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ESES Review of Recently Published Literature

Collection: T. Clerici, F. Triponez, 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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SR: systematic review, **MA**: meta-analysis, **RCT**: randomized controlled trial, **CG**: consensus statement/guidelines

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

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Collectors

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

Frédéric Triponez, MD
Department of Thoracic and Endocrine Surgery, University Hospital 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

Journals covered

Journal	IF2012	Journal	IF2012
Acta Cytol	0.69	J Bone Miner Res	6.128
Am J Kidney Dis	5.294	J Clin Endocrinol Metab	6.430
Am J Nephrol	2.623	J Clin Oncol	18.038
Am J Surg	2.516	J Endocrinol	4.058
Am Surgeon	0.92	J Endocrinol Invest	1.654
Ann Surg	6.329	J Nephrol	2.015
Ann Surg Oncol	4.12	J Nucl Med	5.774
Anz J Surg	1.098	J Surg Oncol	2.644
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	1.779	Lancet	39·06
JAMA Surg (*prev:* Arch Surg)	4.42	Langenbecks Arch Surg	1.891
Br J Surg	4.839	Laryngoscope	1.979
Cancer	5.201	N Engl J Med	51.658
Chirurg	0.517	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	11.025
Clin Endocrinol Oxf	3.396	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	15.031
Clin Nucl Med	2.955	Nephrol Dial Transplant	3.371
Curr Opin Oncol	4.027	Nephron Clin Pract	1.652
Endocr Relat Cancer	5.261	Neuroendocrinology	3.537
Endocr Rev	14.873	Oncologist	4.10
Eur Arch Otorhinolaryngol	1.458	Otolaryngol Head Neck Surg	1.625
Eur J Endorcrinol	3.136	Surg Clin North Am	2.019
Eur J Surg Oncol	2.614	Surg Endosc	3.427
Gland Surg	---	Surg Laparosc Endosc Percutan Tech	0.876
Head Neck	2.833	Surg Oncol	2.136
Horm Metab Res	2.145	Surg Oncol Clin N Am	1.22
Int J Cancer	6.198	Surgery	3.373
J Am Coll Surg	4.5	Thyroid	3.544
J Am Soc Nephrol	8.98	Updates In Surgery	---
J Bone Miner Metab	2.219	World J Surg	2.228

Journal names are links to the journal's homepage!, IF2012: Impact factor 2012

Thyroid

Meta-Analyses

A Systematic Review and Meta-Analysis Evaluating Completeness and Outcomes of Robotic Thyroidectomy.
Laryngoscope, 125(2):509-18.
Lang BH, Wong CK, Tsang JS, Wong KP, Wan KY. 2015.
OBJECTIVES/HYPOTHESIS: Despite immense interest, robotic-assisted thyroidectomy (RT) remains controversial in differentiated thyroid carcinoma (DTC). This systematic review and meta-analysis compared surgical completeness and/or oncological outcomes between RT and open thyroidectomy (OT) in low-risk DTC. STUDY DESIGN: Systematic review. METHODS: A systematic review was performed to identify studies that compared surgical completeness and/or oncological outcomes between RT and OT in DTC. Any study that compared at least one parameter relating to surgical completeness and/or oncological outcome for DTC was considered. Number of central lymph nodes (CLNs) retrieved during central neck dissection (CND), preablation stimulated thyroglobulin (sTg) level, radioiodine uptake on post-therapy scan, and locoregional recurrence (LRR) were examined. Meta-analysis was performed using a fixed or random-effects model depending on heterogeneity between studies. RESULTS: Ten studies were eligible. Of the 2,205 DTCs, 752 (34.1%) had RT, whereas 1,453 (65.9%) had OT. Relative to OT, RT had significantly fewer CLNs retrieved during CND (4.7 +/- 3.2 vs. 5.5 +/- 3.8, standardized mean difference [SMD] = -0.240, 95% confidence interval [CI]: -0.364 to -0.116, P < .001) and higher preablation sTg level (3.6 +/- 6.7 ng/mL vs. 2.0 +/- 5.0 ng/mL, SMD = 0.272, 95% CI: 0.022 to 0.522, P = .033). Interestingly, these differences were more evident in the robotic transaxillary approach (RTAA) than the robotic bilateral axillo-breast approach. After a mean follow-up of 17.7 months, no LRR was found in RT, whereas after 18.6 months, one LRR was found in OT. CONCLUSIONS: Relative to OT, total thyroidectomy by RTAA was associated with fewer CLNs retrieved and less-complete thyroid resection. However, using RTAA is unlikely to compromise the outcomes of low-risk DTC because of its inherently good prognosis.
PubMed-ID: 25236330
http://dx.doi.org/10.1002/lary.24946

Contrast-Enhanced Ultrasound for Differentiation of Benign and Malignant Thyroid Lesions: Meta-Analysis.
Otolaryngol Head Neck Surg, 151(6):909-15.
Yu D, Han Y, Chen T. 2014.
OBJECTIVE: Contrast-enhanced ultrasound (CEUS) is a new noninvasive modality for the diagnosis of thyroid nodules. However, the performance of CEUS in differentiating malignant and benign thyroid nodules has not been systematically evaluated. This meta-analysis was performed to assess the accuracy of CEUS in diagnosing thyroid nodules. DATA SOURCES: PubMed, Embase, and the references of included studies were examined. REVIEW METHODS: We recorded the characteristics of the included studies and assessed the quality of each study using the Quality Assessment of Diagnostic Accuracy Studies tool. The pooled sensitivity, specificity, positive likelihood ratio (LR), negative LR, diagnostic odds ratio (DOR), and area under the curve (AUC) were calculated. We also evaluated the publication bias. RESULTS: This meta-analysis included 7 studies with a total of 597 thyroid nodules. The pooled the sensitivity, specificity, and positive and negative LR were 0.853, 0.876, 5.822, and 0.195, respectively. The DOR and AUC were 34.730 and 0.9162, respectively. Heterogeneity existed between the included studies. The results of subgroup analyses indicated that the evaluation processes are likely the predominant source of heterogeneity. No significant publication bias was observed. CONCLUSION: Contrast-enhanced ultrasound is a promising noninvasive technique for the differential diagnosis of benign and malignant thyroid nodules and could be a valuable supplemental method to fine-needle aspiration.
PubMed-ID: 25344590
http://dx.doi.org/10.1177/0194599814555838

Randomized controlled trials

Lateral Neck Sentinel Lymph Node Biopsy in Papillary Thyroid Carcinoma, Is It Really Necessary? A Randomized, Controlled Study.
Surgery, 157(3):518-25.
Lee SK, Lee JH, Bae SY, Kim J, Kim M, Lee HC, Jung YY, Kil WH, Kim SW, Lee JE, Nam SJ, Choe JH, Kim JH, Kim JS. 2015.
BACKGROUND: Although occult metastasis to lymph node in the lateral neck compartment is common in papillary thyroid carcinoma (PTC), the clinical impact of these metastasis is unknown. We hypothesized that sentinel lymph node biopsy (SLNB) of the lateral neck compartment with radioisotopes may detect occult metastasis, which could prevent recurrence. METHODS: This randomized, controlled study was conducted from June 2009 to January 2011 and included 283 patients with PTC who were receiving treatment at the Samsung Medical Center. RESULTS: Of the 283 patients enrolled in the study, 141 were randomized to a lateral SLNB (LSLNB) group and 142 patients were to the control group. Lateral sentinel lymph nodes (LSLNs) were identified in 80 of the 127 patients (63.0%) for whom stimulated thyroglobulin (sTg) levels were available. Among the 80 patients with LSLNs, 24 (30.0%) had metastases and underwent an ipsilateral modified radical neck dissection. Among the 191 patients for whom repeated sTg test results were available, the first median level of sTg in the LSLNB study group was less compared with the control group (P = .012, adjusted for duration). However, the second sTg level (after the first radioactive iodine ablation) was not different between the 2 groups. Moreover, the sTg levels were not significantly different between the LSLN-positive (n = 23) and other patients (n = 168) after the first and second ablations. During patient follow-up (median, 39 months; range, 7-55), 3 cases of recurrence were observed in the control group and 1 case in the study group (a LSLN had not been detected in this case). CONCLUSION: Although LSLNB was able to remove occult metastasis in PTC, this procedure had no effect on either sTg levels or on recurrence rates at a mean follow-up of 39 months. Additional long-term studies are needed to explore fully the clinical usefulness of LSLNB in the prevention of PTC recurrence.
PubMed-ID: 25633731
http://dx.doi.org/10.1016/j.surg.2014.10.013

Consensus Statements/Guidelines

Consensus Statement on Intra-Operative Electrophysiological Recurrent Laryngeal Nerve Monitoring During Thyroid Surgery.
ANZ J Surg, 84(9):603-4.
Serpell J, Sidhu S, Vallance N, Panizza B, Randolph G. 2014.
PubMed-ID: 25302349

Other Articles

Risk Factors for Central Neck Lymph Node Metastasis of Clinically Noninvasive, Node-Negative Papillary Thyroid Microcarcinoma.
Am J Surg, 208(3):412-8.
Park JP, Roh JL, Lee JH, Baek JH, Gong G, Cho KJ, Choi SH, Nam SY, Kim SY. 2014.
BACKGROUND: To examine predictive factors for subclinical central neck lymph node metastases (LNM) of papillary thyroid microcarcinoma (PTMC). METHODS: The clinical and pathological findings of 287 patients with clinically noninvasive, node-negative, solitary papillary thyroid carcinoma (PTC), who had undergone thyroidectomy plus central compartment neck dissection and showed pathologically confirmed nodal metastases, were analyzed. Predictive risk factors for central LNM were quantified. RESULTS: Pathologic LNM was identified in 63 (32.6%) PTMC patients and 48 (51.0%) PTC patients (tumor size >1 cm; P = .003). Tumor size (>.7 cm; P = .011), multifocality (P = .010), and microscopic extracapsular extension (P = .050) were significant variables predictive of central LNM from PTMC in univariate analysis. Tumor size (odds ratio 2.28, 95% confidence interval 1.19 to 4.38; P = .014) and multifocality (odds ratio 2.38, 95% confidence interval 1.14 to 4.93; P = .020) were independent variables predictive of central LNM in multivariate analysis. CONCLUSIONS: Cervical LNM is highly prevalent in clinically noninvasive, node-negative PTC. Central neck LNM is associated with larger tumor size and multifocality of PTMC.
PubMed-ID: 24602323
http://dx.doi.org/10.1016/j.amjsurg.2013.10.032

Can a Surgeon Predict the Risk of Postoperative Hypoparathyroidism During Thyroid Surgery? A Prospective Study on Self-Assessment by Experts.
Am J Surg, 208(1):13-20.
Promberger R, Ott J, Bures C, Kober F, Freissmuth M, Seemann R, Hermann M. 2014.
BACKGROUND: Thyroid surgery can cause postoperative hypocalcemia (POH) and permanent hypoparathyroidism (PEH). Surgeons implicitly assess the risk and adapt their surgical strategy accordingly. METHODS: The outcome of this intraoperative decision-making process (the surgeons' ability to predict the risk of POH and PEH on a numerical rating scale and their actual incidence) was studied prospectively in 2,558 consecutive thyroid operations. RESULTS: POH and PEH occurred in 723 and 64 patients, respectively. In multivariate analysis, the surgeons' risk assessment score was an independent predictive factor for both complications ($P < .05$). Surgeons' differed significantly ($P = .015$) in their rates of POH but not of PEH ($P = .062$). Six and 3 (of 9) surgeons correctly predicted an increased risk of PEH and POH (adjusted odds ratios 1.67 to 2.21 and 1.47 to 12.73), respectively. CONCLUSION: The risk for hypoparathyroidism can be estimated, but surgeons differ substantially in this ability and in the extent to which this implicit knowledge is translated into lower complication rates.
PubMed-ID: 24746378
http://dx.doi.org/10.1016/j.amjsurg.2013.11.007

Prediction of Permanent Hypoparathyroidism After Total Thyroidectomy.
World J Surg, 38(10):2613-20.
Almquist M, Hallgrimsson P, Nordenstrom E, Bergenfelz A. 2014.
BACKGROUND: Hypoparathyroidism is a common complication with thyroid surgery. The ability to predict a high risk of permanent hypoparathyroidism is important for individual prognosis and follow-up. METHODS: Permanent hypoparathyroidism, defined as continuing need for vitamin D medication at 1-year post-operatively, was investigated in patients after total thyroidectomy. Blood levels of calcium and parathyroid hormone (PTH) were measured intra-operatively, the day after surgery and at 1 month post-operatively. Logistic regression analysis was performed to investigate the risk of vitamin D treatment at last follow-up, calculated as odds ratios (ORs) with 95 % confidence intervals (CIs). Patients were followed until cessation of vitamin D and/or calcium medication, until death, loss to follow-up, or end of follow-up, whichever came first. RESULTS: A total of 519 patients were included. The median (range) follow-up in patients unable to cease vitamin D was 2.7 (1.2-10.3) years. The rate of permanent hypoparathyroidism was 10/519, 1.9 %. Parathyroid auto-transplantation was.
PubMed-ID: 24791907
http://dx.doi.org/10.1007/s00268-014-2622-z

PAX8/PPARgamma Rearrangement in Thyroid Nodules Predicts Follicular-Pattern Carcinomas, in Particular the Encapsulated Follicular Variant of Papillary Carcinoma.
Thyroid, 24(9):1369-74.
Armstrong MJ, Yang H, Yip L, Ohori NP, McCoy KL, Stang MT, Hodak SP, Nikiforova MN, Carty SE, Nikiforov YE. 2014.
BACKGROUND: PAX8/PPARgamma rearrangement is a common genetic alteration in follicular thyroid carcinoma (FTC) and has been reported with variable frequency in papillary thyroid carcinoma (PTC). The diagnostic and phenotypic features of thyroid nodules positive for PAX8/PPARgamma on preoperative examination are not well understood. METHODS: The prevalence of PAX8/PPARgamma rearrangement was analyzed in a series of 2015 consecutive thyroid nodules that underwent molecular analysis on cytology specimens and in 446 surgically removed PTCs. For all PAX8/PPARgamma positive cases, cytology and surgical pathology slides were examined and the available clinical records were reviewed. RESULTS: Twenty-two PAX8/PPARgamma rearrangements were identified, including 16 detected preoperatively and 6 postoperatively. The incidence of PAX8/PPARgamma in PTC was 1.1%. Cytologically, most of these nodules were diagnosed as a follicular neoplasm (73%), followed by the diagnosis of atypia of undetermined significance (19%), and none of the cases was diagnosed as cytologically malignant. All nodules with PAX8/PPARgamma detected preoperatively and surgical follow-up available were found to be malignant, among which the most common diagnosis was the encapsulated follicular variant of PTC. Overall, among 20 PAX8/PPARgamma-positive tumors that were surgically excised, 17 (85%) were PTC and 3 (15%) were FTC. On follow-up available for 17 patients (mean, 22.4 months), 16 PAX8/PPARgamma-positive cancers showed no evidence of biochemical or structural recurrence, whereas 1 patient with FTC developed bone metastasis. CONCLUSIONS: In this series, PAX8/PPARgamma rearrangement found in thyroid nodules had a 100% predictive value for differentiated thyroid cancer, and was more predictive of PTC than FTC. However, almost all PTC carrying PAX8/PPARgamma were encapsulated follicular-pattern tumors, distinguished from FTC only by nuclear features. Although most tumors carrying this mutation appear to be clinically indolent, at least on short-term

follow-up, distant metastasis can develop from FTC positive for PAX8/PPARgamma.
PubMed-ID: 24798894
http://dx.doi.org/10.1089/thy.2014.0067

Does Preoperative Neutrophil Lymphocyte Ratio Predict Risk of Recurrence and Occult Central Nodal Metastasis in Papillary Thyroid Carcinoma?
World J Surg, 38(10):2605-12.
Lang BH, Ng CP, Au KB, Wong KP, Wong KK, Wan KY. 2014.
BACKGROUND: Preoperative neutrophil to lymphocyte ratio (NLR) might be prognostic in papillary thyroid carcinoma (PTC). Given the controversy of prophylactic central neck dissection (pCND) in clinically nodal-negative (cN0) PTC, our study evaluated whether preoperative NLR predicted disease-free survival (DFS) and occult central nodal metastasis (CNM) in cN0 PTC. METHODS: A total of 191 patients who underwent pCND were analyzed. Complete blood counts with differential counts were taken before operation. NLR was calculated by dividing preoperative neutrophil count with lymphocyte count. Patients were categorized into NLR tertiles: first (NLR < 1.93; n = 63), second (NLR = 1.93-2.79; n = 64), and third tertile (NLR > 2.79; n = 64). Four other patient types, namely, benign nodular goiter, clinically nodal-positive (cN1) PTC, poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma (ATC), were used as references. RESULTS: Age at operation ($p < 0.001$) and tumor size ($p = 0.037$) significantly increased with higher NLR. First tertile had significantly more TNM stage I tumors ($p = 0.01$) and lowest MACIS score ($p = 0.002$). Tumor size [hazard ratio (HR) 1.422, 95% confidence interval (CI) 1.119-1.809, $p = 0.004$] and multicentricity (HR = 2.545, 95% CI 1.073-6.024, $p = 0.034$) independently predicted DFS, whereas old age [odds ratio (OR) 1.026, 95% CI 1.006-1.046, $p = 0.009$), male (OR 2.882, 95% CI 1.348-6.172, $p = 0.006$), and large tumor (OR 1.567, 95% CI 1.209-2.032, $p = 0.001$) independently predicted occult CNM. NLR was not significantly associated with DFS or occult CNM. ATC had significantly higher NLR than cN1 PTC (7.28 vs. 2.74, $p < 0.001$). CONCLUSIONS: Although a higher NLR may imply a poorer tumor profile, it was not significantly associated with a worse DFS or higher risk of occult CNM in cN0 PTC. Perhaps, future research should focus on the prognostic value in other thyroid cancer types with a poorer prognosis.
PubMed-ID: 24809487
http://dx.doi.org/10.1007/s00268-014-2630-z

Centralized Molecular Testing for Oncogenic Gene Mutations Complements the Local Cytopathologic Diagnosis of Thyroid Nodules.
Thyroid, 24(10):1479-87.
Beaudenon-Huibregtse S, Alexander EK, Guttler RB, Hershman JM, Babu V, Blevins TC, Moore P, Andruss B, Labourier E. 2014.
BACKGROUND: Molecular testing for oncogenic gene mutations and chromosomal rearrangements plays a growing role in the optimal management of thyroid nodules, yet lacks standardized testing modalities and systematic validation data. Our objective was to assess the performance of molecular cytology on preoperative thyroid nodule fine-needle aspirates (FNAs) across a broad range of variables, including independent collection sites, clinical practices, and anatomic pathology interpretations. METHODS: Single-pass FNAs were prospectively collected from 806 nodules 1 cm or larger by ultrasonography at five independent sites across the United States. Specimens were shipped in a nucleic acid stabilization solution and tested at a centralized clinical laboratory. Seventeen genetic alterations (BRAF, KRAS, HRAS, and NRAS mutations, PAX8-PPARG and RET-PTC rearrangements) were evaluated by multiplex polymerase chain reaction and liquid bead array cytometry in 769 FNAs that met inclusion criteria. Cytology.
PubMed-ID: 24811481
http://dx.doi.org/10.1089/thy.2013.0640

