUSIONS: PET/CT represents a preoperative, non-invasive tool that when combined with sonographic features can identify indeterminate nodules at low risk for malignancy.
PubMed-ID: 27762671
http://dx.doi.org/10.1089/thy.2016.0379

Should Level V Be Routinely Dissected in N1b Papillary Thyroid Carcinoma?
Thyroid, 27(2):253-60.
S. K. Kim, I. Park, N. Hur, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2017.
BACKGROUND: For N1b papillary thyroid carcinoma (PTC) patients, modified radical neck dissection (MRND) encompassing levels II-V is generally recommended. However, routine level V dissection is controversial because of the low incidence of metastasis/recurrence in level V and the increased morbidities associated with level V dissection. METHODS: This study retrospectively reviewed 646 N1b PTC patients who underwent unilateral MRND between January 1997 and June 2015. Specifically, to assess surgery-related outcomes of level V dissection, outcomes from N1b PTC patients who underwent unilateral MRND (levels II-V) were compared with those who underwent unilateral selective neck dissection (SND; levels II-IV) using propensity score matching. RESULTS: Overall and occult level V metastases were observed in 13.9% and 8.6% of patients, respectively. Level V recurrences were observed in only 2.26 (7.7%) recurred N1b PTC patients who underwent unilateral MRND. In multivariate analysis, three-level (II, III, and IV) simultaneous metastasis (adjusted odds ratio = 3.079, p = 0.003) was an independent predictor for level V metastasis. Under a matched condition, "shoulder syndrome" encompassing shoulder dysfunction and pain (9.1% vs. 2.7%, p = 0.002) was significantly more frequent in the MRND group than it was in the SND group. CONCLUSIONS: Because of the low incidence of metastasis/recurrence in level V and the clear evidence of increased morbidities, level V dissection in N1b PTC patients may be reserved for those with three-level simultaneous metastasis or clinically/radiologically evident level V metastasis.
PubMed-ID: 27762727
http://dx.doi.org/10.1089/thy.2016.0364

Elevated serum tetrac in Graves' disease: potential pathogenic role in thyroid-associated ophthalmopathy.
J Clin Endocrinol Metab:jc20162762.
R. Fernando, E. Placzek, E. A. Reese, A. T. Placzek, S. Schwartz, A. Trierweiler, L. M. Niziol, S. Atkins, T. S. Scanlan and T. J. Smith. 2016.
CONTEXT: The sources and biological impact of 3,3',5,5' tetraiodothyroacetic acid (TA4) are uncertain. CD34+ fibrocytes express several proteins involved in the production of thyroid hormones. They infiltrate the orbit in Graves' disease (GD), an autoimmune process known as thyroid-associated ophthalmopathy. It appears that the thyrotropin receptor (TSHR) plays an important role in the pathogenesis of TAO. OBJECTIVE: To quantify levels of TA4 in healthy subjects and those with Graves' disease. To determine whether fibrocytes generate this TH analogue. To determine whether TA4 influences the actions of TSH and thyroid-stimulating immunoglobulins in orbital fibroblasts. DESIGN/SETTING/PARTICIPANTS: Patients with GD and healthy donors in an academic medical center clinical practice were recruited. MAIN OUTCOME MEASURES: liquid chromatography-tandem mass spectrometry, autoradiography, real-time PCR, hyaluronan immunoassay Results: Serum levels of TA4 are elevated in GD. TA4 levels are positively correlated with those of thyroxine and negatively correlated with serum levels of triiodothyronine. Several cell types in culture generate TA4 from ambient thyroxine, including fibrocytes, HELA cells, human Muller stem cells, and retinal pigmented epithelial cells. Propylthiouracil inhibited TA4 generation. TA4 enhances the induction by thyrotropin and thyroid-stimulating immunoglobulins of several participants in the pathogenesis of TAO, including IL-6, hyaluronan synthase-1, prostaglandin endoperoxide H synthase-2, and haluronan production. CONCLUSION: TA4 may be ubiquitously generated in many tissues and enhances the biological impact of thyrotropin and thyroid-stimulating immunoglobulins in orbital connective

tissue. These findings may identify a physiologically important determinant of extra-thyroidal TSH action.
PubMed-ID: 27768856
http://dx.doi.org/10.1210/jc.2016-2762

The role of lateral neck ultrasound in detecting single or multiple lymph nodes in papillary thyroid cancer.
Am J Surg, 212(6):1147-53.
Z. Al-Hilli, V. Strajina, T. J. McKenzie, G. B. Thompson, D. R. Farley and M. L. Richards. 2016.
BACKGROUND: Lateral neck dissection (LND) for papillary thyroid cancer (PTC) transitioned from isolated lymphadenectomy or "berry picking" based on clinical examination to multicompartment lymphadenectomy. We aimed to assess ultrasound (US) as a predictor of solitary (SLN) or multiple lymph node (MLN) metastases. METHODS: Demographics, US findings, extent of LND, and pathology were collected in patients with PTC who underwent LND. US sensitivity and specificity were calculated, and accuracy was correlated with US findings and patient characteristics. RESULTS: A total of 462 patients underwent 590 LNDs. US showed an SLN in 179 patients (30%) and MLNs in 411 patients (70%). Sensitivity, positive predictive value, and accuracy were 61%, 43%, and 75% for US detected SLN and 78%, 89%, and 75% for US detected MLNs. US accuracy for MLNs increased as node size increased (<10 mm, 63%; 10 to 20 mm, 71%; >20 mm, 89%; P < .0001). CONCLUSIONS: US has limited accuracy in the detection SLN metastasis in the lateral neck. Care should be taken when considering a focused compartment dissection.
PubMed-ID: 27771031
http://dx.doi.org/10.1016/j.amjsurg.2016.09.014

Propensity score-matched analysis of robotic versus endoscopic bilateral axillo-breast approach (BABA) thyroidectomy in papillary thyroid carcinoma.
Langenbecks Arch Surg, 402(2):243-50.
S. K. Kim, J. W. Woo, I. Park, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2017.
PURPOSE: The da Vinci surgical robot system was developed to overcome the weaknesses of endoscopic surgery. However, whether robotic surgery is superior to endoscopic surgery remains uncertain. Therefore, the purpose of this study was to compare the surgical and oncologic outcomes between endoscopic and robotic thyroidectomy using bilateral axillo-breast approach (BABA). METHODS: Between January 2008 and June 2015, papillary thyroid carcinoma patients who underwent thyroidectomy with central neck dissection using endoscopic (n = 480) or robotic (n = 705) BABA were primarily reviewed. We performed 1:1 propensity score matching and 289 matched pairs were yielded. RESULTS: Operation time was significantly longer in the robotic thyroidectomy than in the endoscopic thyroidectomy (184.9 vs. 128.9 min, P < 0.001). A significantly higher number of central lymph nodes (CLNs) were resected in the robotic thyroidectomy than in the endoscopic thyroidectomy (5.3 vs. 4.4, P = 0.003). However, the incidence of other outcomes including hospital stay, postoperative duration, thyroglobulin level, radioactive iodine ablation, hemorrhage, chyle leakage, wound infection, recurrent laryngeal nerve injury, and loco-regional recurrence did not significantly differ between the endoscopic thyroidectomy and the robotic thyroidectomy. CONCLUSIONS: Endoscopic thyroidectomy is comparable with robotic thyroidectomy in view of surgical complications and LRR. Because robotic thyroidectomy resected a larger number of CLNs than did endoscopic thyroidectomy, further long-term follow-up studies will be required to clarify the possible prognostic benefits of robotic thyroidectomy.
PubMed-ID: 27774578
http://dx.doi.org/10.1007/s00423-016-1528-7

Total thyroidectomy alone versus ipsilateral versus bilateral prophylactic central neck dissection in clinically node-negative differentiated thyroid carcinoma. A retrospective multicenter study.
Eur J Surg Oncol, 43(1):126-32.
P. G. Calo, G. Conzo, M. Raffaelli, F. Medas, C. Gambardella, C. De Crea, L. Gordini, R. Patrone, L. Sessa, E. Erdas, E. Tartaglia and C. P. Lombardi. 2017.
BACKGROUND: Central neck dissection (CND) remains controversial in clinically node-negative differentiated thyroid carcinoma (DTC) patients. The aim of this multicenter retrospective study was to determine the rate of central neck metastases, the morbidity and the rate of recurrence in patients treated with total thyroidectomy (TT) alone or in combination with bilateral or ipsilateral CND. METHODS: The clinical records of 163 clinically node-negative consecutive DTC patients treated between January 2008 and December 2010 in three endocrine surgery referral units were retrospectively evaluated. The patients were divided into three groups: patients who had undergone TT alone (group A), TT with ipsilateral CND (group B), and TT with bilateral CND (group C). RESULTS: The respective incidences of transient hypoparathyroidism and unilateral recurrent nerve injury were 12.6% and 1% in group A, 23.3% and 3.3% in B, and 36.7% and 0% in C. Node metastases were observed in

8.7% in group A, 23.3% in B, and 63.3% in C. Locoregional recurrence was observed in 3.9% of patients in group A and in 0% in B and C. CONCLUSIONS: We found no statistically significant differences in the rates of locoregional recurrence between the three groups. Therefore, TT appears to be an adequate treatment for these patients; CND is associated with higher rates of transient hypoparathyroidism and cannot be considered the treatment of choice even if it could help for more appropriate selection of patients for RAI. Ipsilateral CND could be an interesting option considering the lower rate of hypocalcemia to be validated by further studies.
PubMed-ID: 27780677
http://dx.doi.org/10.1016/j.ejso.2016.09.017

Hypoparathyroidism after total thyroidectomy in patients with previous gastric bypass.
Langenbecks Arch Surg, 402(2):273-80.
R. A. Droeser, J. Ottosson, A. Muth, H. Hultin, K. Lindwall-Ahlander, A. Bergenfelz and M. Almquist. 2017.
PURPOSE: Case reports suggest that patients with previous gastric bypass have an increased risk of severe hypocalcemia after total thyroidectomy, but there are no population-based studies. The prevalence of gastric bypass before thyroidectomy and the risk of hypocalcemia after thyroidectomy in patients with previous gastric bypass were investigated. METHODS: By cross-linking The Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery with the Scandinavian Obesity Surgery Registry patients operated with total thyroidectomy without concurrent or previous surgery for hyperparathyroidism were identified and grouped according to previous gastric bypass. The risk of treatment with intravenous calcium during hospital stay, and with oral calcium and vitamin D at 6 weeks and 6 months postoperatively was calculated by using multiple logistic regression in the overall cohort and in a 1:1 nested case-control analysis. RESULTS: We identified 6115 patients treated with total thyroidectomy. Out of these, 25 (0.4 %) had undergone previous gastric bypass surgery. In logistic regression, previous gastric bypass was not associated with treatment with i.v. calcium (OR 2.05, 95 % CI 0.48-8.74), or calcium and/or vitamin D at 6 weeks (1.14 (0.39-3.35), 1.31 (0.39-4.42)) or 6 months after total thyroidectomy (1.71 (0.40-7.32), 2.28 (0.53-9.75)). In the nested case-control analysis, rates of treatment for hypocalcemia were similar in patients with and without previous gastric bypass. CONCLUSION: Previous gastric bypass surgery was infrequent in patients undergoing total thyroidectomy and was not associated with an increased risk of postoperative hypocalcemia.
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http://dx.doi.org/10.1007/s00423-016-1517-x

Cell Cycle M-Phase Genes Are Highly Upregulated in Anaplastic Thyroid Carcinoma.
Thyroid, 27(2):236-52.
P. Weinberger, S. R. Ponny, H. Xu, S. Bai, R. Smallridge, J. Copland and A. Sharma. 2017.
BACKGROUND: Anaplastic thyroid carcinoma (ATC) accounts for only 3% of thyroid cancers, yet strikingly, it accounts for almost 40% of thyroid cancer deaths. Currently, no effective therapies exist. In an effort to identify ATC-specific therapeutic targets, we analyzed global gene expression data from multiple studies to identify ATC-specific dysregulated genes. METHODS: The National Center for Biotechnology Information Gene Expression Omnibus database was searched for high-throughput gene expression microarray studies from human ATC tissue along with normal thyroid and/or papillary thyroid cancer (PTC) tissue. Gene expression levels in ATC were compared with normal thyroid or PTC using seven separate comparisons, and an ATC-specific gene set common in all seven comparisons was identified. We investigated these genes for their biological functions and pathways. RESULTS: There were three studies meeting inclusion criteria, (including 32 ATC patients, 69 PTC, and 75 normal). There were 259 upregulated genes and 286 downregulated genes in ATC with at least two-fold change in all seven comparisons. Using a five-fold filter, 36 genes were upregulated in ATC, while 40 genes were downregulated. Of the 10 top globally upregulated genes in ATC, 4/10 (MMP1, ANLN, CEP55, and TFPI2) are known to play a role in ATC progression; however, 6/10 genes (TMEM158, CXCL5, E2F7, DLGAP5, MME, and ASPM) had not been specifically implicated in ATC. Similarly, 3/10 (SFTA3, LMO3, and C2orf40) of the most globally downregulated genes were novel in this context, while 7/10 genes (SLC26A7, TG, TSHR, DUOX2, CDH1, PDE8B, and FOXE1) have been previously identified in ATC. We experimentally validated a significant correlation for seven transcription factors (KLF16, SP3, ETV6, FOXC1, SP1, EGFR1, and MAFK) with the ATC-specific genes using microarray analysis of ATC cell lines. Ontology clustering of globally altered genes revealed that "mitotic cell cycle" is highly enriched in the globally upregulated gene set (44% of top upregulated genes, p-value <10-30). CONCLUSIONS: By focusing on globally altered genes, we have identified a set of consistently altered biological processes and pathways in ATC. Our data are consistent with an important role for M-phase cell cycle genes in ATC, and may provide direction for future studies to identify novel therapeutic targets for this disease.
PubMed-ID: 27796151
http://dx.doi.org/10.1089/thy.2016.0285

Familial non-medullary thyroid cancer: unraveling the genetic maze.
Endocr Relat Cancer, 23(12):R577-R95.
S. Peiling Yang and J. Ngeow. 2016.
Familial non-medullary thyroid cancer (FNMTC) constitutes 3-9% of all thyroid cancers. Out of all FNMTC cases, only 5% in the syndromic form has well-studied driver germline mutations. These associated syndromes include Cowden syndrome, familial adenomatous polyposis, Gardner syndrome, Carney complex type 1, Werner syndrome and DICER1 syndrome. It is important for the clinician to recognize these phenotypes so that genetic counseling and testing can be initiated to enable surveillance for associated malignancies and genetic testing of family members. The susceptibility chromosomal loci and genes of 95% of FNMTC cases remain to be characterized. To date, 4 susceptibility genes have been identified (SRGAP1 gene (12q14), TITF-1/NKX2.1 gene (14q13), FOXE1 gene (9q22.33) and HABP2 gene (10q25.3)), out of which only the FOXE1 and the HABP2 genes have been validated by separate study groups. The causal genes located at the other 7 FNMTC-associated chromosomal loci (TCO (19q13.2), fPTC/ PRN (1q21), FTEN (8p23.1-p22), NMTC1 (2q21), MNG1 (14q32), 6q22, 8q24) have yet to be identified. Increasingly, gene regulatory mechanisms (miRNA and enhancer elements) are recognized to affect gene expression and FNMTC tumorigenesis. With newer sequencing technique, along with functional studies, there has been progress in the understanding of the genetic basis of FNMTC. In our review, we summarize the FNMTC studies to date and provide an update on the recently reported susceptibility genes including novel germline SEC23B variant in Cowden syndrome, SRGAP1 gene, FOXE1 gene and HABP2 genes in non-syndromic FNMTC.
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http://dx.doi.org/10.1530/ERC-16-0067

Initial and Dynamic Risk Stratification of Pediatric Patients with Differentiated Thyroid Cancer.
J Clin Endocrinol Metab:jc20162666.
T. Y. Sung, M. J. Jeon, Y. H. Lee, Y. M. Lee, H. Kwon, J. H. Yoon, K. W. Chung, W. G. Kim, D. E. Song and S. J. Hong. 2016.
BACKGROUND: The objective of this study was to evaluate the usefulness of American Thyroid Association (ATA) risk classification and dynamic risk stratification (DRS) based on the response to initial therapy in pediatric patients with differentiated thyroid cancer (DTC). METHODS: This historical cohort study included 77 pediatric patients with DTC who underwent thyroid surgery. Clinical outcomes during median 5.3 years of follow-up were assessed according to three ATA risk groups and four DRS groups. RESULTS: In ATA risk classification, 22%, 48%, and 30% of patients were low, intermediate and high risk group. There was no significant difference in disease-free survival (DFS) between indeterminate and low risk group. The risk of recurrent/persistent disease was significantly higher only in high risk group (HR=18.4, p=0.005). In DRS, 49%, 13%, 6% and 31% of patients were classified in excellent, indeterminate, biochemical incomplete, and structural incomplete response group, respectively. The risk of recurrent/persistent disease was significantly higher in indeterminate group (HR=10.2, p=0.045), and structural incomplete group (HR=98.7, p=0.005) compared by excellent response group. CONCLUSION: DRS based on the response to initial therapy could be useful in addition to initial ATC pediatric risk classification to predict recurrent/persistent disease in pediatric patients with DTC.
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http://dx.doi.org/10.1210/jc.2016-2666

Low Elasticity of Thyroid Nodules on Ultrasound Elastography Is Correlated with Malignancy, Degree of Fibrosis, and High Expression of Galectin-3 and Fibronectin-1.
Thyroid, 27(1):103-10.
T. Rago, M. Scutari, V. Loiacono, F. Santini, M. Tonacchera, L. Torregrossa, R. Giannini, N. Borrelli, A. Proietti, F. Basolo, P. Miccoli, P. Piaggi, F. Latrofa and P. Vitti. 2017.
BACKGROUND: Thyroid ultrasound (US) elastography provides an estimation of tissue stiffness and is helpful to differentiate malignant from benign lesions. Tissue proprieties and molecules causing stiffness are not established. The aim of the study was to correlate US elastography findings with tissue properties in thyroid nodules. METHODS: A total of 115 thyroid nodules from 112 patients who underwent surgery for the presence of Thy 3 (indeterminate) cytology (n = 67), Thy 4-5 (suspicious-indicative of carcinoma) cytology (n = 47), or large goiter in the presence of Thy 2 cytology (n = 1) and suspicious US features were examined by US elastography. Tissues obtained after surgery were characterized for cell number, microvessel density, fibrosis, and expression of galectin-3 (Gal-3) and fibronectin-1 (FN-1). RESULTS: Low elasticity on qualitative US elastography (LoEl) was found in 66 nodules (one benign and 65 carcinomas); high elasticity (HiEl) was found in 49 nodules (46 benign and three carcinomas; $p < 0.0001$). Quantitative analysis, performed in 24 nodules and expressed as elastic ratio between the strain of the nodule and that of the surrounding thyroid parenchyma,

showed a mean of 1.90 (interquartile range [IQR] 1.18-2.77) in 14 nodules with LoEl, and a mean of 1.01 (IQR 0.91-1.10) in 10 nodules with HiEl (p = 0.002). Stiffness did not correlate with cell number and was inversely correlated with microvessel density. Fibrosis was higher in nodules with LoEl than in those with HiEl (p = 0.009) and in carcinomas than in benign nodules (p = 0.02). Fibrosis was higher in nodules with high expression of Gal-3 (p < 0.001) and FN-1 (p = 0.004). Fibrosis and expression of Gal-3 and FN-1 were higher in the classic compared with the follicular variant of papillary thyroid carcinoma and lower in follicular adenomas. CONCLUSIONS: Low elasticity at US elastography is highly correlated with malignancy. Nodule stiffness is correlated with fibrosis and expression of Gal-3 and FN-1. These features are more evident in the classic than in the follicular variant of papillary thyroid carcinoma.
PubMed-ID: 27809694
http://dx.doi.org/10.1089/thy.2016.0341

Cost-effectiveness of active surveillance versus hemithyroidectomy for micropapillary thyroid cancer.
Surgery, 161(1):116-26.
S. Venkatesh, J. D. Pasternak, T. Beninato, F. T. Drake, W. P. Kluijfhout, C. Liu, J. E. Gosnell, W. T. Shen, O. H. Clark, Q. Y. Duh and I. Suh. 2017.
BACKGROUND: The management of low-risk micropapillary thyroid cancer <1 cm in size has come into question, because recent data have shown that nonoperative active surveillance of micropapillary thyroid cancer is a viable alternative to hemithyroidectomy. We conducted a cost-effectiveness analysis to help decide between observation versus operation. METHODS: We constructed Markov models for active surveillance and hemithyroidectomy. The reference case was a 40-year-old patient with recently diagnosed, low-risk micropapillary thyroid cancer. Costs and health utilities were determined using extensive literature review. The willingness-to-pay threshold was set at $100,000/quality-adjusted life year gained. Deterministic and probabilistic sensitivity analyses were performed to account for uncertainty in the model's variables. RESULTS: Active surveillance is dominant (less expensive and more quality-adjusted life years) for a health utility <0.01 below that for disease-free, posthemithyroidectomy state, or for a remaining life expectancy of <2 years. For a utility difference >/=0.02, the incremental cost-effectiveness ratio (the ratio of the difference in costs between active surveillance and hemithyroidectomy divided by the difference in quality-adjusted life years) for hemithyroidectomy is <$100,000/QALY gained and thus cost-effective. For a utility difference of 0.11-the reference case scenario-the incremental cost-effectiveness ratio for hemithyroidectomy is $4,437/quality-adjusted life year gained. CONCLUSION: The cost-effectiveness of hemithyroidectomy is highly dependent on patient disutility associated with active surveillance. In patients who would associate nonoperative management with at least a modest decrement in quality of life, hemithyroidectomy is cost-effective.
PubMed-ID: 27839930
http://dx.doi.org/10.1016/j.surg.2016.06.076

Germline polymorphisms of the VEGF-pathway predict recurrence in non-advanced differentiated thyroid cancer.
J Clin Endocrinol Metab:jc20162555.
V. Marotta, C. Sciammarella, M. Capasso, A. Testori, C. Pivonello, M. G. Chiofalo, C. Gambardella, M. Grasso, A. Antonino, A. Annunziata, P. E. Macchia, R. Pivonello, L. Santini, G. Botti, S. Losito, L. Pezzullo, A. Colao and A. Faggiano. 2016.
CONTEXT: Angiogenesis is an hallmark of cancer and is mainly determined by genetic background, rather than environment. Germline single nucleotide polymorphisms (SNPs) of VEGF-pathway have demonstrated prognostic value in different tumours. OBJECTIVES: Main: testing prognostic value of germline SNPs of VEGF-pathway in non-advanced DTC. Secondary: correlating analyzed SNPs with microvessel density (MVD). DESIGN: Multicenter, retrospective, observational study. SETTING: Four referral centers. PATIENTS: Blood samples were obtained from consecutive DTC patients. SNP genotyping was performed according to TaqMan protocol, including 4 VEGF-A (-2578C>A, -460T>C, +405G>C, and +936C>T) and 2 VEGFR-2 (+1192 C>T and +1719 T>A) SNPs. MVD was estimated by means of CD34 staining. Main outcome meausures: Rate of recurrent structural disease/disease free survival (DFS). Difference in MVD between tumours from patients with different genotype. RESULTS: Two-hundred four AJCC/UICC stage I-II (mean follow-up 73+/-64 months) and 240 ATA low-intermediate risk DTC (mean follow-up 70+/-60 months) were enrolled. We identified 2 "risk" genotypes by combining VEGF-A SNPs -2578 C>A, -460 T>C, and +405 G>C. ACG homozygous genotype was protective in both stage I-II (p=0.018, OR=0.08, 95% CI 0.01-1.43) and ATA low-intermediate risk (p=0.035, OR=0.14, 95% CI 0.01-1.13) patients. CTG homozygous genotype was significantly associated to recurrence in stage I-II (p=0.018, OR=5.47, 95% CI 1.15-26.04), and was slightly deleterious in ATA low-intermediate risk (p=0.079, OR=3.39, 95% 0.8-14.33) subjects. MVD of primary tumours from patients harbouring protective genotype was significantly lower (median MVD 76.5+/-12.7 and 86.7+/-27.9, respectively; p=0.024).

CONCLUSIONS: Analysis of germline VEGF-A SNPs could empower prognostic approach to DTC. Further validation is required.
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http://dx.doi.org/10.1210/jc.2016-2555

Epitope-specific antitumor immunity suppresses tumor spread in papillary thyroid cancer.
J Clin Endocrinol Metab:jc20162469.
M. Ehlers, A. Kuebart, H. Hautzel, J. Enczmann, A. C. Reis, M. Haase, S. Allelein, T. Dringenberg, C. Schmid and M. Schott. 2016.
CONTEXT: Papillary thyroid cancer (PTC) is characterized by a lymphocytic infiltration. PTC patients with lymphocytic infiltration may have a better clinical outcome. OBJECTIVE: Characterization of tumor epitope-specific immunity and correlation analyses with the clinical outcome. PATIENTS: 150 PTC patients; 40 Hashimoto's thyroiditis (HT) patients; 21 healthy controls; 27.239 healthy Caucasians (for HLA typing). MAIN OUTCOME MEASURES: HLA class I restricted thyroperoxidase (TPO) and thyroglobulin (Tg) epitope-specific T cells (tetramer analyses), correlation analyses between HLA class II phenotypes, T cell immunity, and the clinical course. RESULTS: The frequency of TPO- and Tg-specific CD8+ T cells in PTC patients was largely increased compared to healthy controls (TPO and Tg: $p < 0.005$ and $p < 0.005$) and was similar to those in HT patients. HLA-DQB1*03 positive PTC patients had a significantly lower risk (RR: 0.170, 95% CI: 0.037 to 0.755, $p < 0.05$) and HLA-DRB1*03 positive and HLA-DQB1*02 positive PTC patients a significantly higher risk (HLA-DRB1*03: RR: 4.400, 95% CI: 1.378 to 14.05, $p < 0.05$; HLA-DQB1*02: RR: 3.692, 95% CI: 1.102 to 12.38, $p < 0.05$) for distant metastases, compared to patients with other haplotypes. HLA-DQB1*03 positive PTC patients revealed an increased responsiveness of tumor epitopes in vitro. These tumor epitope-specific CD8+ T cells were also found in lymph node metastases of HLA-DQB1*03 positive PTC patients. CONCLUSION: We demonstrate a tumor epitope-specific immunity in PTC patients and the protective role of HLA-DQB1*03 against metastatic spread. These results have direct implications for new treatment options with immune check point inhibitors.
PubMed-ID: 27860539
http://dx.doi.org/10.1210/jc.2016-2469

Preoperative detection of RAS mutation may guide extent of thyroidectomy.
Surgery, 161(1):168-75.
S. G. Patel, S. E. Carty, K. L. McCoy, N. P. Ohori, S. O. LeBeau, R. R. Seethala, M. N. Nikiforova, Y. E. Nikiforov and L. Yip. 2017.
BACKGROUND: Preoperative detection of RAS mutations can contribute to cancer risk assessment in indeterminate thyroid nodules, although RAS is not always associated with malignancy. METHODS: Fine-needle aspiration samples classified in 1 of 3 indeterminate cytology categories were prospectively tested for N-, H-, and K-RAS mutations using next-generation sequencing assay. RESULTS: In the study, 93 patients with 94 nodules had preoperative RAS detected, of whom 86 patients had an operation (69% total thyroidectomy, 29% lobectomy). In total, 76% of RAS-positive nodules were malignant and follicular variant papillary thyroid cancer was the most common cancer type (83%). HRAS mutations had the greatest risk of cancer (92%) followed by NRAS (74%) and KRAS (64%; P = .05). No preoperative variables were associated with malignancy including age (P = .07), sex (P = .49), RAS isoform (P = .05), mutational allelic frequency (P = .49), nodule size (P = .14), cytology category (P = .63), or ultrasound bilaterality (P = .24), multifocality (P = .23), or presence of >/=1 suspicious feature (P = .86). Only 60% of patients with a unifocal nodule on ultrasound had single focus low-risk encapsulated follicular variant papillary thyroid cancer or benign disease. CONCLUSION: Preoperative RAS mutation detection in thyroid nodules carries a substantial risk of cancer with a greater risk associated with HRAS and NRAS. Most RAS malignancies are follicular variant papillary thyroid cancer, which may inform the extent of operation.
PubMed-ID: 27863786
http://dx.doi.org/10.1016/j.surg.2016.04.054