Postoperative Vocal Cord Dysfunction Despite Normal Intraoperative Neuromonitoring: an Unexpected Complication With the Risk of Bilateral Palsy.
World J Surg, 38(10):2597-602.
Melin M, Schwarz K, Pearson MD, Lammers BJ, Goretzki PE. 2014.
BACKGROUND: Intraoperative neuromonitoring (IONM) has become standard practice in thyroid surgery for many surgeons. It reduces the risk of vocal cord palsy in high-risk patients and has led to two-stage operations to prevent bilateral palsies. The specificity of detecting nerve injuries is not 100 %, leading to patients with vocal cord dysfunction (VCD) despite regular neuromonitoring (false-negative IONM). We aimed to evaluate possible risk factors for this phenomenon and its importance regarding bilateral palsies. METHODS: We performed a retrospective analysis of all patients with false-negative IONM. RESULTS: A total of 2152 patients (3426 nerves at risk) underwent surgery for benign disease between January 2008 and October 2010. Sensitivity for predicting

VCD was 85.4 % and specificity 99.0 %. The positive predictive value was 68.0 % and the negative predictive value 99.6 %. We were not able to identify risk factors for false-negative IONM. We found four patients with delayed occurrence of VCD after regular IONM (1-8 weeks). We registered two patients with bilateral VCD after false negative IONM on the first side of bilateral resections (2/7) and four patients with bilateral palsy after correct IONM (4/1256). The relative risk for bilateral VCD between patients with false-negative IONM on the primary resection side and patients with correct IONM was 89.7. CONCLUSIONS: Although seldom, false-negative IONM is of clinical importance as it bears a high risk of bilateral VCD if it occurs on the first side of a bilateral resection. It can also have a latent occurrence after surgery.
PubMed-ID: 24867468
http://dx.doi.org/10.1007/s00268-014-2591-2

The Incidence of Papillary Thyroid Carcinoma and Outcomes in Operative Patients According to Their Body Mass Indices.
Surgery, 156(5):1145-52.
Tresallet C, Seman M, Tissier F, Buffet C, Lupinacci RM, Vuarnesson H, Leenhardt L, Menegaux F. 2014.
BACKGROUND: The connection between high body mass index (BMI), risk of papillary thyroid carcinoma (PTC), and the aggressiveness of PTC is still debated. We aimed to establish the relationship between excess BMI and the risk of PTC in an operative population, and the impact of obesity on histopathologic aggressiveness of PTC and on the outcome of patients. METHODS: All consecutive patients who underwent thyroid operation from June 2002 to December 2009 were reviewed in this retrospective study. BMI groupings were based on standardized categories: normal-weight, overweight, and obesity. We performed a total thyroidectomy with lymph node dissection in patients with preoperative or operative diagnosis of PTC. Radioiodine ablation was performed in every N1 patient, in case of tumor size greater than 10 mm, and if there was extrathyroidal invasion. During a median follow-up of 6.2 years, patients who were retreated by operation or (131)I were considered to have a persistent (<18 months of the initial operative treatment) or recurrent (>/= 18 months) disease. RESULTS: Of 6,684 patients who had a thyroid gland resection, we identified 1,216 (18.2%) patients with PTC. Patients who were overweight or obese were not at greater risk of PTC than normal-weight subjects. Indications for operation or radioiodine therapy were similar in the three BMI groups. During follow-up, 86 patients (7.1%) experienced persistent (4.5%) or recurrent (2.5%) disease. When excluding micro-PTCs (</= 10 mm), we found an association between recurrent or residual locoregional thyroid cancer and BMI: 18.7% in obese patients versus 8.5% if BMI <25 kg/m(2) and 9.8% if 25 >/= BMI < 30 kg/m(2) (P = .03). This difference was clearly marked for persistence. When adjusted for other cofounder factors, we observed that BMI was an independent factor associated with the risk of postoperative locoregional event (odds ratio 3.8, 95% confidence interval 1.6-8.8), with sex, age, lymph node metastasis, and tumor bilaterality. CONCLUSION: In macro-PTC, obese patients had an increased risk of developing a locoregional event during the follow-up, specifically a persistence of the disease. According to these results, overweight and obese patients with macro-PTC should be monitored more carefully for early detection of cancer persistence.
PubMed-ID: 24878452
http://dx.doi.org/10.1016/j.surg.2014.04.020

Factors Contributing to Surgical Outcomes of Transaxillary Robotic Thyroidectomy for Papillary Thyroid Carcinoma.
Surg Endosc, 28(11):3134-42.
Son H, Park S, Lee CR, Lee S, Kim JW, Kang SW, Jeong JJ, Nam KH, Chung WY, Park CS. 2014.
INTRODUCTION: Transaxillary robotic thyroidectomy is considered a technically feasible and safe treatment option for patients with low-risk papillary thyroid carcinoma (PTC). The aim of the present study was to determine the factors that contribute to the perioperative surgical outcomes of robotic thyroidectomy and to suggest guidelines for patient selection to be used by surgeons inexperienced in the technique. METHOD: We reviewed the records of 275 patients with PTC who underwent robotic total thyroidectomy using a gasless, transaxillary single-incision approach at Yonsei University Health System, South Korea, between January 2011 and May 2012. The association between surgical outcomes and clinicopathologic factors was assessed using linear and logistic regression analysis. RESULTS: The contributing factors for surgical outcomes of robotic thyroidectomy were categorized as patient factors, including gender and body mass index (BMI), and thyroid-specific factors, including thyroid gland size, coexistent thyroiditis, tumor size, and serum anti-thyroglobulin antibody and anti-microsomal antibody titers. Of these, male gender, a large thyroid gland, and thyroiditis significantly increased the total operation time. Male gender, thyroiditis, and overweight BMI increased the working space time, and a large thyroid gland and overweight BMI affected the console time. A large thyroid gland and histological thyroiditis were associated with increased intraoperative blood loss. There was no association between postoperative complications and clinicopathologic parameters. CONCLUSION: Male

gender, overweight BMI, a large thyroid gland, and coexistent thyroiditis adversely affected the surgical outcome of robotic thyroidectomy. Surgeons inexperienced in the technique should avoid or carefully approach individuals with these factors.
PubMed-ID: 24879136
http://dx.doi.org/10.1007/s00464-014-3567-x

Early Prediction of Oral Calcium and Vitamin D Requirements in Post-Thyroidectomy Hypocalcaemia.
Otolaryngol Head Neck Surg, 151(3):407-14.
Al-Dhahri SF, Mubasher M, Al-Muhawas F, Alessa M, Terkawi RS, Terkawi AS. 2014.
OBJECTIVE: To optimize and individualize post-thyroidectomy hypocalcemia management. STUDY DESIGN: A multicenter prospective cohort study. SETTING: Two tertiary care hospitals. SUBJECTS AND METHODS: parathyroid hormone (PTH) was measured preoperatively, then at 1 and 6 hours after surgery. The required doses of calcium and vitamin D were defined as those maintaining the patients asymptomatic and their cCa >/= 2 mmol/L. They were used as an endpoint in a generalized linear mixed effect model (GLIMMEX) aiming to identify the best predictors of these optimal required doses. Models were evaluated by goodness of fit and Receiver Operating Characteristic (ROC) curves. RESULTS: One hundred and sixty-eight patients were analyzed; 85.1% were female, 49.3% had BMI > 30, and 64% had vitamin D deficiency. Post-thyroidectomy hypocalcemia was found in 25.6%, of whom 18 (41.9%) were symptomatic and received intravenous calcium. First hour.
PubMed-ID: 24903452
http://dx.doi.org/10.1177/0194599814536848

Clinical Value of Visually Identifiable 18F-Fluorodeoxyglucose Uptake in Primary Papillary Thyroid Microcarcinoma.
Otolaryngol Head Neck Surg, 151(3):415-20.
Hwang SO, Lee SW, Kang JK, Choi HH, Kim WW, Park HY, Jung JH. 2014.
OBJECTIVE: This study evaluates the relationship between visually identifiable (18)F-fluorodeoxyglucose (FDG) uptake in primary papillary thyroid microcarcinoma (PTMC) and tumor aggressiveness. STUDY DESIGN: Historical cohort study. SETTING: Tertiary care center. METHODS: Clinicopathological factors and PET/CT findings of 219 PTMC surgical patients who underwent preoperative (18)F-FDG positron emission tomography/computed tomography (PET/CT) were retrospectively reviewed. RESULTS: (18)F-FDG uptake was observed in the tumors of 124 (56.6%) patients. Tumor size (odds ratio [OR] = 1.774; 95% confidence interval [CI], 1.416-2.223; P < .0001) and Hashimoto thyroiditis (OR = 2.815; CI, 1.237-6.404; P = .014) independently predicted (18)F-FDG uptake. Tumor size (OR = 1.495; CI, 1.217-1.835; P < .0001) and BRAF(V600E) mutation (OR = 3.320; CI, 1.056-10.432; P = .040) independently predicted extrathyroidal invasion. Multiplicity (OR = 2.375; CI, 1.278-4.415; P = .006) independently predicted central lymph node metastasis. CONCLUSION: (18)F-FDG uptake in PTMC depends on tumor size and Hashimoto thyroiditis. Therefore, preoperative PET/CT for PTMC may not help in evaluating tumor aggressiveness.
PubMed-ID: 24903453
http://dx.doi.org/10.1177/0194599814537224

The Effect of Patient Age on the Success of Laryngeal Reinnervation.
Eur Arch Otorhinolaryngol, 271(12):3241-7.
Li M, Chen D, Song X, Wang W, Zhu M, Liu F, Li Y, Chen S, Zheng H. 2014.
The objective of the study was to investigate the influence of patient age on the efficacy of laryngeal reinnervation with ansa cervicalis in unilateral vocal fold paralysis (UVFP) patients. We retrospectively reviewed 349 consecutive UVFP cases of laryngeal reinnervation with ansa cervicalis to the recurrent laryngeal nerve anastomosis. Preoperative and postoperative videostroboscopy, perceptual evaluation, acoustic analysis, maximum phonation time (MPT) and laryngeal electromyography (EMG) data were collected. Gender, age, preoperative EMG status [preoperative voluntary motor unit recruitment (VMUR)] and denervation duration were analyzed in previous multivariable logistic regression analysis. Stratification analysis was performed on patient age in the present study. All patients were divided into four groups according to their age: Group A included patients with an age less than 30 years; Group B, 30-44 years; Group C, 45-59 years; Group D, >/=60 years. Stratification analysis on patient age showed significant differences between Group A and D, Group B and D, Group C and D (P < 0.05), but no significant difference between Group A and B, Group A and C, Group B and C (P > 0.05), respectively, with regard to parameters including glottal closure, overall grade, shimmer, noise-to-harmonics ratio; but there are no significant differences among the four groups with regard to jitter. However, for MPT and postoperative VMUR, there are significant differences among the four groups expect between Group A and B. In addition, glottal closure, perceptual and acoustic parameters, MPT values and VMUR data, were

significantly improved postoperatively in each age group (P < 0.01). The data from this study indicate that patient age is an influential factor of the surgical outcome of laryngeal reinnervation for UVFP patients. Laryngeal reinnervation is less effective when patient age is more than 60 years.
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http://dx.doi.org/10.1007/s00405-014-3091-6

Interest of Sentinel Node Biopsy in Apparently Intrathyroidal Medullary Thyroid Cancer: a Pilot Study.
J Endocrinol Invest, 37(9):829-34.
Puccini M, Manca G, Ugolini C, Candalise V, Passaretti A, Bernardini J, Boni G, Buccianti P. 2014.
PURPOSE: Initial surgery for medullary thyroid cancer (MTC) with no evidence of lymph node involvement in neck compartments consists of total thyroidectomy and prophylactic central neck dissection. This study evaluated the reliability of a radiotracer technique for the intraoperative detection of sentinel lymph nodes (SLNs) in lateral compartments in patients with early MTC. METHODS: Patients with limited (cT1 N0) MTC entered the study (2009-2012). A 0.1-0.3 ml suspension of macrocolloidal technetium-99-labeled human albumin was injected (under echo-guide) in the tumor 5 h before surgery. Preoperative lymphoscintigraphy confirmed the identification of SLNs in the lateral neck. The operation consisted of total thyroidectomy and central neck dissection, and a hand-held gamma-probe (Neoprobe) guide was used to remove the SLNs from the lateral neck. RESULTS: Four patients were recruited. The tracer always indicated a SLN. Pathology reports indicated micrometastases from MTC in SLN in three patients. At a mean follow-up of 30.5 months, all patients were biochemically cured. The technique we describe to detect and remove neck SLN from MTC seemed to be very accurate. It always showed the SLNs (usually two) in the lateral compartments. Micrometastases were detected in three of four patients, allowing their correct staging. CONCLUSIONS: The method described here for the detection of SLNs in early MTC seems effective and reliable and can be used for a more precise N staging of the patients. It could play a role, alone or combined with other techniques, in driving the extent of prophylactic neck dissection or other potential applications.
PubMed-ID: 24950750
http://dx.doi.org/10.1007/s40618-014-0112-7

BRAF V600E in Papillary Thyroid Carcinoma Is Associated With Increased Programmed Death Ligand 1 Expression and Suppressive Immune Cell Infiltration.
Thyroid, 24(9):1385-93.
Angell TE, Lechner MG, Jang JK, Correa AJ, LoPresti JS, Epstein AL. 2014.
BACKGROUND: There remain a small number of patients with papillary thyroid cancer (PTC) who suffer recurrence, metastases, or death. While mutation of the BRAF gene, corresponding to the constitutively active BRAF(V600E) protein, has been associated with worse clinical outcomes in thyroid cancer, the reasons underlying this observation are presently unknown. Disruption of endogenous host immune surveillance and promotion of tumor immune escape is one mechanism by which BRAF(V600E) tumors may achieve more aggressive behavior. This study evaluated the relationship between BRAF(V600E) status and known strategies of tumor-mediated immune suppression. METHODS: Tissue sections of PTC tumors from 33 patients were evaluated by immunohistochemistry for tumor-expressed suppressive ligands and enzymes and effector and suppressor populations of tumor-infiltrating immune cells. Presence of BRAF(V600E) was evaluated by direct DNA sequencing of PTC specimens and the results correlated with tumor-expressed molecules and.
PubMed-ID: 24955518
http://dx.doi.org/10.1089/thy.2014.0134

External Beam Radiotherapy With or Without Concurrent Chemotherapy in Advanced or Recurrent Non-Anaplastic Non-Medullary Thyroid Cancer.
J Surg Oncol, 110(4):375-82.
Romesser PB, Sherman EJ, Shaha AR, Lian M, Wong RJ, Sabra M, Rao SS, Fagin JA, Tuttle RM, Lee NY. 2014.
BACKGROUND AND OBJECTIVES: To review clinical outcomes and toxicities in locally advanced differentiated thyroid cancer patients treated with external beam radiotherapy (EBRT) with or without concurrent chemotherapy (CCRT). METHODS: Between 1990 and 2012, 66 patients with gross residual/unresectable non-anaplastic non-medullary thyroid cancer were treated with EBRT. RESULTS: The median overall survival was 42.0 months. The overall locoregional progression-free survival (LPFS) at 3 years was 77.3%. CCRT resulted in a non-significant improvement in LPFS (90.0% vs. 73.0%, P = 0.347). Poorly differentiated histology had significantly improved LPFS (89.4% vs. 66.1%, P = 0.020), despite a significantly worse distant metastasis-free survival (43.9% vs. 82.5%, P = 0.023). Acute treatment-related toxicity included dermatitis, mucositis, and dysphagia with grade three rates of 12.1%, 19.7%, and 16.7%, respectively. The incidence of late toxicity was low. CCRT was only

associated with a significant greater rate of acute grade 3 hoarseness (10.0% vs. 0.0%, P = 0.033), but with no difference in the rate of grade 2 late toxicity. CONCLUSIONS: EBRT is a safe and effective treatment modality with 90% LPFS at 3 years in patients with gross residual or unresectable non-anaplastic, non-medullary thyroid carcinoma treated with CCRT. Further incorporation of EBRT with concurrent chemotherapy may result in improved disease control.
PubMed-ID: 24961938
http://dx.doi.org/10.1002/jso.23656

Changing Trends in Thyroid and Parathyroid Surgery Over the Decade: Is Same-Day Discharge Feasible in the United Kingdom?
World J Surg, 38(11):2825-30.
Rajeev P, Sutaria R, Ezzat T, Mihai R, Sadler GP. 2014.
BACKGROUND: A recent British Association of Endocrine and Thyroid Surgeons consensus document suggested that day-case thyroidectomy is feasible in a small proportion of patients but has to be balanced against risks. Currently, there is no large reported series of same-day discharge in thyroid and parathyroid surgery from the UK. The aim of this study was to assess the outcomes of day-case thyroid and parathyroid surgery. METHODS: We conducted a retrospective study of patients who underwent thyroid or parathyroid surgery between January 2000 and December 2011 at Oxford University Hospitals. The end points analysed were complications in the form of bleeding, hypocalcaemia, wound infection, and seroma. RESULTS: A total of 2,102 patients (495 males and 1,607 females, age range = 13-90 years) underwent surgery for parathyroid (n = 776) or thyroid (n = 1,326) conditions. The operations included minimally invasive parathyroidectomy (MIP) (n = 331), open parathyroidectomy (n = 445), lobectomy (n = 687), isthmusectomy (n = 23), total thyroidectomy (n = 580) and thyroglossal cyst excision (n = 36). Routine arrangements were in place for consideration of same-day discharge for lobectomies, thyroglossal cyst surgery, and MIPs; lobectomies accounted for 63 % of same-day cases, followed by parathyroidectomy (35 %). Over the decade, day-case surgery increased from 4 to 17 % for thyroid surgery and from 20 to 40 % for parathyroid surgery. None of the 435 patients who had same-day discharge was readmitted for bleeding [confidence interval (CI) 0-0.6 %]. There was no 30-day mortality for the whole cohort. Complications in patients who underwent surgery in the whole cohort versus those who were discharged the same day were temporary hypocalcaemia (4 vs. 0.2 %), permanent hypocalcaemia (1 vs. 0.4 %), bleeding (0.4 vs. 0 %), seroma (0.3 vs. 0 %), and wound infection (0.3 vs. 0 %). CONCLUSION: Current protocols for thyroid or parathyroid surgery make same-day discharge feasible and safe in carefully selected patients.
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http://dx.doi.org/10.1007/s00268-014-2673-1

Striving Toward Standardization of Reporting of Ultrasound Features of Thyroid Nodules and Lymph Nodes: a Multidisciplinary Consensus Statement.
Thyroid, 24(9):1341-9.
Su HK, Dos Reis LL, Lupo MA, Milas M, Orloff LA, Langer JE, Brett EM, Kazam E, Lee SL, Minkowitz G, Alpert EH, Dewey EH, Urken ML. 2014.
BACKGROUND: The use of high-resolution ultrasound (US) imaging is a mainstay of the initial evaluation and long-term management of thyroid nodules and thyroid cancer. To fully capitalize on the diagnostic capabilities of a US examination in the context of thyroid disease, many clinicians consider it desirable to establish a universal format and standard of US reporting. The goals of this interdisciplinary consensus statement are twofold. First, to create a standardized set of US features to characterize thyroid nodules and cervical lymph nodes accurately, and second, to create a standardized system for tracking sequential changes in the US examination of thyroid nodules and cervical lymph nodes for the purpose of determining risk of malignancy. SUMMARY: The Thyroid, Head and Neck Cancer (THANC) Foundation convened a panel of nine specialists from a variety of medical disciplines that are actively involved in the diagnosis and treatment of thyroid nodules and thyroid cancer. Consensus was achieved on the following topics: US evaluation of the thyroid gland, US evaluation of thyroid nodules, US evaluation of cervical lymph nodes, US-guided fine needle aspiration (FNA) of thyroid nodules, and US-guided FNA of cervical lymph nodes. CONCLUSION: We propose that this statement represents a consensus within a multidisciplinary team on the salient and essential elements of a comprehensive and clinically significant thyroid and neck US report with regards to content, terminology, and organization. This reporting protocol supplements previous US performance guidelines by not only capturing categories of findings that may have important clinical implications, but also delineating findings that are clinically relevant within those categories as specifically as possible. Additionally, we have included the specific features of diagnostic and therapeutic interventions that have not been previously addressed.