Can we consider immediate complications after thyroidectomy as a quality metric of operation?
Surgery, 161(1):156-65.
J. C. Lifante, C. Payet, F. Menegaux, F. Sebag, J. L. Kraimps, J. L. Peix, F. Pattou, C. Colin and A. Duclos. 2017.
BACKGROUND: Permanent recurrent laryngeal nerve palsy and hypoparathyroidism are 2 major complications after thyroid operation. Assuming that the rate of immediate complications can predict the permanent complication rate, some authors consider these complications as a valid metric for assessing the performance of individual surgeons. This study aimed to determine the correlation between rates of immediate and permanent complications after thyroidectomy at the surgeon level. METHODS: We conducted a prospective, cross-sectional

study in 5 academic hospitals between April 2008 and December 2009. The correlation between the rates of immediate and permanent complications for each of the 22 participating surgeons was calculated using the Pearson correlation test (r). RESULTS: The study period included 3,605 patients. There was a fairly good correlation between rates of immediate and permanent recurrent laryngeal nerve palsy (r = 0.70, P = .004), but no correlation was found for immediate and permanent hypoparathyroidism (r = 0.18, P = .427). CONCLUSION: The immediate hypoparathyroidism rate does not reflect the permanent hypoparathyroidism rate. Consequently, immediate hypoparathyroidism should not be used to assess the quality of thyroidectomy or to monitor the performance of surgeons.
PubMed-ID: 27866716
http://dx.doi.org/10.1016/j.surg.2016.04.049

Intraoperative neural monitoring in thyroid surgery: lessons learned from animal studies.
Gland Surg, 5(5):473-80.
C. W. Wu, G. W. Randolph, I. C. Lu, P. Y. Chang, Y. T. Chen, P. C. Hun, Y. C. Lin, G. Dionigi and F. Y. Chiang. 2016.
Recurrent laryngeal nerve (RLN) injury remains a significant morbidity associated with thyroid and parathyroid surgery. In the past decade, surgeons have increasingly used intraoperative neural monitoring (IONM) as an adjunct technique for localizing and identifying the RLN, detecting RLN injury, and predicting the outcome of vocal cord function. In recent years, many animal studies have investigated common pitfalls and new applications of IONM. For example, the use of IONM technology in animal models has proven valuable in studies of the electrophysiology of RLN injury. The advent of animal studies has substantially improved understanding of IONM technology. Lessons learned from animal studies have immediate clinical applications in establishing reliable strategies for preventing intraoperative RLN injury. This article gives an overview of the research progress on IONM-relevant animal models.
PubMed-ID: 27867861
http://dx.doi.org/10.21037/gs.2016.09.06

Metastasis to the Thyroid Gland: A Critical Review.
Ann Surg Oncol,
I. J. Nixon, A. Coca-Pelaz, A. I. Kaleva, A. Triantafyllou, P. Angelos, R. P. Owen, A. Rinaldo, A. R. Shaha, C. E. Silver and A. Ferlito. 2016.
BACKGROUND: Metastasis to the thyroid gland from nonthyroid sites is an uncommon clinical presentation in surgical practice. The aim of this review was to assess its incidence management and outcomes. METHODS: A literature review was performed to identify reports of metastases to the thyroid gland. Both clinical and autopsy series were included. RESULTS: Metastases to the gland may be discovered at the time of diagnosis of the primary tumor, after preoperative investigation of a neck mass, or on histologic examination of a thyroidectomy specimen. The most common primary tumors in autopsy studies are from the lung. In clinical series, renal cell carcinoma is most common. For patients with widespread metastases in the setting of an aggressive malignancy, surgery is rarely indicated. However, when patients present with an isolated metastasis diagnosed during follow-up of indolent disease, surgery may achieve control of the central neck and even long-term cure. Other prognosticators include features of the primary tumor, time interval between initial diagnosis and metastasis, and extrathyroid extent of disease. CONCLUSIONS: In patients with thyroid metastases, communication among clinicians treating the thyroid and the index primary tumor is essential. The setting is complex, and decisions must be made considering the features of the primary tumor, overall burden of metastases, and comorbidities. Careful balancing of these factors influences individualized approaches.
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http://dx.doi.org/10.1245/s10434-016-5683-4

Diagnostic value of conventional chest radiography in intrathoracic goiters-retrospective analysis of 2570 patients.
Langenbecks Arch Surg, 402(2):251-5.
F. Benmiloud, M. Grino, C. Oliver and A. Denizot. 2017.
PURPOSE: Since intrathoracic goiters (IG), either cervico-mediastinal goiters (CMGs) or mediastinal nodules (MNs), can lead to sternotomies and/or evitable reoperations, their detection is mandatory before thyroid surgery. A systematic screening by CT scan or MRI is not conceivable because of their expensiveness. We tested if conventional chest radiography (CCR) could remain a good screening tool for IG before thyroid surgery. METHODS: In this retrospective study (2554 patients), CCR usefulness was evaluated in relation with patients' complaints, clinical examination, neck US, and anatomical and surgical findings. RESULTS: CMGs (n = 67) and MNs (n = 42) were symptomatic in 10 and 5 patients, respectively. Clinical examination or neck US suspected

their existence in 25 and 13 and 45 and 17 patients, respectively. Among the 50 IG detected by CCR (42 CMGs and 8 MNs), 4 CMGs and 2 MNs were missed by clinical examination or neck US. CCR failed to detect IG in 59 patients (54%): 25 CMGs (37%) and 34 MNs (80%). Twenty-eight IG (9 CMGs and 19 MNs) were discovered during surgery. CCR resulted in false positive in 88 out of 2445 patients (3.5%). CCR potentially avoided reoperation in two patients (a maximum saving of 6160 euro, whereas the total cost of CCR was 54,895 euro). CONCLUSIONS: CCR should not be used routinely for the preoperative detection of IG. Surgeons should preferably use clinical examination or neck US and directly perform CT scan when a mediastinal extension is suspected.
PubMed-ID: 27882431
http://dx.doi.org/10.1007/s00423-016-1534-9

Is it time to reconsider lobectomy in low-risk paediatric thyroid cancer?
Clin Endocrinol (Oxf), 86(4):591-6.
W. P. Kluijfhout, J. D. Pasternak, D. van der Kaay, M. R. Vriens, E. J. Propst and J. D. Wasserman. 2017.
OBJECTIVE: Current guidelines recommend total thyroidectomy for nearly all children with well-differentiated thyroid cancer (WDTC). These guidelines, however, derive from older data accrued prior to current high-resolution imaging. We speculate that there is a subpopulation of children who may be adequately treated with lobectomy. DESIGN: Retrospective analysis of prospectively maintained database. PATIENTS: Seventy-three children with WDTC treated between 2004 and 2015. MEASUREMENTS: We applied two different risk-stratification criteria to this population. First, we determined the number of patients meeting American Thyroid Association (ATA) 'low-risk' criteria, defined as disease grossly confined to the thyroid with either N0/Nx or incidental microscopic N1a disease. Second, we defined a set of 'very-low-risk' histopathological criteria, comprising unifocal tumours </=4 cm without predefined high-risk factors, and determined the proportion of patients that met these criteria. RESULTS: Twenty-seven (37%) males and 46 (63%) females were included in this study, with a mean age of 13.4 years. Ipsilateral- and contralateral multifocality were identified in 27 (37.0%) and 19 (26.0%) of specimens. Thirty-seven (51%) patients had lymph node metastasis (N1a = 18/N1b = 19). Pre-operative ultrasound identified all cases with clinically significant nodal disease. Of the 73 patients, 39 (53.4%) met ATA low-risk criteria and 16 (21.9%) met 'very-low-risk' criteria. All 'very-low-risk' patients demonstrated excellent response to initial therapy without persistence/recurrence after a mean follow-up of 36.4 months. CONCLUSIONS: Ultrasound and histopathology identify a substantial population that may be candidates for lobectomy, avoiding the risks and potential medical and psychosocial morbidity associated with total thyroidectomy. We propose a clinical framework to stimulate discussion of lobectomy as an option for low-risk patients.
PubMed-ID: 27896825
http://dx.doi.org/10.1111/cen.13287

Diagnostic accuracy of Thyroid Imaging Reporting and Data System in the prediction of malignancy in nodules with atypia and follicular lesion of undetermined significance cytologies.
Clin Endocrinol (Oxf), 86(4):584-90.
H. Baser, B. Cakir, O. Topaloglu, A. Alkan, S. B. Polat, H. T. Dogan, M. O. Yazicioglu, C. Aydin and R. Ersoy. 2017.
OBJECTIVE: Thyroid Imaging Reporting and Data System (TIRADS) is a simple and reliable reporting system for the prediction of malignancy. We aimed to determine the role of TIRADS in the prediction of malignancy in subcategories of Bethesda Category III, atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS). DESIGN & PATIENTS: A total of 461 nodules with AUS cytology in 450 patients and 179 nodules with FLUS cytology in 168 patients were included. Ultrasonography (US) features and postoperative histopathology results were documented. Every suspicious US feature was scored as 1 and 0 according to the presence or not, respectively. TIRADS category of each nodule was determined. RESULTS: In AUS subcategory, histopathologically malignant nodules had significantly different TIRADS categories compared to benign nodules (P = 0.001), but this was not the case in FLUS subcategory (P = 0.121). In AUS group, malignant nodules had significantly higher prevalance of microcalcification, hypoechogenicity and anteroposterior/transverse ratio than benign ones (P < 0.001, P < 0.001 and P = 0.003, respectively) and TIRADS categories of 4c and 5 were more frequent in malignant nodules (P < 0.05). Microcalcification, hypoechogenicity and TIRADS were found to be associated with malignancy in multivariate logistic regression analysis in this subcategory. TIRADS category >/=4c was associated with malignancy (AUC +/- SE: 0.584 +/- 0.028). In FLUS subcategory, there was no significant difference between histopathologically malignant and benign nodules with respect to suspicious US features (P > 0.05, all). CONCLUSION: TIRADS seems to be useful in predicting malignancy and planning further management in the AUS subcategory, but not quite so in the FLUS subcategory.

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http://dx.doi.org/10.1111/cen.13274

Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany.
Eur J Endocrinol, 175(6):521-9.
J. Wendler, M. Kroiss, K. Gast, M. C. Kreissl, S. Allelein, U. Lichtenauer, R. Blaser, C. Spitzweg, M. Fassnacht, M. Schott, D. Fuhrer and V. Tiedje. 2016.
CONTEXT: Anaplastic thyroid carcinoma (ATC) is an orphan disease and confers a dismal prognosis. Standard treatment is not established. OBJECTIVE: The aim of this study is to describe clinical characteristics, current treatment regimens and outcome of ATC and to identify clinical prognostic markers and treatment factors associated with improved prognosis. DESIGN: Retrospective cohort study at five German tertiary care centers. PATIENTS AND METHODS: Totally 100 ATC patients diagnosed between 2000 and 2015 were included in the analysis. Disease-specific overall survival (OS) was compared with the Kaplan-Meier method and log-rank test; Cox proportional hazard model was used to identify risk factors. RESULTS: The 6-month, 1-year and 5-year disease-specific OS rates were 37, 28 and 5%, respectively. Stage-dependent OS at 6 months was 78, 54 and 18% for stage IVA, B and C, respectively. 29% patients survived >1 year. Multivariate analysis of OS identified age >/=70 years, incomplete local resection status and the presence of distant metastasis as significant risk factors associated with shorter survival. Radical surgery (hazard ratio [HR] 2.20, 95% confidence interval (CI) 1.19-4.09, P = 0.012), external beam radiation therapy (EBRT) >/=40 Gy (HR = 0.34, 0.15-0.76, P = 0.008) and any kind of chemotherapy (CTX) (HR = 11.64, 2.42-60.39, P = 0.003) were associated with longer survival in multivariate analyses adjusted for age and tumor stage. A multimodal treatment regimen was significantly associated with a survival benefit (HR = 1.04, 1.01-1.08, P < 0.0001) only in IVC patients. CONCLUSION: Disease-specific OS is still poor in ATC. Treatment factors associated with improved OS provide a rationale to devise treatment pathways for routine care. Collaborative research structures should be aimed to advance treatment of ATC.
PubMed-ID: 27926471
http://dx.doi.org/10.1530/EJE-16-0574

[Active surveillance versus primary surgery for papillary microcarcinoma of the thyroid gland].
Chirurg, 88(1):71.
H. Dralle and F. Weber. 2017.
PubMed-ID: 27928601
http://dx.doi.org/10.1007/s00104-016-0331-x

Postoperative thyroglobulin and neck ultrasound in the risk re-stratification and decision to perform 131I ablation.
J Clin Endocrinol Metab:jc20162860.
A. Matrone, C. Gambale, P. Piaggi, D. Viola, C. Giani, L. Agate, V. Bottici, F. Bianchi, G. Materazzi, P. Vitti, E. Molinaro and R. Elisei. 2016.
CONTEXT: For many years, total thyroidectomy (TTx) and radioiodine remnant ablation (RRA) represented the initial treatment of differentiated thyroid cancer (DTC). There is currently much debate surrounding the clinical impact of RRA, particularly in low (LR) and intermediate (IR) risk DTC. OBJECTIVE: To evaluate the role of postoperative High-Sensitive Thyroglobulin on L-thyroxine (LT4-HSTg) and postoperative neck ultrasound (nUS) in risk re-stratification and decision to perform RRA. PATIENTS: 505 patients with LR or IR DTC were evaluated 3-4 months after TTx. All patients underwent RRA and a post-therapeutic whole body scan (ptWBS). RESULTS: After TTx, 29.7% DTC patients had LT4-HSTg <0.1 ng/ml (Group A) and could be re-stratified as cured: 1/150 had lymphnode metastases (LN-mets) detected by nUS but negative at ptWBS. 56.8% DTC patients had LT4-HSTg between 0.1 and </=1 ng/ml (Group B) and could be re-stratified either as cured or not cured according to Tg cut-off. In this group, 15/287(5.2%) had metastases but only 7 were detected by ptWBS alone: the diagnosis of these lesions (7/287;2.4%) would be delayed if RRA was not performed. 13.5% DTC patients had LT4-HSTg >1 ng/ml (Group C) and could not be considered as cured by definition. LN-mets were present in 11/68(16.2%) cases, all detected by nUS. No correlation was found with the presence of metastases and serum LT4-HSTg values or with the level of risk. CONCLUSIONS: LT4-HSTg measured 3-4 months after TTx is important in the risk re-stratification of DTC patients but is less relevant than nUS in the decision to perform RRA.
PubMed-ID: 27929713
http://dx.doi.org/10.1210/jc.2016-2860

ATF4 Targets RET for Degradation and is a Candidate Tumor Suppressor Gene in Medullary Thyroid Cancer.
J Clin Endocrinol Metab:jc20162878.
R. Bagheri-Yarmand, M. D. Williams, E. G. Grubbs and R. F. Gagel. 2016.
CONTEXT: Medullary thyroid cancer (MTC) is an aggressive tumor that harbors activating mutations of the RET proto-oncogene. We previously reported that RET inhibits transcriptional activity of ATF4, the master regulator of the stress response pathway, to prevent cell death. OBJECTIVE: We hypothesized that loss of function of ATF4 play a role in initiation of MTC. DESIGN: Targeted deletion of ATF4 in mice was used to assess ATF4 function in the thyroid gland. ATF4 overexpression was achieved by adenoviral and lentiviral vectors. We used immunohistochemical analysis and western blotting of MTC tumors to determine protein levels of RET and ATF4 and the Kaplan-Meier method to determine their association with clinical outcome. RESULTS: Targeted deletion of ATF4 in mice causes C-cell hyperplasia, a precancerous lesion for MTC. Forced ATF4 expression decreased survival of MTC cells and blocked the activation of RET downstream signaling pathways (phosphorylated ERK, phosphorylated AKT, and p70S6K). ATF4 knockdown decreased sensitivity to tyrosine kinase inhibitor-induced apoptosis. Moreover, ATF4 expression decreased RET protein levels by promoting RET ubiquitination. We found decreased or loss of ATF4 in 52% of MTC tumors (n=39) compared with normal thyroid follicle cells. A negative correlation was observed between RET and ATF4 protein levels in MTC tumors, and low ATF4 expression was associated with poor overall survival in MTC patients. CONCLUSIONS: ATF4 was identified as a negative regulator of RET, a candidate tumor suppressor gene, and may be a molecular marker that distinguishes patients at high risk of MTC from those with a longer survival prognosis.
PubMed-ID: 27935748
http://dx.doi.org/10.1210/jc.2016-2878

Long-term Quality of Life in Adult Survivors of Pediatric Differentiated Thyroid Carcinoma.
J Clin Endocrinol Metab:jc20162246.
M. Nies, M. S. Klein Hesselink, G. A. Huizinga, E. Sulkers, A. H. Brouwers, J. G. Burgerhof, E. W. van Dam, B. Havekes, M. M. van den Heuvel-Eibrink, E. P. Corssmit, L. C. Kremer, R. T. Netea-Maier, H. J. van der Pal, R. P. Peeters, J. T. Plukker, C. M. Ronckers, H. M. van Santen, W. J. Tissing, T. P. Links and G. Bocca. 2016.
INTRODUCTION: Little is known about long-term quality of life (QoL) of survivors of pediatric differentiated thyroid carcinoma (DTC). Therefore, this study aimed to evaluate generic health-related QoL (HRQoL), fatigue, anxiety, and depression in adult survivors of pediatric DTC compared with matched controls, and to evaluate thyroid cancer-specific HRQoL in survivors only. MATERIALS AND METHODS: Adult survivors of pediatric DTC, diagnosed between 1970-2013 at age <18 years were included. Exclusion criteria were a follow-up <5 years, attained age <18 years or diagnosis of DTC as a second malignant neoplasm. Controls were matched by age, gender, and socio-economic status. Survivors and controls were asked to complete three questionnaires (SF-36(HRQoL), MFI-20 (fatigue) and HADS(anxiety/depression)). Survivors were also asked to complete the THYCA-QoL (thyroid cancer-specific HRQoL). RESULTS: Sixty-seven survivors and 56 controls were included. Median age of survivors at evaluation was 34.2 years (range18.8-61.7). Median follow-up was 17.8 years (range 5.0-44.7). On most QoL subscales, scores of survivors and controls did not differ significantly. However, survivors had more physical problems (P =.031), role limitations due to physical problems (P =.021), and mental fatigue (P =.016) than controls. Some thyroid cancer-specific complaints(e.g. sensory complaints, headache and chilliness) were present in survivors. Unemployment and more extensive disease- or treatment characteristics were most frequently associated with worse QoL. CONCLUSIONS: Overall, long-term QoL in survivors of pediatric DTC was normal. Survivors experienced impairment of QoL in some domains(physical problems, mental fatigue and various thyroid cancer-specific complaints), but mostly in mild forms. Factors possibly affecting QoL need further exploration.
PubMed-ID: 28001468
http://dx.doi.org/10.1210/jc.2016-2246

Is the reproducibility of shear wave elastography of thyroid nodules high enough for clinical use? A methodological study.
Clin Endocrinol (Oxf), 86(4):606-13.
K. Z. Swan, V. E. Nielsen, B. M. Bibby and S. J. Bonnema. 2017.
OBJECTIVE: To systematically assess the reproducibility of thyroid ultrasonographic shear wave elastography (SWE). CONTEXT: SWE has been suggested as a potential tool for thyroid nodule evaluation, but assessment of its reproducibility has been insufficiently addressed. DESIGN: SWE examinations were performed prospectively by two investigators. PATIENTS: Seventy-two patients (male/female: 19/53; mean age: 53 +/- 14 years; malignant/benign 17/55) undergoing thyroid surgery were enrolled in the study. MEASUREMENTS: Repeated and blinded measurements of elasticity index (EI) in predefined regions of interest (ROI) were

collected. The inter- and intrarater agreement, along with the day-to-day agreement, was evaluated in terms of the 95% limits of agreement (LOA). Results are presented as a ratio, by which 1.0 indicates perfect agreement. RESULTS: The interrater, intrarater and day-to-day LOA showed ratios between repeated measurements of 1.7-3.6, 1.8-3.7 and 2.2-2.9, respectively. These values reflect a low to moderate degree of agreement for all EI outcomes. The interrater LOA was higher for malignant nodules compared with benign nodules for six of seven EI outcomes ($P < 0.001$-0.03). The proportion of agreement calculated from the optimum cutoff point for differentiating malignant from benign nodules was 63-88% for the investigated EI outcomes. CONCLUSIONS: In this methodological study, EI measured by thyroid SWE seems suboptimal for clinical use, due to a low inter- and intrarater agreement. That EI varies from day to day furthermore jeopardizes the validity of the method. Although the proportion of agreement was acceptable for some EI parameters, it is questionable whether EI assessments can reliably differentiate malignant from benign nodules in the individual patient.
PubMed-ID: 28002625
http://dx.doi.org/10.1111/cen.13295

Thyroid Surgery in a Resource-Limited Setting.
Otolaryngol Head Neck Surg, 156(3):464-71.
A. Jafari, D. Campbell, B. H. Campbell, H. N. Ngoitsi, T. M. Sisenda, M. Denge, B. C. James and S. R. Cordes. 2017.
Objective The present study reviews a series of patients who underwent thyroid surgery in Eldoret, Kenya, to demonstrate the feasibility of conducting long-term (>1 year) outcomes research in a resource-limited setting, impact on the quality of life of the recipient population, and inform future humanitarian collaborations. Study Design Case series with chart review. Setting Tertiary public referral hospital in Eldoret, Kenya. Subjects and Methods Twenty-one patients were enrolled during the study period. A retrospective chart review was performed for all adult patients who underwent thyroid surgery during humanitarian trips (2010-2015). Patients were contacted by mobile telephone. Medical history and physical examination, including laryngoscopy, were performed, and the SF-36 was administered (a quality-of-life questionnaire). Laboratory measurements of thyroid function and neck ultrasound were obtained. Results The mean follow-up was 33.6 +/- 20.2 months after surgery: 37.5% of subtotal thyroidectomy patients and 15.4% of lobectomy patients were hypothyroid postoperatively according to serologic studies. There were no cases of goiter recurrence or malignancy. All patients reported postoperative symptomatic improvement and collectively showed positive pre- and postoperative score differences on the SF-36. Conclusion Although limited by a small sample size and the retrospective nature, our study demonstrates the feasibility of long-term surgical and quality-of-life outcomes research in a resource-limited setting. The low complication rates suggest minimal adverse effects of performing surgery in this context. Despite a considerable rate of postoperative hypothyroidism, it is in accordance with prior studies and emphasizes the need for individualized, longitudinal, and multidisciplinary care. Quality-of-life score improvements suggest benefit to the recipient population.
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Parathyroids

Meta-Analyses

Focused Versus Bilateral Parathyroid Exploration for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis.
Ann Surg Oncol,
M. Jinih, E. O'Connell, D. P. O'Leary, A. Liew and H. P. Redmond. 2016.
BACKGROUND: Focused exploration (FE) and bilateral parathyroid exploration (BE) are the standard surgical options for patients with primary hyperparathyroidism. However, the relative risk of recurrence, persistence, overall failure, reoperation, and any complications associated with either surgical approach is unclear. This study compared the outcomes and complication rates after FE and BE for patients with primary hyperparathyroidism. METHODS: PubMed and Embase were searched for studies comparing these outcomes between FE and BE. A meta-analysis was performed using RevMan 5.3 software. Published data were pooled using the DerSimonian random-effect model, and results were presented as odds ratio (OR) or mean difference with 95% confidence interval (CI). RESULTS: A total of 12,743 patients from 19 studies were included in this meta-analysis. In comparison with BE, the FE arm had comparable rates of recurrence (OR 1.08; 95% CI 0.59-2.00; p = 0.80; n = 9 studies), persistence (OR 0.89; 95% CI 0.58-1.35; p = 0.58; n = 13), overall failure (OR 0.88; 95% CI 0.58-1.34; p = 0.56; n = 13), and reoperation (OR 1.05; 95% CI 0.25-4.32; p = 0.95, n = 4). The operative time was significantly shorter (mean difference = -39.86; 95% CI -53.05 to -26.84; p < 0.01, n = 9), with a lower overall complication rate in the FE arm (OR 0.35; 95% CI 0.15-0.84; p = 0.02; n = 12). The latter was attributed predominantly to a lower risk of transient hypocalcemia (OR 0.36; 95% CI 0.14-0.90; p = 0.03; n = 9). There was a significant heterogeneity among these studies for all outcomes except for disease recurrence. CONCLUSIONS: Compared with BE, FE has similar recurrence, persistence, and reoperation rates but significantly lower overall complication rates and shorter operative time.
PubMed-ID: 27896505
http://dx.doi.org/10.1245/s10434-016-5694-1

Use of PET tracers for parathyroid localization: a systematic review and meta-analysis.
Langenbecks Arch Surg, 401(7):925-35.
W. P. Kluijfhout, J. D. Pasternak, F. T. Drake, T. Beninato, J. E. Gosnell, W. T. Shen, Q. Y. Duh, I. E. Allen, M. R. Vriens, B. de Keizer, M. H. Pampaloni and I. Suh. 2016.
PURPOSE: The great spatial and temporal resolution of positron emission tomography might provide the answer for patients with primary hyperparathyroidism (pHPT) and non-localized parathyroid glands. We performed a systematic review of the evidence regarding all investigated tracers. METHODS: A study was considered eligible when the following criteria were met: (1) adults >/=17 years old with non-familial pHPT, (2) evaluation of at least one PET isotope, and (3) post-surgical and pathological diagnosis as the gold standard. Performance was expressed in sensitivity and PPV. RESULTS: Twenty-four papers were included subdivided by radiopharmaceutical: 14 studies investigated L-[11C]Methionine (11C-MET), one [11C]2-hydroxy-N,N,N-trimethylethanamium (11C-CH), six 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG), one 6-[18F] fluoro-L-DOPA (18F-DOPA), and three N-[(18F)Fluoromethyl]-2-hydroxy-N,N-dimethylethanaminium (18F-FCH). The 14 studies investigating MET included a total of 327 patients with 364 lesions. Sensitivity for the detection of a lesion in the correct quadrant had a pooled estimate of 69 % (95 % CI 60-78 %). Heterogeneity was overall high with I2 of 51 % (p = 0.01) for all 14 studies. Pooled PPV ranged from 91 to 100 % with a pooled estimate of 98 % (95 % CI 96-100 %). Of the other investigated tracers, 18-FCH seems the most promising with high diagnostic performance. CONCLUSIONS: The results of our meta-analysis show that 11C-MET PET has an overall good sensitivity and PPV and may be considered a reliable second-line imaging modality to enable minimally invasive parathyroidectomy. Our literature review suggests that 18F-FCH PET may produce even greater accuracy and should be further investigated using both low-dose CT and MRI for anatomical correlation.
PubMed-ID: 27086309
http://dx.doi.org/10.1007/s00423-016-1425-0

Outcomes of Parathyroidectomy in Patients with Primary Hyperparathyroidism: A Systematic Review and Meta-analysis.
World J Surg, 40(10):2359-77.
N. M. Singh Ospina, R. Rodriguez-Gutierrez, S. Maraka, A. E. Espinosa de Ycaza, S. Jasim, A. Castaneda-Guarderas, M. R. Gionfriddo, A. Al Nofal, J. P. Brito, P. Erwin, M. Richards, R. Wermers and V. M. Montori.

2016.
BACKGROUND: Parathyroidectomy is a definitive treatment for primary hyperparathyroidism. Patients contemplating this intervention will benefit from knowledge regarding the expected outcomes and potential risks of the currently available surgical options. PURPOSE: To appraise and summarize the available evidence regarding benefits and harms of minimally invasive parathyroidectomy (MIP) and bilateral neck exploration (BNE). DATA SOURCES: A comprehensive search of multiple databases (MEDLINE, EMBASE, and Scopus) from each database's inception to September 2014 was performed. STUDY SELECTION: Eligible studies evaluated patients with primary hyperparathyroidism undergoing MIP or BNE. DATA EXTRACTION: Reviewers working independently and in duplicate extracted data and assessed the risk of bias. DATA SYNTHESIS: We identified 82 observational studies and 6 randomized trials at moderate risk of bias. Most of them reported outcomes after MIP (n = 71). Using random-effects models to pool results across studies, the cure rate was 98 % (95 % CI 97-98 %, I (2) = 10 %) with BNE and 97 % (95 % CI 96-98 %, I (2) = 86 %) with MIP. Hypocalcemia occurred in 14 % (95 % CI 10-17 % I (2) = 93 %) of the BNE cases and in 2.3 % (95 % CI 1.6-3.1 %, I (2) = 87 %) with MIP (P < 0.001). There was a statistically significant lower risk of laryngeal nerve injury with MIP (0.3 %) than with BNE (0.9 %), but similar risk of infection (0.5 vs. 0.5 %) and mortality (0.1 vs. 0.5 %). LIMITATIONS: The available evidence, mostly observational, is at moderate risk of bias, and limited by indirect comparisons and inconsistency for some outcomes (cure rate, hypocalcemia). CONCLUSION: MIP and BNE are both effective surgical techniques for the treatment of primary hyperparathyroidism. The safety profile of MIP appears superior to BNE (lower rate of hypocalcemia and recurrent laryngeal nerve injury).
PubMed-ID: 27094563
http://dx.doi.org/10.1007/s00268-016-3514-1

Randomized controlled trials

Total Parathyroidectomy With Routine Thymectomy and Autotransplantation Versus Total Parathyroidectomy Alone for Secondary Hyperparathyroidism: Results of a Nonconfirmatory Multicenter Prospective Randomized Controlled Pilot Trial.
Ann Surg, 264(5):745-53.
K. Schlosser, D. K. Bartsch, M. K. Diener, C. M. Seiler, T. Bruckner, C. Nies, M. Meyer, J. Neudecker, P. E. Goretzki, G. Glockzin, R. Konopke and M. Rothmund. 2016.
OBJECTIVE: This randomized controlled multicenter pilot trial was conducted to find robust estimates for the rates of recurrence of 2 surgical strategies for secondary hyperparathyroidism (SHPT) within 36 months of follow-up. BACKGROUND: SHPT is a frequent consequence of chronic renal failure. Total parathyroidectomy with autotransplantation (TPTX+AT) and subtotal parathyroidectomy (SPTX) are the standard surgical procedures. Total parathyroidectomy alone (TPTX) might be a good alternative, as morbidity and recurrence rates are low according to small-scale retrospective studies. METHODS: The trial was performed as a nonconfirmatory randomized controlled pilot trial with 100 patients on long-term dialysis with otherwise uncontrollable SHPT to generate data on the rate of recurrent disease within a 3-year follow-up period after TPTX or TPTX+AT. Parathyroid hormone (PTH) and calcium levels, recurrent or persistent hyperparathyroidism, parathyroid reoperations, morbidity, and mortality were evaluated during a 3-year follow-up. RESULTS: A total of 52 patients underwent TPTX and 48 TPTX+AT. Patient characteristics, preoperative baseline data, duration of surgery (02:29 vs 02:47 hrs, P = 0.17) and mean hospital stay (10 +/- 7.1 vs 8 +/- 3.7 days, P = 0.11) did not differ significantly. Persistent SHPT developed in 1 TPTX and 2 TPTX+AT patients. None of the TPTX patients required delayed parathyroid AT to treat permanent hypoparathyroidism. Serum-calcium values were similar (2.1 +/- 0.3 vs 2.1 +/- 0.2, P = 0.95) whereas PTH rose by time in the TPTX+AT group and was significantly higher at the end of follow-up when compared with the TPTX group (31.7 +/- 43.6 vs 98.2 +/- 156.8, P = 0.02). Recurrent SHPT developed in 4 TPTX+AT and none of the TPTX patients. CONCLUSIONS: TPTX+AT and TPTX seem to be safe and equally effective for the treatment of otherwise uncontrollable SHPT. TPTX seems to suppress PTH more effectively and showed no recurrences after 3 years. The hypothesis that TPTX is superior to TPTX+AT referring to the rate of recurrent SHPT has to be tested in a large-scale confirmatory trial. Nevertheless, TPTX seems to be a feasible alternative therapeutic option for the surgical treatment of SHPT.
PubMed-ID: 27741007
http://dx.doi.org/10.1097/SLA.0000000000001875

Consensus Statements/Guidelines

The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism.
JAMA Surg, 151(10):959-68.
S. M. Wilhelm, T. S. Wang, D. T. Ruan, J. A. Lee, S. L. Asa, Q. Y. Duh, G. M. Doherty, M. F. Herrera, J. L. Pasieka, N. D. Perrier, S. J. Silverberg, C. C. Solorzano, C. Sturgeon, M. E. Tublin, R. Udelsman and S. E. Carty. 2016.
Importance: Primary hyperparathyroidism (pHPT) is a common clinical problem for which the only definitive management is surgery. Surgical management has evolved considerably during the last several decades. Objective: To develop evidence-based guidelines to enhance the appropriate, safe, and effective practice of parathyroidectomy. Evidence Review: A multidisciplinary panel used PubMed to review the medical literature from January 1, 1985, to July 1, 2015. Levels of evidence were determined using the American College of Physicians grading system, and recommendations were discussed until consensus. Findings: Initial evaluation should include 25-hydroxyvitamin D measurement, 24-hour urine calcium measurement, dual-energy x-ray absorptiometry, and supplementation for vitamin D deficiency. Parathyroidectomy is indicated for all symptomatic patients, should be considered for most asymptomatic patients, and is more cost-effective than observation or pharmacologic therapy. Cervical ultrasonography or other high-resolution imaging is recommended for operative planning. Patients with nonlocalizing imaging remain surgical candidates. Preoperative parathyroid biopsy should be avoided. Surgeons who perform a high volume of operations have better outcomes. The possibility of multigland disease should be routinely considered. Both focused, image-guided surgery (minimally invasive parathyroidectomy) and bilateral exploration are appropriate operations that achieve high cure rates. For minimally invasive parathyroidectomy, intraoperative parathyroid hormone monitoring via a reliable protocol is recommended. Minimally invasive parathyroidectomy is not routinely recommended for known or suspected multigland disease. Ex vivo aspiration of resected parathyroid tissue may be used to confirm parathyroid tissue intraoperatively. Clinically relevant thyroid disease should be assessed preoperatively and managed during parathyroidectomy. Devascularized normal parathyroid tissue should be autotransplanted. Patients should be observed postoperatively for hematoma, evaluated for hypocalcemia and symptoms of hypocalcemia, and followed up to assess for cure defined as eucalcemia at more than 6 months. Calcium supplementation may be indicated postoperatively. Familial pHPT, reoperative parathyroidectomy, and parathyroid carcinoma are challenging entities that require special consideration and expertise. Conclusions and Relevance: Evidence-based recommendations were created to assist clinicians in the optimal treatment of patients with pHPT.
PubMed-ID: 27532368
http://dx.doi.org/10.1001/jamasurg.2016.2310

Other Articles

Evaluation of malignant parathyroid tumours in two European cohorts of patients with sporadic primary hyperparathyroidism.
Langenbecks Arch Surg, 401(7):943-51.
A. Ozolins, Z. Narbuts, A. Vanags, Z. Simtniece, Z. Visnevska, A. Akca, D. Wirowski, J. Gardovskis, I. Strumfa and P. E. Goretzki. 2016.
PURPOSE: Parathyroid carcinoma (PC) is remarkable for its rare occurrence and challenging diagnostics. PC accounts for 0.1-5 % cases of primary hyperparathyroidism (PHPT). The differentiation from benign tumours is difficult even by morphological criteria. To address these issues, we assessed the PC frequency in two separate European PHPT cohorts and evaluated the demographic, clinical, morphological and molecular background. METHODS: A retrospective study was carried out, using continuously maintained database (2005-2014) of PHPT patients from two tertiary referral university hospitals in Europe. The demographic, clinical data and frequency of PC among surgically treated PHPT was detected. Immunohistochemistry (IHC) was performed to detect parafibromin, representing protein product of HRPT2 gene and proliferation marker Ki-67. RESULTS: Both PHPT cohorts were characterised by close mean age values (58.6 and 58.0 years) and female predominance. The frequency of PC differed significantly between the cohorts: 2.1 vs. 0.3 %; p = 0.004. PC was characterised by invariable complete loss of parafibromin contrasting with parathyroid adenomas. The proliferation fraction was similar in both PC cohorts (10.6 and 11.0 %). PC showed significantly higher proliferation fraction than typical parathyroid adenomas (1.6 %), atypical adenomas (1.6 %) or adenomas featuring focal loss of parafibromin (2.2 %). CONCLUSIONS: PC frequency can range significantly between the

two European cohorts. The differences can be attributable to selection bias of patients referred for surgery and are not caused by discordant definition of malignant parathyroid histology. Diffuse loss of parafibromin and increased proliferation fraction by Ki-67 are valuable adjuncts in PC diagnostics due to significant differences with various clinical and morphological subtypes of adenoma.
PubMed-ID: 26658808
http://dx.doi.org/10.1007/s00423-015-1361-4

Compliance with recommendations on surgery for primary hyperparathyroidism-from guidelines to real practice: results from an Iberian survey.
Langenbecks Arch Surg, 401(7):953-63.
J. Villar-Del-Moral, J. Capela-Costa, A. Jimenez-Garcia, A. Sitges-Serra, D. Casanova-Rituerto, J. Rocha, J. M. Martos-Martinez, A. de la Quintana-Basarrate, J. Rosa-Santos, X. Guirao-Garriga, J. M. Bravo-de-Lifante, O. Vidal-Perez, A. Moral-Duarte and J. Polonia. 2016.
PURPOSE: Knowledge about compliance with recommendations derived from the positional statement of the European Society of Endocrine Surgeons on modern techniques in primary hyperparathyroidism surgery and the Third International Workshop on management of asymptomatic primary hyperparathyroidism is scarce. Our purpose was to check it on a bi-national basis and determine whether management differences may have impact on surgical outcomes. METHODS: An online survey including questions about indications, preoperative workup, surgical approach, intraoperative adjuncts, and outcomes was sent to institutions affiliated to the endocrine surgery divisions of the National Surgical Societies from Spain and Portugal. A descriptive evaluation of the responses was performed. Finally, we assessed the correlation between the different types of management with the achievement of optimal results, defined as a cure rate equal or greater than the median of all interviewed institutions. RESULTS: Fifty-seven hospitals (41 Spanish, 16 Portuguese) answered the survey. First-ordered imaging tests were neck ultrasound and sestamibi scan. Facing negative or non-concordant results, 44 % of surgeons ordered additional tests before first-time surgery, and 84 % before reoperations. When indicated, selective parathyroidectomy was an acceptable option for 95 % of institutions as first-time surgery and for 51 % in reoperations. Intraoperative parathormone measurements were used by 92 % of departments. The surgical outcomes were good in most institutions (median cure rate 97 %) and were influenced mostly by the presence of an endocrine surgery unit in the surgical department (p = 0.038). CONCLUSIONS: Practice of Iberian endocrine surgeons is consistent with current recommendations on surgery for primary hyperparathyroidism, with variability in some areas.
PubMed-ID: 26686853
http://dx.doi.org/10.1007/s00423-015-1362-3

The CaPTHUS score as predictor of multiglandular primary hyperparathyroidism in a European population.
Langenbecks Arch Surg, 401(7):937-42.
M. Mogollon-Gonzalez, P. Notario-Fernandez, M. Dominguez-Bastante, A. Molina-Raya, M. Serradilla-Martin, N. Munoz-Perez, J. I. Arcelus-Martinez, J. Villar-Del-Moral and J. A. Jimenez-Rios. 2016.
PURPOSE: Focused parathyroidectomy has been proven to be a safe technique for the treatment of single-gland primary hyperparathyroidism (PHPT). The CaPTHUS scoring model has been reported to be an accurate preoperative diagnostic tool for distinguishing single-gland (SGD) from multiglandular disease (MGD), including preoperative serum calcium and PTH values plus ultrasound and Sestamibi scanning. The purpose of the present study was to validate the CaPTHUS model for the population in southern Europe, since the North American and the European populations show different clinicopathological profiles in PHPT. METHODS: This is a retrospective review of a prospectively maintained database of patients diagnosed with PHPT who underwent surgical treatment in a single referral center. Differences between SGD and MGD groups were analyzed using chi-square and Fisher's exact tests for categorical variables and Student's t test for continuous variables. Overall diagnostic accuracy of the scoring model was assessed by the area under the receiver operating characteristic (ROC) curve (AUC). A p < 0.05 level was accepted as significant. RESULTS: From January 2001 to November 2014, 241 patients were included in the study, of whom 92.1 % had SGD and 71.8 % had a CaPTHUS score >/=3. SGD was distinguished from MGD (p < 0.001) using the dichotomous scoring model based on an AUC value of 0.762. Scores >/=3 had a sensitivity of 76.5 % and a positive predictive value of 96 % for SGD. CONCLUSIONS: Despite good test performance, a CaPTHUS score >/=3 does not discard MGD definitely. Intraoperative adjuncts are still needed to further reduce the risk of missing MGD during selective parathyroidectomy.
PubMed-ID: 27080995
http://dx.doi.org/10.1007/s00423-016-1426-z

Differentiating Atypical Parathyroid Neoplasm from Parathyroid Cancer.
Ann Surg Oncol, 23(9):2889-97.
I. Christakis, N. Bussaidy, C. Clarke, L. J. Kwatampora, C. L. Warneke, A. M. Silva, M. D. Williams, E. G. Grubbs, J. E. Lee and N. D. Perrier. 2016.
INTRODUCTION: The differentiation of benign parathyroid gland atypia and true parathyroid carcinoma (PC) can be challenging. In some instances, patients are classified as having 'atypical parathyroid neoplasms' (APNs), explicitly acknowledging that the distinction between benign and malignant disease appears impossible to determine. This 'grey area' diagnosis makes rendering an accurate prognosis difficult, and clouds clinical management and treatment planning. METHODS: We performed a retrospective chart review of all patients undergoing operation for primary hyperparathyroidism in our institution (2000-2014). Patients with a histopathological diagnosis of PC or APN were included. Demographics, clinical characteristics, and survival rates were analyzed, and analysis was conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). RESULTS: Fifty-four patients were included in the study-31 (57.41 %) with PC and 23 (42.59 %) with APN. PC versus APN was associated with higher parathyroid hormone (PTH) (p = 0.005) and with males (p = 0.002). Five-year overall survival (OS) from diagnosis was 82.64 % [95 % confidence interval (CI) 59.82-93.17] for the PC group and 93.33 % (95 % CI 61.26-99.03) for the APN group, while the 5-year recurrence-free survival rate was 59.63 % (95 % CI 36.32-76.81) in the PC group and 90.91 % (95 % CI 50.81-98.67) in the APN group. CONCLUSION: PC and APN are distinct clinical entities with differences in tumor biology reflected in overall recurrence rates, disease-free survival, and OS. APNs present with a less accentuated biochemical profile and demonstrate an indolent clinical course compared with PCs. Efforts to improve categorization and staging of PC and APN are needed.
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http://dx.doi.org/10.1245/s10434-016-5248-6

More Extensive Surgery May Not Improve Survival Over Parathyroidectomy Alone in Parathyroid Carcinoma.
Ann Surg Oncol, 23(9):2898-904.
S. Young, J. X. Wu, N. Li, M. W. Yeh and M. J. Livhits. 2016.
BACKGROUND: Parathyroid carcinoma is a rare cause of hyperparathyroidism. Surgery is the only effective therapy, and en bloc resection has previously been recommended. METHODS: A retrospective cohort study of patients with parathyroid carcinoma in the California Cancer Registry and California Office of Statewide Health Planning and Development database from 1999 to 2012 was performed. Patients were stratified by surgical procedure: parathyroidectomy alone, thyroid resection with en bloc parathyroidectomy, and parathyroidectomy with delayed thyroid resection within 6 months. The primary outcome was overall survival stratified by surgical procedure. Secondary outcomes included perioperative complications within 30 days of initial surgery and disease-related complications. RESULTS: Among our study cohort (n = 136), 60 patients underwent parathyroidectomy alone, 58 patients had en bloc resection, and 18 patients had parathyroidectomy followed by delayed thyroid resection. For the entire cohort, the 5-year and 10-year overall survival rates were 86.9 and 72.0 %. The overall survival rates did not differ between the surgical procedures. Factors that were independently associated with decreased survival included age (hazard ratio 1.05, P = 0.017) and distant metastases (hazard ratio 4.73, P = 0.017), while en bloc resection and delayed thyroid resection were not associated with improved survival over parathyroidectomy alone. There were no differences in perioperative or disease-related complications across procedures. CONCLUSIONS: The addition of thyroid resection to parathyroidectomy may not improve survival for patients with parathyroid carcinoma over complete parathyroid resection alone. A larger prospective study is necessary to determine the optimal treatment to achieve long-term survival with minimal complications.
PubMed-ID: 27177488
http://dx.doi.org/10.1245/s10434-016-5256-6

Autosomal dominant hypocalcaemia due to a novel CASR mutation: clinical and genetic implications.
Clin Endocrinol (Oxf), 85(3):495-7.
L. Gagliardi, M. G. Burt, J. Feng, N. K. Poplawski and H. S. Scott. 2016.
PubMed-ID: 27177819
http://dx.doi.org/10.1111/cen.13104

Intraoperative Near-infrared Imaging for Parathyroid Gland Identification by Auto-fluorescence: A Feasibility Study.
World J Surg, 40(9):2131-8.
F. De Leeuw, I. Breuskin, M. Abbaci, O. Casiraghi, H. Mirghani, A. Ben Lakhdar, C. Laplace-Builhe and D. Hartl. 2016.
BACKGROUND: Parathyroid glands (PGs) can be particularly hard to distinguish from surrounding tissue and thus can be damaged or removed during thyroidectomy. Postoperative hypoparathyroidism is the most common complication after thyroidectomy. Very recently, it has been found that the parathyroid tissue shows near-infrared (NIR) auto-fluorescence which could be used for intraoperative detection, without any use of contrast agents. The work described here presents a histological validation ex vivo of the NIR imaging procedure and evaluates intraoperative PG detection by NIR auto-fluorescence using for the first time to our knowledge a commercially available clinical NIR imaging device. METHODS: Ex vivo study on resected operative specimens combined with a prospective in vivo study of consecutive patients who underwent total or partial thyroid, or parathyroid surgery at a comprehensive cancer center. During surgery, any tissue suspected to be a potential PG by the surgeon was imaged with the Fluobeam 800 ((R)) system. NIR imaging was compared to conventional histology (ex vivo) and/or visual identification by the surgeon (in vivo). RESULTS: We have validated NIR auto-fluorescence with an ex vivo study including 28 specimens. Sensitivity and specificity were 94.1 and 80 %, respectively. Intraoperative NIR imaging was performed in 35 patients and 81 parathyroids were identified. In 80/81 cases, the fluorescence signal was subjectively obvious on real-time visualization. We determined that PG fluorescence is 2.93 +/- 1.59 times greater than thyroid fluorescence in vivo. CONCLUSIONS: Real-time NIR imaging based on parathyroid auto-fluorescence is fast, safe, and non-invasive and shows very encouraging results, for intraoperative parathyroid identification.
PubMed-ID: 27220510
http://dx.doi.org/10.1007/s00268-016-3571-5

Subtotal parathyroidectomy for secondary renal hyperparathyroidism: a 20-year surgical outcome study.
Langenbecks Arch Surg, 401(7):965-74.
A. Konturek, M. Barczynski, M. Stopa and W. Nowak. 2016.
AIM: The aim of this study was to evaluate the outcomes of surgery for patients with secondary renal hyperparathyroidism (rHPT). METHODS: This is a retrospective cohort study. Our institutional database was searched for eligible patients treated in 1995-2014. The inclusion criterion was initial parathyroidectomy for rHPT. Clinical and follow-up data were analyzed to estimate the cure rate (primary outcome), and morbidity (secondary outcome). RESULTS: The study group comprised 297 patients (154 females, age 44.5 +/- 13.7 years, follow-up 24.6 +/- 10.5 months), including 268 (90.2 %) patients who had underwent subtotal parathyroidectomy, and 29 (9.8 %) who had had incomplete parathyroidectomy. Intraoperative iPTH assay was utilized in 207 (69.7 %) explorations. Persistent rHPT occurred in 12/268 (4.5 %) patients after subtotal parathyroidectomy and 5/29 (17.2 %) subjects after incomplete parathyroidectomy (p = 0.005). The patients operated on with intraoperative iPTH assay had a higher cure rate than non-monitored individuals, 201/207 (97.1 %) vs. 79/90 (87.8 %), respectively (p = 0.001). In-hospital mortality occurred in 1/297 (0.3 %) patient. The hungry bone syndrome occurred in 84/268 (31.3 %) patients after subtotal parathyroidectomy and 2/29 (6.9 %) subjects after incomplete parathyroidectomy (p = 0.006). Transient recurrent laryngeal nerve paresis occurred in 14/594 (2.4 %) and permanent in 5/594 (0.8 %) nerves at risk. CONCLUSIONS: Subtotal parathyroidectomy is a safe and efficacious treatment for patients with rHPT. Utilization of intraoperative iPTH assay can guide surgical exploration and improve the cure rate.
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http://dx.doi.org/10.1007/s00423-016-1447-7

Parathyroid 4D-CT: Multi-institutional International Survey of Use and Trends.
Otolaryngol Head Neck Surg, 155(6):956-60.
J. K. Hoang, K. Williams, F. Gaillard, A. Dixon and J. A. Sosa. 2016.
Four-dimensional computed tomography (4D-CT) is a new modality for preoperative localization of parathyroid adenomas. We performed a survey study to describe the role and trends in the utilization of 4D-CT. Of 361 radiologists, 200 (55%) reported that 4D-CT was used in their practices. Nineteen (10%) used 4D-CT as the first-line imaging study; 155 (76%) reported that 4D-CT played a secondary role; and 26 (13%) reported that it is performed routinely in combination with ultrasound and scintigraphy. Early adopters of 4D-CT (use for >3 years) were 3 times more likely to use 4D-CT in a first-line role (18%) when compared with radiologists who used 4D-CT for </=3 years (6%; P < .05). In conclusion, more than half of radiologists perform 4D-CT, and a majority reported that 4D-CT plays a secondary role. However, this role may change, as utilization is increasing and radiologists may follow early adopters, who are more likely to use it as a first-line study.

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Selective Parathyroid Hormone Venous Sampling in Patients with Persistent or Recurrent Primary Hyperparathyroidism and Negative, Equivocal or Discordant Noninvasive Imaging.
World J Surg, 40(12):2956-63.
P. Y. Sun, S. M. Thompson, J. C. Andrews, R. A. Wermers, T. J. McKenzie, M. L. Richards, D. R. Farley and G. B. Thompson. 2016.
BACKGROUND: In patients with persistent (P-PHPT) or recurrent (R-PHPT) primary hyperparathyroidism, preoperative localization is important. Selective parathyroid hormone venous sampling (sPVS) is an invasive technique that can be used to regionalize and/or lateralize the source of PHPT when noninvasive imaging studies are nonlocalizing. The aim of the present study was to assess the role of sPVS in the preoperative evaluation of patients with P-PHPT or R-PHPT and negative, equivocal, or discordant noninvasive imaging localization. METHODS: After IRB-approval a retrospective review of all patients with P-PHPT or R-PHPT and nonlocalizing noninvasive imaging that underwent sPVS from 2000 to 2014 was performed. The location of the source of PHPT at sPVS was predicted by a parathyroid hormone (PTH) gradient and compared to the surgical, pathology, and biochemical follow-up data as the gold standard. Sensitivity and positive predictive value (PPV) were calculated. RESULTS: Of 30 patients who underwent sPVS, 12 patients did not undergo surgical exploration due to negative or non-localizing PTH gradient (n = 8) or opted for medical management (n = 4). Of the 18 patients who underwent surgical exploration, 17 (94 %) had a positive PTH gradient and pathologic parathyroid tissue identified at surgery. Sensitivity and PPV of sPVS were 93 and 77 %, respectively, for all surgical cases, 86 and 60.0 % for cervical cases (n = 11), and 100 and 100 % for mediastinal cases (n = 7). Sixteen patients (89 %) were surgically cured. CONCLUSIONS: In patients with P-PHPT or R-PHPT and nonlocalizing imaging studies, sPVS is a sensitive test for localizing the source of PHPT when a positive PTH gradient is present.
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http://dx.doi.org/10.1007/s00268-016-3621-z

Unilateral Clearance for Primary Hyperparathyroidism in Selected Patients with Multiple Endocrine Neoplasia Type 1.
World J Surg, 40(12):2964-9.
W. P. Kluijfhout, T. Beninato, F. T. Drake, M. R. Vriens, J. Gosnell, W. T. Shen, I. Suh, C. Liu and Q. Y. Duh. 2016.
BACKGROUND: Primary hyperparathyroidism is the most common manifestation of multiple endocrine neoplasia type 1 (MEN1). Guidelines advocate subtotal parathyroidectomy (STP) or total parathyroidectomy with autotransplantation due to high prevalence of multiglandular disease; however, both are associated with a significant risk of permanent hypoparathyroidism. More accurate imaging and use of intraoperative PTH levels may allow a less extensive initial parathyroidectomy (unilateral clearance, removing both parathyroids with cervical thymectomy) in selected MEN1 patients with primary hyperparathyroidism. METHODS: We performed a retrospective cohort study at a high-volume tertiary medical center including patients with MEN1 and primary hyperparathyroidism, who underwent STP or unilateral clearance as their initial surgery from 1995 to 2015. Unilateral clearance was offered to patients who had concordant sestamibi and ultrasound showing a single enlarged parathyroid gland. For both the groups, we compared rates of persistent/recurrent disease and permanent hypoparathyroidism. RESULTS: Eight patients had unilateral clearance and 16 had STP. Subtotal parathyroidectomy patients were younger (37 vs 52 years). One patient in each group had persistent disease. One (13 %) unilateral clearance and five (31 %) STP patients had recurrent hyperparathyroidism after a mean follow-up of 47 and 68 months (p = 0.62). No unilateral clearance patients and two of 16 SPT patients had permanent hypoparathyroidism (p = 0.54). CONCLUSIONS: Some MEN1 patients with primary hyperparathyroidism who have concordant localizing studies may be selected for unilateral clearance as an alternative to STP. For appropriately selected MEN1 patients, unilateral clearance can achieve similar results as STP and has no risk of permanent hypoparathyroidism, and may facilitate possible future reoperations.
PubMed-ID: 27402205
http://dx.doi.org/10.1007/s00268-016-3624-9

Reoperative Surgery in Patients with Multiple Endocrine Neoplasia Type 1 Associated Primary Hyperparathyroidism.
Ann Surg Oncol, 23(Suppl 5):701-7.
X. M. Keutgen, N. Nilubol, S. Agarwal, J. Welch, C. Cochran, S. J. Marx, L. S. Weinstein, W. F. Simonds and E. Kebebew. 2016.
BACKGROUND: Persistent/recurrent primary hyperparathyroidism (pHPT) occurs frequently in multiple endocrine neoplasia type 1 (MEN1). We assessed the usefulness of intraoperative PTH (IOPTH) and preoperative localizing studies based on the outcome of patients with MEN1-associated pHPT undergoing reoperative surgery. METHODS: A retrospective analysis identified MEN1 patients with persistent/recurrent pHPT. Patient outcome was defined as postoperative serum calcium and PTH levels (cured, persistent or recurrent) at last follow-up. Positive predictive value (PPV) was calculated for imaging studies and IOPTH. RESULTS: Thirty patients with MEN1-associated recurrent/persistent pHPT underwent 69 reoperative parathyroidectomies. Median follow-up time was 33 months. Persistent pHPT occurred in four (13 %) patients. IOPTH had a 92 % PPV for postoperative eucalcemia. Ultrasound and Tc99m-sestamibi had sensitivities of 100 and 85 % for localizing an enlarged parathyroid gland. However, five (17 %) patients had additional enlarged glands, not visualized preoperatively that were removed after IOPTH did not drop appropriately. Bone mineral density scores did not improve after reoperation (p = 0.60), but the rate of postoperative nephrocalcinosis did (p = 0.046). Patients with pancreatic neuroendocrine tumors had significantly higher rates of persistent/recurrent pHPT compared with those without (40 vs. 0 %, p = 0.021). Intraoperative and delayed parathyroid autotransplantation was performed in nine (30 %) and four (14 %) patients, respectively. CONCLUSIONS: Although preoperative localizing studies are helpful for guiding reoperative strategy in MEN1 with persistent/recurrent pHPT, additional enlarged glands may be missed by conventional imaging. IOPTH should therefore be employed routinely in this setting. Routine cryopreservation should be considered in all patients. Pancreatic manifestation may be associated with earlier recurrence or persistent disease.
PubMed-ID: 27464610
http://dx.doi.org/10.1245/s10434-016-5467-x