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BRAF V600E and TERT Promoter Mutations Cooperatively Identify the Most Aggressive Papillary Thyroid Cancer With Highest Recurrence.
J Clin Oncol, 32(25):2718-26.
Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, Pai S, Bishop J. 2014.
PURPOSE: To investigate the prognostic value of the BRAF V600E mutation and the recently identified TERT promoter mutation chr5:1,295,228C>T (C228T), individually and in their coexistence, in papillary thyroid cancer (PTC). PATIENTS AND METHODS: We performed a retrospective study of the relationship of BRAF and TERT C228T mutations with clinicopathologic outcomes of PTC in 507 patients (365 women and 142 men) age 45.9 +/- 14.0 years (mean +/- SD) with a median follow-up of 24 months (interquartile range, 8 to 78 months). RESULTS: Coexisting BRAF V600E and TERT C228T mutations were more commonly associated with high-risk clinicopathologic characteristics of PTC than they were individually. Tumor recurrence rates were 25.8% (50 of 194;77.60 recurrences per 1,000 person-years; 95% CI, 58.81 to 102.38) versus 9.6% (30 of 313; 22.88 recurrences per 1,000 person-years; 95% CI, 16.00 to 32.72) in BRAF mutation-positive versus -negative patients (hazard ratio [HR], 3.22; 95% CI, 2.05 to 5.07) and 47.5% (29 of 61; 108.55 recurrences per 1,000 person-years; 95% CI, 75.43 to 156.20) versus 11.4% (51 of 446; 30.21 recurrences per 1,000 person-years; 95% CI, 22.96 to 39.74) in TERT mutation-positive versus -negative patients (HR, 3.46; 95% CI, 2.19 to 5.45). Recurrence rates were 68.6% (24 of 35; 211.76 recurrences per 1,000 person-years; 95% CI, 141.94 to 315.94) versus 8.7% (25 of 287; 21.60 recurrences per 1,000 person-years; 95% CI, 14.59 to 31.97) in patients harboring both mutations versus patients harboring neither mutation (HR, 8.51; 95% CI, 4.84 to 14.97), which remained significant after clinicopathologic cofactor adjustments. Disease-free patient survival curves displayed a moderate decline with BRAF V600E or TERT C228T alone but a sharp decline with two coexisting mutations. CONCLUSION: Coexisting BRAF V600E and TERT C228T mutations form a novel genetic background that defines PTC with the worst clinicopathologic outcomes, providing unique prognostic and therapeutic implications.
PubMed-ID: 25024077
http://dx.doi.org/10.1200/JCO.2014.55.5094

What Is the Gold Standard for Comprehensive Interinstitutional Communication of Perioperative Information for Thyroid Cancer Patients? A Comparison of Existing Electronic Health Records With the Current American Thyroid Association Recommendations.
Thyroid, 24(10):1466-72.
Dos Reis LL, Tuttle RM, Alon E, Bergman DA, Bernet V, Brett EM, Cobin R, Doherty G, Harris JR, Klopper J, Lee SL, Lupo M, Milas M, Machac J, Mechanick JI, Orloff L, Randolph G, Ross DS, Smallridge RC, Terris DJ, Tufano RP, Mehra S, Scherl S, Clain JB, Urken ML. 2014.
BACKGROUND: Appropriate management of well-differentiated thyroid cancer requires treating clinicians to have access to critical elements of the patient's presentation, surgical management, postoperative course, and pathologic assessment. Electronic health records (EHRs) provide an effective method for the storage and transmission of patient information, although most commercially available EHRs are not intended to be disease-specific. In addition, there are significant challenges for the sharing of relevant clinical information when providers involved in the care of a patient with thyroid cancer are not connected by a common EHR. In 2012, the American Thyroid Association (ATA) defined the critical elements for optimal interclinician communication in a position paper entitled, "The Essential Elements of Interdisciplinary Communication of Perioperative Information for Patients Undergoing Thyroid Cancer Surgery." SUMMARY: We present a field-by-field comparison of the ATA's essential elements as applied to three contemporary electronic reporting systems: the Thyroid Surgery e-Form from Memorial Sloan-Kettering Cancer Center (MSKCC), the Alberta WebSMR from the University of Calgary, and the Thyroid Cancer Care Collaborative (TCCC). The MSKCC e-form fulfills 21 of 32 intraoperative fields and includes an additional 14 fields not specifically mentioned in the ATA's report. The Alberta WebSMR fulfills 45 of 82 preoperative and intraoperative fields outlined by the ATA and includes 13 additional fields. The TCCC fulfills 117 of 120 fields outlined by the ATA and includes 23 additional fields. CONCLUSIONS: Effective management of thyroid cancer is a highly collaborative, multidisciplinary effort. The patient information that factors into clinical decisions about thyroid cancer is complex. For these reasons, EHRs are particularly favorable for the management of patients with thyroid cancer. The MSKCC Thyroid Surgery e-Form, the Alberta WebSMR, and the TCCC each meet all of the general recommendations for effective reporting of the specific domains that they cover in the management of thyroid cancer, as recommended by the ATA. However, the TCCC format is the most comprehensive. The TCCC is a new Web-based disease-specific database to enhance communication of patient information between clinicians in a Health Insurance Portability and Accountability Act

(HIPAA)-compliant manner. We believe the easy-to-use TCCC format will enhance clinician communication while providing portability of thyroid cancer information for patients.
PubMed-ID: 25036190
http://dx.doi.org/10.1089/thy.2014.0209

Stretch of the Minimally Invasive Incision During Thyroid and Parathyroid Surgery.
Otolaryngol Head Neck Surg , 151(4):582-5.
Chen N, Stephenson LA, Jorgensen JB, Zitsch RP, III. 2014.
OBJECTIVE: Identify and quantify changes in length of the skin incision following minimally invasive thyroid and parathyroid surgery and determine whether these changes persist postoperatively. STUDY DESIGN: Cohort study. SETTING: Tertiary care teaching hospital. SUBJECTS AND METHODS: Between July 2012 and June 2013, a prospective, nonrandomized study was performed on 44 consecutive patients undergoing open cervical minimally invasive thyroidectomy (incision approximately 6 cm or less) or minimally invasive parathyroidectomy (incision approximately 3 cm or less). Incision length was measured following initial incision, immediately after wound closure, and on postoperative follow-up at 2-week and 14-week visits. RESULTS: Thirty-one patients underwent minimally invasive thyroidectomy or parathyroidectomy with initial incision lengths ranging from 20 mm to 60 mm. Seven patients (21%) underwent total thyroidectomy with a mean length of 45 +/- 8 mm, 15 patients (44%) underwent unilateral thyroid lobectomy with a mean length of 37 +/- 5 mm, and 9 patients (26%) underwent parathyroidectomy with a mean length of 28 +/- 2 mm. On average, the skin incision lengthened by 3.0 +/- 0.9 mm during surgery representing an intraoperative stretch of 8.0% (P < .0001). Incision lengths decreased by an average of 0.3 mm at 2-week postoperative follow-up (ns) and 6.3 mm at 14-week postoperative follow-up (P < .0001). CONCLUSION: Significant intraoperative incision stretch is likely to occur during minimally invasive thyroid and parathyroid surgery. Postoperative follow-up data suggest that the increase in incision length is not permanent and resolves upon postoperative follow-up.
PubMed-ID: 25052513
http://dx.doi.org/10.1177/0194599814544453

A Single Parathyroid Hormone Level Obtained 4 Hours After Total Thyroidectomy Predicts the Need for Postoperative Calcium Supplementation.
J Am Coll Surg, 219(4):757-64.
Carr AA, Yen TW, Fareau GG, Cayo AK, Misustin SM, Evans DB, Wang TS. 2014.
BACKGROUND: Parathyroid hormone (PTH) levels after total thyroidectomy have been shown to predict the development of symptomatic hypocalcemia and the need for calcium supplementation. This study aimed to determine whether a PTH level drawn 4 hours postoperatively is as effective as a level drawn on postoperative day 1 (POD1) in predicting this need. STUDY DESIGN: This is a single-institution retrospective review of 4-hour and POD1 PTH levels in patients who underwent total thyroidectomy from January 2012 to September 2012. If POD1 PTH was >/=10 pg/mL, patients did not routinely receive supplementation; if PTH was <10 pg/mL, patients received oral calcium with or without calcitriol. RESULTS: Of 77 patients, 20 (26%) had a 4-hour PTH <10 pg/mL; 18 (90%) of these patients had a POD1 PTH <10 pg/mL. No patient with a 4-hour PTH >/=10 pg/mL had a POD1 PTH <10 pg/mL. All 18 patients with POD1 PTH <10 pg/mL received calcium supplementation. Three additional patients received supplementation due to reported symptoms or surgeon preference. A 4-hour PTH >/=10 pg/mL compared with a POD1 PTH had a similar ability to predict which patients would not need calcium supplementation; sensitivity was 98% vs 98%, specificity was 90% vs 86%, and and negative predictive value was 95% vs 95%. Of 21 patients who received supplementation, 13 (62%) also received calcitriol, including 9 patients (69%) with a 4-hour PTH <6 pg/mL. CONCLUSIONS: A single PTH level obtained 4 hours after total thyroidectomy that is >/=10 pg/mL accurately identifies patients who do not need calcium supplementation or additional monitoring of serum calcium levels. Same-day discharge, if deemed safe, can be accomplished with or without calcium supplementation based on the 4-hour PTH level. Greater consideration should be given to calcitriol supplementation in patients with a 4-hour PTH <6 pg/mL.
PubMed-ID: 25053220
http://dx.doi.org/10.1016/j.jamcollsurg.2014.06.003

The 2009 American Thyroid Association Guidelines Modestly Reduced Radioactive Iodine Use for Thyroid Cancers Less Than 1 Cm.
Thyroid, 24(10):1549-50.
Roman BR, Feingold JH, Patel SG, Shaha AR, Shah JP, Tuttle RM, Epstein AJ. 2014.
PubMed-ID: 25065817
http://dx.doi.org/10.1089/thy.2014.0237

Can Ultrasound Be Used to Predict Malignancy in Patients With a Thyroid Nodule and an Indeterminate Fine-Needle Aspiration Biopsy?
Surgery, 156(4):967-70.
Khoncarly SM, Tamarkin SW, McHenry CR. 2014.
PURPOSE: The purpose of this study was to evaluate whether ultrasonography is helpful in predicting malignancy in patients with a thyroid nodule and atypia/follicular lesion of undetermined significance (AFLUS). METHODS: All patients with a preoperative ultrasound who underwent thyroidectomy for a nodule with AFLUS comprised the study population. A blinded review of gray-scale and color-Doppler sonographic images of the thyroid nodule was performed by an expert sonographer; results were compared with the original interpretation and were correlated with histopathology. All images were reviewed for hypoechogenicity, irregular margins, shape that was taller than wide, micro and macrocalcifications, absent halo, and intranodular hypervascularity. RESULTS: From 2010 to 2012, 61 patients underwent thyroidectomy for AFLUS with an ultrasound examination for review; 6 (10%) with cancer. Nodule shape that was taller than wide, was associated with cancer ($P < .05$). The original sonographer commented on an average of two of seven features important in assessment of a thyroid nodule. CONCLUSION: With the exception of nodule height greater than width, sonographic criteria were not helpful in deciding which patients with AFLUS should undergo thyroidectomy. Thyroidectomy is recommended in lieu of repeat biopsy for a nodule that is taller than wide. Standardized sonographic reporting should be implemented.
PubMed-ID: 25074360
http://dx.doi.org/10.1016/j.surg.2014.06.043

Diagnosis of Thyroid Follicular Neoplasm: Fine-Needle Aspiration Versus Core-Needle Biopsy.
Thyroid, 24(11):1612-7.
Yoon RG, Baek JH, Lee JH, Choi YJ, Hong MJ, Song DE, Kim JK, Yoon JH, Kim WB. 2014.
BACKGROUND: Although fine-needle aspiration (FNA) is a safe and accurate diagnostic procedure for assessing thyroid nodules, it has limitations in diagnosing follicular neoplasms due to its relatively high false-positive rate. The purpose of the present study was to evaluate the diagnostic role of core-needle biopsy (CNB) for thyroid nodules with follicular neoplasm (FN) in comparison with FNA. METHODS: A series of 107 patients (24 men, 83 women; mean age, 47.4 years) from 231 FNAs and 107 patients (29 men, 78 women; mean age, 46.3 years) from 186 CNBs with FN readings, all of whom underwent surgery, from October 2008 to December 2013 were retrospectively analyzed. The false-positive rate, unnecessary surgery rate, and malignancy rate for the FNA and CNB patients according to the final diagnosis following surgery were evaluated. RESULTS: The CNB showed a significantly lower false-positive and unnecessary surgery rate than the FNA (4.7% versus 30.8%, 3.7% versus 26.2%, $p < 0.001$, respectively). In the FNA group, 33 patients (30.8%) had non-neoplasms, including nodular hyperplasia ($n = 32$) and chronic lymphocytic thyroiditis ($n = 1$). In the CNB group, 5 patients (4.7%) had non-neoplasms, all of which were nodular hyperplasia. Moreover, the CNB group showed a significantly higher malignancy rate than FNA (57.9% versus 28%, $p < 0.001$). CONCLUSIONS: CNB showed a significantly lower false-positive rate and a higher malignancy rate than FNA in diagnosing FN. Therefore, CNB could minimize unnecessary surgery and provide diagnostic confidence when managing patients with FN to perform surgery.
PubMed-ID: 25089716
http://dx.doi.org/10.1089/thy.2014.0140

Is Malignant Nodule Topography an Additional Risk Factor for Metastatic Disease in Low-Risk Differentiated Thyroid Cancer?
Thyroid, 24(11):1607-11.
Campenni A, Giovanella L, Siracusa M, Stipo ME, Alibrandi A, Cucinotta M, Ruggeri RM, Baldari S. 2014.
BACKGROUND: Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. In recent decades, the incidence has been increasing, largely due to increased detection of patients with low-risk or very low-risk DTC. According to European Thyroid Association and American Thyroid Association guidelines, radioiodine (RAI) thyroid remnant ablation is not indicated in very low-risk patients, while its role is still debated in low-risk patients. Accordingly, risk stratification of DTC patients is pivotal when deciding for or against RAI ablation. Presently, risk stratification is based on pTNM staging integrated with clinical parameters. The aim of our study was to evaluate the relationship between location of malignant thyroid nodules within the thyroid gland and the presence of loco-regional and/or distant metastases in patients with pT1a-pT1b DTCs. METHODS: We reviewed the records of 246 patients (214 women, 32 men; female-to-male ratio 6.7:1) affected by unifocal DTC </= 2 cm, who had undergone RAI thyroid remnant ablation (activity ranged 555-4588 MBq) after levothyroxine withdrawal or after recombinant human TSH (rhTSH) stimulation. The majority of the patients (91.5%) were affected by papillary thyroid carcinoma. RESULTS: Metastases were discovered by posttreatment whole-body

scintigraphy in 29 out of 246 (11.8%) patients. In patients with metastases, malignant thyroid nodules were located in the right lobe (14/123, 11.4%), left lobe (7/95, 7.4%), and isthmus (8/27, 29.6%). The prevalence of metastases was significantly higher in patients with DTC located in the isthmus, compared to other sites (chi(2) = 9.6, p = 0.002). CONCLUSIONS: Our data show for the first time that a location of a thyroid cancer in the isthmus is an additional risk factor for RAI avid metastatic disease in pT1a-pT1b DTC patients, regardless of the presence or absence of other risk factors.
PubMed-ID: 25089829
http://dx.doi.org/10.1089/thy.2014.0217

A Phase I Study of Cabozantinib (XL184) in Patients With Differentiated Thyroid Cancer.
Thyroid, 24(10):1508-14.
Cabanillas ME, Brose MS, Holland J, Ferguson KC, Sherman SI. 2014.
BACKGROUND: Cabozantinib targets tyrosine kinases including MET, vascular endothelial growth factor (VEGF) receptor 2, and rearranged during transfection (RET). Differentiated thyroid cancer (DTC) is a tumor type that may be sensitive to cabozantinib. Therefore, we evaluated cabozantinib in a cohort of heavily pretreated patients with metastatic DTC. METHODS: This single-arm open-label phase I trial assessed the safety, tolerability, and antitumor activity of cabozantinib in DTC patients taking part in a drug-drug interaction study. Adult patients with histologically confirmed metastatic or surgically unresectable DTC (including papillary, follicular, or Hurthle cell) were enrolled. Patients received daily oral dosing of 140 mg cabozantinib. Safety was assessed by evaluation of adverse events (AEs), vital signs, electrocardiograms, laboratory tests, and concomitant medications. Tumor response by magnetic resonance imaging or computed tomography scan was investigator assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.0. RESULTS: The study enrolled 15 patients who had failed standard radioactive iodine therapy. Patients had received a median of two prior systemic agents, and 11 patients (73%) had previously received at least one VEGF pathway inhibiting therapy. Common AEs included diarrhea, nausea, fatigue, and decreased appetite. Partial response was reported in eight patients (53%). Median progression-free survival and median overall survival were not reached. CONCLUSIONS: Cabozantinib demonstrates a safety profile similar to other multitargeted VEGFR inhibitors in advanced DTC patients. The antitumor activity observed in this study warrants further investigation of cabozantinib in patients with advanced DTC.
PubMed-ID: 25102375
http://dx.doi.org/10.1089/thy.2014.0125