Genetics of primary hyperaldosteronism.
Endocr Relat Cancer, 23(10):R437-54.
R. K. Dutta, P. Soderkvist and O. Gimm. 2016.
Hypertension is a common medical condition and affects approximately 20% of the population in developed countries. Primary aldosteronism is the most common form of secondary hypertension and affects 8-13% of patients with hypertension. The two most common causes of primary aldosteronism are aldosterone-producing adenoma and bilateral adrenal hyperplasia. Familial hyperaldosteronism types I, II and III are the known genetic syndromes, in which both adrenal glands produce excessive amounts of aldosterone. However, only a minority of patients with primary aldosteronism have one of these syndromes. Several novel susceptibility genes have been found to be mutated in aldosterone-producing adenomas: KCNJ5, ATP1A1, ATP2B3, CTNNB1, CACNA1D, CACNA1H and ARMC5 This review describes the genes currently known to be responsible for primary aldosteronism, discusses the origin of aldosterone-producing adenomas and considers the future clinical implications based on these novel insights.
PubMed-ID: 27485459
http://dx.doi.org/10.1530/ERC-16-0055

How Best to Approach Surgery for Primary Hyperparathyroidism-Can We All Agree?
JAMA Surg, 151(10):969.
J. A. Sosa. 2016.
PubMed-ID: 27533602
http://dx.doi.org/10.1001/jamasurg.2016.2360

Indocyanine Green Angiography in Subtotal Parathyroidectomy: Technique for the Function of the Parathyroid Remnant.
J Am Coll Surg, 223(5):e43-e9.
J. Vidal Fortuny, S. M. Sadowski, V. Belfontali, W. Karenovics, S. Guigard and F. Triponez. 2016.
PubMed-ID: 27568330
http://dx.doi.org/10.1016/j.jamcollsurg.2016.08.540

Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment.
Endocr Rev, 37(5):521-47.
P. J. Tebben, R. J. Singh and R. Kumar. 2016.
Hypercalcemia occurs in up to 4% of the population in association with malignancy, primary hyperparathyroidism, ingestion of excessive calcium and/or vitamin D, ectopic production of 1,25-dihydroxyvitamin D [1,25(OH)2D], and impaired degradation of 1,25(OH)2D. The ingestion of excessive amounts of vitamin D3 (or vitamin D2) results in hypercalcemia and hypercalciuria due to the formation of supraphysiological amounts of 25-hydroxyvitamin D [25(OH)D] that bind to the vitamin D receptor, albeit with lower affinity than the active form of the vitamin, 1,25(OH)2D, and the formation of 5,6-trans 25(OH)D, which binds to the vitamin D receptor more tightly than 25(OH)D. In patients with granulomatous disease such as sarcoidosis or tuberculosis and tumors such as lymphomas, hypercalcemia occurs as a result of the activity of ectopic 25(OH)D-1-hydroxylase (CYP27B1) expressed in macrophages or tumor cells and the formation of excessive amounts of 1,25(OH)2D. Recent work has identified a novel cause of non-PTH-mediated hypercalcemia that occurs when the degradation of 1,25(OH)2D is impaired as a result of mutations of the 1,25(OH)2D-24-hydroxylase cytochrome P450 (CYP24A1). Patients with biallelic and, in some instances, monoallelic mutations of the CYP24A1 gene have elevated serum calcium concentrations associated with elevated serum 1,25(OH)2D, suppressed PTH concentrations, hypercalciuria, nephrocalcinosis, nephrolithiasis, and on occasion, reduced bone density. Of interest, first-time calcium renal stone formers have elevated 1,25(OH)2D and evidence of impaired 24-hydroxylase-mediated 1,25(OH)2D degradation. We will describe the biochemical processes associated with the synthesis and degradation of various vitamin D metabolites, the clinical features of the vitamin D-mediated hypercalcemia, their biochemical diagnosis, and treatment.
PubMed-ID: 27588937
http://dx.doi.org/10.1210/er.2016-1070

Intraoperative Real-Time Localization of Normal Parathyroid Glands With Autofluorescence Imaging.
J Clin Endocrinol Metab, 101(12):4646-52.
S. W. Kim, S. H. Song, H. S. Lee, W. J. Noh, C. Oak, Y. C. Ahn and K. D. Lee. 2016.
CONTEXT: This biomedical investigation is valuable for identification and localization of parathyroid glands during thyroidectomy, which can provide an intraoperative real-time visual guidance. OBJECTIVE: The objective of the study was to investigate the feasibility of real-time autofluorescence imaging of the parathyroid glands without exogenous contrast dye for their localization and demonstration of relation to the background tissues. SETTING: This research was undertaken at Kosin University Gospel Hospital. METHODS: Sixteen normal parathyroid glands from eight patients with papillary thyroid carcinoma were enrolled. Photo images of the surgical field including the parathyroid and background tissues were taken with a digital camera, 780 nm light-emitting diode to excite the parathyroid, and infrared illuminator to visualize the entire neck. The area-averaged autofluorescence intensity of parathyroid over the area-averaged fluorescence intensity of background tissues was measured. MAIN OUTCOME MEASURE: The location of the parathyroid gland was verified with a single image. RESULTS: The area-averaged autofluorescence intensity of parathyroid over the area-averaged fluorescence intensity of background tissues for all parathyroid glands was higher than 1, with a minimum of 1.95 and a maximum of 5.20 (average 2.76, SD 0.79). By our technique, all 16 parathyroid glands were detected (positive predictive value of 100%), and the entire surgical field including the parathyroid and background tissues was visualized as well. The parathyroid glands that were exposed or even covered by connective tissues or blood vessels could be detected with strong emission. CONCLUSIONS: This method showed the precise localization of the parathyroid glands and demonstrated their relation to background tissue. We believe that this simple, nonexogenous dye technique of anatomical guidance can aid surgeons to preserve parathyroid glands during thyroidectomy.
PubMed-ID: 27648967
http://dx.doi.org/10.1210/jc.2016-2558

Ambulatory bilateral neck exploration for primary hyperparathyroidism: is it safe?
Am J Surg, 212(4):722-7.
C. M. Kiernan, C. Schlegel, C. Isom, S. Kavalukas, M. F. Peters and C. C. Solorzano. 2016.
BACKGROUND: We sought to determine if bilateral neck exploration (BNE) for hyperparathyroidism could be performed safely in an ambulatory setting (same-day discharge) when compared with focused parathyroidectomy. METHODS: A retrospective review of 503 patients who underwent parathyroidectomy from 2010 to 2015 was performed. Focused parathyroidectomy was compared with BNE. Only patients with positive localization and no prior operations were included. RESULTS: Forty-nine percent of patients underwent focused parathyroidectomy and 51% had BNE. BNE patients were more likely to have 1 or more glands removed (35% vs 14%, P < .01) and longer operative times (median 50 vs 41 minutes, P < .01). There were no differences in

the rate of same-day discharge, transient hypocalcemia, emergency department visits, and readmissions. CONCLUSIONS: In this study, BNE for hyperparathyroidism was associated with excision of more parathyroid glands and slightly longer operative times. However, BNE had equal rates of same-day discharges and safety profile.
PubMed-ID: 27659156
http://dx.doi.org/10.1016/j.amjsurg.2016.06.021

Primary hyperparathyroidism with normal baseline intraoperative parathyroid hormone: A challenging population.
Surgery, 161(2):493-8.
M. Javid, G. Callender, C. Quinn, T. Carling, P. Donovan and R. Udelsman. 2017.
BACKGROUND: Patients with primary hyperparathyroidism and baseline intraoperative parathyroid hormone levels in the normal range are challenging. This study compares the predictive value of a commonly used intraoperative parathyroid hormone algorithm, a software model for cure prediction, and surgeon judgment in this population. METHODS: This was a retrospective review of consecutive patients who underwent parathyroidectomy for primary hyperparathyroidism at a single institution from March 2013 to October 2014. RESULTS: Of 541 operative patients, 114 (21.1%) had a mean normal baseline intraoperative parathyroid hormone of </=69 pg/mL (median 59.0 +/- 10.3; range 26-69). Of the 114 patients, 93 (81.6%) were women, median age was 61 years (range 18-88). Overall, 107/108 (99.1%) patients were cured; 47 (41.2%) patients had single adenomas, 16 (14%) had double adenomas, and 51 (44.7%) had multigland hyperplasia. Using the 50% decline algorithm, a correct prediction was made in 86 (75.4%) patients. Using the computer software, a correct prediction was made in 88 (77.2%) patients. Surgeon judgment, however, was 99.1% accurate. CONCLUSION: Patients with normal baseline intraoperative parathyroid hormone have a high incidence of multigland disease (58.8%), greater than reported previously. Current software modeling and the 50% decline algorithm are insufficient to predict cure in this population; intraoperative parathyroid hormone interpretation combined with operative findings and surgical judgment yield optimal outcomes.
PubMed-ID: 27712879
http://dx.doi.org/10.1016/j.surg.2016.08.018

"Silent" kidney stones in "asymptomatic" primary hyperparathyroidism-a comparison of multidetector computed tomography and ultrasound.
Langenbecks Arch Surg, 402(2):289-93.
A. Selberherr, M. Hormann, G. Prager, P. Riss, C. Scheuba and B. Niederle. 2017.
PURPOSE: The purpose of this study was to demonstrate the high number of kidney stones in primary hyperparathyroidism (PHPT) and the low number of in fact "asymptomatic" patients. METHODS: Forty patients with PHPT (28 female, 12 male; median age 58 (range 33-80) years; interquartile range 17 years [51-68]) without known symptoms of kidney stones prospectively underwent multidetector computed tomography (MDCT) and ultrasound (US) examinations of the urinary tract prior to parathyroid surgery. Images were evaluated for the presence and absence of stones, as well as for the number of stones and sizes in the long axis. The MDCT and US examinations were interpreted by two experienced radiologists who were blinded to all clinical and biochemical data. Statistical analysis was performed using the Wilcoxon signed-rank test. RESULTS: US revealed a total of 4 kidney stones in 4 (10 %) of 40 patients (median size 6.5 mm, interquartile range 11.5 mm). MDCT showed a total of 41 stones (median size was 3 mm, interquartile range 2.25 mm) in 15 (38 %) of 40 patients. The number of kidney stones detected with MDCT was significantly higher compared to US (p = 0.00124). CONCLUSIONS: MDCT is a highly sensitive method for the detection of "silent" kidney stones in patients with PHPT. By widely applying this method, the number of asymptomatic courses of PHPT may be substantially reduced. MDCT should be used primarily to detect kidney stones in PHPT and to exclude asymptomatic PHPT.
PubMed-ID: 27734157
http://dx.doi.org/10.1007/s00423-016-1520-2

Rates of secondary hyperparathyroidism after bypass operation for super-morbid obesity: An overlooked phenomenon.
Surgery, 161(3):720-6.
M. G. White, M. A. Ward, M. K. Applewhite, H. Wong, V. Prachand, P. Angelos, E. L. Kaplan and R. H. Grogan. 2017.
BACKGROUND: With over 110,000 bariatric operations performed in the United States annually, it is important to understand the biochemical abnormalities causing endocrine dysfunction associated with these procedures. Here we compare 2 malabsorptive procedures, duodenal switch and Roux-en-Y gastric bypass, to determine the

role malabsorption plays in secondary hyperparathyroidism in this population. METHODS: Data from all super-obese patients undergoing duodenal switch or Roux-en-Y gastric bypass between August 2002 and October 2005 were prospectively collected. Postoperatively, all patients received 1,200 mg of calcium citrate and 1,000 IU vitamin D3 per American Society for Metabolic and Bariatric Surgery guidelines. Beginning in 2007, duodenal switch patients were instructed to add daily vitamin D3 10,000 IU. Statistical analyses included Student t test, multivariate, and univariate logistic regression. RESULTS: Of 283 patients with a body mass index >/=50, 170 (60.1%) underwent duodenal switch, while 113 (39.9%) underwent Roux-en-Y gastric bypass. Of 132 (46.6%) patients with secondary hyperparathyroidism, 101 (59.4%) had undergone duodenal switch and 31 (27.4%) had undergone Roux-en-Y gastric bypass. Symptoms were more common in the duodenal switch group (33 patients [19.4%]) than Roux-en-Y gastric bypass (11 patients [9.7%]). Multivariate logistic regression demonstrated that the extent of bypass and duration of follow-up were the only 2 independent predictive risk factors for developing secondary hyperparathyroidism. Although vitamin D levels improved with increased vitamin D3 supplementation in 2007, rates of secondary hyperparathyroidism increased. CONCLUSION: Despite routine postoperative calcium and vitamin D3 supplementation, secondary hyperparathyroidism is common after Roux-en-Y gastric bypass and duodenal switch. The degree of iatrogenic malabsorption correlates with the incidence of secondary hyperparathyroidism. These rates suggest current supplementation guidelines are not sufficient in preventing secondary hyperparathyroidism. Further work is needed to better define the sequelae of long-term hyperparathyroidism.
PubMed-ID: 27769660
http://dx.doi.org/10.1016/j.surg.2016.08.046

Focused parathyroidectomy without intraoperative parathormone testing is safe after pre-operative localization with 18F-Fluorocholine PET/CT.
Eur J Surg Oncol, 43(1):133-7.
M. Hocevar, L. Lezaic, S. Rep, K. Zaletel, T. Kocjan, M. J. Sever, J. Zgajnar and B. Peric. 2017.
A focused surgical approach based on pre-operative localization replaced the classical four-gland exploration in patients with primary hyperparathyroidism (PHP). Sestamibi scanning and ultrasound are most often used localization modalities with reported sensitivity of 54-100% for identification of single gland disease. The aim of this study was to analyze the results of pre-operative localization with 18F-Fluorocholine PET/CT (FCh-PET) in patients with PHP. A retrospective review of 151 patients with PHP who underwent surgery after pre-operative localization with FCh-PET was performed. Only a focused parathyroidectomy without ioPTH testing had been done in patients with single adenoma on FCh-PET. Primary outcome was operative failure, defined as persistent PHP. According to pre-operative FCh-PET 126 (83,4%) patients had single adenoma, 22 (14,5%) multiglandular disease and the test was negative in only two patients. Intraoperative failure experienced 4/126 patients (3,3%) with single adenoma. Removed parathyroid glands were normal in three and hyperplastic in one patient with intraoperative failure. A limited bilateral neck exploration with ioPTH testing was used in 14/22 patients with double adenoma and a classical four-gland exploration without ioPTH testing was used in 8/22 patients with more than two pathological glands according to pre-operative FCh-PET. Intraoperative failure experienced 2/22 patients (9,1%). In two patients with negative FCh-PET a classical four-gland exploration without ioPTH testing was used and one experienced intraoperative failure. A preoperative localization with FCh-PET is a reliable test in patients with PHP. Patients with a single adenoma on FCh-PET can safely undergo a focused parathyroidectomy without ioPTH testing.
PubMed-ID: 27776943
http://dx.doi.org/10.1016/j.ejso.2016.09.016

Central venous parathyroid hormone monitoring using a novel, specific anatomic method accurately predicts cure during minimally invasive parathyroidectomy.
Am J Surg, 212(6):1154-61.
C. M. Edwards, J. Folek, S. Dayawansa, C. M. Govednik, C. E. Quinn, B. R. Sigmond, C. Y. Lee, M. S. Angel, J. C. Hendricks and T. C. Lairmore. 2016.
BACKGROUND: Measurement of intraoperative parathyroid hormone (PTH) levels is an important adjunct to confirm biochemical cure during parathyroidectomy. The purpose of this study was to evaluate a simplified anatomic technique for PTH sampling from the central veins through the minimally invasive neck incision, and to compare the predictive accuracy of central and peripheral PTH values. METHODS: A specific anatomic method for central PTH sampling was employed in 48 patients. Samples were drawn simultaneously from peripheral and central veins at baseline and 10 minutes postexcision of all hyperfunctioning parathyroid glands. RESULTS: The central venous PTH levels independently predicted biochemical cure according to the Miami criterion in all the patients. There was no significant difference in the postexcision central and peripheral values, which were 24.40 + 1.86 and 21.69 + 1.74, respectively (P = .877, ANOVA test). CONCLUSIONS: This study provides the original

description of a simplified technique for measurement of intraoperative PTH levels in the central veins with direct comparison to peripheral venous levels, and confirmation of accuracy in predicting biochemical cure when relying on centrally obtained values alone.
PubMed-ID: 27793324
http://dx.doi.org/10.1016/j.amjsurg.2016.09.015

Normohormonal primary hyperparathyroidism is a distinct form of primary hyperparathyroidism.
Surgery, 161(1):62-9.
M. K. Applewhite, M. G. White, J. Tseng, M. K. Mohammed, F. Mercier, E. L. Kaplan, P. Angelos, T. Vokes and R. H. Grogan. 2017.
BACKGROUND: Normohormonal primary hyperparathyroidism presents diagnostic and intraoperative challenges, and current literature is conflicting about management. We aim to better define normohormonal primary hyperparathyroidism in order to improve the care for these patients. METHODS: In the study, 516 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism were divided into 2 groups: classic primary hyperparathyroidism (classic primary hyperparathyroidism, increased serum levels of calcium, and parathyroid hormone) and normohormonal primary hyperparathyroidism (hypercalcemia, normal serum levels of parathyroid hormone). We evaluated inter-group differences in presentation, gland weight, pathology, and complications. RESULTS: The normohormonal primary hyperparathyroidism group was comprised of 116 (22.5%) patients. Mean serum levels of parathyroid hormone and calcium were 62.1 pg/mL +/- 10.1 and 10.6 mg/dL +/- 0.63 in normohormonal primary hyperparathyroidism, and 142 +/- 89.0pg/mL and 11.0 +/- 0.88 (both P < .01) for classic primary hyperparathyroidism. Nephrolithiasis was more common in normohormonal primary hyperparathyroidism. Multigland hyperplasia was more common in normohormonal primary hyperparathyroidism 23 (19.8%) vs 44 (11%; P = .04). Concordant imaging studies were less likely in normohormonal primary hyperparathyroidism (82 [73.2%] vs 337 [87.1%; P < .01]), had a lesser total gland weight (531.8 mg +/- 680.0 vs 1,039.6 mg +/- 1,237.3; P < .01), and lesser 2-week parathyroid hormone (32.5 pg/mL +/- 18.95 vs 41.0 pg/mL +/- 27.8; P = .01). There was no difference in hypoparathyroidism (parathyroid hormone <15 pg/mL; P = .93) at 2 weeks postoperatively. CONCLUSION: Normohormonal primary hyperparathyroidism represents 22.5% of our primary hyperparathyroidism population, which is greater than reported previously. It is a distinct disease process from classic primary hyperparathyroidism in presentation, imaging, and operative findings. More hyperplasia and a lesser gland weight make it challenging to resect the ideal amount of tissue. Studies with long-term follow-up are needed to determine optimal operative management.
PubMed-ID: 27866715
http://dx.doi.org/10.1016/j.surg.2016.03.038

AP2S1 and GNA11 mutations - not a common cause of familial hypocalciuric hypercalcemia.
Eur J Endocrinol, 176(2):177-85.
S. Hovden, L. Rejnmark, S. A. Ladefoged and P. H. Nissen. 2017.
OBJECTIVE: Familial hypocalciuric hypercalcemia (FHH) type 1 is caused by mutations in the gene encoding the calcium-sensing receptor (CASR). Recently, mutations affecting codon 15 in the gene AP2S1 have been shown to cause FHH type 3 in up to 26% of CASR-negative FHH patients. Similarly, mutations in the gene GNA11 have been shown to cause FHH type 2. We hypothesized that mutations in AP2S1 and GNA11 are causative in Danish patients with suspected FHH and that these mutations are not found in patients with primary hyperparathyroidism (PHPT), which is the main differential diagnostic disorder. DESIGN: Cross-sectional study. METHODS: We identified patients with unexplained hyperparathyroid hypercalcemia and a control group of verified PHPT patients through review of 421 patients tested for CASR mutations in the period 2006-2014. DNA sequencing of all amino acid coding exons including intron-exon boundaries in AP2S1 and GNA11 was performed. RESULTS: In 33 CASR-negative patients with suspected FHH, we found two (~6%) with a mutation in AP2S1 (p.Arg15Leu and p.Arg15His). Family screening confirmed the genotype-phenotype correlations. We did not identify any pathogenic mutations in GNA11. No pathogenic mutations were found in the PHPT control group. CONCLUSIONS: We suggest that the best diagnostic approach to hyperparathyroid hypercalcemic patients suspected to have FHH is to screen the CASR and AP2S1 codon 15 for mutations. If the results are negative and there is still suspicion of an inherited condition (i.e. family history), then GNA11 should be examined.
PubMed-ID: 27913609
http://dx.doi.org/10.1530/EJE-16-0842

Thiazide Treatment in Primary Hyperparathyroidism - A New Indication for an Old Medication?
J Clin Endocrinol Metab:jc20162481.
G. Tsvetov, D. Hirsch, I. Shimon, C. Benbassat, H. Masri-Iraqi, A. Gorshtein, D. Herzberg, T. Shochat, I. Shraga-Slutzky and T. Diker-Cohen. 2016.
CONTEXT: There is no available targeted therapy for control of hypercalciuria in nonoperable patients with primary hyperparathyroidism (PHPT). Thiazide diuretics are used for idiopathic hypercalciuria but avoided in PHPT to prevent exacerbating hypercalcemia. Nevertheless, several reports suggested that thiazides may be safe in patients with PHPT. OBJECTIVE: To test the safety and efficacy of thiazides in PHPT. DESIGN: Retrospective analysis of medical records. SETTING: Endocrine clinic at a tertiary hospital. PATIENTS: 72 patients (58 female, 14 male) with PHPT treated with thiazides for hypercalciuria or hypertension. INTERVENTIONS: Laboratory data were compared for each patient before and after thiazide administration. MAIN OUTCOME MEASURES: Effect of thiazide on urine and serum calcium levels. RESULTS: Mean patient age was 68.9+/-9.1 years. Patients were treated with hydrochlorothiazide 12.5-50mg/day for 3.1+/-2.3 years. Treatment led to a decrease in mean levels of urine calcium (427+/-174 to 251+/-114mg/day, p<0.001) and parathyroid hormone (115+/-57 to 74+/-36ng/L, p<0.001), with no change in serum calcium level (mean: 10.7+/-0.4 off-treatment, 10.5+/-1.2mg/dL on-treatment, p=0.4; maximum: 11.1+/-0.5 off-treatment, 11+/-0.5mg/dL on-treatment, p=0.8). Findings were consistent over all doses, with no difference in the extent of reduction in urine calcium level or change in serum calcium level by thiazide dose. CONCLUSION: Thiazides may be effective and safe for controlling hypercalciuria in patients with PHPT and may have an advantage in decreasing serum PTH level. Effectiveness can be achieved even at a dose of 12.5mg/day, and safety maintained at doses of up to 50mg/day; however, careful monitoring for hypercalcemia is required.
PubMed-ID: 27967299
http://dx.doi.org/10.1210/jc.2016-2481

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

Adrenal gland: New guidelines for adrenal incidentalomas.
Nat Rev Endocrinol, 12(10):561-2.
Q. Y. Duh. 2016.
PubMed-ID: 27564712
http://dx.doi.org/10.1038/nrendo.2016.148

Other Articles

Addison's disease with polyglandular autoimmunity carries a more than 2.5-fold risk for adrenal crises: German Health insurance data 2010-2013.
Clin Endocrinol (Oxf), 85(3):347-53.
G. Meyer, K. Badenhoop and R. Linder. 2016.
OBJECTIVE: Adrenal crises are potentially life-threatening complications in patients with adrenal insufficiency (AI). Our objective was to investigate the frequency of adrenal crises in different forms of AI.
DESIGN/PATIENTS: The Statutory Health Insurance (SHI) database of the Techniker Krankenkasse - covering more than 12% of the German population - was analysed for diagnostic codes from 1 January 2010 to 31 December 2013. MEASUREMENTS: By analysis of routine data from a large healthcare provider. Diagnoses of AI were recorded and classified in primary AI, secondary AI and autoimmune polyglandular syndrome (APS). The ICD-code E27.2 (AC) was retrieved in all cohorts. RESULTS: We found a prevalence of 222/million for secondary and 126/million for primary AI. AC was documented with a frequency of 4.8/100 patient years. Crises were significantly more frequent in patients with primary (7.6/100 patient years) compared to those with secondary AI (3.2/100 patient years; P < 0.0001). Prevalence of crises was higher in individuals with APS (10.9/100 patient years) and highest in patients with primary AI and type 1 diabetes (12.5/100 patient years). CONCLUSIONS: Applying a SHI database comprising more than 9 million individuals, we identified robust data about the risk of AC in different groups of patients with AI. Our data confirm and extend the clinical observation that patients with APS are at highest risk for AC. Approximately 1 of 8 patients with primary AI and type 1 diabetes suffers from an AC each year. Specific targeting of efforts aiming at the prevention of AC is necessary.
PubMed-ID: 26896640
http://dx.doi.org/10.1111/cen.13043

Bilateral aldosterone suppression and its resolution in adrenal vein sampling of patients with primary aldosteronism: analysis of data from the WAVES-J study.
Clin Endocrinol (Oxf), 85(5):696-702.
Y. Shibayama, N. Wada, H. Umakoshi, T. Ichijo, Y. Fujii, K. Kamemura, T. Kai, R. Sakamoto, A. Ogo, Y. Matsuda, T. Fukuoka, M. Tsuiki, T. Suzuki and M. Naruse. 2016.
CONTEXT: In adrenal vein sampling (AVS) for patients with primary aldosteronism, the contralateral ratio of aldosterone/cortisol (A/C) between the nondominant adrenal vein and the inferior vena cava is one of the best criteria for determining lateralized aldosterone secretion. Despite successful cannulation in some patients, the A/C ratios in the adrenal veins are bilaterally lower than that in the inferior vena cava (bilateral aldosterone

suppression; BAS). OBJECTIVES: To investigate the prevalence of BAS in AVS and how to resolve this condition. DESIGN AND SETTING: Retrospective study involving nine referral centres. PATIENTS: Four hundred and ninety-one patients who were confirmed as having primary aldosteronism and had an AVS between January 2006 and December 2013. MEASUREMENTS: The prevalence of BAS before and after ACTH stimulation was compared. In addition, we investigated other methods for overcoming BAS. RESULTS: In 304 patients with successful AVS before ACTH stimulation, BAS was observed in 29 (9.5%). BAS was resolved after ACTH stimulation in 22 patients. In 276 patients with successful AVS both before and after ACTH stimulation, the frequency of BAS was significantly reduced after ACTH (8.7% vs 2.5%, P < 0.01). In a few patients, BAS was also resolved by adding a sampling point at the common trunk of the left adrenal vein and by an alternative drainage vein from the adrenal tumour. CONCLUSIONS: BAS sometimes occurs in AVS without ACTH stimulation. ACTH stimulation significantly reduces BAS with a single AVS procedure.
PubMed-ID: 27128234
http://dx.doi.org/10.1111/cen.13090

A delayed diagnosis of salt-wasting congenital adrenal hyperplasia.
Clin Endocrinol (Oxf), 85(3):497-9.
K. J. Pijnenburg-Kleizen, C. Noordam, B. J. Otten and H. L. Claahsen-van der Grinten. 2016.
PubMed-ID: 27197923
http://dx.doi.org/10.1111/cen.13108

Does ACTH improve the diagnostic performance of adrenal vein sampling for subtyping primary aldosteronism?
Clin Endocrinol (Oxf), 85(5):703-9.
M. J. Wolley, A. H. Ahmed, R. D. Gordon and M. Stowasser. 2016.
OBJECTIVE: Adrenal vein sampling (AVS) is used for determining treatment options for primary aldosteronism (PA), but is a difficult procedure. Adrenocorticotropic hormone (ACTH) infusion or bolus has been reported to improve AVS success rates by increasing cortisol secretion, but effects on lateralization are controversial. We therefore assessed the effects of ACTH in regard to AVS success and lateralization in our unit, after a change in protocol to ACTH-stimulated AVS. SETTING: AVS was performed after overnight recumbency in patients with PA confirmed by fludrocortisone suppression testing. Bilateral sequential sampling was performed before and after an intravenous bolus of 250 mcg of ACTH. Lateralization was defined as an aldosterone/cortisol ratio in one adrenal vein at least twice peripheral, combined with a contralateral adrenal ratio no higher than peripheral (contralateral suppression). RESULTS: In 47 AVS procedures, the median adrenal/peripheral cortisol gradient increased on the left (11.6 vs 18.2 mug/100 ml, P < 0.001) and right (15.6 vs 31.5 mug/100 ml, P < 0.001) after ACTH. A total of 34 of 47 studies were diagnostic pre-ACTH (six failing because of low aldosterone levels bilaterally and seven failing to cannulate one or both sides) vs 44 of 47 (P = 0.011) studies diagnostic post-ACTH (failure to cannulate one or both sides in 3). Concordance between diagnostic studies pre- and post-ACTH was 91%, but two bilateral cases became unilateral after ACTH and one unilateral case before ACTH was bilateral afterwards. CONCLUSIONS: ACTH improved cortisol gradients and aldosterone secretion, resulting in a reduction in the proportion of nondiagnostic studies. There was a low proportion of discordance between pre- and post-ACTH diagnoses, the significance of which is unclear.
PubMed-ID: 27213822
http://dx.doi.org/10.1111/cen.13110