Minimally Invasive, Nonendoscopic Thyroidectomy: a Cosmetic Alternative to Robotic-Assisted Thyroidectomy.
Surgery, 156(4):1030-7.
Govednik CM, Snyder SK, Quinn CE, Saxena S, Jupiter DC. 2014.
BACKGROUND: The desire to improve cosmesis has driven the introduction of robotic-assisted and video-assisted thyroidectomy techniques. We report on minimally invasive thyroidectomy (MIT) through a 2-cm incision without the added need for video assistance and hypothesize similar clinical results to standard open thyroidectomy. METHODS: Between May 2012 and December 2013, 62 nonendoscopic MIT were evaluated for demographics, clinical outcomes, and patient satisfaction on a 1-10 scale. The results were compared with a case-matched control group who underwent conventional open thyroidectomy by the same surgeon. RESULTS: The 124 study patients demonstrated no differences between groups for demographics or clinical outcomes except a smaller thyroid lobe in the MIT group (9.2 vs 11.7 g.
PubMed-ID: 25104462
http://dx.doi.org/10.1016/j.surg.2014.06.056

Early Surgery and Survival of Patients With Anaplastic Thyroid Carcinoma: Analysis of a Case Series Referred to a Single Institution Between 1999 and 2012.
Thyroid, 24(11):1600-6.
Brignardello E, Palestini N, Felicetti F, Castiglione A, Piovesan A, Gallo M, Freddi M, Ricardi U, Gasparri G, Ciccone G, Arvat E, Boccuzzi G. 2014.
BACKGROUND: Extensive resection of the tumor has been associated with better survival of anaplastic thyroid carcinoma (ATC) patients. However, surgery is not the rule for ATC patients with distant metastases at the time of diagnosis (stage IV-C), regardless of tumor resectability. The aim of this work was to explore the potential role of surgery in ATC patients, including those in stage IV-C. METHODS: We considered all the consecutive ATC patients referred to our institution from June 1999 to July 2012. Patients with stage IV-A incidentally discovered ATC were excluded because of their better prognosis. All patients eligible for surgery at the time of diagnosis were first operated with the intent to obtain a macroscopically complete resection (R0, R1), or a R2 resection

with minimal macroscopical residual tumor. These operations were defined as "maximal debulking," whereas operations that did not achieve this goal were defined as "partial debulking." After surgery, almost all patients received adjuvant chemotherapy, associated to radiotherapy in more than 50% of patients. RESULTS: There were 55 eligible patients (34 women; median age 73.15 years). Thirty-one patients had distant metastases (stage IV-C). The median overall survival was 5.55 months [CI 4.94-6.60], with no difference according to stage. "Maximal debulking" was obtained in 70.73% of operated patients as a first modality and resulted associated with better survival than "partial debulking" (6.57 months [CI 5.52-12.09] vs. 3.25 months [CI 0.66-4.80]), without any difference between stage IV-B and IV-C patients. Furthermore, 21% of patients submitted to "maximal debulking" died secondary to local progression of the tumor, whereas this was the case for 69% of patients treated with "partial debulking" or not operated at all. CONCLUSIONS: Early "maximal debulking," followed by adjuvant therapy, can improve the survival and ameliorate the quality of residual life preventing the risk of suffocation. This effect is also observed in patients with distant metastasis at diagnosis and treated with this approach: they have an outcome similar to that observed in stage IV-B patients. We thus suggest that surgery may be considered in the management of all ATC patients, and should not be restricted a priori to stages IV-A and IV-B.
PubMed-ID: 25110922
http://dx.doi.org/10.1089/thy.2014.0004

Gas in the Retropharyngeal Space: Descending Necrotising Mediastinitis.
Lancet, 384(9958):1952.
Watanabe K, Kimura Y, Obara T. 2014.
PubMed-ID: 25132504
http://dx.doi.org/10.1016/S0140-6736(14)61138-7

Is Age Associated With Risk of Malignancy in Thyroid Cancer?
Otolaryngol Head Neck Surg, 151(5):746-50.
Do BA, Payne RJ, Bastianelli M, Mlynarek AM, Tamilia M, Hier M, Forest VI. 2014.
OBJECTIVES: Many predictive models for risk of malignancy in well-differentiated thyroid cancer (WDTC) have been proposed, and many scoring systems for thyroid cancer prognosis have been established. Age is taken in consideration in all. Our main goal is to establish whether patients' age has a correlation with the rate of malignancy, size, and aggressiveness of the tumor. STUDY DESIGN: Case series with chart review. SETTING: McGill University Thyroid Teaching Hospitals. SUBJECTS AND METHODS: A retrospective analysis of 1022 patients undergoing consecutive thyroidectomy was performed. The patients were divided based on age (<45 and >/= 45 years). Data were gathered for the size of thyroid nodules, the presence of lymph node (LN) metastasis, and the final thyroid pathology, including the presence of extrathyroidal extension. RESULTS: There were 396 patients younger than 45 years and 626 patients 45 years or older. The rates of malignancy were 67.2% in the first group and 68.7% in the second group (P = .111). When patients were stratified according to different age cutoffs, WDTC and LN metastasis occurred more often in patients younger than 50 years (50.2% vs 43.2%, P = .031 and 18.9% vs 14.1%, P = .0496, respectively). Micropapillary carcinoma occurred more often in patients 50 years or older (23.6% vs 16.1%, P = .0035). CONCLUSIONS: Tumor behavior and rates of WDTC were similar in patients aged <45 and >/= 45 years. Well-differentiated thyroid cancer occurred more often in patients younger than 50 years, whereas the rate of micropapillary carcinoma occurred more often in patients 50 years or older.
PubMed-ID: 25151485
http://dx.doi.org/10.1177/0194599814547503

Thyrotoxicosis Does Not Protect Against Incidental Papillary Thyroid Cancer.
Surgery, 156(5):1153-6.
Preece J, Grodski S, Yeung M, Bailey M, Serpell J. 2014.
BACKGROUND: Thyroid cancer is the 10th most commonly diagnosed cancer in Australia, and many studies have linked thyroid-stimulating hormone (TSH) and papillary thyroid cancer (PTC). Low TSH is thought to be protective against thyroid cancer. Our aim was to evaluate the relationship between thyrotoxicosis, in particular Graves' disease, and the incidence of incidental PTC. METHODS: After ethics approval, a review of the thyroid database at Monash University Endocrine Surgery Unit was performed. Data was obtained for the period September 1994 to August 2012 and identified those patients who underwent total thyroidectomy (n = 1,898). Those patients with known or suspected malignancy were excluded from the study (n = 390). The remaining patients (n = 1,508) were divided into 3 groups: Graves' disease (n = 250), toxic multinodular goiter (MNG; n = 295), and nontoxic MNG (n = 963) based on indication for surgery and thyroid status. Data were analyzed for the presence of malignancy in each group. RESULTS: Of the 1,508 patients included in the study, 96 (6.4%) had

thyroid cancer, and the incidence of PTC was similar between the 3 groups. There were 16 cases (6.4%) in the Graves' group, 48 cases (5%) in the nontoxic MNG group, and 20 cases (6.8%) in the toxic MNG group (P = .41). CONCLUSION: The incidence of malignancy, particularly PTC, is similar in patients with Graves' disease, toxic MNG, and nontoxic MNG. This study demonstrates no protective effect of thyrotoxicosis on the incidence of incidental thyroid cancer.
PubMed-ID: 25151553
http://dx.doi.org/10.1016/j.surg.2014.04.025

Impact of Invasive Extranodal Extension on the Prognosis of Patients With Papillary Thyroid Carcinoma.
Thyroid, 24(12):1779-83.
Moritani S. 2014.
BACKGROUND: Although 20-50% of papillary thyroid carcinoma (PTC) patients initially present with lymph node metastases, prognosis is excellent. Thus, the significance of lymph node metastasis in PTC remains controversial. In this study, we examined the impact of extranodal extension to surrounding organs (invasive extranodal extension) on the prognosis for PTC patients. METHODS: Medical records of PTC patients who underwent surgery as their initial treatment at our institution between 1981 and 2008 were retrospectively reviewed. Patients with or without invasive extranodal extension were selected. Our therapeutic strategy for PTC with invasive extranodal extension included complete resection and functional reconstruction. Intergroup comparison was performed using Student's t-test or the chi-square test as appropriate. Survival curves determined by the Kaplan-Meier method were compared for statistical significance using the log-rank test. A Cox-hazard regression model with the forward stepwise method was used for multivariate analysis. RESULTS: The study cohort included 60 (12.3%) patients with and 428 (87.7%) without invasive extranodal extension. The most common site of invasive extranodal extension in the central neck compartment was the recurrent laryngeal nerve, whereas the internal jugular vein was the most frequently invaded site in the lateral neck compartment. The locoregional recurrence rate did not differ significantly between patients with and without invasive extranodal extension, but the distant recurrence rate was higher for those with invasive extranodal extension. The 10-year disease-specific survival rate was significantly lower for patients with invasive extranodal extension than for those without invasive extranodal extension. Furthermore, multivariate analysis revealed that being aged >/=45 years, poor differentiation, and extrathyroidal extension were independent predictive factors for disease-specific death in PTC. Invasive extranodal extension had no effect on the survival of PTC patients. CONCLUSIONS: Invasive extranodal extension did not affect the survival of patients with PTC. Despite a negative impact on distant recurrence, invasive extranodal extension did not affect locoregional recurrence in PTC patients.
PubMed-ID: 25157399
http://dx.doi.org/10.1089/thy.2014.0167

Examining National Outcomes After Thyroidectomy With Nerve Monitoring.
J Am Coll Surg, 219(4):765-70.
Chung TK, Rosenthal EL, Porterfield JR, Carroll WR, Richman J, Hawn MT. 2014.
BACKGROUND: Previous intraoperative nerve monitoring (IONM) studies have demonstrated modest-to-no benefit and did not include a nationwide sample of hospitals representative of broad thyroidectomy practices. This national study was designed to compare vocal cord paralysis (VCP) rates between thyroidectomy with IONM and without monitoring (conventional). STUDY DESIGN: We performed a retrospective analysis of 243,527 thyroidectomies during 2008 to 2011 using the Nationwide Inpatient Sample. RESULTS: Use of IONM increased yearly throughout the study period (2.6% [2008], 5.6% [2009], 6.1% [2010], 6.9% [2011]) and during this time, VCP rates in the IONM group initially increased year-over-year (0.9% [2008], 2.4% [2009], 2.5% [2010], 1.4% [2011]). In unadjusted analyses, IONM was associated with significantly higher VCP rates (conventional 1.4% vs IONM 1.9%, $p < 0.001$). After propensity score matching, IONM remained associated with higher VCP rates in partial thyroidectomy and lower VCP rates for total thyroidectomy with neck dissection. Hospital-level analysis revealed that VCP rates were not explained by differential laryngoscopy rates, decreasing the likelihood of ascertainment bias. Additionally, for hospitals in which IONM was applied to more than 50% of thyroidectomies, lower VCP rates were observed (1.1%) compared with hospitals that applied IONM to less than 50% (1.6%, $p = 0.016$). Higher hospital volume correlated with lower VCP rates in both groups (<75, 75 to 299, >300 thyroidectomies/year: IONM, 2.1%, 1.7%, 1.7%; conventional, 1.5%, 1.3%, 1.0%, respectively). CONCLUSIONS: According to this study, IONM has not been broadly adopted into practice. Overall, IONM was associated with a higher rate of VCP even after correction for numerous confounders. In particular, low institutional use of IONM and use in partial thyroidectomies are associated with higher rates of VCP. Further studies are warranted to support the broader application of IONM in patients where benefit can be reliably achieved.

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http://dx.doi.org/10.1016/j.jamcollsurg.2014.04.013

Multi-Organ Distant Metastases Confer Worse Disease-Specific Survival in Differentiated Thyroid Cancer.
Thyroid, 24(11):1594-9.
Wang LY, Palmer FL, Nixon IJ, Thomas D, Patel SG, Shaha AR, Shah JP, Tuttle RM, Ganly I. 2014.
BACKGROUND: Differentiated thyroid cancer (DTC) is usually associated with an excellent prognosis. With appropriate management of disease in the neck, death from thyroid cancer is more commonly related to the impact of distant metastases rather than locoregional recurrence. However, many patients with distant metastases can have very long periods of progression-free survival. The aims of this study were to determine the impact of single and multi-organ distant metastases (SODM and MODM) on survival, and identify factors that predict SODM progressing to MODM. METHODS: An institutional database of 3664 previously untreated patients with DTC who had surgery between 1986 and 2010 was reviewed. One hundred and twenty-five (3.4%) patients developed distant metastases, of whom 93 developed SODM and 32 MODM. Overall survival was determined for each group by the Kaplan-Meier method. Factors predictive of MODM were identified by univariate and multivariate analysis. Multi-organ recurrence-free survival (MORFS) is a measure of SODM progressing to MODM disease. MORFS was calculated from the time of first distant metastasis to the time of second organ involvement by distant metastases. RESULTS: The median age was 56 years (range 5-86 years). The median follow-up was 77 and 79 months (range 2-318 months) for the SODM and MODM groups respectively. SODM patients had five-year survival of 77.6% from the time of first distant metastasis, whereas MODM patients had a significantly poorer survival of just 15.3% from the time of second organ distant metastasis to death (p<0.001). The median time from first to second distant metastasis was 14.7 months (range 1-121 months). Seventy-one (57%) patients had M1 disease at presentation. Being aged >/= 45 years (p = 0.05) and having an unstimulated serum thyroglobulin (Tg) level of >/= 30 ng/mL at the time of diagnosis of initial distant metastasis (p<0.001) were univariate predictors of developing MODM. Controlling for age, an unstimulated serum Tg level of >/= 30 ng/mL conferred a hazard ratio of 5.77 ([CI 2.13-15.64]; p = 0.001) for diagnosis of MODM. CONCLUSIONS: MODM are associated with a poorer survival compared to patients with SODM. A serum Tg level >30 ng/mL at the time of first distant metastases confers more than a fivefold risk of having MODM identified during follow-up.
PubMed-ID: 25162180
http://dx.doi.org/10.1089/thy.2014.0173

MTOR Activation in Medullary Thyroid Carcinoma With RAS Mutation.
Eur J Endocrinol, 171(5):633-40.
Lyra J, Vinagre J, Batista R, Pinto V, Prazeres H, Rodrigues F, Eloy C, Sobrinho-Simoes M, Soares P. 2014.
OBJECTIVE: Rearranged during transfection (RET) mutations are well-known genetic events in sporadic and familial medullary thyroid carcinoma (FMTC). The presence of RAS mutations in sporadic cases, challenging the RET paradigm in these tumors, has been recently reported. We intend to evaluate mTOR pathway activation in RET- and RAS-mutated MTC. MATERIALS AND METHODS: In this study, we analysed the presence of RET, H-RAS, and K-RAS mutations in a series of 87 MTCs (82 apparently sporadic and five FMTCs; five apparently sporadic MTCs were eventually found to be familial). We also evaluated mTOR activation--using the expression of its downstream effector phospho-S6 ribosomal protein (p-S6) and the expression of the mTOR inhibitor, phosphatase and tensin homologue deleted on chromosome 10 (PTEN)--by immunohistochemistry. RESULTS: Our results revealed that RET mutations were present in 52.9% of the cases (46/87) and RAS mutations in 12.6% (11/87) of the whole series of MTCs and 14.3% of the 77 sporadic MTCs. The presence of RET and RAS mutations was mutually exclusive. RAS mutations were significantly associated with higher intensity of p-S6 expression (P=0.007), suggesting that the mTOR pathway is activated in such MTCs. We observed also an increased expression of p-S6 in invasive tumors (P=0.042) and in MTCs with lymph node metastases (P=0.046). Cytoplasmic PTEN expression was detected in 58.8% of the cases; cases WT for RAS showed a significantly lower expression of PTEN (P=0.045). CONCLUSIONS: We confirmed the presence of RAS mutation in 14.3% of sporadic MTCs and report, for the first time, an association between such mutations and the activation of the mTOR pathway. The evaluation of the mTOR activation by pS6 expression may serve as an indicator of invasive MTC.
PubMed-ID: 25163725
http://dx.doi.org/10.1530/EJE-14-0389

Secular Trends in the Prognostic Factors for Papillary Thyroid Cancer.
Eur J Endocrinol, 171(5):667-75.

Choi H, Lim JA, Ahn HY, Cho SW, Lee KE, Kim KW, Yi KH, Sung MW, Youn YK, Chung JK, Park YJ, Park dJ, Cho BY. 2014.
OBJECTIVE: With the recent increasing rates of screening for thyroid cancer, the cancers now tend to be smaller and less aggressive than those that are diagnosed when presented with symptoms, suggesting changes in the clinical validity of conventional prognostic factors for outcomes. We performed the retrospective study to identify the secular trends in the prognostic factors of thyroid cancer. METHODS: We used medical records of 3147 patients diagnosed with papillary thyroid cancer (PTC) at the Seoul National University Hospital Thyroid Cancer Clinic between 1962 and 2009. RESULTS: During the median 5.1-year follow-up, the overall recurrence rate was 13.3%, and male sex, tumor size, lymph node (LN) involvement, and extrathyroidal extension (ETE) were the significant prognostic factors for recurrence. Thyroid cancer-specific mortality was 1.4%, and the associated prognostic factors were older age, male sex, and LN involvement. For tumor recurrence, the hazard ratio (HR) for male sex decreased from 2.809 (95% CI, 1.497-5.269) in the pre-1989 period to 1.142 (95% CI, 0.736-1.772) in the post-1999 period. The pathologic characteristics, such as tumor size, LN involvement, and ETE, showed similar or increasing HRs over the time periods. For cancer-specific mortality, the HR for male sex decreased from 6.460 (95% CI, 1.714-24.348) in the pre-1990 period to 0.781 (95% CI, 0.083-7.379) in the post-1999 period. CONCLUSION: The risk for poor outcomes in PTC associated with male sex decreased over time; in contrast, the risk associated with pathologic characteristics remained the same or increased over time. These trends might be associated with recent changes in the characteristics of patients with thyroid cancer.
PubMed-ID: 25163726
http://dx.doi.org/10.1530/EJE-14-0225

Latencies Longer Than 3.5 Ms After Vagus Nerve Stimulation Does Not Exclude a Nonrecurrent Inferior Laryngeal Nerve.
BMC Surg, 14:61.
Brauckhoff M, Naterstad H, Brauckhoff K, Biermann M, Aas T. 2014.
BACKGROUND: It has recently been reported that a signal latency shorter than 3.5 ms after electrical stimulation of the vagus nerve signify a nonrecurrent course of the inferior laryngeal nerve. We present a patient with an ascending nonrecurrent inferior laryngeal nerve. In this patient, the stimulation latency was longer than 3.5 ms. CASE PRESENTATION: A 74-years old female underwent redo surgery due to a right-sided recurrent nodular goitre. The signal latency on electrical stimulation of the vagus nerve at the level of the carotid artery bifurcation was 3.75 ms. Further dissection revealed a nonrecurrent but ascending course of the inferior laryngeal nerve. Caused by the recurrent goitre, the nerve was elongated to about 10 cm resulting in this long latency. CONCLUSION: This case demonstrates that the formerly proposed "3.5 ms rule" for identifying a nonrecurrent course of the inferior laryngeal nerve has exceptions. A longer latency does not necessarily exclude a nonrecurrent laryngeal nerve.
PubMed-ID: 25168966
http://dx.doi.org/10.1186/1471-2482-14-61

Recombinant Human TSH and Radioactive Iodine Therapy in the Management of Benign Multinodular Goiter.
Eur J Endocrinol, 172(2):R47-R52.
Graf H. 2015.
Multinodular goiter (MNG) is a very common thyroid disorder determined by diverse goitrogenic factors, the most important one being iodine deficiency. The clinical presentation of a patient with MNG varies from a completely asymptomatic goiter to a life-threatening disease due to upper airway compression. Patients can develop underlying subclinical or overt hyperthyroidism due to autonomously hyperfunctioning nodules. In the absence of clinical, ultrasonographic, or cytological findings suggestive of malignancy, the best therapeutic approach for a patient with MNG will depend on the size and location of the goiter, the presence and severity of compressive symptoms, and the presence or absence of thyrotoxicosis. There is still no consensus regarding the treatment of atoxic MNGs. Hence, its optimal management remains controversial; possible therapies include levothyroxine (lT4), surgery, and radioactive iodine ((131)I).
PubMed-ID: 25189867
http://dx.doi.org/10.1530/EJE-14-0608

BRAF Mutation Analysis in Thyroid Nodules With Indeterminate Cytology: Our Experience on Surgical Management of Patients With Thyroid Nodules From an Area of Borderline Iodine Deficiency.
J Endocrinol Invest, 37(10):1009-14.
Agretti P, Niccolai F, Rago T, De MG, Molinaro A, Scutari M, Di CC, Di CG, Vitale M, Maccheroni M, Vitti P, Tonacchera M. 2014.

PURPOSE: Fine-needle aspiration (FNA) with cytologic evaluation is the most reliable tool for malignancy prediction in thyroid nodules, but cytologic diagnosis remains indeterminate for 12-18 % of nodules. BRAF V600E mutation has been reported to show a high specificity for malignant thyroid nodules and the use of this marker to refine indeterminate FNA cytology results may be a useful diagnostic adjunctive tool in the pre-operative evaluation of thyroid nodules. The aim of this study was to estimate the prevalence of BRAF exon 15 mutation (V600E) and its clinical value as a diagnostic tool in a series of thyroid nodules with indeterminate cytology from an area of borderline iodine deficiency. SUBJECTS AND METHODS: One hundred and fifty-three thyroid samples obtained by FNA of thyroid nodules from 151 patients were subjected to the analysis of BRAF V600E mutation by direct sequencing. In the study 54 nodules with indeterminate cytology, 56 benign and 43 malignant thyroid nodules were included. RESULTS: V600E BRAF gene mutation was demonstrated in 19/43 malignant nodules, in 0/56 benign nodules and in only 1/54 indeterminate nodules that, after histology, turned out to be at a papillary thyroid carcinoma. CONCLUSIONS: The application of BRAF exon 15 analysis showed limitations when applied to discriminate thyroid nodules with indeterminate cytology if wild-type BRAF is found, and there is no role for avoiding diagnostic thyroid surgery.
PubMed-ID: 25194426
http://dx.doi.org/10.1007/s40618-014-0166-6

High Prevalence of Papillary Thyroid Cancer in Korean Women With Insulin Resistance.
Head Neck,
Bae MJ, Kim SS, Kim WJ, Yi YS, Jeon YK, Kim BH, Lee BJ, Lee JC, Kim IJ, Wang SG, Kim YK. 2014.
Background: The objective of this study was to determine if hyperinsulinemia and/or insulin resistance are/is associated with the prevalence of papillary thyroid cancer (PTC) in Korean women. Methods: This study included 735 female PTC patients and 537 female non-PTC control subjects. Multiple logistic regression analysis was performed to evaluate the associations between hyperinsulinemia/insulin resistance and the occurrence of PTC. Results: The prevalence of PTC was significantly correlated with increased insulin, glucose levels and a high HOMA-IR. The multivariate adjusted odds ratios for the prevalence of PTC in the highest quartile groups for insulin, glucose, and HOMA-IR were 2.88, 9.32, and 4.07 (all P<0.001), respectively, compared with the lowest quartile groups. Pathological analyses revealed that increased serum glucose, insulin levels and a higher HOMA-IR were associated with the multifocality of PTC. Conclusions: Hyperinsulinemia and/or insulin resistance may be associated with the development of PTC, but not disease severity in Korean women. Head Neck, 2014.
PubMed-ID: 25196854
http://dx.doi.org/10.1002/hed.23848

Papillary Thyroid Cancer in Identical Adolescent Twins With Osteogenesis Imperfecta and Hashimoto's Thyroiditis: Is There a Genetic Link?
Am Surg, 80(9):849-50.
Diegidio P, Kolok D, Brown W, Camps JI. 2014.
The relationship between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC) remains controversial. Researchers have identified multiple genes that could put patients with HT at risk for PTC. None are related to osteogenesis imperfecta (OI). We present identical twin sisters with OI who developed PTC in the setting HT.
PubMed-ID: 25197868

Recurrent Laryngeal Nerve: Its History.
World J Surg, 38(12):3138-41.
Sterpetti AV, De TG, De CA. 2014.
PubMed-ID: 25201468
http://dx.doi.org/10.1007/s00268-014-2758-x

Extent of Surgery for Papillary Thyroid Cancer Is Not Associated With Survival: an Analysis of 61,775 Patients.
Ann Surg, 260(4):601-5.
Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, Scheri R, Roman SA, Sosa JA. 2014.
OBJECTIVE: To examine the association between the extent of surgery and overall survival in a large contemporary cohort of patients with papillary thyroid cancer (PTC). BACKGROUND: Guidelines recommend total thyroidectomy for PTC tumors >1 cm, based on older data demonstrating an overall survival advantage for total thyroidectomy over lobectomy. METHODS: Adult patients with PTC tumors 1.0-4.0 cm undergoing thyroidectomy in the National Cancer Database, 1998-2006, were included. Cox proportional hazards models were applied to measure the association between the extent of surgery and overall survival while adjusting for patient demographic and clinical factors, including comorbidities, extrathyroidal extension, multifocality, nodal

and distant metastases, and radioactive iodine treatment. RESULTS: Among 61,775 PTC patients, 54,926 underwent total thyroidectomy and 6849 lobectomy. Compared with lobectomy, patients undergoing total thyroidectomy had more nodal (7% vs 27%), extrathyroidal (5% vs 16%), and multifocal disease (29% vs 44%) (all Ps < 0.001). Median follow-up was 82 months (range, 60-179 months). After multivariable adjustment, overall survival was similar in patients undergoing total thyroidectomy versus lobectomy for tumors 1.0-4.0 cm [hazard ratio (HR) = 0.96; 95% confidence interval (CI), 0.84-1.09); P = 0.54] and when stratified by tumor size: 1.0-2.0 cm [HR = 1.05; 95% CI, 0.88-1.26; P = 0.61] and 2.1-4.0 cm [HR = 0.89; 95% CI, 0.73-1.07; P = 0.21]. Older age, male sex, black race, lower income, tumor size, and presence of nodal or distant metastases were independently associated with compromised survival (P < 0.0001). CONCLUSIONS: Current guidelines suggest total thyroidectomy for PTC tumors >1 cm. However, we did not observe a survival advantage associated with total thyroidectomy compared with lobectomy. These findings call into question whether tumor size should be an absolute indication for total thyroidectomy.
PubMed-ID: 25203876
http://dx.doi.org/10.1097/SLA.0000000000000925

Well-Differentiated Thyroid Cancer With Aerodigestive Tract Invasion: Long-Term Control and Functional Outcomes.
Head Neck,
Su SY, Milas ZL, Bhatt N, Roberts D, Clayman GL. 2014.
BACKGROUND: Well-differentiated thyroid cancer (WDTC) invading the aerodigestive tract is an uncommon entity associated with significant morbidity and reduced survival. METHODS: We reviewed the surgical treatment, oncologic control, and functional outcomes of 69 consecutive patients with WDTC invading the upper aerodigestive tract. RESULTS: Complete tumor excision with negative margins was achieved in 62% of patients. Tracheostomy dependence (27%) and permanent hypoparathyroidism (49%) were present or the result of surgery. Seventy-one percent of patients ate a regular diet, 59% had normal speech, and the majority (62%) reported normal activities of daily living. The local, regional, and distant recurrence was 1%, 14%, and 23%, respectively. The 5-year overall survival (OS) and disease-free survival (DFS) was 71% and 45%, respectively. CONCLUSION: Surgical resection and appropriate adjuvant treatment can achieve excellent locoregional control while preserving function and quality of life. Long-term survival is limited by the high incidence of distant metastasis. (c) 2014 Wiley Periodicals, Inc. Head Neck, 2014.
PubMed-ID: 25204531
http://dx.doi.org/10.1002/hed.23851

Conditional Survival in Patients With Thyroid Cancer.
Thyroid, 24(12):1784-9.
Banerjee M, Muenz DG, Worden FP, Wong SL, Haymart MR. 2014.
BACKGROUND: Thyroid cancer is an increasingly common malignancy. Although likelihood of survival from well-differentiated thyroid cancer can vary by disease severity, it is not known how patients' life expectancies change the farther they are from time of diagnosis. METHODS: Using data from the Surveillance, Epidemiology, End Results (SEER) registry, we selected patients diagnosed with well-differentiated thyroid cancer (N=43,392) between 1998 and 2005. Patients were followed for up to 12 years. Conditional survival estimates by SEER stage and age were obtained based on Cox proportional hazards regression model of disease-specific survival. RESULTS: Patients with localized thyroid cancer have excellent conditional 5-year survival, irrespective of where they are in their survivorship phase. Patients with regional thyroid cancer have relatively stable conditional 5-year survival, whereas for patients with distant thyroid cancer there is gradual improvement the farther from time of diagnosis. Age and gender influence conditional survival. Similarly, age has a strong effect on disease-specific survival for patients with thyroid cancer with localized (hazard ratio [HR] 88.7 [95% confidence interval {CI} 26.3-552), comparing age >/=80 with <30 years), regional (HR 105 [95% CI 52.6-250]), and distant disease [HR 86.8 (95% CI 32.5-354)]. Male gender is also associated with a significantly worse disease-specific survival among patients with regional disease (HR 1.56 [95% CI 1.31-1.85]) but not among patients with localized or distant disease. CONCLUSION: Cancer stage, gender, age at diagnosis, and length of time already survived can influence conditional survival for patients with thyroid cancer. Understanding the conditional 5-year disease-specific survival of well-differentiated thyroid cancer is key to creating treatment plans and tailoring surveillance.
PubMed-ID: 25208475
http://dx.doi.org/10.1089/thy.2014.0264

Combined Effect of Hashimoto's Thyroiditis and BRAF Mutation Status on Aggressiveness in Papillary Thyroid Cancer.
Head Neck,

Kim SJ, Myong JP, Jee HG, Chai YJ, Choi JY, Min HS, Lee KE, Youn YK. 2014.
Background: This study was conducted to evaluate association between Hashimoto's thyroiditis (HT), BRAFV600E mutation status in papillary thyroid cancer (PTC) patients, and to determine their combined association with tumor aggressiveness in PTC. Patients and methods: A total of 1,780 PTC patients who underwent surgery were enrolled. Simple and multiple analyses were performed to determine association between HT and the BRAFV600E mutation in PTC. Results: HT was present in 11.5% (204/1,780) of PTC patients. Multiple logistic regressions showed that BRAFV600E (OR = 0.493; 95% CI: 0.360-0.678) and female gender (OR = 7.146; 95% CI: 3.408-18.347) were independent factors associated with HT in PTC. BRAFV600E mutation and HT-negative PTC group were associated with aggressive disease (OR = 3.069; 95% CI: 1.654-5.916) Conclusion: HT associated less frequently with BRAFV600E , and frequently with female gender in PTC patients. HT and BRAFV600E status may help to predict clinical outcome of PTC. Head Neck, 2014.
PubMed-ID: 25213729
http://dx.doi.org/10.1002/hed.23854

Influence of Superior Laryngeal Nerve Injury on Glottal Configuration/Function of Thyroidectomy-Induced Unilateral Vocal Fold Paralysis.
Otolaryngol Head Neck Surg, 151(6):996-1002.
De VA, Chang MH, Jiang RS, Wang CP, Wu SH, Liu SA, Wang CC. 2014.
OBJECTIVE: Recurrent laryngeal nerve (RLN) injury may induce unilateral vocal fold paralysis (UVFP). During thyroidectomy, the most common cause of UVFP, the superior laryngeal nerve (SLN), is also at risk of injury. In the literature, the influence of SLN injury on glottal configuration and function in patients with UVFP remains controversial. The present study investigates SLN injury influence on glottal configuration and function in patients with UVFP after thyroidectomy. STUDY DESIGN: Prospective controlled study. SETTING: Tertiary medical center. SUBJECTS AND METHODS: The SLN and RLN function of 34 patients with UVFP after thyroidectomy was determined by laryngeal electromyography. The subjects were dichotomized into the isolated RLN injury group (n = 26) or the concurrent SLN/RLN injury group (n = 8). We evaluated glottal angle and paralyzed vocal fold shape during inspiration, normalized glottal gap area, and glottal shape during phonation. The glottal function measurements included voice acoustic and aerodynamic analyses and the Voice Handicap Index. The aforementioned parameters of the RLN and concurrent SLN/RLN injury groups were compared. RESULTS: There were no statistical differences in glottal configuration such as glottal angle, paralyzed vocal fold shape, normalized glottal gap area, and glottal shape between the RLN and concurrent SLN/RLN injury groups. There were also no significant differences in other glottal function analyses including fundamental frequency, mean airflow rate, phonation quotient, maximal phonation time, and Voice Handicap Index. CONCLUSION: In the present study, we did not find any evidence that SLN injury could significantly influence the glottal configuration and function in patients with UVFP.
PubMed-ID: 25214548
http://dx.doi.org/10.1177/0194599814549740

Management of the Compromised Airway and Role of Tracheotomy in Anaplastic Thyroid Carcinoma.
Head Neck,
Mani N, McNamara K, Lowe N, Loughran S, Yap BK. 2014.
BACKGROUND: Anaplastic thyroid carcinoma (ATC) is an uncommon thyroid malignancy with a poor prognosis. American Thyroid Association (ATA) guidelines acknowledge the complexity of airway management in these patients. We studied our local experience with the aim of providing guidance in airway management in ATC. METHODS: Patients with histologically confirmed ATC from January 2004 to December 2011 were identified from our institutional database. The data were retrospectively analyzed using hospital case notes. RESULTS: Twenty-six patients were identified with ATC, 25 of who died from the disease. Five of 26 patients (19%) had stridor at presentation. A further 6 of 26 patients (23%) developed stridor during or soon after radiotherapy. Nine patients (36%) died of airway obstruction. CONCLUSION: Tracheotomy can facilitate completion of palliative treatment in those patients with ATC and stridor. Given the short life expectancy of these patients, a balanced decision must be made regarding the role and timing of tracheotomy. (c) 2014 Wiley Periodicals, Inc. Head Neck, 2014.
PubMed-ID: 25215461
http://dx.doi.org/10.1002/hed.23857

Association of Hashimoto's Thyroiditis With Thyroid Cancer.
Endocr Relat Cancer, 21(6):845-52.
Azizi G, Keller JM, Lewis M, Piper K, Puett D, Rivenbark KM, Malchoff CD. 2014.
This prospective study investigates the relationship between Hashimoto's thyroiditis (HT) and thyroid cancer

(TC) in patients with thyroid nodules (TNs). We prospectively examined 2100 patients with 2753 TNs between January 5, 2010 and August 15, 2013. A total of 2023 patients with 2669 TNs met the inclusion criteria of TN >/=5 mm and age >/=18 years. Each patient had blood drawn before fine-needle aspiration biopsy (FNAB) for the following measurements: TSH, free thyroxine, free tri-iodothyronine, thyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Diagnosis of TC was based on pathology analysis of thyroidectomy tissue. The associations of TC with the independent variables were determined by univariate and multivariate logistic regression analysis and reported as adjusted odds ratio (OR) with 95% CI. A total of 248 malignant nodules were found in 233 patients. There was an association of TC with both increased serum TgAb concentration and age<45 years. An elevated serum TgAb.
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http://dx.doi.org/10.1530/ERC-14-0258

Malignancy Risk and Reproducibility Associated With Atypia of Undetermined Significance on Thyroid Cytology.
Surgery, 156(6):1471-6.
Mathur A, Najafian A, Schneider EB, Zeiger MA, Olson MT. 2014.
BACKGROUND: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) describes several subcategories within atypia of undetermined significance (AUS), including (1) presence of focal nuclear atypia (AUS-N), (2) focal microfollicular proliferation (AUS-F), (3) focal Hurthle cell proliferation (AUS-HC), and (4) other (AUS-O). Several publications suggest that 5-15% is an underestimate of the malignancy risk for AUS, and that the underestimation is owing to the similarity between AUS-N and suspicious for malignancy (SFM). Thus, we investigated the AUS subcategories during morphologic re-review at a tertiary care center and their associated malignancy risk. METHODS: Of 4,827 fine-needle aspiration specimens were sent between January 2009 and August 2013 for morphologic re-review, 806 were categorized as AUS. Comparison of AUS subcategory diagnoses were made between outside and re-review results. The malignancy risk was also determined for 255 nodules with available surgical pathology. RESULT: The outside diagnoses of the 806 cases read as AUS on second review were as follows: 5 insufficient (0.1%), 149 benign (19%), 463 AUS (57%), 124 SFN or suspicious for follicular or Hurthle cell neoplasm (15%), 56 SFM (7%), and 9 malignant (1%). Of the 463 cases in which both the outside and re-review diagnosis was AUS, the distribution of the subcategories in order of increasing frequency was 53 AUS-HC (11%), 74 AUS-O (16%), 79 AUS-F (17%), and 257 AUS-N (56%). Of the 255 resected nodules, 99 (39%) were malignant. Subcategory malignancy rates were: AUS-HC, 19% (9/47); AUS-O, 26% (14/54); AUS-F, 39% (19/49); and AUS-N, 54% (57/105). Cases in which both the referring institution and re-review agreed about the AUS-N subcategory had an even greater risk of malignancy (68%; 17/25). CONCLUSION: Disagreement about the diagnosis of AUS between institutions is frequent. The malignancy risk for AUS is higher than originally proposed by TBSRTC and attributable to the high risk of AUS-N. Furthermore, agreement on AUS-N after re-review portends a malignancy risk that borders on that of SFM. This suggests that AUS-N may have discrete features that can provide specific morphologic predictors and enable the consolidation of AUS-N into SFM.
PubMed-ID: 25218896
http://dx.doi.org/10.1016/j.surg.2014.08.026

Late-Onset Palsy of the Recurrent Laryngeal Nerve After Thyroid Surgery.
Br J Surg, 101(12):1556-9.
Bures C, Bobak-Wieser R, Koppitsch C, Klatte T, Zielinski V, Freissmuth M, Friedrich G, Repasi R, Hermann M. 2014.
BACKGROUND: A small subset of patients may develop late-onset palsy of the recurrent laryngeal nerve (RLN) after thyroid surgery. However, no conclusive data have been published regarding the incidence of, and possible risk factors for, this complication. METHODS: Preoperative, intraoperative and postoperative data from consecutive patients who underwent thyroid surgery at a single centre between 1999 and 2012 were analysed. Late-onset palsy of the RLN was defined as deterioration of RLN function after normal vocal cord function as investigated by routine preoperative and postoperative laryngoscopy. RESULTS: The cohort included 16 692 patients with 28 757 nerves at risk. Early postoperative palsy of the RLN was diagnosed in 1183 nerves at risk (4.1 per cent), whereas late-onset RLN palsy was found in 41 (0.1 per cent). Late-onset palsy of the RLN was diagnosed after a median interval of 2.5 (range 0.5-12) weeks and nerve function recovered completely in 28 patients after a median interval of 3 months. This recovery rate was significantly lower than that for early-onset RLN palsy: 1068 (90.3 per cent) of 1183 nerves (P < 0.001). No particular risk factor for late-onset RLN palsy was identified. CONCLUSION: Late-onset palsy of the RLN was diagnosed in a small subset of patients after thyroid surgery, and recovery of nerve function occurred less frequently than in patients with early-onset RLN palsy.