Impact of Laparoscopic Adrenalectomy on Overall Survival in Patients with Nonmetastatic Adrenocortical Carcinoma.
J Am Coll Surg, 223(3):485-92.
K. T. Huynh, D. Y. Lee, B. J. Lau, D. C. Flaherty, J. Lee and M. Goldfarb. 2016.
BACKGROUND: Appropriate use of laparoscopic adrenalectomy (LA) for adrenocortical carcinoma (ACC) remains controversial because complete resection with negative margins is the best chance for potential cure. This study compared the oncologic outcomes and overall survival (OS) of LA and open adrenalectomy (OA) for ACC. STUDY DESIGN: A retrospective analysis of the National Cancer Data Base (NCDB) between 2010 and 2014 identified 423 European Network for the Study of Adrenal Tumors (ENSAT) stage I to III ACC patients who had LA (n = 137) or OA (n = 286). Outcomes and OS were compared between the 2 groups. RESULTS: Patients who underwent OA had more advanced stage disease (p = 0.0001), larger (>/=5 cm) tumors (p < 0.0001), and were younger (age less than 55 years, p = 0.05). Nodal assessment was rare in LA (n = 4) compared with OA (n = 88) (p < 0.0001). Margin positivity was affected only by surgical approach in patients with T3 tumors (LA 54.6% vs OA 21.7%; p = 0.0009). Neither surgical procedure nor any socio-demographic factor(s) affected OS for the entire cohort. Only positive margins (p = 0.007), positive nodes (p = 0.02), tumor extension (p = 0.01), and more

advanced ENSAT stage (p = 0.004) increased mortality. When stratified by disease stage, LA decreased OS for patients with stage II disease (p = 0.04), and remained an independent risk factor for death on multivariate analysis (hazard ratio [HR] 1.86, 95% CI 1.02 to 3.38; p = 0.04). Only positive margins decreased OS in the entire cohort (HR 2.17, 95% CI 1.32 to 3.57; p = 0.002). CONCLUSIONS: Use of LA may decrease OS in select patients with ACC. Because margin status remains the strongest predictor of mortality, caution should be used in selecting LA for patients with ACC.
PubMed-ID: 27238874
http://dx.doi.org/10.1016/j.jamcollsurg.2016.05.015

Procedural and clinical outcomes of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy.
Clin Endocrinol (Oxf), 85(5):710-6.
D. A. Delivanis, D. Erickson, T. D. Atwell, N. Natt, S. Maraka, G. D. Schmit, P. W. Eiken, M. A. Nathan, W. F. Young, Jr. and I. Bancos. 2016.
OBJECTIVE: The role of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy has not been fully investigated. Our aim was to describe the clinical presentation leading to the adrenal biopsy and evaluate the diagnostic performance, complications and non diagnostic rate of adrenal biopsy. DESIGN: Single-centre, retrospective cohort study. PATIENTS AND MEASUREMENTS: Medical records of patients who underwent adrenal biopsy between 1994 and 2014 were reviewed. Adrenal biopsy outcome was compared to a predefined reference standard. RESULTS: Biopsy was performed in 418 patients [62% men, median age 69 years (range, 15-91)] on 419 adrenal lesions, median size 3.1 cm (range, 0.6-24). The main indication for adrenal mass biopsy was (349/419, 83%) suspected adrenal metastasis from a known or suspected extra-adrenal primary source. Only 116 of 419, 28% of cases had prebiopsy biochemical testing for pheochromocytoma. Biopsy-related complications occurred in 4% of the patients. Histology revealed a metastasis in 231 of 419 (55%), benign adrenal tissue in 137 of 419 (33%), adrenocortical carcinoma in eight of 419 (2%), other lesions in 23 of 419 (5%) including seven cases of pheochromocytoma and six cases of infectious process. Biopsy was nondiagnostic in 20 of 419 (5%). All adrenal masses with unenhanced radiodensity </=10 HU (42/137, 31%) proved to be benign adrenal adenomas. Adrenal biopsy diagnosed malignancy with a sensitivity of 88.5%, specificity of 91.5%, positive predictive value of 93.4% and negative predictive value of 85.5%. CONCLUSION: When used in the appropriate clinical setting, adrenal biopsy is a powerful tool in the diagnostic algorithm of the evaluation of adrenal masses with features suspicious for malignancy. Efforts to increase awareness to perform biochemical testing for pheochromocytoma prior to adrenal biopsy are needed.
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Functional characterization of two novel germline mutations of the KCNJ5 gene in hypertensive patients without primary aldosteronism but with ACTH-dependent aldosterone hypersecretion.
Clin Endocrinol (Oxf), 85(6):845-51.
A. Sertedaki, A. Markou, D. Vlachakis, S. Kossida, E. Campanac, D. A. Hoffman, M. L. Sierra, P. Xekouki, C. A. Stratakis, G. Kaltsas, G. P. Piaditis, G. P. Chrousos and E. Charmandari. 2016.
BACKGROUND: Germline mutations of the KCNJ5 gene encoding Kir3.4, a member of the inwardly rectifying K+ channel, have been identified in 'normal' adrenal glands, patients with familial hyperaldosteronism (FH) type III, aldosterone-producing adenomas (APAs) and sporadic cases of primary aldosteronism (PA). OBJECTIVE: To present two novel KCNJ5 gene mutations in hypertensive patients without PA, but with Adrenocorticotropic hormone (ACTH)-dependent aldosterone hypersecretion. DESIGN AND PATIENTS: Two hypertensive patients without PA, who exhibited enhanced ACTH-dependent response of aldosterone secretion, underwent genetic testing for the presence of the CYP11B1/CYP11B2 chimeric gene and KCNJ5 gene mutations. Genomic DNA was isolated from peripheral white blood cells, and the exons of the entire coding regions of the above genes were amplified and sequenced. Electrophysiological studies were performed to determine the effect of identified mutation(s) on the membrane reversal potentials. Structural biology studies were also carried out. RESULTS: Two novel germline heterozygous KCNJ5 mutations, p.V259M and p.Y348N, were detected in the two subjects. Electrophysiological studies showed that the Y348N mutation resulted in significantly less negative reversal potentials, suggesting loss of ion selectivity, while the V259M mutation did not affect the Kir3.4 current. In the mutated structural biology model, the N348 mutant resulted in significant loss of the ability for hydrogen bonding, while the M259 mutant was capable of establishing weaker interactions. The CYP11B1/CYP11B2 chimeric gene was not detected. CONCLUSIONS: These findings expand on the clinical spectrum of phenotypes associated with KCNJ5 mutations and implicate these mutations in the pathogenesis of hypertension associated with increased aldosterone response to ACTH stimulation.

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http://dx.doi.org/10.1111/cen.13132

Clinical characteristics of PRKACA mutations in Chinese patients with adrenal lesions: a single-centre study.
Clin Endocrinol (Oxf), 85(6):954-61.
X. Li, B. Wang, L. Tang, B. Lang, Y. Zhang, F. Zhang, L. Chen, J. Ouyang and X. Zhang. 2016.
CONTEXT: Recent studies have identified that the somatic PRKACA L206R mutation can cause cortisol-producing adenomas (CPAs). This study investigated the prevalence and characteristics of PRKACA, GNAS and CTNNB1 mutations in adrenal lesions in patients from a single centre in China. DESIGN, PATIENTS AND MEASUREMENTS: We sequenced PRKACA, GNAS and CTNNB1 genes in 108 patients, including 60 patients with CPAs (57 with unilateral and three with bilateral adenomas), 13 with nonfunctional adenomas, 12 with adrenocortical carcinomas (ACCs), 15 with primary bilateral macronodular hyperplasia (PBMAH) and eight with aldosterone and cortisol cosecreting adenomas. Mutations in PRKACA, GNAS and CTNNB1 were examined, and clinical characteristics were compared. RESULTS: Among the unilateral CPAs, we identified somatic mutations in PRKACA (L206R) in 23 cases (40.4%), GNAS (R201C and R201H) in six cases (10.5%), CTNNB1 (S45C, L46P and S45P) in six cases (10.5%) and CTNNB1 plus GNAS in two cases (3.5%). PRKACA and GNAS mutations were mutually exclusive. Among the patients with nonfunctional adenoma, two carried CTNNB1 mutations. Among the patients with ACC, two carried GNAS and CTNNB1 mutations but none carried PRKACA mutations. One patient showed bilateral CPA, and one PBMAH patient carried PRKACA mutations. No mutations in PRKACA, GNAS or CTNNB1 were identified in the eight patients with aldosterone and cortisol cosecreting adenomas. PRKACA-mutant adenomas were associated with young age, overt Cushing's syndrome and high cortisol levels compared with non-PRKACA-mutant or CTNNB1-mutant lesions. CONCLUSIONS: PRKACA mutations are present in CPAs and bilateral adrenal macronodular hyperplasia. PRKACA mutation is associated with more severe autonomous cortisol secretion.
PubMed-ID: 27296931
http://dx.doi.org/10.1111/cen.13134

Inappropriate adrenoreceptor blockade prior to phaeochromocytoma removal is perhaps a 'timely reappraisal'?
Clin Endocrinol (Oxf), 85(6):989-90.
C. Lentschener, S. Gaujoux, C. Baillard and B. Dousset. 2016.
PubMed-ID: 27332792
http://dx.doi.org/10.1111/cen.13142

Surgeon volume impact on outcomes and cost of adrenal surgeries.
Eur J Surg Oncol, 42(10):1483-90.
Z. Al-Qurayshi, R. Robins, J. Buell and E. Kandil. 2016.
INTRODUCTION: The number of adrenal surgeries performed in the United Stated is continuing to increase. Identifying factors associated with favorable outcomes can have a major impact on cost-differences. We aim to assess the impact of surgeon volume on both clinical outcomes and cost following adrenal surgery. MATERIALS AND METHODS: A cross-sectional analysis was performed utilizing data from the Nationwide Inpatient Sample, 2003-2009. Surgeon volumes included (adrenalectomies/year): low-volume (1), intermediate-volume (2-6), and high-volume (>/=7). RESULTS: A total of 7045 patients were included. Surgeries performed by low-volume surgeons were associated with a higher risk of postoperative complications [OR: 1.66, 95% CI: (1.23, 2.24)]. During the study period, if all operations performed by low-volume surgeons were selectively referred to intermediate-volume surgeons, a 7.7% cost savings would have been incurred. Potential savings were even higher (8.1%) if the operations had been performed by the high-volume surgeons. With the conservative assumption that there are 5000 adrenalectomies per year in the United States, the high-volume surgeons would produce savings of $8.8 million over a span of 14 years. CONCLUSION: A surgeon's expertise is associated with favorable outcomes. Our model estimates that considerable cost savings are attainable with appropriate referrals to high volume endocrine surgeons.
PubMed-ID: 27378161
http://dx.doi.org/10.1016/j.ejso.2016.06.392

A Novel Phenotype of Familial Hyperaldosteronism Type III: Concurrence of Aldosteronism and Cushing's Syndrome.
J Clin Endocrinol Metab, 101(11):4290-7.
A. Tong, G. Liu, F. Wang, J. Jiang, Z. Yan, D. Zhang, Y. Zhang and J. Cai. 2016.
CONTEXT: To date, all the familial hyperaldosteronism type III (FH-III) patients reported presenting with typical primary aldosteronism (PA), without showing other adrenal hormone abnormalities. OBJECTIVE: This study characterized a novel phenotype of FH-III and explored the possible pathogenesis. PATIENTS AND METHODS: A male patient presented with severe hypertension and hypokalemia at the age of 2 years and developed Cushing's syndrome at 20 years. He was diagnosed with PA and Cushing's syndrome on the basis of typical biochemical findings. He had massive bilateral adrenal hyperplasia and underwent left adrenalectomy. KCNJ5 was sequenced, and secretion of aldosterone and cortisol were observed both in vivo and in vitro. RESULTS: A heterozygous germline p.Glu145Gln mutation of KCNJ5 was identified. ARMC5, PRKAR1A, PDE8B, PDE11A, and PRKACA genes and beta-catenin, P53 immunoactivity were normal in the adrenal. CYP11B2 was highly expressed, whereas mRNA expression of CYP11B1, CYP17A1, and STAR was relatively low in the hyperplastic adrenal, compared with normal adrenal cortex and other adrenal diseases. In the primary cell culture of the resected hyperplastic adrenal, verapamil and nifedipine, two calcium channel blockers, markedly inhibited the secretion of both aldosterone and cortisol and the mRNA expression of CYP11B1, CYP11B2, CYP17A1, and STAR. CONCLUSIONS: We presented the first FH-III patient who had both severe PA and Cushing's syndrome. Hypersecretion of cortisol might be ascribed to overly large size of the hyperplastic adrenal because CYP11B1 expression was relatively low in his adrenal. Like aldosterone, synthesis and secretion of cortisol in the mutant adrenal may be mediated by voltage-gated Ca2+ channels.
PubMed-ID: 27403928
http://dx.doi.org/10.1210/jc.2016-1504

Adrenocortical carcinoma surgery-surgical extent and approach.
Langenbecks Arch Surg, 401(7):991-7.
C. Vanbrugghe, A. J. Lowery, C. Golffier, D. Taieb and F. Sebag. 2016.
PURPOSE: Adequate tumour resection is the gold standard of care for adrenocortical carcinoma (ACC). However, the optimal surgical strategy remains debatable. In our opinion, the extent of surgery (adequate tumour resection) is the primary concern, rather than the surgical approach (laparoscopic or open). We propose that both surgical approaches have a role in the management of ACC provided the extent of resection is selected based on patient and tumour characteristics and accurate pre-operative investigations. METHODS: A review of 25 curative intent resections for ACC between 2002 and 2013 was done. Group A (16 patients-64 %) included all patients who underwent planned radical adrenalectomy without any other resection and group B (9 patients-36 %) included all patients who underwent a planned extensive resection based on pre-operative investigations. RESULTS: Of 471 adrenalectomies, 25 were performed for ACC with curative intent. Tumours were significantly larger in group B with mean size of 119.6 versus 62.4 mm in group A (p = 0.002). Tumours in group B also had higher WEISS scores (mean score 7 vs 5.2, p = 0.033) and almost always required multi-organ resection. The recurrence rate was 37.5 % (n = 6) for group A and 44.4 % for group B (n = 4), p = 1.00. Poor prognosis was associated with significantly higher WEISS scores (p = 0.016) and a trend towards more advanced ENSAT disease stage (p = 0.06). Estimated overall survival was 74.17 months (group A 67.3 vs group B 70.1, p = 0.244). CONCLUSIONS: Accurate pre-operative staging is critical to select a tailored surgical strategy. Multi-organ resection remains the preferred approach for large and potentially invasive ACC. Some patients presenting with smaller ACC may benefit from a more extensive resection.
PubMed-ID: 27412357
http://dx.doi.org/10.1007/s00423-016-1462-8

Radiofrequency ablation compared with laparoscopic adrenalectomy for aldosterone-producing adenoma.
Br J Surg, 103(11):1476-86.
S. Y. Liu, C. M. Chu, A. P. Kong, S. K. Wong, P. W. Chiu, F. C. Chow and E. K. Ng. 2016.
BACKGROUND: Radiofrequency ablation (RFA) is an emerging treatment for primary aldosteronism owing to aldosterone-producing adenoma. Whether RFA could be an alternative treatment to laparoscopic adrenalectomy is unknown. METHODS: This was a retrospective comparative study in patients with aldosterone-producing adenoma undergoing either laparoscopic adrenalectomy or CT-guided percutaneous RFA between 2004 and 2012. Short-term outcomes and long-term resolution rates of primary aldosteronism (normalized aldosterone to renin ratio), hypokalaemia and hypertension (BP lower than 140/90 mmHg without antihypertensive medical therapy) were evaluated. RESULTS: Some 63 patients were included, 27 in the laparoscopic adrenalectomy group and 36 in the RFA group. RFA was associated with shorter duration of operation (median 12 versus 124

min; P < 0.001), shorter hospital stay (2 versus 4 days; P < 0.001), lower analgesic requirements (13 of 36 versus 23 of 27 patients; P < 0.001) and earlier resumption of work (median 4 versus 14 days; P = 0.006). Morbidity rates were similar in the two groups. With median follow-up of 5.7 (range 1.9-10.6) years, resolution of primary aldosteronism was seen in 33 of 36 patients treated with RFA and all 27 patients who had laparoscopic adrenalectomy (P = 0.180). Hypertension was resolved less frequently after treatment with RFA compared with laparoscopic adrenalectomy (13 of 36 versus 19 of 27 patients; P = 0.007). Hypokalaemia was resolved in all patients. CONCLUSION: For patients with aldosterone-producing adenoma the efficacy of resolution of primary aldosteronism and hypertension was inferior after treatment with RFA compared with laparoscopic adrenalectomy.
PubMed-ID: 27511444
http://dx.doi.org/10.1002/bjs.10219

Robotic assisted versus pure laparoscopic surgery of the adrenal glands: a case-control study comparing surgical techniques.
Langenbecks Arch Surg, 401(7):999-1006.
L. Morelli, D. Tartaglia, J. Bronzoni, M. Palmeri, S. Guadagni, G. Di Franco, A. Gennai, M. Bianchini, L. Bastiani, A. Moglia, V. Ferrari, E. Fommei, A. Pietrabissa, G. Di Candio and F. Mosca. 2016.
PURPOSE: The role of the da Vinci Robotic System (R) in adrenal gland surgery is not yet well defined. The goal of this study was to compare robotic-assisted surgery with pure laparoscopic surgery in a single center. METHODS: One hundred and 16 patients underwent minimally invasive adrenalectomies in our department between June 1994 and December 2014, 41 of whom were treated with a robotic-assisted approach (robotic adrenalectomy, RA). Patients who underwent RA were matched according to BMI, age, gender, and nodule dimensions, and compared with 41 patients who had undergone laparoscopic adrenalectomies (LA). Statistical analysis was performed using the Student's t test for independent samples, and the relationship between the operative time and other covariates were evaluated with a multivariable linear regression model. P < 0.05 was considered significant. RESULTS: Mean operative time was significantly shorter in the RA group compared to the LA group. The subgroup analysis showed a shorter mean operative time in the RA group in patients with nodules >/=6 cm, BMI >/= 30 kg/m2 and in those who had previous abdominal surgery (p < 0.05). Results from the multiple regression model confirmed a shorter mean operative time with RA with nodules >/=6 cm (p = 0.010). Conversion rate and postoperative complications were 2.4 and 4.8 % in the LA group and 0 and 4.8 % in the RA group. CONCLUSIONS: In our experience, RA shows potential benefits compared to classic LA, in particular on patients with nodules >/=6 cm, BMI >/= 30 kg/m2, and with previous abdominal surgery.
PubMed-ID: 27516077
http://dx.doi.org/10.1007/s00423-016-1494-0

The Author's Reply: inappropriate adrenoreceptor blockade prior to pheochromocytoma removal - 'A timely reappraisal'.
Clin Endocrinol (Oxf), 85(6):990-1.
H. V. Luiz, R. Yu, K. Wolf, N. Miao, A. Mannes and K. Pacak. 2016.
PubMed-ID: 27623515
http://dx.doi.org/10.1111/cen.13234

Rapid-sequence MRI for long-term surveillance for paraganglioma and phaeochromocytoma in patients with succinate dehydrogenase mutations.
Eur J Endocrinol, 175(6):561-70.
E. Daniel, R. Jones, M. Bull and J. Newell-Price. 2016.
BACKGROUND: Patients with SDHx mutations need long-term radiological surveillance for the development of paragangliomas and phaeochromocytomas, but no longitudinal data exist. The aim of the study was to assess the performance of rapid-sequence non-contrast magnetic resonance imaging (MRI) in the long-term monitoring of patients with SDHx mutations. METHODS: Retrospective study between 2005 and 2015 at a University Hospital and regional endocrine genetics referral centre. Clinical and imaging data of 47 patients with SDHx mutations (SDHB (36), SDHC (6) and SDHD (5)) who had surveillance for detection of paragangliomas by rapid-sequence non-contrast MRI (base of skull to pubic symphysis) were collected. RESULTS: Twelve index cases (nine SDHB, one SDHC and two SDHD) and 35 mutation-positive relatives were monitored for a mean of 6.4 years (range 3.1-10.0 years). Mean age at the end of the study: SDHB 46.9 +/- 17.6 years; SDHC 42.3 +/- 24.4 years; SDHD 54.9 +/- 10.6 years. On excluding imaging at initial diagnosis of index cases, 42 patients underwent 116 rapid-sequence MRI scans: 83 scans were negative and 31 scans were positive for sPGL/HNPGL in 13 patients. Most patients had multiple scans (n = number of patients (number of rapid-sequence MRI scans during screening)): n = 9 (2), n = 20 (3), n = 6 (4), n = 1 (6). Nine patients (three index)

were diagnosed with new paragangliomas during surveillance and non-operated tumour size was monitored in nine patients. There were two false-positive scans (1.6%). Scans were repeated every 27 +/- 9 months. CONCLUSIONS: Biannual rapid-sequence non-contrast MRI is effective to monitor patients with SDHx mutations for detection of new tumours and monitoring of known tumours.
PubMed-ID: 27634942
http://dx.doi.org/10.1530/EJE-16-0595

Aldosterone-Producing Adenoma With a Somatic KCNJ5 Mutation Revealing APC-Dependent Familial Adenomatous Polyposis.
J Clin Endocrinol Metab, 101(11):3874-8.
J. Vouillarmet, F. Fernandes-Rosa, J. Graeppi-Dulac, P. Lantelme, M. Decaussin-Petrucci, C. Thivolet, J. L. Peix, S. Boulkroun, E. Clauser and M. C. Zennaro. 2016.
CONTEXT: Recurrent somatic mutations in KCNJ5, CACNA1D, ATP1A1, and ATP2B3 have been identified in aldosterone-producing adenomas (APAs). The question as to whether they are responsible for both nodulation and aldosterone production is not solved. CASE DESCRIPTION: We describe the case of a young patient who was diagnosed with severe arterial hypertension due to primary aldosteronism at age 26 years, followed by hemorrhagic stroke 4 years later. Abdominal computed tomography showed bilateral macronodular adrenal hyperplasia. Identification of lateralized aldosterone secretion led to right adrenalectomy, followed by normalization of biochemical and hormonal parameters and amelioration of blood pressure. The resected adrenal showed three nodules, one of them expressing aldosterone synthase and harboring a somatic KNCJ5 mutation. A Weiss revisited index of 3 of the APA prompted us to perform a second 18F-2-fluoro-2-deoxy-D-glucose-positron emission tomography after surgery, which revealed abnormal rectal activity despite the absence of clinical symptoms. Gastrointestinal exploration showed multiple polyps with severe dysplasia, and the diagnosis of familial adenomatous polyposis was established in the presence of a germline heterozygous APC gene mutation. Sequencing of somatic DNA from the APA and a second adrenal nodule revealed biallelic APC inactivation due to loss of heterozygosity in both nodules. CONCLUSIONS: This case report underlines the need for establishing the frequency of germline APC variants in patients with primary aldosteronism and bilateral macronodular adrenal hyperplasia because their presence may predispose to APA development and severe hypertension well before the first familial adenomatous polyposis symptoms appear. From a mechanistic point of view, it supports a two-hit model for APA development, whereby the first hit drives increased cell proliferation whereas the second hit specifies the pattern of hormonal secretion.
PubMed-ID: 27648962
http://dx.doi.org/10.1210/jc.2016-1874

Towards a universally accepted definition of subclinical Cushing's syndrome - subclinical autonomous hypercortisolism.
Clin Endocrinol (Oxf), 86(1):7-9.
W. J. Inder. 2017.
PubMed-ID: 27662258
http://dx.doi.org/10.1111/cen.13244

Is there an optimal preoperative management strategy for phaeochromocytoma/paraganglioma?
Clin Endocrinol (Oxf), 86(2):163-7.
B. G. Challis, R. T. Casey, H. L. Simpson and M. Gurnell. 2017.
Phaeochromocytomas and paragangliomas (PPGLs) are catecholamine secreting neuroendocrine tumours that predispose to haemodynamic instability. Currently, surgery is the only available curative treatment, but carries potential risks including hypertensive and hypotensive crises, cardiac arrhythmias, myocardial infarction and stroke, due to tumoral release of catecholamines during anaesthetic induction and tumour manipulation. The mortality associated with surgical resection of PPGL has significantly improved from 20-45% in the early 20th century (Apgar & Papper, AMA Archives of Surgery, 1951, 62, 634) to 0-2.9% in the early 21st century (Kinney et al. Journal of Cardiothoracic and Vascular Anesthesia, 2002, 16, 359), largely due to availability of effective pharmacological agents and advances in surgical and anaesthetic practice. However, surgical resection of PPGL still poses significant clinical management challenges. Preoperatively, alpha-adrenoceptor blockade is the mainstay of management, although various pharmacological strategies have been proposed, based largely on reports derived from retrospective data sets. To date, no consensus has been reached regarding the 'ideal' preoperative strategy due, in part, to a paucity of data from high-quality evidence-based studies comparing different treatment regimens. Here, based on the available literature, we address the Clinical Question: Is there an optimal preoperative management strategy for PPGL?