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http://dx.doi.org/10.1002/bjs.9648

Risk Factors for and Occurrence of Postoperative Cervical Hematoma After Thyroid Surgery: A Single-Institution Study Based on 5156 Cases From the Past 2 Years.
Head Neck,
Liu J, Li Z, Liu S, Wang X, Xu Z, Tang P. 2014.
BACKGROUND: The occurrence of and risk factors for postoperative cervical hematoma remain unclear. METHODS: We conducted a retrospective analysis of 5156 patients treated at a single institution. RESULTS: The occurrence of postoperative cervical hematoma was 0.85% (44 of 5156 patients). The multivariate analysis showed that male sex, benign pathology, hypertension, and previous thyroid surgery are individual risk factors with odds ratios of 1.906, 2.004, 7.962, and 4.407, respectively. The majority (88.7%) of hematomas occurred within 12 hours after surgery. Obvious bleeding points were detected in 28 cases (73.6%) during reexploration, surface of the strap muscle, superior thyroid vessel, and end of the recurrent laryngeal nerve were the most frequent bleeding sources. CONCLUSION: Hematoma often occurs within 12 hours after thyroid surgery. Hypertension, previous thyroid surgery, male sex, and benign pathology may increase the risk of hematoma. (c) 2014 Wiley Periodicals, Inc. Head Neck, 2014.
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http://dx.doi.org/10.1002/hed.23868

Frequent Silencing of RASSF1A Via Promoter Methylation in Follicular Thyroid Hyperplasia: a Potential Early Epigenetic Susceptibility Event in Thyroid Carcinogenesis.
JAMA Surg, 149(11):1146-52.
Brown TC, Juhlin CC, Healy JM, Prasad ML, Korah R, Carling T. 2014.
IMPORTANCE: Follicular thyroid hyperplasia (FTH) refers to enlargement of the thyroid gland due to cellular hyperplasia. It is frequently encountered in clinical practice in nontoxic uninodular or multinodular goiter. The genetic and epigenetic events associated with the origin and malignant potential of FTH are poorly understood. OBJECTIVE: To analyze FTH samples for known recurrent genetic and epigenetic driver events in thyroid neoplasms such as activating mutations in proto-oncogenes BRAF and NRAS and promoter hypermethylation of tumor suppressor genes CDKN2A, PTEN, and RASSF1A. DESIGN, SETTING, AND PARTICIPANTS: Clinical characteristics and thyroid specimens were prospectively obtained from 43 patients who underwent thyroid surgery at Yale-New Haven Hospital. MAIN OUTCOMES AND MEASURES: Presence of BRAF(V600E) and NRAS codon 61 mutations were assessed in FTH. Methylation status of CDKN2A, PTEN, and RASSF1A gene promoters in FTH, follicular thyroid adenoma, and follicular thyroid carcinoma was quantified. Regulation of RASSF1A messenger RNA (mRNA) and protein expression and its potential neoplastic role in FTH were examined. RESULTS: An exploratory cohort of FTH (n = 10) was negative for BRAF(V600E) and NRAS codon 61 mutations. In contrast, epigenetic analysis displayed significant promoter hypermethylation of the tumor-suppressor gene RASSF1A in 6 FTH samples (60%) compared with their adjacent normal tissue (P = .01). The overall genome CpG methylation and promoter methylation of PTEN and CDKN2A were unaffected in the lesions. Further analysis of an expanded cohort of patients with FTH (n = 23), follicular thyroid adenoma (n = 10), and follicular thyroid carcinoma (n = 10) showed RASSF1A promoter hypermethylation in 14 (61%), 9 (90%), and 7 (70%), respectively (P < .001). The overall hypermethylation level in FTH showed a statistically significant inverse correlation with RASSF1A mRNA expression (P = .005). Immunohistochemistry demonstrated minimal or no protein expression in most FTH samples studied. To explore the potential neoplastic contribution of RASSF1A downregulation, we analyzed the expression pattern of thyroid proliferation markers Ki-67 and NF-kappaB in representative samples. Although Ki-67 expression was undetectable, similar to normal tissue, FTH samples expressed high levels of NF-kappaB, similar to the expression levels in thyroid tumors. CONCLUSIONS AND RELEVANCE: We demonstrate silencing of tumor suppressor RASSF1A in a subset of FTH in the absence of other known thyroid cancer-associated genetic and epigenetic changes. Silencing of RASSF1A and concurrent NF-kappaB activation demonstrate that a subset of FTH shares epigenetic changes and downstream signaling events associated with malignant lesions, suggesting that FTH may have the potential to be a premalignant lesion.
PubMed-ID: 25229773
http://dx.doi.org/10.1001/jamasurg.2014.1694

Practice Patterns in the Surgical Treatment of Papillary Thyroid Microcarcinoma.
Thyroid, 24(12):1816-7.
Nguyen C, Wang M. 2014.

PubMed-ID: 25232803
http://dx.doi.org/10.1089/thy.2014.0388

Intraoperative Neuromonitoring of the Recurrent Laryngeal Nerve in Robotic Thyroid Surgery.
Surg Laparosc Endosc Percutan Tech, 25(1):23-6.
Bae DS, Kim SJ. 2015.
This study evaluated the technical feasibility and efficacy of intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) to aid its identification and preservation during robotic thyroidectomy (RoT). IONM of the RLN was evaluated in 30 consecutive patients undergoing RoT. All patients underwent an indirect laryngoscope examination to objectively assess vocal cord function. Their Voice Handicap Index-10 (VHI-10) was measured to subjectively assess vocal cord function preoperatively and at postoperative months 1 and 3. Of the 56 RLNs at risk in 30 patients undergoing RoT, all were visualized and identified by IONM. The IONM sensitivity for postoperative permanent RLN palsy was 100%, with a positive predictive value of 100%. The mean VHI-10 scores preoperatively and at postoperative months 1 and 3 were 0.20+/-0.66, 3.47+/-5.04, and 1.53+/-2.47, respectively (P<0.001). IONM of the RLN during RoT is technically feasible and effective for identifying this nerve.
PubMed-ID: 25238177
http://dx.doi.org/10.1097/SLE.0000000000000074

A Meta-Analysis of Thyroid Imaging Reporting and Data System in the Ultrasonographic Diagnosis of 10,437 Thyroid Nodules.
Head Neck,
Wei X, Li Y, Zhang S, Gao M. 2014.
Background: The meta-analysis was preformed to review the diagnostic accuracy of ultrasound reporting and data system in the diagnosis of thyroid nodules. Methods: We identified the diagnostic accuracy of ultrasound reporting and data system in five databases. Meta-analyses were used in selected studies to obtain pooled sensitivity, specificity, and summary receiver operating characteristic curves. Fixed or random-effects models were performed to analyze our data. Results: Twelve eligible studies were identified, including 10,437 thyroid nodules. A pooled sensitivity of 0.79 (95% confidence interval:0.77-0.81) and a pooled specificity of 0.71 (95% confidence interval: 0.70-0.72) of ultrasound reporting system in differentiated diagnosis of thyroid nodules were showed in meta-analyses. Subgroup analyses showed the most important factor of heterogeneity in studies was final diagnostic references (histological and cytological standards or only histological results). Conclusion: The thyroid imaging reporting and data system has a good sensitivity and specificity in diagnosis of patients with thyroid nodules. Head Neck, 2014.
PubMed-ID: 25244250
http://dx.doi.org/10.1002/hed.23878

Thyroid Tumors: Are We Unveiling the Puzzle?
Endocr Relat Cancer, 21(5):E7-E8.
Ward LS. 2014.
PubMed-ID: 25245018
http://dx.doi.org/10.1530/ERC-14-0407

Accuracy of PET and PET-CT in the Detection of Differentiated Thyroid Cancer Recurrence With Negative I Whole Body Scan Results: A Meta-Analysis.
Head Neck,
Caetano R, Bastos CR, de Oliveira IA, da Silva RM, Fortes CP, Pepe VL, Reis LG, Braga JU. 2014.
Background A meta-analysis aimed to evaluate the accuracy of positron emission tomography (PET) and PET-CT for detecting recurrence of differentiated thyroid carcinoma (DTC) not identified by 131 I whole body scintigraphy (WBS). Methods MEDLINE, EMBASE, LILACS and Cochrane databases were searched for studies published between January/1985 and March/2012. Systematic methods were used to select and evaluate the quality of studies. Pooled sensitivity and specificity for conventional PET and PET-CT was estimated using random effects model. Results Twenty studies were included in the systematic review; the data of 18 were used in the meta-analysis. The combined sensitivity and specificity for conventional PET were both found to be 84%; for PET-CT, they were 93% and 81%, respectively. The overall accuracies were 91% and 93%, respectively. Conclusions 18 FDG-PET and PET-CT are highly accurate diagnostics tools for DTC recurrence in patients who present a negative WBS and could impact the clinical and therapeutic management of DTC. Head Neck, 2014.
PubMed-ID: 25251544
http://dx.doi.org/10.1002/hed.23881

Risk-Adapted Management of Papillary Thyroid Carcinoma According to Our Own Risk Group Classification System: Is Thyroid Lobectomy the Treatment of Choice for Low-Risk Patients?
Surgery, 156(6):1579-88.
Ebina A, Sugitani I, Fujimoto Y, Yamada K. 2014.
BACKGROUND: Our original system for risk group classification for predicting cause-specific death from papillary thyroid carcinoma (PTC) defined patients with distant metastasis and older patients (>/= 50 years) with either massive extrathyroidal extension or large (>/= 3 cm) lymph node metastasis as high risk; all others are low risk. For unilateral, low-risk PTC, the extent of thyroidectomy (less-than-total thyroidectomy vs total or near-total thyroidectomy) has been determined based on the choice of the patient since 2005. PATIENTS: Of 1,187 patients who underwent initial thyroidectomy for PTC (tumor size [T] >1 cm) between 1993 and 2010, 967 (82%) were classified as low risk. Among low-risk patients, 791 (82%) underwent less than total thyroidectomy. RESULTS: The 10-year cause-specific survival and disease-free survival rates did not differ between patients who underwent total thyroidectomy versus less than total thyroidectomy (cause-specific survival, 99% vs 99% [P = .61]; disease-free survival, 91% vs 87% [P = .90]). Age >/= 60 years, T >/= 3 cm, and lymph node metastases >3 cm represented significant risk factors for distant recurrence. CONCLUSION: The favorable overall survival of low-risk patients, regardless of the extent of thyroidectomy, supports patient autonomy in treatment-related decision making. Low-risk patients possessing risk factors for distant recurrence would be likely to benefit from total thyroidectomy followed by radioactive iodine.
PubMed-ID: 25262223
http://dx.doi.org/10.1016/j.surg.2014.08.060

A Single Surgeon's Experience and Surgical Outcomes of 300 Robotic Thyroid Surgeries Using a Bilateral Axillo-Breast Approach.
J Surg Oncol, 111(2):135-40.
Kim WW, Jung JH, Park HY. 2015.
OBJECTIVES: We introduce surgical outcomes regarding 300 cases of robotic thyroidectomy using a bilateral axillo-breast approach (BABA). METHODS: From April 2010 to October 2013, 300 patients who underwent robotic thyroidectomy were analyzed and compared with 300 cases of open total thyroidectomy. Robotic surgery was performed with a snake retractor to allow for complete central lymph node dissection. We performed robotic surgery using BABA without drains in 170 cases; subfascial dissection was performed to reduce post-operative wound adhesion. RESULTS: The learning curve for robotic thyroidectomy was 40 cases; after that, the operation time significantly decreased (233 min vs. 185 min, P=0.001). A snake retractor was selectively useful for the dissection of paratracheal lymph nodes located in the deep areas. In patients who underwent drainless BABA, additional aspirations were required in only 19 (6.3%). The number of retrieved lymph nodes of robot and open surgery were 6.7 +/- 0.2 and 8.9 +/- 0.3, respectively (P<0.001). The mean serum thyroglobulin of thyroid hormone was 0.80 +/- 0.19 and 1.77 +/- 0.29 ng/ml, respectively (P=0.001). Post-operative complications of robot surgery, including transient hypocalcemia (n=33, 23.0%) in total thyroidectomy, transient recurrent laryngeal nerve palsy (n=8, 2.6%) without permanent palsy rarely observed. CONCLUSION: Robotic thyroidectomy using BABA is an effective and comparable treatment option. J. Surg. Oncol. 2015 111:135-140.
PubMed-ID: 25262911
http://dx.doi.org/10.1002/jso.23793

Impact of Surgeon Volume on Incidence of Neck Hematoma After Thyroid and Parathyroid Surgery: Ten Years' Analysis of Nationwide in-Patient Sample Database.
Am Surg, 80(10):948-52.
Dehal A, Abbas A, Al-Tememi M, Hussain F, Johna S. 2014.
The study's objective is to examine the impact of surgeon experience on the incidence and the severity of neck hematoma after thyroid and parathyroid surgery using a nationwide database. The Nationwide In-patient Sample is a nationwide clinical and administrative database. We used the International Classification of Diseases, 9th Revision diagnosis and procedures codes to identify adult patients who underwent thyroid and parathyroid surgery and subsequently developed neck hematoma. Patient and hospital characteristics were collected along with surgeon volume to predict patient outcomes. Surgical procedures were stratified into three groups according to surgeon volume: low (less than 10 operations), intermediate (10 to 99), and high (100 or more). We identified 147,344 thyroid and parathyroid surgery performed between 2000 and 2009 nationwide. Overall incidence of postoperative neck hematoma was 1.5 per cent (n = 2210). This was 2.1, 1.4, and 0.9 per cent among procedures performed by low-volume, intermediate-volume, and high-volume surgeons, respectively. After adjusting for other confounders, compared with procedures performed by low-volume surgeons, those performed by intermediate- (odds ratio [OR], 0.7; 95% confidence interval [CI], 0.6 to 0.8; P < 0.01) and high-volume surgeons (OR, 0.5; 95% CI, 0.4 to 0.6; P < 0.01) were less to likely to develop neck hematoma. Surgeon

experience is significantly associated with the development of neck hematoma after thyroid and parathyroid surgery.
PubMed-ID: 25264636

Quantification of BRAF V600E Alleles Predicts Papillary Thyroid Cancer Progression.
Endocr Relat Cancer, 21(6):891-902.
Kim MH, Bae JS, Lim DJ, Lee H, Jeon SR, Park GS, Jung CK. 2014.
The BRAF V600E mutation is the most common genetic alteration in thyroid cancer. However, its clinicopathological significance and clonal mutation frequency remain unclear. To clarify the inconsistent results, we investigated the association between the allelic frequency of BRAF V600E and the clinicopathological features of classic papillary thyroid carcinoma (PTC). Tumour tissues from two independent sets of patients with classic PTC were manually microdissected and analysed for the presence or absence of the BRAF mutation and the mutant allelic frequency using quantitative pyrosequencing. For external validation, the Cancer Genome Atlas (TCGA) data were analysed. The BRAF V600E mutation was found in 264 (82.2%) out of 321 classic PTCs in the training set. The presence of BRAF V600E was only associated with extrathyroidal extension and the absence of thyroiditis. In BRAF V600E-positive tumours, the mutant allelic frequency varied from 8 to 41% of the total BRAF alleles (median, 20%) and directly correlated with tumour size and the number of metastatic lymph nodes. Lymph node metastases were more frequent in PTCs with a high (>/=20%) abundance of mutant alleles than in those with a low abundance of mutant alleles (P=0.010). These results were reinforced by validation dataset (n=348) analysis but were not reproduced in the TCGA dataset. In a population with prevalent BRAF mutations, quantitative analysis of the BRAF mutation could provide additional information regarding tumour behaviour, which is not reflected by qualitative analysis. Nonetheless, prospective studies are needed before the mutated allele percentage can be considered as a prognostic factor.
PubMed-ID: 25266729
http://dx.doi.org/10.1530/ERC-14-0147

A New Strategy to Estimate Levothyroxine Requirement After Total Thyroidectomy for Benign Thyroid Disease.
Thyroid, 24(12):1759-64.
Di D, V, Santoro MG, de WC, Ricciato MP, Paragliola RM, Pontecorvi A, Corsello SM. 2014.
BACKGROUND: The current approach for calculating the starting dose of levothyroxine (LT4) after total thyroidectomy is based on the patient's body weight (BW). The aim of the study was to identify the major predictive factors of LT4 requirement and to elaborate a new method to improve the accuracy of the LT4 starting dose after total thyroidectomy. METHODS: The study consists of two parts. The first part consisted of the retrospective identification of 92 adult patients (retrospective cohort) who had undergone a total thyroidectomy for benign disease and who had begun LT4 treatment at a dose of 1.6 mug/kg/day. Adjustments to optimize the LT4 dose were then performed at the post-surgery follow-up on the basis of serum thyrotropin (TSH) levels. The results of this retrospective analysis were used to formulate a nomogram for a proper calculation of the LT4 starting dose that was then used prospectively in the second part of the study on 31 consecutive patients (prospective cohort). RESULTS: At the first follow-up, 37 (40%) patients from the retrospective cohort were euthyroid. Univariate analysis indicated significant correlations between the optimal dose of LT4 and BW, body mass index (BMI), age, preoperative mean corpuscular volume, and free triiodothyronine (fT3). The optimal dose of LT4, analyzed for BMI and age, showed an inverse relationship with these two parameters, and ranged from 1.4 to 1.8 mug/kg/day. In the prospective cohort, the use of an age- and BMI-related nomogram improved the prediction of the optimal LT4 starting dose, with 68% of patients being euthyroid at the first follow-up compared to 41% of patients reported to have reached euthyroid state using the best strategy proposed in the literature. CONCLUSIONS: This study confirms that BW is not the only variable for predicting LT4 requirement, as it decreases with the increase in age and BMI, probably due to the relative decrease of lean body mass. A new correlation between optimal dose and presurgical levels of fT3 and mean corpuscular volume was observed. We propose an easy and more efficient method of calculating LT4 starting dose after total thyroidectomy for benign disease.
PubMed-ID: 25268754
http://dx.doi.org/10.1089/thy.2014.0111

Central Lymph Node Characteristics Predictive of Outcome in Patients With Differentiated Thyroid Cancer.
Thyroid, 24(12):1790-5.
Wang LY, Palmer FL, Nixon IJ, Thomas D, Shah JP, Patel SG, Tuttle RM, Shaha AR, Ganly I. 2014.
BACKGROUND: The aim of our study was to determine central compartment lymph node (LN) characteristics

predictive of outcomes in patients with differentiated thyroid cancer (DTC) and pathologically confirmed positive central LNs, in the absence of lateral neck disease or distant metastases at presentation. METHODS: An institutional database of 3664 previously untreated patients with DTC operated between 1986 and 2010 was reviewed. Six hundred patients with central compartment nodal disease on histopathology were identified. Patient demographics, number of positive LNs, size of largest LN, and presence of extranodal spread (ENS) were recorded for each patient. Variables predictive of recurrence-free survival (RFS) were identified using the Kaplan-Meier method. Univariate analysis was carried out by the log-rank test and multivariable analysis was carried out using cox proportional hazard model. RESULTS: The median age of the cohort was 41 years (range 12-91 years). The median follow-up was 61 months (range 1-330 months). Neck recurrence occurred in 43 patients. Recurrence occurred in the central neck in 11 patients, lateral neck in 27 patients, and both compartments in five patients. Factors predictive of neck RFS on univariate analysis were higher T stage (p=0.007), increased number of positive LNs, increased LN diameter, and presence of ENS (p=0.001). Multivariable analysis of LN characteristics showed that the only statistically significant predictor of neck recurrence was the presence of ENS. Neck RFS at five years for patients with and without ENS was 84.7% and 94.5% respectively (p=0.001). CONCLUSION: The LN feature most predictive of neck recurrence appears to be the presence of ENS in the positive central neck.
PubMed-ID: 25268855
http://dx.doi.org/10.1089/thy.2014.0256

Benign Intranodal Thyroid Tissue Mimicking Nodal Metastasis in a Patient With Papillary Thyroid Carcinoma: A Case Report.
Head Neck,
Lee YJ, Kim DW, Park HK, Ha TK, Kim DH, Jung SJ, Bae SK. 2014.
Background: A case of benign intranodal thyroid tissue mimicking nodal metastasis on ultrasound (US) and computed tomography (CT) in a patient with papillary thyroid carcinoma has not been reported. Methods: The clinical, imaging, and histopathological findings of the patient are presented. Results: A 52-year-old woman who underwent US-guided fine-needle aspiration for two small, suspicious thyroid nodules in both lobes at a local clinic was referred to our hospital for surgical treatment. US-guided fine-needle aspiration for a suspicious lymph node in the left upper neck was performed. According to the imaging and cytology results, total thyroidectomy and nodal dissection for both central and left lateral nodes were performed. In the histopathology, the lymph node was confirmed as a benign lymph node with intranodal thyroid tissue. Conclusion: This case illustrates that benign intranodal thyroid tissue may mimic nodal metastasis on US or CT in a patient with papillary thyroid carcinoma. Head Neck, 2014.
PubMed-ID: 25270676
http://dx.doi.org/10.1002/hed.23886

Current Controversies in the Initial Post-Surgical Radioactive Iodine Therapy for Thyroid Cancer: a Narrative Review.
Endocr Relat Cancer, 21(6):R473-R484.
Blumhardt R, Wolin EA, Phillips WT, Salman UA, Walker RC, Stack BC, Jr., Metter D. 2014.
Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and the fifth most common cancer in women. DTC therapy requires a multimodal approach, including surgery, which is beyond the scope of this paper. However, for over 50 years, the post-operative management of the DTC post-thyroidectomy patient has included radioactive iodine (RAI) ablation and/or therapy. Before 2000, a typical RAI post-operative dose recommendation was 100 mCi for remnant ablation, 150 mCi for locoregional nodal disease, and 175-200 mCi for distant metastases. Recent recommendations have been made to decrease the dose in order to limit the perceived adverse effects of RAI including salivary gland dysfunction and inducing secondary primary malignancies. A significant controversy has thus arisen regarding the use of RAI, particularly in the management of the low-risk DTC patient. This debate includes the definition of the low-risk patient, RAI dose selection, and whether or not RAI is needed in all patients. To allow the reader to form an opinion regarding post-operative RAI therapy in DTC, a literature review of the risks and benefits is presented.
PubMed-ID: 25277792
http://dx.doi.org/10.1530/ERC-14-0286

Response and Acquired Resistance to Everolimus in Anaplastic Thyroid Cancer.
N Engl J Med, 371(15):1426-33.
Wagle N, Grabiner BC, Van Allen EM, Amin-Mansour A, Taylor-Weiner A, Rosenberg M, Gray N, Barletta JA, Guo Y, Swanson SJ, Ruan DT, Hanna GJ, Haddad RI, Getz G, Kwiatkowski DJ, Carter SL, Sabatini DM, Janne PA, Garraway LA, Lorch JH. 2014.

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is effective in treating tumors harboring alterations in the mTOR pathway. Mechanisms of resistance to everolimus remain undefined. Resistance developed in a patient with metastatic anaplastic thyroid carcinoma after an extraordinary 18-month response. Whole-exome sequencing of pretreatment and drug-resistant tumors revealed a nonsense mutation in TSC2, a negative regulator of mTOR, suggesting a mechanism for exquisite sensitivity to everolimus. The resistant tumor also harbored a mutation in MTOR that confers resistance to allosteric mTOR inhibition. The mutation remains sensitive to mTOR kinase inhibitors.
PubMed-ID: 25295501
http://dx.doi.org/10.1056/NEJMoa1403352

How Do We Improve Patient Access to High-Volume Thyroid Surgeons?
Surgery, 156(6):1450-2.
Oltmann SC, Holt SA. 2014.
PubMed-ID: 25304840
http://dx.doi.org/10.1016/j.surg.2014.08.083

Tall Cell Variant of Papillary Thyroid Carcinoma: a Population-Based Study in Iceland.
Thyroid, 25(2):216-20.
Axelsson TA, Hrafnkelsson J, Olafsdottir EJ, Jonasson JG. 2015.
BACKGROUND: The tall cell variant (TCV) of papillary thyroid carcinoma (PTC) is an aggressive variant of PTC that is believed to have worse outcomes than classical PTC. The objective of this study was to investigate the incidence, survival, and disease recurrence of patients with TCV and compare them with other PTC in a whole population. METHODS: Information on all thyroid carcinomas diagnosed in Iceland from 1990 to 2009 was obtained from the Icelandic Cancer Registry. PTC diagnosed postmortem was excluded. The date of diagnosis, sex, and age at diagnosis were registered. All histopathology material was re-evaluated, and papillary thyroid tumors classified as either TCV or other types of PTC. Tumors were classified as TCV if >50% of cells were tall (height > twice the width). TNM stage was determined for all the cases. Endpoints were thyroid cancer-specific death and thyroid cancer recurrence. RESULTS: Out of 376 patients diagnosed with PTC in the study period, 49 (13%) were classified as TCV. Patients with TCV were older (66 years vs. 49 years, p<0.001), more often had pT4 tumors (71% vs. 15%, p<0.001), had higher rates of nodal metastasis (51% vs. 22%, p<0.001), and more often distant metastasis (14% vs. 2%, p<0.001). The age-adjusted incidence of TCV for men was 0.5/100,000 [confidence interval (CI) 0.3-0.7] and for women 0.7/100,000 [CI 0.4-1.0] between 1990 and 2009. The five-year disease-specific survival for TCV was 83% [CI 68-91] compared to 98% [CI 96-99] for other PTC respectively (p<0.001). In multivariate analysis, TCV histology was an independent risk factor for recurrence (hazard ratio (HR) 3.18 [CI 1.48-6.84]) but not for disease specific survival (HR 1.86 [CI 0.77-4.73]). CONCLUSIONS: TCV comprises 13% of all diagnosed PTC in Iceland with an incidence of 0.5/100,000 for men and 0.7/100,000 for women. Patients diagnosed with TCV have worse five-year disease-specific survival than patients with other PTC. TCV histology is an independent risk factor for disease recurrence but not for disease-specific survival.
PubMed-ID: 25322334
http://dx.doi.org/10.1089/thy.2014.0075

Additional Lateral Neck Dissection Unnecessary for Papillary Thyroid Carcinoma Patients With Lateral Neck Lymph Node Metastases but Negative Intraoperative Frozen Section Findings.
Head Neck,
Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, Chang HS, Park CS. 2014.
Background. This study aimed to investigate the outcomes of papillary thyroid cancer (PTC) patients with lateral neck metastasis (LNM) according to their permanent pathology report but negative frozen section findings who did not undergo lateral neck dissection (LND). Methods. Between September 2009 and December 2011, 575 patients at Gangnam Severance Hospital (Seoul, Korea) underwent frozen section analysis for a suspicious lateral neck lymph node. In 16 patients, the intraoperative findings were negative, but LNM was diagnosed on the basis of permanent pathology findings. The outcomes of these patients who underwent thyroidectomy but not LND were retrospectively investigated. Results. One patient underwent a subsequent LND. After a mean (standard deviation) follow-up period of 42.1 (8.5) months, none of the patients had distant metastasis. Conclusion Total thyroidectomy with subsequent LND is not necessary in PTC patients who are diagnosed with LNM according to their permanent pathology report but have negative intraoperative frozen section findings. Head Neck, 2014.
PubMed-ID: 25327877
http://dx.doi.org/10.1002/hed.23893

Clinical Management and Outcomes in Patients With Hyperfunctioning Distant Metastases From Differentiated Thyroid Cancer After Total Thyroidectomy and Radioactive Iodine Therapy.
Thyroid, 25(2):229-37.
Qiu ZL, Shen CT, Luo QY. 2015.
BACKGROUND: Hyperfunctioning distant metastasis (HFDM) from differentiated thyroid cancer (DTC) is a rare entity. This study aimed to assess the outcomes of DTC patients presenting with HFDM after total thyroidectomy and radioactive iodine therapy. METHODS: A total of 5367 DTC patients treated with (131)I after total thyroidectomy were analyzed retrospectively from January 1991 to June 2013. Therapeutic efficacy was evaluated based on changes in serum thyroglobulin (Tg) and anatomical imaging changes in metastatic lesions. The relationships between survival time and several variables were assessed by univariate and multivariate analyses using the Kaplan-Meier method and Cox's proportional hazards model respectively. RESULTS: Thirty-eight patients with HFDM from DTC were diagnosed, including four with hyperthyroidism, four with subclinical hyperthyroidism, and three with subclinical hypothyroidism. The remaining 27 were euthyroid. Of 25 patients with lung metastases, 84% (21/25) showed disappearance or shrinkage of lung nodules; of 24 patients with bone metastases, 66.67% (16/24) exhibited no obvious imaging changes in metastatic bone lesions after (131)I therapy. Serum Tg decreased significantly in 81.58% (31/38) and increased in 18.42% (7/38) after (131)I therapy. The 10-year survival rate of DTC patients with HFDM was 65.79% (25/38). Multivariate analyses identified age at occurrence of distant metastases (<45 years), only lung metastases, and papillary thyroid cancer (PTC; p=0.032, NA, and 0.043) as independent predictors of survival. CONCLUSION: The response of hyperfunctioning lung metastases to (131)I treatment was better than that of non-hyperfunctioning lung metastases in DTC, while hyperfunctioning bone metastases responded similarly compared to non-hyperfunctioning bone metastases. Patients younger than 45 years at occurrence of distant metastases, those with only lung metastases, and patients with PTC had better prognoses.
PubMed-ID: 25331724
http://dx.doi.org/10.1089/thy.2014.0233

Assessment of Lesion Response in the Initial Radioiodine Treatment of Differentiated Thyroid Cancer Using 124I PET Imaging.
J Nucl Med, 55(11):1759-65.
Jentzen W, Hoppenbrouwers J, van LP, van d, V, van de Kolk R, Poeppel TD, Nagarajah J, Brandau W, Bockisch A, Rosenbaum-Krumme S. 2014.
(124)I PET/CT images from differentiated thyroid cancer patients were retrospectively analyzed to assess the relationship between absorbed radiation dose (AD) to lesions and their response after radioiodine therapy. METHODS: Patients received serial (124)I PET/CT scans before and after their first radioiodine treatment. The pretherapy PET data were used to segment the lesion volumes and to predict the therapy-delivered ADs after administration of the therapeutic (131)I activity. The segmentation method's lower volume limit of determinability was a sphere of 0.80 mL, which classified the lesions into a known-volume group (>0.80 mL) or a small-volume group (</=0.80 mL) with their respective average and minimum ADs. The posttherapy PET data were used to assess the lesion-based therapy success. In the known-volume group, the response rate was calculated on the basis of lesions that received average ADs above the generally accepted threshold of 85 Gy for metastases and 300 Gy for thyroid remnants (TRs) and was expressed as the percentage of completely responding lesions. In the small-volume group, the metastasis and TR responses were evaluated for 3 minimum-AD groups: 5 to 10 Gy (TR, 5 to 30 Gy), >10 to 85 Gy (TR, >30 to 300 Gy), and >85 Gy (TR, >300 Gy). Their response rates were calculated in terms of the percentage of completely responding lesions in each minimum-AD group. RESULTS: In total, 59 lesions in 17 patients were amenable to reliable volume estimation. The response rates were 63%, 88%, and 90% for lymph node metastases (LMs), pulmonary metastases, and TRs, respectively. The response rates of 168 small lesions in 34 patients were more than 82% for LMs and more than 91% for TRs in each of the 3 minimum-AD groups; all small pulmonary metastases responded completely. CONCLUSION: In the known-volume group, the response rate for TRs matched well with historical data derived using (131)I scintigraphy imaging, whereas the response rate for LMs was not as high as expected, which may be explained by too short a follow-up time for a few LMs and a higher sensitivity of PET imaging. Small lesions were treated effectively, suggesting that they are considerably smaller than 0.80 mL.
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http://dx.doi.org/10.2967/jnumed.114.144089

Relevance of BRAF(V600E) Mutation Testing Versus RAS Point Mutations and RET/PTC Rearrangements Evaluation in the Diagnosis of Thyroid Cancer.
Thyroid, 25(2):221-8.
Rossi M, Buratto M, Tagliati F, Rossi R, Lupo S, Trasforini G, Lanza G, Franceschetti P, Bruni S, Degli UE,

Zatelli MC. 2015.
BACKGROUND: A molecular profile including BRAF and RAS mutations as well as RET/PTC rearrangement evaluation has been proposed to provide an accurate presurgical assessment of thyroid nodules and to reduce the number of unnecessary diagnostic surgeries, sparing patients' health and saving healthcare resources. However, the application of such molecular analyses may provide different results among different centers and populations in real-life settings. Our aims were to evaluate the diagnostic utility of assessing the presence of BRAF and RAS mutations and RET/PTC1 and RET/PTC3 rearrangements in all cytological categories in an Italian group of thyroid nodule patients assessed prospectively, and to understand whether and which mutation testing might be helpful in cytologically indeterminate nodules. METHODS: A total of 911 patients were submitted to ultrasound and fine-needle aspiration biopsy examination. Cytological evaluation was performed in parallel with molecular testing and compared to pathological results in 940 thyroid nodules, including 140 indeterminate lesions. RESULTS: BRAF mutation testing provided the best contribution to cancer diagnosis, allowing the disease to be detected at an early stage, and identifying indeterminate nodules in which diagnostic lobectomy could be spared. On the contrary, RAS and RET/PTC analysis did not further increase diagnostic sensitivity for thyroid cancer. In addition, we found RET/PTC rearrangements in benign lesions, indicating that this molecular marker might not be useful for the detection of thyroid cancer. CONCLUSION: BRAF(V600E) mutation analysis is superior to RAS point mutations and evaluation of RET/PTC rearrangements in the diagnosis of thyroid cancer, even in indeterminate lesions.
PubMed-ID: 25333496
http://dx.doi.org/10.1089/thy.2014.0338

Response to Initial Therapy Predicts Clinical Outcomes in Medullary Thyroid Cancer.
Thyroid, 25(2):242-9.
Lindsey SC, Ganly I, Palmer F, Tuttle RM. 2015.
BACKGROUND: Risk stratification in medullary thyroid cancer (MTC) has traditionally relied on standardized anatomic staging systems that, despite providing valuable prognostic information, do not adequately predict the risk of persistent or recurrent disease. As dynamic risk stratification has been demonstrated to be clinically valuable in nonmedullary thyroid cancer, we adapted our response to therapy definitions in order to apply them to MTC. In this study, we evaluate and compare the clinical utility of our previously proposed MTC response to therapy stratification with a traditional standardized anatomic staging system. METHODS: Both the Tumor, Node, Metastasis/American Joint Cancer Committee (TNM/AJCC) staging system and our previously proposed response to initial therapy staging system was evaluated in 287 MTC patients followed for a median of five years. RESULTS: The TNM/AJCC staging system provided adequate risk stratification with regard to disease-specific mortality and the likelihood of having no evidence of disease at final follow-up, but did not adequately stratify patients with regard to the likelihood of having structural persistent disease, biochemical persistent disease, or recurrence. However, the response to initial therapy risk stratification system provided clinically useful risk stratification with regard to disease-specific mortality, the likelihood of having no evidence of disease at final follow-up, the likelihood of having a biochemical persistent disease at final follow-up, and the likelihood of having structural persistent disease at final follow-up. Furthermore, the response to therapy risk stratification system demonstrated a higher proportion of variance explained (54.3%) than the TNM/AJCC system (23.9%). CONCLUSION: Our data demonstrate that a dynamic risk stratification system that uses response to therapy variables to adjust risk estimates over time provides more useful clinical prognostic information than static initial anatomic staging in MTC thyroid cancer.
PubMed-ID: 25338223
http://dx.doi.org/10.1089/thy.2014.0277

Morbidity of Reoperation for Thyroid Disease.
Am Surg, 80(11):1178-9.
Abboud B, Sleilaty G, Eid T. 2014.
PubMed-ID: 25347515

Hereditary Thyroid Cancer Syndromes and Genetic Testing.
J Surg Oncol, 111(1):51-60.
Rowland KJ, Moley JF. 2015.
This review focuses on both hereditary medullary thyroid cancer (MTC) and hereditary nonmedullary thyroid cancer (NMTC) and discusses the genetics, clinical diagnosis and evaluation, and surgical approach to treatment of these malignancies. Areas of innovation as well as areas of debate are highlighted and management recommendations are made.