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A SDHC Founder Mutation Causes Paragangliomas (PGLs) in the French Canadians: New Insights on the SDHC-Related PGL.
J Clin Endocrinol Metab, 101(12):4710-8.
I. Bourdeau, S. Grunenwald, N. Burnichon, E. Khalifa, N. Dumas, M. C. Binet, S. Nolet and A. P. Gimenez-Roqueplo. 2016.
BACKGROUND: More than 40% of patients with paragangliomas (PGLs) harbor a germline mutation of the known PGL susceptibility genes, mainly in the SDHB or SDHD genes. OBJECTIVE: The objective of the study was to characterize the genetic background of the French Canadian (FC) patients with PGLs and provide new clinical and paraclinical insights on SDHC-related PGLs. METHODS: Genetic testing has been offered to FC patients affected with PGLs followed up at the adrenal genetics clinic at Centre hospitalier de l'Universite de Montreal. After genetic counseling, 29 FC patients consented for PGL genetic testing. RESULTS: Thirteen of 29 patients (44.8%) carried a germline mutation. The same heterozygous nonsense mutation at codon 133 of exon 5 of the SDHC gene (c.397C>T, p.[Arg133Ter]) was found in nine patients, representing 69.2% of the patients having a germline mutation. Seventy percent of these patients had head and neck PGLs. Twenty percent had multiple and 30% had malignant PGLs. We traced back the ascending genealogy of 10 index cases (nine patients from our cohort and one patient referred to us) and found that this mutation was most probably introduced in Nouvelle France by a couple of French settlers who established themselves in the 17th century. CONCLUSIONS: We found that 31% of the PGLs in the French Canadian can be explained by the SDHC mutation (c.397C>T, p.[Arg133Ter]). The dominance of the SDHC mutation is unique to the FCs and is most likely due to a French founder effect. SDHC gene analysis should be prioritized in FC patients with PGL.
PubMed-ID: 27700540
http://dx.doi.org/10.1210/jc.2016-1665

Pheochromocytomas are diagnosed incidentally and at older age in neurofibromatosis type 1.
Clin Endocrinol (Oxf), 86(3):332-9.
J. Moramarco, N. El Ghorayeb, N. Dumas, S. Nolet, L. Boulanger, N. Burnichon, A. Lacroix, Z. Elhaffaf, A. P. Gimenez Roqueplo, P. Hamet and I. Bourdeau. 2017.
INTRODUCTION: Guidelines do not currently recommend routine systematic hormonal screening for pheochromocytoma (PHEO) in all/normotensive patients with neurofibromatosis type 1 (NF1), in contrast to other PHEO-predisposing genetic syndromes such as Von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2. OBJECTIVES: To characterize and compare parameters of PHEO in patients with NF1 to patients with or without other germline mutations. METHODS: A retrospective chart review of patients with histologically proven PHEO at the Centre hospitalier de l'Universite de Montreal from 2000 through 2015. RESULTS: Neurofibromatosis type 1 was diagnosed clinically in nine patients in our cohort of 145 PHEO (6.2%). The mean age at diagnosis was 48 +/- 14 years, and seven patients had hypertension. No PHEO was diagnosed by systematic clinical screening. The mode of presentation was adrenal incidentalomas in five patients. Urinary metanephrines were elevated in 5/9 cases. Mean tumour diameter was 3.5 cm (min-max 1.5-12.5 cm). One had bilateral PHEO and none were malignant to date. Statistically significant differences were noted when comparing PHEO in NF1 to other genetic syndromes (n = 20), in terms of age at diagnosis (mean 48 vs 30 years $P < 0.05$), initial mode of presentation (no PHEO detected by routine screening in NF1 vs 40% in other genetic syndromes $P < 0.05$) and familial history of catecholamine-secreting tumour (none in NF1 vs 55% in patients with other genetic syndrome $P < 0.05$). CONCLUSIONS: Pheochromocytoma in NF1 occurs in older patients with no family history compared to other syndromes; it is mostly unilateral, secretory and benign. The older age at diagnosis of PHEO could be secondary to delay in identification due to lack of systematic screening for PHEO in NF1.
PubMed-ID: 27787920
http://dx.doi.org/10.1111/cen.13265

SDHB mutation status and tumor size but not tumor grade are important predictors of clinical outcome in pheochromocytoma and abdominal paraganglioma.
Surgery, 161(1):230-9.
Y. Assadipour, S. M. Sadowski, M. Alimchandani, M. Quezado, S. M. Steinberg, N. Nilubol, D. Patel, T. Prodanov, K. Pacak and E. Kebebew. 2017.
BACKGROUND: A staging/prognostic system has long been desired to better categorize pheochromocytoma/paraganglioma which can be very aggressive in the setting of SDHB mutations. METHODS: A retrospective analysis was conducted of clinical characteristics and outcomes including results of genetic

testing, tumor recurrence/metastasis, Ki67/MIB1% staining, and tumor mitotic index in patients with pheochromocytoma/paraganglioma. RESULTS: Patients with SDHB mutation presented at younger age (33.0 years old vs 49.6 years old, P < .001), had increased local recurrence and distant metastases (47.6% vs 9.1%, P < .001, and 56.3% vs 9.1%, P < .001, respectively), and lesser median disease-free interval (89.8 months, 95% confidence interval 36.0-96.4 vs not reached, P < .001). SDHB mutation, greatest tumor diameter, and open operative resection were associated with a greater rate of local recurrence and distant metastases (P < .006 each). SDHB mutation and tumor diameter were independent risk factors for local recurrence (P </= .04 each) and metastases. Ki67% and mitotic index were not associated with SDHB mutation (P >/= .09 each), local recurrence (P = .48, P = .066, respectively), metastases (P >/= .22 each), or disease-free interval (P >/= .19 each). CONCLUSION: SDHB status and primary tumor size are more predictive of patient outcome than Ki67% or mitotic index and should be part of any clinically relevant, prognostic scoring system.
PubMed-ID: 27839933
http://dx.doi.org/10.1016/j.surg.2016.05.050

Surgery for recurrent adrenocortical carcinoma: A multicenter retrospective study.
Surgery, 161(1):249-56.
G. Simon, F. Pattou, E. Mirallie, J. C. Lifante, C. Nomine, V. Arnault, L. de Calan, C. Caillard, B. Carnaille, L. Brunaud, N. Laplace, R. Caiazzo and C. Blanchard. 2017.
BACKGROUND: Adrenocortical carcinoma is a rare neoplasm with a high rate of recurrence. We studied the impact of surgery on the survival in recurrent adrenocortical carcinoma patients. METHODS: We performed a retrospective review of patients with recurrent adrenocortical carcinoma, managed in 5 French University Hospitals between 1980 and 2014. We compared surgery and medical management for ACC recurrence. RESULTS: Fifty-nine patients were included, 46 of whom had an initial R0 resection. Twenty-nine patients underwent reoperation for recurrence, while 30 had nonoperative treatments. Operated patients had a greater median overall survival after recurrence than nonoperated patients (91 vs 15 months; P < .001). Patients operated on for local or distant recurrence had similar overall survival (110 vs 91 months; P = .81). In nonoperated patients, types of medical managements did not impact survival. Surgery for recurrence (P = .037) and a disease-free interval between initial resection and recurrence >12 months (P = .059) were both prognostic factors for improved survival, whereas age, stage, and tumor size (P >/= .2 each) were not. A Ki67 <25% tended to be associated with better overall survival (P = .051). CONCLUSION: Both surgery for recurrence and disease-free interval between the initial resection of an adrenocortical carcinoma and recurrence >12 months are associated with better overall survival.
PubMed-ID: 27855966
http://dx.doi.org/10.1016/j.surg.2016.08.058

Scoring system for the diagnosis of bilateral primary aldosteronism in the outpatient setting before adrenal venous sampling.
Clin Endocrinol (Oxf), 86(4):467-72.
H. Kobayashi, A. Haketa, T. Ueno, Y. Ikeda, Y. Hatanaka, S. Tanaka, H. Otsuka, M. Abe, N. Fukuda and M. Soma. 2017.
OBJECTIVE: The only reliable method for subtyping primary aldosteronism (PA) is adrenal venous sampling (AVS), which is costly and time-consuming. Considering the limited availability of AVS, it would be helpful to obtain information on the diagnosis of bilateral hyperaldosteronism (BHA) from routine tests. We aimed to establish new, simple criteria for outpatients to diagnose BHA from PA before AVS. DESIGN: We retrospectively analysed 82 patients who were diagnosed with PA and underwent AVS. Thirty-seven patients were diagnosed with unilateral hyperaldosteronism (UHA), and 36 with BHA and nine were undetermined. Among the variables that were significantly different between UHA and BHA in the univariate analysis, we chose three variables to be included in multivariate logistic regression models and constructed a subtype prediction score. RESULTS: The subtype prediction score was calculated as follows: 3 points for no adrenal nodules on computed tomography imaging, 2 for serum potassium of >/=3.5 mmol/l and 2 for aldosterone-to-renin ratio of <490 after a captopril challenge test. Receiver operating characteristic curve analysis for the ability to discriminate BHA from UHA showed that a score of 7 points had 50% sensitivity and 100% specificity and a score of 5 points had 67% sensitivity and 94% specificity (area under the curve: 0.922; 95% CI: 0.863-0.980). CONCLUSIONS: Our new, simple criteria specifically distinguished BHA from UHA in the outpatient setting before AVS. Furthermore, not only endocrinologists but also general internists can use this convenient, safe scoring system.
PubMed-ID: 27862131
http://dx.doi.org/10.1111/cen.13278

Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary?
Clin Endocrinol (Oxf), 86(3):309-14.
M. Isaacs and P. Lee. 2017.
Resection of phaeochromocytoma and paraganglioma (PPGL) is traditionally preceded by alpha-blockade to prevent complications of haemodynamic instability intraoperatively. While there is general agreement on preoperative alpha-blockade for classic PPGLs presenting with hypertension, it is less clear whether alpha-blockade is necessary in predominantly dopamine-secreting tumours, normotensive PPGLs, as well as tumours that appear to be biochemically 'silent'. Preoperative management of these 'atypical' PPGLs is challenging and the treatment approach must be individualized, carefully weighing the risk of intraoperative hypertension against the possibility of orthostatic and prolonged postoperative hypotension. Consideration of antihypertensive medication pharmacology in the light of catecholamine physiology and PPGL secretory profile will facilitate the formulation of individualized preoperative preparatory strategies.
PubMed-ID: 27864838
http://dx.doi.org/10.1111/cen.13284

Outcome of adrenalectomy for subclinical hypercortisolism and Cushing syndrome.
Surgery, 161(1):264-71.
M. Raffaelli, C. De Crea, G. D'Amato, P. Gallucci, C. P. Lombardi and R. Bellantone. 2017.
BACKGROUND: We compared operative and metabolic outcomes in patients with subclinical Cushing syndrome and Cushing syndrome caused by unilateral adrenal lesion, aiming to clarify the role of glucocorticoid replacement treatment in patients with subclinical Cushing syndrome after adrenalectomy. METHODS: The medical records of all the patients who underwent unilateral adrenalectomy for subclinical Cushing syndrome or Cushing syndrome were reviewed. Diagnostic criteria for subclinical Cushing syndrome were a pathologic dexamethasone suppression test plus 2 additional criteria. RESULTS: Twenty-nine patients with subclinical Cushing syndrome and 50 with Cushing syndrome were identified. No significant difference was found between patients with subclinical Cushing syndrome and Cushing syndrome regarding lesion size, operative time, and hospital stay. Two patients out of 29 with subclinical Cushing syndrome and 3 out of 50 patients with Cushing syndrome experienced Clavien-Dindo grade II complications (P = .87). All the patients required postoperative glucocorticoid replacement that was discontinued within 6 months in 28 of the 29 patients with subclinical Cushing syndrome and in 3 out of 50 Cushing syndrome patients (P < .005). At long-term follow-up, adrenalectomy significantly improved hypertension and diabetes in affected patients, with no differences between subclinical Cushing syndrome and Cushing syndrome. Hypercortisolism was resolved in all the cases. CONCLUSION: Operative and metabolic outcomes of adrenalectomy are similar in subclinical Cushing syndrome and Cushing syndrome. Postoperative glucocorticoid replacement treatment is advisable in all patients with subclinical Cushing syndrome. Prolonged adrenal insufficiency is more frequent in Cushing syndrome patients.
PubMed-ID: 27865591
http://dx.doi.org/10.1016/j.surg.2016.07.042

Laparoscopic anterior versus endoscopic posterior approach for adrenalectomy: a shift to a new golden standard?
Langenbecks Arch Surg,
O. M. Vrielink, K. P. Wevers, J. W. Kist, I. H. Borel Rinkes, P. H. Hemmer, M. R. Vriens, J. de Vries and S. Kruijff. 2016.
PURPOSE: There has been an increased utilization of the posterior retroperitoneal approach (PRA) for adrenalectomy alongside the "classic" laparoscopic transabdominal technique (LTA). The aim of this study was to compare both procedures based on outcome variables at various ranges of tumor size. METHODS: A retrospective analysis was performed on 204 laparoscopic transabdominal (UMC Groningen) and 57 retroperitoneal (UMC Utrecht) adrenalectomies between 1998 and 2013. We applied a univariate and multivariate regression analysis. Mann-Whitney and chi-squared tests were used to compare outcome variables between both approaches. RESULTS: Both mean operation time and median blood loss were significantly lower in the PRA group with 102.1 (SD 33.5) vs. 173.3 (SD 59.1) minutes (p < 0.001) and 0 (0-200) vs. 50 (0-1000) milliliters (p < 0.001), respectively. The shorter operation time in PRA was independent of tumor size. Complication rates were higher in the LTA (19.1%) compared to PRA (8.8%). There was no significant difference in recovery time between both approaches. CONCLUSIONS: Application of the PRA decreases operation time, blood loss, and complication rates compared to LTA. This might encourage institutions that use the LTA to start using PRA in patients with adrenal tumors, independent of tumor size.
PubMed-ID: 27888343
http://dx.doi.org/10.1007/s00423-016-1533-x

Risk factors for complications after adrenalectomy: results from a comprehensive national database.
Langenbecks Arch Surg, 402(2):315-22.
L. H. Thompson, E. Nordenstrom, M. Almquist, H. Jacobsson and A. Bergenfelz. 2017.
PURPOSE: Most knowledge regarding outcome after adrenal surgery stems from retrospective studies reported by highly specialized centres. The aim of this study was to report a national experience of adrenalectomy with particular attention to predictive factors for postoperative complications, conversion from endoscopic to open surgery and length of hospital stay. METHODS: Adrenalectomies reported in the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) 2009-2014 were included. Risk factors for complications, conversion and hospital stay >3 days were assessed using univariable and multivariable logistic regression analysis. RESULTS: There were 659 operations. Endoscopic adrenalectomy was performed in 513 (77.8%) operations and almost half of these were robotic assisted. The median length of hospital stay was 3 (range 1-30) days. There was no 30-day mortality. In 43 (6.6%) patients, at least one complication was registered. The only factor associated with complications in multivariable analysis was conversion to open surgery odds ratio (OR) 3.61 (95% confidence interval 1.07 to 12.12). The risk for conversion was associated with tumour size OR 1.03 (1.00 to 1.06) and with malignancy on histopathology OR 8.33 (2.12 to 32.07). Length of hospital stay increased in patients with operation of bilateral tumours OR 3.13, left-sided tumours OR 1.98, hyper secretion of catecholamines OR 2.32, conversion to open surgery OR 42.05 and open surgery OR 115.18. CONCLUSIONS: The present study shows that endoscopic surgery is widely used. Complications were associated with conversion and the risk for conversion was associated with tumour size and malignant tumour. Hospital stay was short.
PubMed-ID: 27896436
http://dx.doi.org/10.1007/s00423-016-1535-8

Bilateral testicular tumors resulting in recurrent Cushing's syndrome after bilateral adrenalectomy".
J Clin Endocrinol Metab:jc20162702.
T. Puar, M. Engels, A. E. van Herwaarden, F. C. Sweep, C. Hulsbergen-van de Kaa, K. Kamphuis-van Ulzen, V. Chortis, W. Arlt, N. Stikkelbroeck, H. L. Claahsen-van der Grinten and A. R. Hermus. 2016.
CONTEXT: Recurrence of hypercortisolism in patients after bilateral adrenalectomy for Cushing's disease is extremely rare. PATIENT: We present a rare case of a 27-year-old man who previously underwent bilateral adrenalectomy for Cushing's disease with complete clinical resolution. Cushingoid features recurred 12 years later, along with bilateral testicular enlargement. Hormonal tests confirmed ACTH-dependent Cushing's. Surgical resection of the testicular tumors led to clinical and biochemical remission. DESIGN AND RESULTS: Gene expression analysis of the tumor tissue by qPCR showed high expression of all key steroidogenic enzymes. Adrenocortical-specific genes were 5.1 x 105 (CYP11B1), 1.8 x 102 (CYP11B2) and 6.3 x 104 (MC2R) times higher than non-steroidogenic fibroblast control. This correlated with urine steroid metabolome profiling showing 2-5 fold increases in the excretion of the metabolites of 11-deoxycortisol, 21-deoxycortisol and total glucocorticoids. Leydig-specific genes were 4.3 x 101 (LHCGR) and 9.3 x 100 (HSD17B3) times higher than control and urinary steroid profiling showed 2-fold increased excretion of the major androgen metabolites androsterone and etiocholanolone. These distinctly increased steroid metabolites were suppressed by dexamethasone, but unresponsive to hCG stimulation, supporting the role of ACTH, but not LH, in regulating tumor-specific steroid excess. CONCLUSION: We report bilateral testicular tumors occurring in a patient with recurrent Cushing's disease 12 years after bilateral adrenalectomy. Using mRNA expression analysis and steroid metabolome profiling, the tumors demonstrated both adrenocortical and gonadal steroidogenic properties, similar to testicular adrenal rest tumors found in patients with congenital adrenal hyperplasia. This suggests the presence of pluripotent cells even in patients without CAH.
PubMed-ID: 27901643
http://dx.doi.org/10.1210/jc.2016-2702

The clinical utility of circulating neuroendocrine gene transcript analysis in well-differentiated paragangliomas and pheochromocytomas.
Eur J Endocrinol, 176(2):143-57.
M. Peczkowska, J. Cwikla, M. Kidd, A. Lewczuk, A. Kolasinska-Cwikla, D. Niec, I. Michalowska, A. Prejbisz, A. Januszewicz, J. Chiarelli, L. Bodei and I. Modlin. 2017.
CONTEXT: Paragangliomas and pheochromocytomas (PPGLs) exhibit variable malignancy, which is difficult to determine by histopathology, amine measurements or tissue genetic analyses. OBJECTIVE: To evaluate whether a 51-neuroendocrine gene blood analysis has clinical utility as a diagnostic and prognostic marker. DESIGN: Prospective cohort study. Well-differentiated PPGLs (n = 32), metastatic (n = 4); SDHx mutation (n = 25); 12 biochemically active, Lanreotide treated (n = 4). Nine patients had multiple sampling. Age- and gender-

matched controls and GEP-NETs (comparators). METHODS: Circulating neuroendocrine tumor mRNA measured (qPCR) with multianalyte algorithmic analysis. Metabolic, epigenomic and proliferative genes as well as somatostatin receptor expression were assessed (averaged, normalized gene expression: mean +/- s.e.m.). Amines were measured by HPLC and chromogranin A by ELISA. Analyses (2-tailed): Fisher's test, non-parametric (Mann-Whitney), receiver-operator curve (ROC) and multivariate analysis (MVA). All data are presented as mean +/- s.e.m. RESULTS: PPGL were NETest positive (100%). All exhibited higher scores than controls (55 +/- 5% vs 8 +/- 1%, P = 0.0001), similar to GEP-NETs (47 +/- 5%). ROC analysis area under curve was 0.98 for differentiating PPGLs/controls (cut-off for normal: 26.7%). Mutation status was not directly linked to NETest. Genetic and molecular clustering was associated (P < 0.04) with NETest scores. Metastatic (80 +/- 9%) and multicentric (64 +/- 9%) disease had significantly (P < 0.04) higher scores than localized disease (43 +/- 7%). Progressive disease (PD) had the highest scores (86 +/- 2%) vs stable (SD, 41 +/- 2%) (P < 0.0001). The area under the curve for PD from SD was 0.93 (cut-off for PD: 53%). Proliferation, epigenetic and somatostatin receptor gene expression was elevated (P < 0.03) in PD. Metabolic gene expression was decreased in SDHx mutations. Repeat NETest measurements defined clinical status in the 9 patients (6 SD and 3 PD). Amine measurement was non-informative. Multivariate analysis identified NETest >53% as an independent prognostic factor. CONCLUSION: Circulating NET transcript analysis is positive (100% diagnostic) in well-differentiated PCC/PGL, scores were elevated in progressive disease irrespective of mutation or biochemical activity and elevated levels were prognostic.
PubMed-ID: 27913608
http://dx.doi.org/10.1530/EJE-16-0727

Histopathological classification of cross-sectional image negative hyperaldosteronism.
J Clin Endocrinol Metab:jc20162986.
Y. Yamazaki, Y. Nakamura, K. Omata, K. Ise, Y. Tezuka, Y. Ono, R. Morimoto, Y. Nozawa, C. E. Gomez-Sanchez, S. A. Tomlins, W. E. Rainey, S. Ito, F. Satoh and H. Sasano. 2016.
CONTEXT: Approximately half of primary aldosteronism (PA) have clinically evident disease according to clinical (hypertension) and/or laboratory (aldosterone and renin levels) findings but do not have nodules detectable in routine cross-sectional imaging. However, the detailed histopathologic, steroidogenic and pathobiological features of cross-sectional image negative PA have not been well characterized. OBJECTIVE: Examine histopathology, steroidogenic enzyme expression and somatic mutation status of aldosterone-driver genes in adrenals from cross-sectional image negative hyperaldosteronism. METHODS: 25 cross-sectional image negative cases were retrospectively reviewed. In situ adrenal aldosterone production capacity was determined using immunohistochemistry (IHC) of steroidogenic enzymes. Somatic mutation status of aldosterone-driver genes (ATP1A1, ATP2B3, CACNA1D and KCNJ5) was determined in the CYP11B2 immunopositive areas (n=35, micronodule: n=32, ZG: n=3) using next-generation sequencing (NGS) after macrodissection. RESULTS: 25 cases were classified as multiple adrenocortical micronodules (MN, n=13) or diffuse hyperplasia of zona glomerulosa (DH, n=12) based upon histopathological evaluation and CYP11B2 IHC. Somatic mutations in aldosterone-driver genes were detected in 21 of 26 (81%) of CYP11B2-positive cortical micronodules in MN, with 17 (65%) mutations in CACNA1D, two (8%) in KCNJ5, and one each (4% each) in ATP1A1 and ATP2B). One of six (17%) of nodules in DH harbored somatic aldosterone-driver gene mutations (in CACNA1D), however no mutations were detected in CYP11B2-positive non-nodular DH areas. CONCLUSION: Morphologic evaluation and CYP11B2 IHC enabled the classification of cross-sectional image negative hyperaldosteronism into MN and DH. Somatic mutations driving renin-independent aldosterone production are common in micronodules of MN, suggesting the novel histological entity possibly related to APCC development.
PubMed-ID: 27967304
http://dx.doi.org/10.1210/jc.2016-2986

DNA methylation is an independent prognostic marker of survival in adrenocortical cancer.
J Clin Endocrinol Metab:jc20163205.
A. Jouinot, G. Assie, R. Libe, M. Fassnacht, T. Papathomas, O. Barreau, D. L. V. B, S. Faillot, N. Hamzaoui, M. Neou, K. Perlemoine, F. Rene-Corail, S. Rodriguez, M. Sibony, F. Tissier, B. Dousset, S. Sbiera, C. Ronchi, M. Kroiss, E. Korpershoek, D. E. K. R, J. Waldmann, D. K. Bartsch, M. Quinkler, M. Haissaguerre, A. Tabarin, O. Chabre, N. Sturm, M. Luconi, F. Mantero, M. Mannelli, R. Cohen, V. Kerlan, P. Touraine, G. Barrande, L. Groussin, X. Bertagna, E. Baudin, L. Amar, F. Beuschlein, E. Clauser, J. Coste and J. Bertherat. 2016.
CONTEXT: Adrenocortical cancer (ACC) is an aggressive tumor with heterogeneous outcome. Prognostic stratification is difficult even based on tumor stage and Ki67 index. Recently integrated genomics studies have demonstrated that CpG islands hypermethylation is correlated with poor survival. OBJECTIVE: To confirm the prognostic value of CpG islands methylation on an independent cohort with a single commonly available methylation assay. DESIGN: CpG islands methylation was measured by methylation-specific-multiplex-ligation-

dependent-probe-amplification (MS-MLPA) using the ME002 kit (MRC-Holland). SETTING: MS-MLPA was performed in a training cohort of 50 ACC to identify the best set of probes correlating with disease-free (DFS) and overall survival (OS). These were then validated in an independent cohort from 21 ENSAT centers. PATIENTS: The validation cohort included 203 ACC: 64% females, median age 50 years, 80% localized tumors. INTERVENTION: None. MAIN OUTCOME MEASURES: DFS and OS (Cox models). RESULTS: In the training cohort, mean methylation in CpG islands of 4 genes (PAX5,GSTP1,PYCARD,PAX6) was the strongest methylation marker. In the validation cohort, methylation was a significant prognostic factor of DFS (p<0.0001) and OS (p<0.0001). Methylation, Ki67 and ENSAT stage were combined in multivariate models. For DFS, methylation (p=0.0005) and ENSAT stage (p<0.0001) but not Ki67 (p=0.19) remained highly significant. For OS, methylation (p=0.0006), ENSAT stage (p<0.0001) and Ki67 (p=0.024) were independent prognostic factors. CONCLUSIONS: Tumor DNA methylation emerges as an independent prognostic factor in ACC. MS-MLPA is readily compatible with clinical routine, and above clinical and pathological features, should enhance our ability for prognostication and precision medicine.
PubMed-ID: 27967600
http://dx.doi.org/10.1210/jc.2016-3205

Long-Term Effect of Adrenalectomy on Cardiovascular Remodeling in Patients with Pheochromocytoma.
J Clin Endocrinol Metab:jc20162422.
B. Majtan, T. Zelinka, J. Rosa, O. Petrak, Z. Kratka, B. Strauch, V. Tuka, A. Vrankova, D. Michalsky, K. Novak, D. Wichterle, J. Widimsky, Jr. and R. Holaj. 2016.
CONTEXT: Catecholamines may contribute to the accumulation of collagen fibers and extracellular matrix in the arterial and myocardial wall due to various mechanisms. Reversibility of this process has not been studied on both structures simultaneously. OBJECTIVE: This study aimed to clarify the long-term effect of catecholamines' excess normalization on carotid and myocardial wall changes in patients with pheochromocytoma or functional paraganglioma (PHEO) after tumor removal. Design, Settings and Patients: Carotid intima-media thickness (IMT) and left ventricle (LV) mass index were studied in 50 patients with PHEO before tumor removal and 5 years after tumor removal and in 50 blood pressure- and age-matched essential hypertensive patients (EH) before follow-up and after 5 years of follow-up. MAIN OUTCOME MEASURES: Common carotid IMT (CCA-IMT) and LV mass indexed to the lean body mass (LBM). RESULTS: Elimination of catecholamine excess in the PHEO group resulted in a significant decrease in CCA-IMT and LV mass index from 0.86 +/- 0.17 to 0.83 +/- 0.18 mm (P <0.05) and from 3.2 +/- 0.9 to 2.9 +/- 0.9 g/LBM (P <0.001), respectively. In contrast, CCA-IMT and LV mass index increased significantly from 0.78 +/- 0.14 to 0.81 +/- 0.15 mm (P <0.05) and from 3.1 +/- 0.7 to 3.2 +/- 0.6 g/LBM (P <0.05), respectively, in patients with essential hypertension. CONCLUSION: In patients with PHEO, carotid IMT and LV mass index can significantly regress after the tumor removal, in contrast to the impairment of these parameters in patients with EH during the same long-term period.
PubMed-ID: 28001459
http://dx.doi.org/10.1210/jc.2016-2422

NET

Meta-Analyses

Surgical treatment of neuroendocrine tumors in the second portion of the duodenum: a single center experience and systematic review of the literature.
Langenbecks Arch Surg,
T. Iwasaki, S. Nara, Y. Kishi, M. Esaki, K. Shimada and N. Hiraoka. 2016.
PURPOSE: The treatment of choice for duodenal neuroendocrine tumors (NETs) ranges from endoscopic resection and local excision to pancreaticoduodenectomy. The aim of this study was to investigate the optimal treatment for this tumor. METHODS: We retrospectively analyzed the clinicopathological data of 14 patients with NETs in the second portion of the duodenum who underwent surgery in our hospital from 2000 to 2015. The duodenal NETs were classified as either ampullary or non-ampullary. Additionally, a systematic review and pooled analysis was conducted. RESULTS: Among eight patients with ampullary NETs and six patients with non-ampullary NETs, seven and three patients underwent pancreaticoduodenectomy and one and three patients underwent local resection, respectively. The maximum tumor diameter were 11-30 mm in ampullary and 10-100 mm in non-ampullary NETs, respectively. In patients with ampullary NETs, lymph node metastases were suspected in only three cases preoperatively, but five patients actually had regional nodal metastases. Among patients with non-ampullary NETs, lymph node metastases were suspected in none preoperatively, but three of the four patients who underwent lymph node dissection had regional nodal metastases. According to a pooled analysis of 1245 patients in 88 studies, even small tumors confined to the submucosal layer and G1 tumors-ampullary and non-ampullary-have been associated with lymph node metastases. In patients with non-ampullary NETs and lymph node metastasis, 10-year recurrence-free survival rate was 51% for patients who underwent pancreaticoduodenectomy (n = 19) and 53% for patients who underwent partial duodenal resection (n = 9), respectively (p = 0.960). CONCLUSION: Lymph node metastases were common in association with both ampullary and non-ampullary NETs, and it was difficult to radiologically diagnose metastases. Additionally, there were no clinicopathological factors that could reliably predict the absence of lymph node metastases preoperatively. Therefore, to maximize the ability to achieve a curative resection, pancreaticoduodenectomy is considered appropriate in well-conditioned patients with NETs in the second portion of the duodenum. However, to further clarify the impact of lymph node dissection on survival after duodenal NET resection, a multi-institutional study with a large number of patients, thorough examination of lymph node metastasis, and a long observation period is warranted.
PubMed-ID: 27915372
http://dx.doi.org/10.1007/s00423-016-1537-6

Randomized controlled trials

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival.
Neuroendocrinology, 104(1):26-32.
A. Rinke, M. Wittenberg, C. Schade-Brittinger, B. Aminossadati, E. Ronicke, T. M. Gress, H. H. Muller and R. Arnold. 2017.
BACKGROUND: Somatostatin analogs have been shown to control the growth of well-differentiated metastatic neuroendocrine tumors. Their effect on overall survival is a matter of debate. We analyzed the prognostic significance of early treatment with octreotide LAR and of hepatic tumor load in the PROMID trial cohort. PATIENTS AND METHODS: Between 2001 and 2008, 85 treatment-naive patients were randomly assigned to monthly octreotide LAR 30 mg or placebo until tumor progression or death. Post-study treatment was at the discretion of the investigator. Upon disease progression, 38 out of 43 placebo patients (88.4%) received octreotide LAR. For survival, patients were followed until May 2014. RESULTS: Forty-eight out of 85 patients (56.5%) died. In 38 patients (79.2%), death was tumor related. The median overall survival (84.7 and 83.7 months) was only slightly different in patients assigned to octreotide and placebo [HR = 0.83 (95% CI: 0.47-1.46); p = 0.51]. The median overall survival was 84.7 months for all 85 patients, 107.6 months in the low-tumor-load (n = 64) and 57.5 months in the high-tumor-load (n = 21) subgroups [HR = 2.49 (95% CI: 1.36-4.55); p =

0.002]. There was a trend towards improved overall survival in patients with a low hepatic tumor load receiving octreotide compared to placebo ['median not reached' and 87.2 months; HR = 0.59 (95% CI: 0.29-1.2); p = 0.142]. CONCLUSION: The extent of tumor burden is a predictor for shorter survival. Overall survival was similar in patients receiving octreotide LAR or placebo treatment at randomization. Crossover of the majority of placebo patients to octreotide LAR may have confounded the data on overall survival.
PubMed-ID: 26731483
http://dx.doi.org/10.1159/000443612

Consensus Statements/Guidelines

- None -

Other Articles

Changes in the Epidemiology of Neuroendocrine Tumours.
Neuroendocrinology, 104(2):105-11.
I. Huguet, A. B. Grossman and D. O'Toole. 2017.
BACKGROUND: The reviewing and assessment of epidemiological characteristics of neuroendocrine tumours (NETs) remains a challenge. Despite the fact that it is an uncommon family of neoplasms, several worldwide series have revealed an increasing incidence of this rare condition. However, the data are difficult to compare over time due to changes in classification. METHODS: We compared the data related to incidence, prevalence, stage of the disease at diagnosis and survival reported in several series, focusing on the differences and trying to examine some of the probable reasons that may explain the variations in the results between studies. RESULTS AND CONCLUSIONS: The incidence of NETs is increasing over time, and their incidental discovery due to improved and more frequent imaging does not seem to be enough to explain this rise. Significant differences can be found between geographic regions and races, suggesting that environmental or genetic factors may contribute to the clinical and biological behaviour of these tumours; increasing our knowledge of oncogenesis will be necessary to explain them. As with other rare diseases, creating specific databases and multidisciplinary working groups would improve the accuracy of the information gained.
PubMed-ID: 26505990
http://dx.doi.org/10.1159/000441897

Trends in Incidence of Neuroendocrine Neoplasms in Norway: A Report of 16,075 Cases from 1993 through 2010.
Neuroendocrinology, 104(1):1-10.
R. Boyar Cetinkaya, B. Aagnes, E. Thiis-Evensen, S. Tretli, D. S. Bergestuen and S. Hansen. 2017.
BACKGROUND: Epidemiological studies show an increasing trend in the incidence of neuroendocrine neoplasms (NENs). A significant number of NENs occur in less common primary sites, but they are often excluded from the population-based studies. We studied the incidence trends of all NENs in Norway according to different primary sites. MATERIALS AND METHODS: Our analyses were based on cancer cases diagnosed between 1993 and 2010 and reported to the national population-based Cancer Registry of Norway. A total of 65 morphological codes were identified as neuroendocrine and stratified into 3 different groups of aggressiveness: low, intermediate and high. RESULTS: We identified 16,075 NENs of which 49.5% were in women. The median age at diagnosis was 65 years. The most common primary sites were the lung (48.1%) and the gastroenteropancreatic system (18.0%). Stage at diagnosis was local in 40.4% of the cases, regional in 17.5% and distant in 42.1%. The stage distribution was stable throughout the study period. The age-standardized (European) incidence rate (per 100,000 person-years) increased from 13.3 in 1993 to 21.3 in 2010 with an estimated annual increase of 5.1% in women and 2.1% in men. The increase was most pronounced for tumors of intermediate aggressiveness from 3.3 in 1993 to 7.3 in 2010. The largest annual increases were estimated for the adrenal gland (8.8%), the pancreas (6.9%) and the lungs (6.1%). CONCLUSION: The incidence of NENs increased. Most primary tumors were found in the lungs or in the gastroenteropancreatic system. The increase in the incidence differed according to the primary site, gender and tumor aggressiveness.
PubMed-ID: 26562558
http://dx.doi.org/10.1159/000442207

Pancreatic Neuroendocrine Neoplasms: Clinical Value of Diffusion-Weighted Imaging.
Neuroendocrinology, 103(6):758-70.
R. De Robertis, M. D'Onofrio, G. Zamboni, P. Tinazzi Martini, S. Gobbo, P. Capelli, G. Butturini, R. Girelli, S. Ortolani, S. Cingarlini, P. Pederzoli and A. Scarpa. 2016.
BACKGROUND/AIMS: Diffusion-weighted imaging (DWI) can depict random motions of water molecules in biological tissues during magnetic resonance (MR) examinations. Few papers have tested its application to pancreatic neuroendocrine neoplasms (PanNENs). The aim of this paper is to assess the clinical value of DWI regarding the identification and characterization of PanNENs and diagnosis of liver metastases. METHODS: Preoperative MR examinations of 30 PanNEN patients were retrospectively reviewed; 30 patients with pathologically proven pancreatic ductal adenocarcinoma (PDAC) were included to compare the imaging features. Qualitative and quantitative MR features were compared between histotypes. A blinded-reader comparison of diagnostic confidence for PanNENs and liver metastases was conducted on randomized image sets. All results were compared with pathological data. RESULTS: PanNEN conspicuity was higher on DW images compared to conventional MR sequences. DWI had higher detection rates for PanNENs than had conventional sequences (93.3 vs. 71.1%). Sharp margins and absence of main pancreatic duct/common bile duct dilation and chronic pancreatitis were more common among PanNENs as compared to PDACs. Arterial iso- or hyperenhancement and portal hyperenhancement were more frequent within PanNENs as compared to PDACs. No differences between histotypes were found for quantitative features. Arterial-phase images had the highest interobserver agreement for the diagnosis of PanNEN (Cohen's kappa = 0.667). DWI provided the highest detection rate for liver metastases as well as excellent interobserver agreement for the diagnosis of liver metastases (kappa = 0.932), with good accuracy (AUC = 0.879-0.869). CONCLUSION: DWI has clinical value regarding the identification of PanNENs and the diagnosis of liver metastases, while conventional MR sequences are fundamental for their characterization.
PubMed-ID: 26646652
http://dx.doi.org/10.1159/000442984

Active Surveillance versus Surgery of Nonfunctioning Pancreatic Neuroendocrine Neoplasms </=2 cm in MEN1 Patients.
Neuroendocrinology, 103(6):779-86.
S. Partelli, D. Tamburrino, C. Lopez, M. Albers, A. C. Milanetto, C. Pasquali, M. Manzoni, C. Toumpanakis, G. Fusai, D. Bartsch and M. Falconi. 2016.
BACKGROUND: The aim of this study was to evaluate the efficacy of conservative treatment for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PNEN) </=2 cm in multiple endocrine neoplasia type 1 (MEN1)-affected patients compared with surgical treatment. METHODS: The databases of 4 tertiary referral institutions (San Raffaele Scientific Institute, Milan; Philipps-Universitat Marburg, Marburg; University of Padua, Padua; Royal Free Hospital, London) were analyzed. A comparison of conservative management and surgery at initial diagnosis of NF-PNEN </=2 cm between 1997 and 2013 was performed. RESULTS: Overall, 27 patients (45%) underwent up-front surgery and 33 patients (55%) were followed up after the initial diagnosis. A higher proportion of patients in the surgery group were female (70 vs. 33%, p = 0.004). Patients were mainly operated on in the period 1997-2007 as compared with the period 2008-2013 (n = 17; 63 vs. 37%; p = 0.040). The rate of multifocal tumors was higher in the surgery group (n = 24; 89%) than in the 'no surgery' group (n = 22; 67%; p = 0.043). After a median follow-up of 126 months, 1 patient deceased due to postoperative complications within 30 days after surgery. The 5-, 10-, and 15-year progression-free survival (PFS) rates were 63, 39, and 10%, respectively. The median PFS was similar in the two groups. Overall, 13 patients (32.5%) were operated on after initial surgical or conservative treatment. The majority of the surgically treated patients had stage 1 (77.5%), T1 (77.5%), and G1 (85%) tumors. CONCLUSIONS: NF-PNEN </=2 cm in MEN1 patients are indolent neoplasms posing a low oncological risk. Surgical treatment of these tumors at initial diagnosis is rarely justified in favor of conservative treatment.
PubMed-ID: 26731608
http://dx.doi.org/10.1159/000443613

Four Neuroendocrine Tumor Types and Neuroendocrine Carcinoma of the Duodenum: Analysis of 203 Cases.
Neuroendocrinology, 104(2):112-25.
A. Vanoli, S. La Rosa, C. Klersy, F. Grillo, L. Albarello, F. Inzani, R. Maragliano, R. Manca, O. Luinetti, M. Milione, C. Doglioni, G. Rindi, C. Capella and E. Solcia. 2017.
BACKGROUND: Several types of neuroendocrine neoplasms (NENs) have been described in the duodenal tract, from low-grade tumors (NETs) to high-grade neuroendocrine carcinomas (NECs). A comprehensive analysis of histology, hormonal profile and prognostic parameters of a sufficiently large duodenal NEN series to

cover all main kinds of neoplasms is however lacking. METHODS: We collected a retrospective series of 203 duodenal wall and ampullary region NENs, from six specialized endocrine pathology centers. All were characterized histopathologically and histochemically, and 190 were followed for a median of 9 years. RESULTS: Twenty-seven poorly differentiated NECs, mostly from the ampullary region, were identified and shown to lead to patient demise in a median of 10 months. Among 176 NETs, four subtypes were characterized, including 20 gastrinomas, 37 ampullary-type somatostatin-producing NETs (ASTs), 12 gangliocytic paragangliomas (GPs) and 106 nonfunctioning NETs (nfNETs). ASTs and GPs were mostly localized in the ampullary/periampullary region, while gastrinomas and nfNETs were mainly from the proximal duodenum. ASTs and gastrinomas showed high rates of local infiltration (especially lymphoinvasion and deep duodenal wall/pancreatic tissue invasion) and lymph node metastasis, while nfNETs had significantly lower and more size-dependent local invasive potential. Disease-specific survival differed significantly between NETs and NECs, though not among NET subtypes. NET cases with distant metastases (n = 23) were significantly associated with larger size, higher proliferative grade, lymphovascular invasion, deep invasion and local lymph node metastasis. CONCLUSION: Our careful analysis of a large series of duodenal NENs identified five histologically and prognostically different histotypes of potential clinical relevance.
PubMed-ID: 26910321
http://dx.doi.org/10.1159/000444803

Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease.
Nat Rev Clin Oncol, 13(9):537-49.
X. M. Keutgen, P. Hammel, P. L. Choyke, S. K. Libutti, E. Jonasch and E. Kebebew. 2016.
von Hippel-Lindau (VHL) disease is a heritable cancer-predisposition syndrome with multiorgan involvement. Pancreatic lesions are detected in approximately two-thirds of patients with VHL disease at some point during their lifetime. In these patients, cystic pancreatic lesions are almost exclusively benign and, unless symptomatic, do not require surgical or endoscopic intervention; however, solid pancreatic lesions can often be recognized through imaging screens, and are commonly found to be nonfunctioning pancreatic neuroendocrine tumours (pNETs) with malignant potential. The natural history of these VHL-associated pNETs is variable, and lacks clinical or imaging features that predict disease progression or metastatic potential, and generally needs to be managed more conservatively than their sporadic counterparts. Treatment options for such lesions, which range from active surveillance to surgical intervention, can nevertheless be associated with considerable morbidity and even mortality. Of note, although several guidelines have been established for the management of tumours associated with VHL syndrome, none of these have specifically focused on pancreatic lesions. Thus, we aim to characterize the types of pancreatic lesions associated with VHL disease and their natural history, to identify particular lesions that necessitate treatment, and to define what forms of treatment should be undertaken.
PubMed-ID: 27030075
http://dx.doi.org/10.1038/nrclinonc.2016.37

NET Blood Transcript Analysis Defines the Crossing of the Clinical Rubicon: When Stable Disease Becomes Progressive.
Neuroendocrinology, 104(2):170-82.
M. Pavel, H. Jann, V. Prasad, I. Drozdov, I. M. Modlin and M. Kidd. 2017.
BACKGROUND/AIMS: A key issue in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is early identification and prediction of disease progression. Clinical evaluation and imaging are limited due to the lack of sensitivity and disease indolence. We assessed the NETest as a predictive and prognostic marker of progression in a long-term follow-up study. METHODS: GEP-NETs (n = 34) followed for a median 4 years (2.2-5.4) were evaluated. WHO tumor grade/stage grade 1: n = 17, grade 2: n = 14, grade 3: n = 1 (for 2, no grade was available); 31 (91%) were stage IV. Baseline and longitudinal imaging and blood biomarkers were available in all, and progression was defined per standard clinical protocols (RECIST 1.0). The NETest was measured by quantitative PCR of blood and multianalyte algorithmic analysis (disease activity scaled 0-100% with low <40% and high activity risk cutoffs >80%); chromogranin A (CgA) was measured by radioimmunoassay (normal <150 microg/l); progression-free survival (PFS) was analyzed by Cox proportional-hazard regression and Kaplan-Meier analysis. RESULTS: At baseline, 100% were NETest positive, and CgA was elevated in 50%. The only baseline variable (Cox modeling) associated with PFS was NETest (hazard ratio = 1.022, 95% confidence interval = 1.005-1.04; p < 0.012). Using Kaplan-Meier analyses, the baseline NETest (>80%) was significantly associated (p = 0.01) with disease progression (median PFS 0.68 vs. 2.78 years with <40% levels). The NETest was more informative (96%) than CgA changes (<under>></under>25%) in consistently predicting disease alterations (40%, p < 2 x 10-5, chi2 = 18). The NETest had an earlier time point change than imaging (1.02 +/- 0.15 years). Baseline NETest levels >40% in stable disease were 100% prognostic of disease progression versus CgA (chi2 = 5, p < 0.03). Baseline NETest values <40% accurately (100%) predicted stability over 5

years (p = 0.05, chi2 = 3.8 vs. CgA). CONCLUSION: The NETest correlated with a well-differentiated GEP-NET clinical status. The NETest has predictive and prognostic utility for GEP-NETs identifying clinically actionable alterations approximately 1 year before image-based evidence of progression.
PubMed-ID: 27078712
http://dx.doi.org/10.1159/000446025

MicroRNAs associated with small bowel neuroendocrine tumours and their metastases.
Endocr Relat Cancer, 23(9):711-26.
H. C. Miller, A. E. Frampton, A. Malczewska, S. Ottaviani, E. A. Stronach, R. Flora, D. Kaemmerer, G. Schwach, R. Pfragner, O. Faiz, B. Kos-Kudla, G. B. Hanna, J. Stebbing, L. Castellano and A. Frilling. 2016.
Novel molecular analytes are needed in small bowel neuroendocrine tumours (SBNETs) to better determine disease aggressiveness and predict treatment response. In this study, we aimed to profile the global miRNome of SBNETs, and identify microRNAs (miRNAs) involved in tumour progression for use as potential biomarkers. Two independent miRNA profiling experiments were performed (n=90), including primary SBNETs (n=28), adjacent normal small bowel (NSB; n=14), matched lymph node (LN) metastases (n=24), normal LNs (n=7), normal liver (n=2) and liver metastases (n=15). We then evaluated potentially targeted genes by performing integrated computational analyses. We discovered 39 miRNAs significantly deregulated in SBNETs compared with adjacent NSB. The most upregulated (miR-204-5p, miR-7-5p and miR-375) were confirmed by qRT-PCR. Two miRNAs (miR-1 and miR-143-3p) were significantly downregulated in LN and liver metastases compared with primary tumours. Furthermore, we identified upregulated gene targets for miR-1 and miR-143-3p in an existing SBNET dataset, which could contribute to disease progression, and show that these miRNAs directly regulate FOSB and NUAK2 oncogenes. Our study represents the largest global miRNA profiling of SBNETs using matched primary tumour and metastatic samples. We revealed novel miRNAs deregulated during SBNET disease progression, and important miRNA-mRNA interactions. These miRNAs have the potential to act as biomarkers for patient stratification and may also be able to guide treatment decisions. Further experiments to define molecular mechanisms and validate these miRNAs in larger tissue cohorts and in biofluids are now warranted.
PubMed-ID: 27353039
http://dx.doi.org/10.1530/ERC-16-0044

Transarterial Chemoembolization for Metastatic Neuroendocrine Tumors With Massive Hepatic Tumor Burden: Is the Benefit Worth the Risk?
Ann Surg Oncol, 23(12):4008-15.
M. Kitano, G. W. Davidson, L. A. Shirley, C. R. Schmidt, G. E. Guy, H. Khabiri, J. D. Dowell, M. H. Shah and M. Bloomston. 2016.
BACKGROUND: Neuroendocrine tumors (NETs) have a propensity to metastasize to the liver, often resulting in massive tumor burden and hepatic dysfunction. While transarterial chemoembolization (TACE) is effective in treating patients with NET metastatic to the liver, there are limited data on its utility and benefit in patients with large hepatic involvement. The aim of our study was to determine the clinical benefit and complication rate of TACE in patients with massive hepatic tumor burden. METHODS: Medical records were reviewed in patients with grade 1 or 2 NETs with hepatic metastasis at our institution from January 2000 to September 2014 who underwent TACE. Of 201 total patients, 68 had massive hepatic tumor burden involving >75 % of liver parenchyma. RESULTS: Carcinoid syndrome was present in 40 (59 %) patients, and 57 (84 %) of the 68 patients were symptomatic from their disease. Complications beyond post-TACE syndrome occurred in 21.7 % of patients, with the most common complication being cardiac arrhythmias. The 30-day mortality rate was 7 %. Biochemical response was observed in 78 % of patients, while symptomatic relief and radiographic response was achieved in 85 and 82 % of patients, respectively. Median overall survival following TACE was 28 months, with 1-, 2-, and 5-year overall survival of 76, 54, and 26 %, respectively. CONCLUSIONS: In spite of massive tumor burden, clinical and biochemical improvements were seen in the majority of patients. Morbidity was acceptable and reversible but with a fairly high mortality rate of 7 %. TACE should still be considered in selective patients with massive hepatic tumor burden from metastatic NET for symptom control and palliation.
PubMed-ID: 27393568
http://dx.doi.org/10.1245/s10434-016-5333-x

Endocrine tumors associated with the vagus nerve.
Endocr Relat Cancer, 23(9):R371-9.
A. Varoquaux, E. Kebebew, F. Sebag, K. Wolf, J. F. Henry, K. Pacak and D. Taieb. 2016.
The vagus nerve (cranial nerve X) is the main nerve of the parasympathetic division of the autonomic nervous system. Vagal paragangliomas (VPGLs) are a prime example of an endocrine tumor associated with the vagus

nerve. This rare, neural crest tumor constitutes the second most common site of hereditary head and neck paragangliomas (HNPGLs), most often in relation to mutations in the succinate dehydrogenase complex subunit D (SDHD) gene. The treatment paradigm for VPGL has progressively shifted from surgery to abstention or therapeutic radiation with curative-like outcomes. Parathyroid tissue and parathyroid adenoma can also be found in close association with the vagus nerve in intra or paravagal situations. Vagal parathyroid adenoma can be identified with preoperative imaging or suspected intraoperatively by experienced surgeons. Vagal parathyroid adenomas located in the neck or superior mediastinum can be removed via initial cervicotomy, while those located in the aortopulmonary window require a thoracic approach. This review particularly emphasizes the embryology, molecular genetics, and modern imaging of these tumors.
PubMed-ID: 27406876
http://dx.doi.org/10.1530/ERC-16-0241

Proteomics Suggests a Role for APC-Survivin in Response to Somatostatin Analog Treatment of Neuroendocrine Tumors.
J Clin Endocrinol Metab, 101(10):3616-27.
O. Fotouhi, H. Kjellin, C. Larsson, J. Hashemi, J. Barriuso, C. C. Juhlin, M. Lu, A. Hoog, L. G. Pastrian, A. Lamarca, V. H. Soto, J. Zedenius, M. Mendiola, J. Lehtio and M. Kjellman. 2016.
CONTEXT: Somatostatin analogs are established in the treatment of neuroendocrine tumors (NETs) including small intestinal NET; however, the molecular mechanisms are not well known. Here, we examined the direct effects of lanreotide in NET cell line models. SETTING AND DESIGN: The cell lines HC45 and H727 were treated with 10nM lanreotide for different time periods and alterations of the proteome were analyzed by in-depth high-resolution isoelectric focusing tandem liquid chromatography-mass spectrometry. We next investigated whether the observed suppression of survivin was mediated by adenomatous polyposis coli (APC) and possible effects on tumor proliferation in vitro. Expression of survivin was assessed by immunohistochemistry in 112 NET cases and compared with patient outcome. RESULTS: We quantified 6451 and 7801 proteins in HC45 and H727, respectively. After short time lanreotide treatment APC was increased and survivin reduced. Overexpression of APC in H727 cells decreased, and APC knock-down elevated the survivin level. The lanreotide regulation of APC-survivin could be suppressed by small interfering RNA against somatostatin receptor 2. Although lanreotide only gave slight inhibition of proliferation, targeting of survivin with the small molecule YM155 dramatically reduced proliferation. Moderate or high as compared with low or absent total survivin expression was associated with shorter progression-free survival, independent of tumor stage, grade, and localization. CONCLUSIONS: We report a proteome-wide analysis of changes in response to lanreotide in NET cell lines. This analysis suggests a connection between somatostatin analog, APC, and survivin levels. Survivin is a possible prognostic factor and a new potential therapeutic target in NETs.
PubMed-ID: 27459532
http://dx.doi.org/10.1210/jc.2016-2028

Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours.
Endocr Relat Cancer, 23(9):R423-36.
G. K. Dimitriadis, M. O. Weickert, H. S. Randeva, G. Kaltsas and A. Grossman. 2016.
Although recent epidemiological evidence indicates that the prevalence of non-functioning gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) is rising, a significant number of GEP-NETs still present with symptoms related to the secretion of biologically active substances leading to the development of distinct clinical syndromes. In the past, these syndromes were associated with substantial morbidity and mortality due to the lack of specific therapies; however, since the introduction of long-acting somatostatin analogues and medications such as proton pump inhibitors, their control has been greatly improved. As a result, nowadays, the main cause of morbidity and mortality in GEP-NETs is mostly directly related to tumour growth and the extent of metastatic disease. However, in some patients with functioning tumours and extensive disease, control of the secretory syndrome still remains problematic, necessitating the employment of several cytoreductive techniques, which may not always be sufficient. Recently, new agents directed against tumour growth, or exerting increased binding activity to receptors expressed in these tumours, or interfering with the synthetic pathway of some of the compounds secreted by these tumours, have been developed. Since there are no specific guidelines addressing the totality of the management of the secretory syndromes related to GEP-NETs, this review aims at critically analysing the medical management of previously recognised secretory syndromes; it also addresses areas of uncertainty, assesses the newer therapeutic developments and also addresses recently described but poorly characterised secretory syndromes related to GEP-NETs.
PubMed-ID: 27461388
http://dx.doi.org/10.1530/ERC-16-0200

Propensity score-matched analysis of robotic versus open surgical enucleation for small pancreatic neuroendocrine tumours.
Br J Surg, 103(10):1358-64.
F. Tian, X. F. Hong, W. M. Wu, X. L. Han, M. Y. Wang, L. Cong, M. H. Dai, Q. Liao, T. P. Zhang and Y. P. Zhao. 2016.
BACKGROUND: Enucleation of pancreatic neuroendocrine tumours (pNETs) via robotic surgery has rarely been described. This study sought to assess the safety and efficiency of robotic surgery for the enucleation of small pNETs. METHODS: A comparison was conducted of enucleation of pNETs smaller than 2 cm by robotic or open surgery between January 2000 and May 2015. Propensity score matching was used to balance sex, age, BMI, tumour location and tumour diameter. Pathological results, safety-related outcomes (postoperative pancreatic fistula (POPF) rate, estimated blood loss, and short-term mortality and morbidity) and efficiency-related outcomes (duration of surgery and postoperative length of hospital stay) were compared between the groups. RESULTS: A cohort of 120 patients with pNET were enrolled in the study (1 : 1 matched for open or robotic surgery, 60 per group). Ninety-three patients (77.5 per cent) had a grade 1 tumour and 114 (95.0 per cent) had an insulinoma. Robotic surgery had a conversion rate of 5 per cent (3 of 60), and was not associated with an increased POPF rate (10 per cent versus 17 per cent after open surgery; P = 0.283) or grade III-V surgical complications according to the Dindo-Clavien classification (3 versus 10 per cent respectively; P = 0.272). Estimated blood loss was reduced with the robotic approach (32.5 versus 80.0 ml in the open group; P = 0.008), as was duration of surgery (117 versus 150 min; P < 0.001). Length of hospital stay after surgery was similar in the two groups (12.0 versus 13.5 days respectively; P = 0.071). CONCLUSION: Robotic surgery for enucleation of pNETs smaller than 2 cm did not increase POPF or major complication rates, and reduced the duration of surgery and estimated blood loss, compared with open surgery. REGISTRATION NUMBER: NCT02125929 (https://www.clinicaltrials.gov/).
PubMed-ID: 27480993
http://dx.doi.org/10.1002/bjs.10220

Perspectives for immunotherapy in endocrine cancer.
Endocr Relat Cancer, 23(10):R469-84.
S. Latteyer, V. Tiedje, B. Schilling and D. Fuhrer. 2016.
The fight against cancer has seen major breakthroughs in recent years. More than a decade ago, tyrosine kinase inhibitors targeting constitutively activated signaling cascades within the tumor inaugurated a new era of oncological therapy. Recently, immunotherapy with immune checkpoint inhibitors has started to revolutionize the treatment of several malignancies, most notably malignant melanoma, leading to the renaissance and the long-awaited breakthrough of immunooncology. This review provides an overview of the basis of immunotherapy from its initial concepts of anti-tumor immunity and cell-based therapy to the development of immune checkpoint inhibitors and discusses published studies and the perspectives of immunooncology for the treatment of endocrine malignancies.
PubMed-ID: 27485460
http://dx.doi.org/10.1530/ERC-16-0169

Localized high-grade gastroenteropancreatic neuroendocrine tumors: Defining prognostic and therapeutic factors for a disease of increasing clinical significance.
Eur J Surg Oncol, 42(10):1471-7.
C. Mosquera, N. J. Koutlas and T. L. Fitzgerald. 2016.
BACKGROUND: Due to the limited sample size in the existing series, the natural history and management of high-grade gastroenteropancreatic neuroendocrine tumors (GEP-NET) is poorly understood. In order to better understand high-grade GEP-NET, a large cohort study was undertaken. OBJECTIVE: To determine the prognostic factors associated with high-grade GEP-NET. METHODS: Patients diagnosed with non-metastatic high-grade GEP-NET from 1988 to 2010 were identified in SEER. RESULTS: Incidence of high-grade GEP-NETs increased from 0.03 to 0.19/100,000 over the study period. The median age was 65 years, and the majority of the patients were white and females. The most common primary site was colorectal, and the most frequent T classification was T3. Surgical resection was performed in 89% of patients that varied by site (p < 0.0001). Nodal involvement was frequent and varied by site (p = 0.0002). The 5-year disease-specific survival was 63.3% and was the greatest for small bowel (p = 0.0003). Survival was associated with age, node status and surgery (p < 0.05). On multivariate analysis, the node status, surgery, and site continued to be associated with survival (p < 0.05); however, age (p = 0.08) no longer influenced the patient's survival. CONCLUSION: High-grade GEP-NETs are neoplasms with exponentially increasing in incidence. Tumor location and nodal status are predictors of survival. Surgery is associated with a survival advantage and could be considered for

localized disease.
PubMed-ID: 27528467
http://dx.doi.org/10.1016/j.ejso.2016.07.137

Diagnosis and surgical management of insulinomas in 33 consecutive patients at a single institution.
Langenbecks Arch Surg, 401(7):1019-25.
J. Wei, X. Liu, J. Wu, W. Xu, W. Gao, K. Jiang, Z. Zhang and Y. Miao. 2016.
PURPOSE: The purpose of this study was to evaluate the diagnosis and surgical management of insulinomas in a single-center setting. METHODS: Demographic details, clinical presentation, preoperative diagnosis, surgical strategy, and outcomes of 33 consecutive patients who underwent surgery for insulinoma were analyzed retrospectively. RESULTS: The median time from the first onset of symptoms to diagnosis was 24 months (range 3 days to 50 years). All cases presented with Whipple's triad and had a fasting insulin to glucose ratio higher than 0.33. The preoperative detection rates of transabdominal ultrasonography, CT, MRI, and EUS were 22 % (2/9), 72 % (23/32), 75 % (9/12), and 80 % (4/5), respectively. Intraoperative manual palpation localized all cases. Enucleation was performed in 58 % of cases (19/33), partial pancreatic resection in 39 % (13/33), and enucleation plus partial resection in 3 % (1/33). Pancreatic fistula was the most common complication and occurred in 15 patients (45 %), including seven grade A, five grade B, and three grade C fistulas. There was no mortality. When compared with partial pancreatectomy, enucleation held a significant advantage in operative time and operative bleeding, with no significant differences in demographic data and postoperative complications. During a median follow-up period of 32 months, two patients were lost to follow-up and the remaining 31 patients were without evidence of recurrence. CONCLUSIONS: A fasting insulin release index larger than 0.3 is a reliable indicator for the diagnosis of insulinoma. Intraoperative palpation by an experienced surgeon can effectively complement an uncertain preoperative localization. Compared with partial pancreatic resection, enucleation showed significant benefit in terms of intraoperative blood loss and operation time.
PubMed-ID: 27539217
http://dx.doi.org/10.1007/s00423-016-1496-y

Pancreatic Neuroendocrine Tumor Secreting Vasoactive Intestinal Peptide and Dopamine With Pulmonary Emboli: A Case Report.
J Clin Endocrinol Metab, 101(10):3564-7.
N. Nilubol, E. M. Freedman, M. M. Quezado, D. Patel and E. Kebebew. 2016.
CONTEXT: The vasoactive intestinal peptide-secreting neuroendocrine tumor (VIPoma) is a very rare pancreatic tumor. We report the first case of a patient with VIPoma that co-secreted dopamine and had pulmonary emboli. CASE DESCRIPTION: A 67-year-old woman presented with 2 months of watery diarrhea, severe generalized weakness,6.8 kg of weight loss, a facial rash, and hypokalemia. Colonoscopy did not reveal the cause of the chronic diarrhea. Initial biochemical testing showed markedly elevated serum vasoactive intestinal peptide (VIP) and pancreatic polypeptide. Computed tomography scan of the abdomen and pelvis revealed a 5.4-cm distal pancreatic mass. Octreoscan showed an intense uptake in the area of the pancreatic mass. Incidental pulmonary emboli were found and treated. Additional biochemical testing revealed a markedly elevated urinary dopamine level. The patient received preoperative alpha-blockade and octreotide. She underwent a successful laparoscopic distal pancreatectomy. Postoperative urinary dopamine and pancreatic polypeptide were within normal limits. Serum VIP decreased by half but remained elevated. Pathology confirmed a grade 1 pancreatic neuroendocrine tumor without lymph node metastasis. The patient's symptoms resolved and no longer required octreotide. Metastatic workup including computed tomography, F18-fluorodeoxglucose positron emission tomography, and Ga68-DOTATATE scans were negative during 4 years of follow-up. CONCLUSIONS: VIPoma is a rare subtype of pancreatic neuroendocrine tumor that can secrete dopamine and can be associated with thromboembolism.
PubMed-ID: 27583474
http://dx.doi.org/10.1210/jc.2016-2051

Resection of the Primary Tumor Followed by Peptide Receptor Radionuclide Therapy as Upfront Strategy for the Treatment of G1-G2 Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases.
Ann Surg Oncol, 23(Suppl 5):981-9.
E. Bertani, N. Fazio, D. Radice, C. Zardini, C. Grana, L. Bodei, L. Funicelli, C. Ferrari, F. Spada, S. Partelli and M. Falconi. 2016.
BACKGROUND: A low burden of disease represents an independent favorable prognostic factor of response to peptide receptor radionuclide therapy (PRRT) in patients affected by gastro-entero-pancreatic neuroendocrine tumors. However, it is not clear whether this is due to a lower diffusion of the disease or thanks to debulking

surgery. METHODS: From 1996 to 2013 those patients diagnosed with G1-G2 pancreatic neuroendocrine tumor (PNET) and synchronous liver metastases who were not deemed eligible for liver radical surgery but were eligible to receive upfront PRRT were prospectively included in the study. Two groups of comparison were identified: those submitted for primary tumor resection before PRRT and those who were not. The outcome was evaluated as: objective response to PRRT (OR), progression-free survival (PFS), and overall survival (OS). RESULTS: Of the 94 subjects, 31 were previously submitted for primary tumor resection. After propensity score adjustments, patients who underwent surgery before PRRT showed higher stabilization or objective responses after PRRT (p = .006), and this translated into a better median PFS (70 vs. 30 months; p = .002) and OS (112 vs. 65 months; p = .011), for operated versus nonoperated patients, respectively. At multivariate analysis, operated patients showed a statistically significantly improved PFS: HR, 5.11 (95 % CI 1.43-18.3); p = .012, whereas Ki-67 in continuous fashion was correlated significantly with OS: 1.13 (95 % CI 1-1.27); p = .048. CONCLUSIONS: Primary tumor resection prior to PRRT can be safely proposed in G1-G2 PNETs with diffuse liver metastases because it seems to enhance response to PRRT and to improve significantly PFS.
PubMed-ID: 27613553
http://dx.doi.org/10.1245/s10434-016-5550-3

Lymphadenectomy during Small Bowel Neuroendocrine Tumor Surgery: The Concept of Skip Metastases.
Ann Surg Oncol, 23(Suppl 5):804-8.
A. Pasquer, T. Walter, P. Rousset, V. Hervieu, J. Forestier, C. Lombard-Bohas and G. Poncet. 2016.
BACKGROUND: More than half of small bowel neuroendocrine tumors (SB-NETs) are metastatic at diagnosis, but complete resection of the primary tumor and lymph node (LN) is recommended by most authors. Our aim was to describe the pattern of involved LN after an extensive LN resection. MATERIALS AND METHODS: Between July 2013 and December 2015, all consecutive patients who underwent resection of at least one SB-NET in our European Neuroendocrine Tumor Society Center of Excellence were prospectively included, while patients with duodenal SB-NETs were excluded. The resection and pathological analysis of LNs were standardized using three groups (group 1, along the small intestine; group 2, along the mesenteric vessel; and group 3, retropancreatic and mesenteric vessel origin). RESULTS: Twenty-eight patients with SB-NET resection were prospectively enrolled in the study, with seven patients being excluded from the analysis because it was impossible to divide the operative piece into nodal groups due to retractile mesenteritis. Among the remaining 21 patients, 20 (95 %) had LNs involved; 8 (38 %) in group 1, 13 (62 %) in group 2, and 12 (57 %) in group 3. Skip metastases were found in 14 patients (67 %): 4 (19 %) with an invasion pattern of group 3+ without group 2+, and 12 (57 %) with an invasion pattern of group 2+ or group 3+ without group 1+. CONCLUSION: As a result of skip metastases, systematic, extensive LN resection in retropancreatic portion may be required to prevent unresectable locoregional recurrence.
PubMed-ID: 27613554
http://dx.doi.org/10.1245/s10434-016-5574-8

18F-FDG PET/CT Volumetric Parameters are Associated with Tumor Grade and Metastasis in Pancreatic Neuroendocrine Tumors in von Hippel-Lindau Disease.
Ann Surg Oncol, 23(Suppl 5):714-21.
K. Satoh, S. M. Sadowski, W. Dieckmann, M. Quezado, N. Nilubol, E. Kebebew and D. Patel. 2016.
BACKGROUND: Approximately 8-17 % of patients with von Hippel-Lindau (VHL) syndrome develop pancreatic neuroendocrine tumors (PNETs), with 11-20 % developing metastases. Tumor grade is predictive of prognosis. OBJECTIVE: The aim of this study was to determine if preoperative metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were associated with metastatic disease and tumor grade. METHODS: Sixty-two patients with VHL-associated PNETs prospectively underwent 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT). MTV, TLG, and maximum standardized uptake value (SUVmax) were measured using a semi-automatic method. Surgically resected PNETs were classified according to 2010 World Health Organization tumor grade classification. MTV, TLG, and SUVmax were analyzed by metastatic disease and tumor grade using the Mann-Whitney test. RESULTS: A total of 88 PNETs were identified by CT and 18F-FDG PET/CT, 10 of which were non-FDG-avid. Histologic grading was available for 20 surgical patients. Patients with metastatic PNETs had a higher TLG (median 25.9 vs. 7.7 mean SUV [SUVmean]*mL; p = 0.0092) compared with patients without metastasis, while patients with grade 2 PNETs had a higher MTV (median 6.9 vs. 2.6 mL; p = 0.034) and TLG (median 41.2 vs. 13.1 SUVmean*mL; p = 0.0035) compared with patients with grade 1 PNETs. No difference in tumor size or SUVmax was observed between the groups. CONCLUSIONS: Patients with metastatic PNETs have a higher TLG compared with patients without metastasis. Grade 2 PNETs have a higher MTV and TLG compared with grade 1 PNETs. Tumor size and SUVmax were not associated with grade. Volumetric parameters on 18F-FDG PET/CT may be useful in detecting higher grade

PNETs with a higher malignant potential that may need surgical intervention.
PubMed-ID: 27638678
http://dx.doi.org/10.1245/s10434-016-5541-4

Parenchyma-sparing surgery for pancreatic endocrine tumors.
Updates Surg, 68(3):313-9.
F. Uccelli, F. Gavazzi, G. Capretti, M. Virdis, M. Montorsi and A. Zerbi. 2016.
Enucleation (EN) and middle pancreatectomy (MP) have been proposed as a treatment for G1 and G2 pancreatic neuroendocrine tumors (PNET). The aim of this study is to analyze the outcomes of parenchyma-sparing surgery (PSS) for PNET in an Italian high-volume center. All patients with a histological diagnosis of PNET who underwent surgical resection in our center between January 2010 and January 2016 were included in the study. Demographic, perioperative, and discharge data were collected in a prospective database. Follow-up was considered until March 31, 2016. 99 patients were included. PSS was performed in 22 cases (22.2 %), 18 EN (82 %), and 4 MP (18 %). 89.8 % patients were staged with CT scan, 69.6 % with endoscopic ultrasonography, 48.4 % with MRI, and 47.4 % with 68Ga-PET. Pre-operative histological diagnosis was obtained in 68.6 %. Most of PSS tumors were G1 (n = 15; 68 %) and there were no G3. Nodal sampling was performed in every PSS. Only two patients showed nodal metastatic disease. The median post-operative length of stay was 7 days after PSS. Eleven (50 %) of these patients developed a complication; two (18.2 %) were major complications. Pancreatic fistula developed in ten patients (45.5 %); two (20 %) were type B. There were no type C fistula and no re-operations after PSS. Readmission rate was 9 %. All patients submitted to PSS are alive and free of recurrence. PSS is a safe technique for G1 and G2 PNETs, but it has to be conducted in experienced centers and an extensive nodal sampling and a long follow-up are required for the best oncologic outcome.
PubMed-ID: 27709476
http://dx.doi.org/10.1007/s13304-016-0400-1

[Importance of tumor size for pancreatic neuroendocrine tumors].
Chirurg, 87(12):1077.
F. Weber. 2016.
PubMed-ID: 27752726
http://dx.doi.org/10.1007/s00104-016-0315-x

Long-term outcomes in patients with multiple endocrine neoplasia type 1 and pancreaticoduodenal neuroendocrine tumours.
Clin Endocrinol (Oxf), 86(2):199-206.
D. Donegan, N. Singh Ospina, R. Rodriguez-Gutierrez, Z. Al-Hilli, G. B. Thompson, B. L. Clarke and W. F. Young, Jr. 2017.
BACKGROUND: In patients with multiple endocrine neoplasia type 1 (MEN-1), pancreaticoduodenal (PD) neuroendocrine tumours (NETs) are associated with early mortality, yet the best treatment strategy remains uncertain. AIM: To assess patient important outcomes (mortality and metastasis) of PD-NETs and predictors of outcomes in patients with MEN-1. METHODS: Retrospective cohort of patients with MEN-1 who attended the Mayo Clinic, Rochester, MN from 1997 to 2014. RESULTS: We identified 287 patients with MEN-1; 199 (69%) patients had 217 PD-NETs. Among those with a PD-NETs, 129 (65%) had surgery of which 90 (70%) had their primary surgery performed at Mayo Clinic. The median postoperative follow-up was 8 years during which 13 (14%) patients died. The mean (+/-standard deviation) age of death was 51 (+/-9) years. Tumour size, metastasis at surgery or tumour type were not predictive of mortality, but for every year older at surgery, the odds of metastasis increased by 6%. Surgery was not performed in 70 (35%) patients. Among those who were observed/medically managed without known metastatic disease, mean tumour growth was 0.02 cm/year (range, -0.13-0.4 cm/year). Four patients (7%) died at a median age of 77 (range, 51-89) years. CONCLUSION: PD-NETs are common in patients with MEN-1 and are associated with early mortality even after surgical intervention. Active surveillance is a viable option in nonaggressive PD-NETs, although definitive factors identifying such patients are lacking. Therefore, counselling regarding risks and benefits of current treatment options remains integral to the care of patients with MEN-1.
PubMed-ID: 27770475
http://dx.doi.org/10.1111/cen.13264

Localization of Insulinoma Using 68Ga-DOTATATE PET/CT Scan.
J Clin Endocrinol Metab:jc20163445.
P. Nockel, B. Babic, C. Millo, P. Herscovitch, D. Patel, N. Nilubol, S. Sadowski, C. Cochran, P. Gorden and E. Kebebew. 2016.
CONTEXT: The reliable localization of insulinoma is critical for the successful surgical treatment. OBJECTIVE: This study compared the accuracy of 68Gallium (Ga)-DOTATATE PET/CT to anatomic imaging modalities, selective arterial secretagogue injection (SASI), and intraoperative ultrasound (IOUS) and palpation for localizing insulinoma in patients who were biochemically cured. DESIGN, SETTING, AND PATIENTS: We conducted a retrospective analysis of 31 patients who had an insulinoma confirmed on histology and were biochemically cured. The results of CT, MRI, transabdominal US, IOUS, 68Ga-DOTATATE PET/CT, SASI, and operative findings were analyzed. Intervention, Main Outcome Measures, Results: The insulinomas were correctly localized in 17 out of 31 (55%) of patients by CT, in 17 out of 28 (61%) by MRI, in 6 out of 28 (21%) by US, and in 9 out of 10 (90%) by 68Ga-DOTATATE. IOUS was performed in 31 patients, and 29 of them had an insulinoma successfully localized (93.5%). Thirty patients underwent SASI, and the insulinoma was regionalized in 28 out of 30 patients (93%). In 19 out of 23 patients (83%), manual palpation identified insulinoma. In patients who had all four noninvasive imaging studies, CT was concordant with 68Ga-DOTATATE in 6 out of 9 patients (67%); MRI in 8 out of 9 (78%); US in 0 out of 9; and in 1 out of 9 patients (11%) the lesion was only seen by 68Ga-DOTATATE. CONCLUSIONS: 68Ga-DOTATATE PET/CT identifies most insulinomas and may be considered as an adjunct imaging study when all imaging studies are negative and when a minimally invasive surgical approach is planned.
PubMed-ID: 27805844
http://dx.doi.org/10.1210/jc.2016-3445

Molecular Imaging of Gastroenteropancreatic Neuroendocrine Tumors: Current Status and Future Directions.
J Nucl Med, 57(12):1949-56.
C. M. Deroose, E. Hindie, E. Kebebew, B. Goichot, K. Pacak, D. Taieb and A. Imperiale. 2016.
Through diagnostic imaging and peptide receptor radionuclide therapy, nuclear medicine has earned a major role in gastroenteropancreatic neuroendocrine tumors (GEP NETs). GEP NETs are diagnosed fortuitously or on the basis of symptoms or hormonal syndrome. The functional tumor characteristics shown by radionuclide imaging allow for more accurate staging and treatment selection. Tumor grade helps determine which tracer should be selected. In the past, 111In-pentetreotide has been successful in well-differentiated (G1 and G2) tumors. However, PET/CT imaging with novel somatostatin analogs (e.g., 68Ga-DOTATOC, 68Ga-DOTATATE, 68Ga-DOTANOC, and 64Cu-DOTATATE) now offers improved sensitivity. 18F-fluorodihydroxyphenylalanine (18F-FDOPA) is another interesting radiopharmaceutical. 18F-FDOPA sensitivity is influenced by a tumor's capacity to take up, decarboxylate, and store amine precursors. 18F-FDOPA sensitivities are highest in ileal NETs and may also be helpful in insulinomas. A high uptake of 18F-FDG with a low uptake of somatostatin analog usually indicates poorly differentiated tumors (G3). Starting from these principles, this article discusses theranostic approaches to GEP NETs, taking into account both primary and metastatic lesions.
PubMed-ID: 27811124
http://dx.doi.org/10.2967/jnumed.116.179234

Early and Late Complications After Surgery For MEN1-related Nonfunctioning Pancreatic Neuroendocrine Tumors.
Ann Surg,
S. Nell, I. H. Borel Rinkes, H. M. Verkooijen, B. A. Bonsing, C. H. van Eijck, H. van Goor, R. H. de Kleine, G. Kazemier, E. J. Nieveen van Dijkum, C. H. Dejong, G. D. Valk and M. R. Vriens. 2016.
OBJECTIVE: To estimate short and long-term morbidity after pancreatic surgery for multiple endocrine neoplasia type 1 (MEN1)-related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs). BACKGROUND: Fifty percent of the MEN1 patients harbor multiple NF-pNETs. The decision to proceed to NF-pNET surgery is a balance between the risk of disease progression versus the risk of surgery-related morbidity. Currently, there are insufficient data on the surgical complications after MEN1 NF-pNET surgery. METHODS: MEN1 patients diagnosed with a NF-pNET who underwent surgery were selected from the DutchMEN1 study group database, including >90% of the Dutch MEN1 population. Early postoperative complications, new-onset diabetes mellitus, and exocrine pancreatic insufficiency were captured. RESULTS: Sixty-one patients underwent NF-pNET surgery at 1 of the 8 Dutch academic centers. Patients were young (median age 41 years) with low American Society of Anesthesiologists scores. Median NF-pNET size on imaging was 22 mm (3-157). Thirty-three percent (19/58) of the patients developed major early-Clavien-Dindo grade III to IV-complications mainly consisting International Study Group of Pancreatic Surgery grade B/C pancreatic fistulas. Twenty-three percent of the patients (14/61)

developed endocrine or exocrine pancreas insufficiency. The development of major early postoperative complications was independent of the NF-pNET tumor size. Twenty-one percent of the patients (12/58) developed multiple major early complications. CONCLUSIONS: MEN1 NF-pNET surgery is associated with high rates of major short and long-term complications. Current findings should be taken into account in the shared decision-making process when MEN1 NF-pNET surgery is considered.
PubMed-ID: 27811505
http://dx.doi.org/10.1097/SLA.0000000000002050

Shape and Enhancement Characteristics of Pancreatic Neuroendocrine Tumor on Preoperative Contrast-enhanced Computed Tomography May be Prognostic Indicators.
Ann Surg Oncol,
H. Okabe, D. Hashimoto, A. Chikamoto, M. Yoshida, K. Taki, K. Arima, K. Imai, Y. Tamura, O. Ikeda, T. Ishiko, H. Uchiyama, T. Ikegami, N. Harimoto, S. Itoh, Y. I. Yamashita, T. Yoshizumi, T. Beppu, Y. Yamashita, H. Baba and Y. Maehara. 2016.
BACKGROUND: Prognostic indicators of the malignant potential of pancreatic neuroendocrine tumors (PNET) are limited. We assessed tumor shape and enhancement pattern on contrast-enhanced computed tomography as predictors of malignant potential. METHODS: Sixty cases of PNET patients undergoing curative surgery from 2001 to 2014 were enrolled onto our retrospective study. Preoperative enhanced CTs were assessed, and criteria defined for regularly shaped and enhancing tumors (group 1), and irregularly shaped and/or enhancing tumors (group 2). The relation of tumor shape and enhancement pattern to outcome was assessed. RESULTS: Interobserver agreement was substantial (kappa = 0.74). Group 2 (n = 24) was significantly correlated with synchronous liver metastasis (23 vs. 0 %), lymph node metastasis (36 vs. 3 %), pathologic capsular invasion (68 vs. 8 %), larger tumor size (30 vs. 12 mm), tumor, node, metastasis classification system (TNM) stage III/IV disease (46 vs. 3 %), and histologic grade 2/3 (41 vs. 0 %). Multivariate analysis revealed that tumor grade 2/3 and group 2 criteria correlated with tumor relapse (hazard ratio 6.5 and 13.6, P = 0.0071 and 0.039, respectively), and that only group 2 criteria were independently correlated with poor overall survival (hazard ratio 5.56e + 9, P = 0.0041). CONCLUSIONS: Irregular tumor shape/enhancement on preoperative computed tomography is a negative prognostic factor after curative surgery for PNET.
PubMed-ID: 27896509
http://dx.doi.org/10.1245/s10434-016-5630-4

Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver.
Eur J Surg Oncol, 43(2):380-7.
D. Citterio, S. Pusceddu, A. Facciorusso, J. Coppa, M. Milione, R. Buzzoni, M. Bongini, F. deBraud and V. Mazzaferro. 2017.
BACKGROUND: Functional well-differentiated neuroendocrine tumours (NET) with liver metastases represent a therapeutic challenge with few alternative options in guidelines. In these patients, the role of surgical resection of the primary tumour is controversial. PATIENTS AND METHODS: From a regional registry collecting somatostatin analogue (SSA)-treated tumours from 1979 to 2005, a series of 139 patients presenting with symptomatic, liver-metastatic, well-differentiated NET (G1-G2, mitoses: </=20, Ki-67: </=20%) was prospectively collected and retrospectively analysed. Surgery on either the primary tumour or liver metastases was chosen: 1) when low perioperative risk was predictable; 2) in presence of an impending risk of obstruction, bleeding, or perforation; or 3) if liver metastases were suitable of curative or subtotal (>90%) tumour removal. Impact of the most relevant clinico-pathological parameters on survival was studied. RESULTS: Median follow-up was 127 months and median survival was 94 months, with 138 vs. 37 months in resected vs. non-resected primary NET ($p < 0.001$), respectively. In the univariate analysis, prolonged survival was significantly associated with primary tumour resection ($p < 0.001$), resection of liver metastases ($p = 0.002$), site of primary (carcinoid vs. pancreatic, $p = 0.018$), basal chromogranin-A (CgA) <200 ng/mL ($p = 0.001$), and absence of diarrhea ($p = 0.012$). Multivariate analysis showed that primary tumour resection was an independent positive prognostic factor (HR = 3.17; 95% CI: 1.77-5.69, $p < 0.001$), whereas diarrhea, basal CgA >/=200 ng/mL, and high tumour load were independent negative prognostic factors. Also, in 103 patients with non-resectable liver metastases, primary tumour resection was significantly associated with prolonged survival (median 137 vs. 32 months, $p < 0.0001$). CONCLUSIONS: Primary tumour resection may improve survival in functional well-differentiated NET with liver metastases.
PubMed-ID: 27956320
http://dx.doi.org/10.1016/j.ejso.2016.10.031

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Risk of Complications after Thyroidectomy and Parathyroidectomy: A Case Series with Planned Chart Review.
Otolaryngol Head Neck Surg, 155(3):391-401.
C. Meltzer, M. Klau, D. Gurushanthaiah, H. Titan, D. Meng, L. Radler and A. Sundang. 2016.
OBJECTIVE: To develop a predictive model for the risk of complications after thyroid and parathyroid surgery. STUDY DESIGN: Case series with planned chart review of patients undergoing surgery, 2007-2013. SETTING: Kaiser Permanente Northern California and Kaiser Permanente Southern California. SUBJECTS AND METHODS: Patients (N = 16,458) undergoing thyroid and parathyroid procedures were randomly assigned to model development and validation groups. We used univariate analysis to assess relationships between each of 28 predictor variables and 30-day complication rates. We subsequently entered all variables into a recursive partitioning decision tree analysis, with P < .05 as the basis for branching. RESULTS: Among patients undergoing thyroidectomies, the most important predictor variable was thyroid cancer. For patients with thyroid cancer, additional risk predictors included coronary artery disease and central neck dissection. For patients without thyroid cancer, additional predictors included coronary artery disease, dyspnea, complete thyroidectomy, and lobe size. Among patients undergoing parathyroidectomies, the most important predictor variable was coronary artery disease, followed by cerebrovascular disease and chronic kidney disease. The model performed similarly in the validation groups. CONCLUSION: For patients undergoing thyroid surgery, 7 of 28 predictor variables accounted for statistically significant differences in the risk of 30-day complications; for patients undergoing parathyroid surgery, 3 variables accounted for significant differences in risk. This study forms the foundation of a parsimonious model to predict the risk of complications among patients undergoing thyroid and parathyroid surgery.
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Limited value for urinary 5-HIAA excretion as prognostic marker in gastrointestinal neuroendocrine tumours.
Eur J Endocrinol, 175(5):361-6.
W. T. Zandee, K. Kamp, R. C. van Adrichem, R. A. Feelders and W. W. de Herder. 2016.
OBJECTIVE: To determine if urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion is of prognostic value for overall survival (OS) in patients with a gastrointestinal neuroendocrine tumour (NET) and to compare the prognostic value with patient characteristics, ENETS/WHO grading, ENETS TNM staging and biomarkers. DESIGN AND METHODS: Data was collected from patients with a gastrointestinal NET or a NET with gastrointestinal metastases and available 5-HIAA excretion in 24-h urine samples. Laboratory results were stratified for urinary 5-HIAA and chromogranin A (CgA): <2x upper limit of normal (ULN), 2-10x ULN, or >10x ULN. For neuron-specific enolase (NSE), this was the reference range or >1x ULN. OS was compared using Kaplan-Meier and log-rank tests, and hazard ratios were calculated using Cox regression for univariate and

multivariate analyses. RESULTS: A total of 371 patients were included, 46.6% female with a mean age of 59.9 years. OS was shortest in patients with urinary 5-HIAA excretion >10x ULN vs reference range (median 83 months vs 141 months, P = 0.002). In univariate analysis, urinary 5-HIAA excretion >10x ULN was a negative predictor (HR 1.62, 95% CI: 1.09-2.39). However, in multivariate analysis, only age (HR 1.04, 95% CI: 1.01-1.08), grade 3 disease (HR 5.09, 95% CI: 2.20-11.79), NSE >1x ULN (HR 2.36, 95% CI: 1.34-4.14) and CgA >10x ULN (HR 3.61, 95% CI: 1.56-8.34) remained as the predictors. CONCLUSION: Urinary 5-HIAA excretion >10x ULN is a negative predictor for OS. However, when added to other biomarkers and grading, it is no longer a predictor for OS. Therefore, it should only be determined to assess carcinoid syndrome and not for prognostic value.
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http://dx.doi.org/10.1530/EJE-16-0392

Joint Meeting of the German Association of Endocrine Surgeons (CAEK) and the British Association of Endocrine and Thyroid Surgeons (BAETS).
Langenbecks Arch Surg, 401(7):1045-91.
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Loss of DPC4/SMAD4 expression in primary gastrointestinal neuroendocrine tumors is associated with cancer-related death after resection.
Surgery, 161(3):753-9.
C. L. Roland, L. F. Starker, Y. Kang, D. Chatterjee, J. Estrella, A. Rashid, M. H. Katz, T. A. Aloia, J. E. Lee, A. Dasari, J. C. Yao and J. B. Fleming. 2017.
BACKGROUND: Gastrointestinal neuroendocrine tumors have frequent loss of DPC4/SMAD4 expression, a known tumor suppressor. The impact of SMAD4 loss on gastrointestinal neuroendocrine tumors aggressiveness or cancer-related patient outcomes is not defined. We examined the expression of SMAD4 in resected gastrointestinal neuroendocrine tumors and its impact on oncologic outcomes. METHODS: Patients who underwent complete curative operative resection of gastrointestinal neuroendocrine tumors were identified retrospectively (n = 38). Immunohistochemical staining for SMAD4 expression was scored by a blinded pathologist and correlated with clinicopathologic features and oncologic outcomes. RESULTS: Twenty-nine percent of the gastrointestinal neuroendocrine tumors were SMAD4-negative and 71% SMAD4-positive. Median overall survival was 155 months (95% confidence interval, 102-208 months). Loss of SMAD4 was associated with both decreased median disease-free survival (28 months; 95% confidence interval, 16-40) months compared with 223 months (95% confidence interval, 3-443 months) for SMAD4-positive patients (P = .03) and decreased median disease-specific survival (SMAD4: 137 [95% confidence interval, 81-194] months versus SMAD4-positive: 204 [95% confidence interval, 143-264] months; P = .04). This translated into a decrease in median overall survival (SMAD4-negative: 125 (95% confidence interval, 51-214) months versus SMAD4-positive: 185 (95% confidence interval, 138-232) months; P = .02). CONCLUSION: Consistent with the known biology of the DPC4/SMAD4 gene, an absence of its protein expression in primary gastrointestinal neuroendocrine tumors was negatively associated with outcomes after curative operative resection.
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