PubMed-ID: 25351655
http://dx.doi.org/10.1002/jso.23769

Korea's Thyroid-Cancer "Epidemic"--Screening and Overdiagnosis.
N Engl J Med, 371(19):1765-7.
Ahn HS, Kim HJ, Welch HG. 2014.
PubMed-ID: 25372084
http://dx.doi.org/10.1056/NEJMp1409841

Transaxillary Thyroidectomy-A Critical Appraisal.
J Surg Oncol, 111(2):131-2.
Shaha AR. 2015.
PubMed-ID: 25411137
http://dx.doi.org/10.1002/jso.23831

Size Distribution of Metastatic Lymph Nodes With Extranodal Extension in Patients With Papillary Thyroid Cancer: a Pilot Study.
Thyroid, 25(2):238-41.
Alpert EH, Wenig BM, Dewey EH, Su HK, Dos RL, Urken ML. 2015.
BACKGROUND: Extranodal extension (ENE) is a documented negative prognostic factor in patients with papillary thyroid cancer (PTC). ENE is presumed to manifest in larger lymph nodes. Yet, to date, no study has proven this. This is a pilot study that specifically examines the size distribution of positive lymph nodes manifesting ENE in patients with PTC. METHODS: An Institutional Review Board approved review examined the size of all lymph nodes demonstrating ENE in postoperative PTC patients that underwent surgery for PTC under the care of a single surgeon between 2004 and 2014. All patients in the study had regional metastatic lymph nodes with ENE. Analysis of the size distribution for all lymph nodes with ENE was performed. RESULTS: A total of 47% of lymph nodes with ENE were </=10 mm. CONCLUSIONS: RESULTS indicate that clinically nonevident, small lymph nodes are at risk of harboring aggressive disease biology reflected in ENE. A total of 47% of all nodes fell within Randolph et al.'s classification of "small" lymph nodes, while 59% of the nodes with ENE were <1.5 cm-the threshold size that was deemed to be prognostically significant by Ito et al. It is apparent that clinically nonevident regional lymph nodes can have adverse histologic features and that the previous presumption that nodes with ENE only appear in clinically evident, macroscopic nodes is flawed.
PubMed-ID: 25422987
http://dx.doi.org/10.1089/thy.2014.0392

Papillary Thyroid Microcarcinomas Located at the Middle Part of the Middle Third of the Thyroid Gland Correlates With the Presence of Neck Metastasis.
Surgery, 157(3):526-33.
Xiang D, Xie L, Xu Y, Li Z, Hong Y, Wang P. 2015.
BACKGROUND: Papillary thyroid microcarcinomas (PTMCs), located at upper poles of the thyroid, are associated with lateral neck metastasis (LNM) according to previous reports. Controversy remains regarding the correlation between the location of PTMCs and central neck metastasis (CNM). METHODS: Medical records of 949 patients with PTMCs diagnosed between 2010 and 2013 were reviewed retrospectively. With a subdivision of the middle third of the thyroid gland, correlations between tumor location and CNM/LNM along with other clinicopathologic factors were analyzed by binary logistic regression. RESULTS: PTMCs located in the middle part of the middle third of the thyroid gland (MPMT) showed the greatest rate of CNM (57.5%) among all locations. PTMCs located at isthmus showed the second greatest rate of CNM (44.3%). In the multivariate.
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http://dx.doi.org/10.1016/j.surg.2014.10.020

Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma Can Be Stratified According to the Number, the Size of Metastatic Foci, and the Presence of Desmoplasia.
Surgery, 157(1):111-8.
Cho SY, Lee TH, Ku YH, Kim HI, Lee GH, Kim MJ. 2015.
BACKGROUND: Lymph node (LN) metastasis is common in papillary thyroid microcarcinoma (PTMC). The aim of this study was to investigate the impact of LN metastasis and its risk stratification on PTMC recurrence. METHODS: We retrospectively reviewed the data of 336 patients with PTMC who underwent surgery from 2005 to 2006 at a single institution. LN metastasis was stratified according to the number of metastatic LNs, the ratio of metastatic to removed LNs, the size of metastatic foci in LNs, and the presence of extranodal extension and

desmoplasia. RESULTS: Of the 336 patients, 93 (28%) had LN metastasis. During the follow-up of 5.3 years, 16 (4.8%) experienced locoregional recurrence. Among several clinicopathologic factors, LN metastasis was the most important risk factor for recurrence (P = .02). Lateral LN metastasis was correlated with recurrence-free survival (P < .01), whereas central LN metastasis was not (P = .20). When central LN metastasis was stratified, a high number of metastatic LNs (>/=3), larger metastatic foci (>/=0.2 cm), and the presence of desmoplasia were associated with recurrence-free survival (P < .05). CONCLUSION: The prognostic significance of central LN metastasis can differ according to the number of metastatic LNs, the size of metastatic foci, and the presence of desmoplasia. Patients with a high number of metastatic LNs, larger metastatic foci, and presence of desmoplasia in LNs should be treated aggressively and supervised carefully for PTMC recurrence.
PubMed-ID: 25444224
http://dx.doi.org/10.1016/j.surg.2014.05.023

BRAF Mutation in Papillary Thyroid Cancer: A Cost-Utility Analysis of Preoperative Testing.
Surgery, 156(6):1569-77.
Lee WS, Palmer BJ, Garcia A, Chong VE, Liu TH. 2014.
BACKGROUND: Papillary thyroid carcinoma (PTC) with BRAF mutation carries a poorer prognosis. Prophylactic central neck dissection (CND) reduces locoregional recurrences, and we hypothesize that initial total thyroidectomy (TT) with CND in patients with BRAF-mutated PTC is cost effective. METHODS: This cost-utility analysis is based on a hypothetical cohort of 40-year-old women with small PTC [2 cm, confined to the thyroid, node(-)]. We compared preoperative BRAF testing and TT+CND if BRAF-mutated or TT alone if BRAF-wild type, versus no testing with TT. This analysis took into account treatment costs and opportunity losses. Key variables were subjected to sensitivity analysis. RESULTS: Both approaches produced comparable outcomes, with costs of not testing being lower (-$801.51/patient). Preoperative BRAF testing carried an excess expense of $33.96 per quality-adjusted life-year per patient. Sensitivity analyses revealed that when BRAF positivity in the testing population decreases to 30%, or if the overall noncervical recurrence in the population increases above 11.9%, preoperative BRAF testing becomes the more cost-effective strategy. CONCLUSION: Outcomes with or without preoperative BRAF testing are comparable, with no testing being the slightly more cost-effective strategy. Although preoperative BRAF testing helps to identify patients with higher recurrence rates, implementing a more aggressive initial operation does not seem to offer a cost advantage.
PubMed-ID: 25444226
http://dx.doi.org/10.1016/j.surg.2014.08.051

Differential Recurrent Laryngeal Nerve Palsy Rates After Thyroidectomy.
Surgery, 156(5):1157-66.
Serpell JW, Lee JC, Yeung MJ, Grodski S, Johnson W, Bailey M. 2014.
INTRODUCTION: Recurrent laryngeal nerve (RLN) palsy is a devastating complication of thyroidectomy. Although neurapraxia is thought to be the most common cause, the underlying mechanisms are poorly understood. The objectives of this study were to examine the differential palsy rates between the left and right RLNs, and the role of intraoperative nerve swelling as a risk factor of postoperative palsy. METHODS: Thyroidectomy data were collected, including demographics, change in RLN diameter, and RLN electromyographic (EMG) reading. Left and right RLNs, as well as bilateral and unilateral subgroup analyses were performed. RESULTS: A total of 5,334 RLNs were at risk in 3,408 thyroidectomies in this study. The overall RLN palsy rate was 1.5%, greater on the right side than the left for bilateral cases (P = .025), and greater on the left side than the right for unilateral cases (P = .007). In a subgroup of 519 RLNs, the diameter and EMG amplitude were measured. The RLN diameter increased by approximately 1.5-fold (P < .001), and corresponded to increased EMG amplitude (P = .01) during the procedure. The diameter of the right RLN was larger than the left RLN, both at the beginning and end of the dissection (P = .001). CONCLUSION: The right-left differential rates of post-thyroidectomy RLN palsy seemed to be due in part to differential RLN diameters, with stretch having a more deleterious effect on RLNs with a smaller diameter; also, edema as a result of stretch might be an underlying mechanism for postoperative neurapraxia and palsy. Thyroid surgeons should be aware of the different vulnerabilities of each RLN and develop practices to avoid iatrogenic injury.
PubMed-ID: 25444315
http://dx.doi.org/10.1016/j.surg.2014.07.018

Surgeon Volume and Adequacy of Thyroidectomy for Differentiated Thyroid Cancer.
Surgery, 156(6):1453-9.
Adkisson CD, Howell GM, McCoy KL, Armstrong MJ, Kelley ML, Stang MT, Joyce JM, Hodak SP, Carty SE, Yip L. 2014.
INTRODUCTION: We aimed to determine influence of surgeon volume on (1) frequency of appropriate initial

surgery for differentiated thyroid cancer (DTC) and (2) completeness of resection. METHODS: We reviewed all initial thyroidectomies (Tx; lobectomy and total) performed in a health system during 2011; surgeons were grouped by number of Tx cases per year. For patients with histologic DTC >/= 1 cm, surgeon volume was correlated with initial extent of the operation, and markers of complete resection including uptake on I(123) prescan, thyrotropin-stimulated thyroglobulin levels, and I(131) dose administered. RESULTS: Of 1,249 patients who underwent Tx by 42 surgeons, 29% had DTC >/= 1 cm without distant metastasis. At a threshold of >/= 30 Tx per year, surgeons were more likely to perform initial total Tx for DTC >/= 1 cm (P = .01), and initial resection was more complete as measured by all 3 quantitative markers. For patients with advanced stage disease, a threshold of >/= 50 Tx per year was needed before observing improvements in I(123) uptake (P = .004). CONCLUSION: Surgeons who perform >/= 30 Tx a year are more likely to undertake the appropriate initial operation and have more complete initial resection for DTC patients. Surgeon volume is an essential consideration in optimizing outcomes for DTC patients, and even higher thresholds (>/= 50 Tx/year) may be necessary for patients with advanced disease.
PubMed-ID: 25456931
http://dx.doi.org/10.1016/j.surg.2014.08.024

Preoperative Laryngoscopy in Thyroid Surgery: Do Patients' Subjective Voice Complaints Matter?
Surgery, 156(6):1477-82.
Lee CY, Long KL, Eldridge RJ, Davenport DL, Sloan DA. 2014.
BACKGROUND: Although routine preoperative laryngoscopy has been standard practice for many thyroid surgeons, there is recent literature that supports selective laryngoscopy. We hypothesize that patients' preoperative voice complaints do not correlate well with abnormalities seen on preoperative laryngoscopy. METHODS: A retrospective chart review of a 3-year, single-surgeon experience was performed. Records of patients undergoing thyroid surgery were reviewed for patient voice complaints, prior neck surgery, surgeon-documented voice quality, and results of laryngoscopy. RESULTS: Of 464 patients, 6% had abnormal laryngoscopy findings, including 11 cord paralyses (2%). Preoperatively, 39% of patients had voice complaints, but only 10% had a corresponding abnormality on laryngoscopy. Only 4% of patients had a surgeon-documented voice abnormality with 72% corresponding abnormalities on laryngoscopy, including 8 cord paralyses. When eliminating patient voice complaints and using only history of prior neck surgery and surgeon-documented voice abnormality as criteria for preoperative laryngoscopy, only 1 cord paralysis is missed and sensitivity (91%) and specificity (86%) were high. Also, when compared with routine laryngoscopy, 84% fewer laryngoscopies are performed. CONCLUSION: When using patients' voice complaints as criteria for preoperative laryngoscopy, the yield is low. We recommend using surgeon-documented voice abnormalities and history of prior neck surgery as criteria for preoperative laryngoscopy.
PubMed-ID: 25456935
http://dx.doi.org/10.1016/j.surg.2014.08.038

Comparable Outcomes for Patients With PT1a and PT1b Differentiated Thyroid Cancer: Is There a Need for Change in the AJCC Classification System?
Surgery, 156(6):1484-9.
Wang LY, Nixon IJ, Palmer FL, Thomas D, Tuttle RM, Shaha AR, Patel SG, Shah JP, Ganly I. 2014.
INTRODUCTION: The current American Joint Committee on Cancer TNM classification for differentiated thyroid cancer (DTC) separates T1 status into T1a and T1b based on a 1-cm cutoff for maximal tumor dimension. In 2009, the American Thyroid Association recommended total thyroidectomy for tumors >1 cm in contrast to the possibility of lobectomy for tumors </= 1 cm. Our aim was to investigate the prognostic significance of a 1-cm tumor cutoff. METHODS: From an institutional database of 3,664 patients with DTC, 1,522 patients with T1 tumors without neck disease or distant metastases were identified. Patient, tumor, and treatment characteristics were compared. Disease-specific survival (DSS) and recurrence-free survival (RFS) outcomes were analyzed. RESULTS: Total thyroidectomy rates were similar between patients with T1a and T1b tumors (P = .307). With a median follow-up of 46 months (range, 1-320), there were no disease-specific deaths in the T1a or T1b groups. In total, 18 patients (1.2%) experienced a recurrence. Five-year RFS was comparable for patients with T1a and T1b tumors (98.6 vs 98.6%; P = .224). CONCLUSION: T1a and T1b tumors have similar prognosis both in terms of DSS and RFS. It seems that a distinction between tumors of <1 and >1 cm is of no prognostic benefit.
PubMed-ID: 25456937
http://dx.doi.org/10.1016/j.surg.2014.08.037

The Utility of Lymph Node Mapping Sonogram and Thyroglobulin Surveillance in Post Thyroidectomy Papillary Thyroid Cancer Patients.
Surgery, 156(6):1491-6.

Miah CF, Zaman JA, Simon M, Davidov T, Trooskin SZ. 2014.
BACKGROUND: The American Thyroid Association recommends lymph node mapping (LNM) ultrasonography 6-12 months after thyroidectomy for patients with papillary thyroid cancer (PTC). The yield of LNM over thyroglobulin (TG) screening is not well defined. We sought to investigate this relationship. METHODS: Post thyroidectomy LNM was performed on 163 patients with PTC. LNM was considered positive based on these criteria: Loss of fatty hilum (LOFH), microcalcifications, hypervascularity, architectural distortion, or short axis (>8 mm). Serum TG levels were compared to LNM and fine needle aspiration (FNA). RESULTS: Sixty-nine patients had suspicious LNM (42%) and 17 had PTC on FNA (25%). There were 135 suspicious lymph nodes described with malignant nodes found in 6 of 65 patients (9%) with LOFH, 13 of 18 patients (76%) with microcalcifications, 11 of 12 patients (92%) with hypervascularity, 16 of 28 patients (52%) with architectural distortion, and 4 of 7 patients (52%) with enlarged size on FNA. The positive predictive value of LNM was 0.34, increasing to 0.66 when LOFH was excluded. Among 152 patients with documented TG data, LNM identified cervical nodal metastasis in 4 patients with TG < 0.5 pg/mL (anti-TG antibody negative, thyroid-stimulating hormone suppressed). Of the 15 patients with positive anti-TG antibody, 3 with recurrence were found on LNM. CONCLUSION: LNM can detect recurrent PTC when TG level is undetectable, and LOFH is a low-yield sonographic characteristic.
PubMed-ID: 25456939
http://dx.doi.org/10.1016/j.surg.2014.08.054

E-Selectin Expression and BRAF Status in Papillary Thyroid Carcinomas: Correlation With Clinicopathologic Features.
Surgery, 156(6):1550-7.
Miccoli P, Torregrossa L, Borrelli N, Materazzi G, Cacciato IA, Miccoli M, Basolo F. 2014.
BACKGROUND: Cell adhesion molecules, represented by the immunoglobulin family and selectins, play an important role in the progression of cancer. A correlation between selectins and tumor aggressiveness has been demonstrated in several reports. METHODS: Eighty-eight patients (mean age, 41.0 +/- 14 years) with papillary thyroid carcinoma (conventional variant and sized approximately 20 mm) were divided in 2 groups: 41 with encapsulated tumors and 47 with tumors with extrathyroidal extension. E-selectin expression was evaluated by immunohistochemical staining and semiquantitative real-time reverse-transcription polymerase chain reaction and normalized by calculating the z-score (positive: value above the population mean; negative: below the mean). RESULTS: Lymph node metastasis (LNM) was found in 2 of 41 encapsulated tumors (4.8%) and in 19 of 47 tumors (40.4%) with extrathyroidal extension. BRAF mutation was present in 21 encapsulated tumors (51.2%) and in 31 tumors with extrathyroidal extension (65.9%). The mean E-selectin z-score was -0.32 for encapsulated tumors and 0.28 for tumors with extrathyroidal extension. E-selectin expression correlates with neoplastic infiltration (P = .04), the American Joint Commission on Cancer stage (P = .02), and BRAF mutation (P = .03). CONCLUSION: E-selectin overexpression in association with BRAF mutation status could promote a more aggressive phenotype in papillary thyroid carcinoma.
PubMed-ID: 25456953
http://dx.doi.org/10.1016/j.surg.2014.08.049

The Importance of Sonographic Landmarks by Transcutaneous Laryngeal Ultrasonography in Post-Thyroidectomy Vocal Cord Assessment.
Surgery, 156(6):1590-6.
Wong KP, Woo JW, Youn YK, Chow FC, Lee KE, Lang BH. 2014.
INTRODUCTION: During examination of the vocal cords (VC) using transcutaneous laryngeal ultrasonography (TLUSG), 3 sonographic landmarks (namely, false VC [FC], true VC [TC], and arytenoids [AR]) are often seen. However, it remains unclear which landmark provides a more reliable assessment and whether seeing more landmarks improves the diagnostic accuracy and reliability. METHODS: We evaluated prospectively 245 patients from 2 centers. One assessor from each center performed all TLUSG examinations and their findings were validated by direct laryngoscopy. All 3 sonographic landmarks were routinely visualized whenever possible. The rate of visualization and diagnostic accuracy between the 3 landmarks were compared. RESULTS: Eighteen patients suffered postoperative VC palsy (VCP). Both centers had comparable visualization or assessability rate of >/= 1 sonographic landmark (94.9 and 95.3%; P = 1.000) and 100% sensitivity on postoperative TLUSG. The rates of FC, TC, and AR visualization were 92.7%, 36.7%, and 89.8%, respectively. The sensitivity, specificity, and diagnostic accuracy and the proportion of true positives, false positives, and true negatives between using 1, 2, landmarks and 3 landmarks were comparable (P > .05). CONCLUSION: Each sonographic landmark had similar reliability and diagnostic accuracy. Identifying all 3 sonographic landmarks was not mandatory and visualizing normal movement in one of the sonographic landmarks would be sufficient to exclude VCP.

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http://dx.doi.org/10.1016/j.surg.2014.08.061

Efficient, Effective, Safe Procedure to Identify Non-Recurrent Inferior Laryngeal Nerve During Thyroid Surgery.
Head Neck,
Watanabe A, Taniguchi M, Kimura Y, Ito S, Hosokawa M, Sasaki S. 2014.
Background: The non-recurrent inferior laryngeal nerve (NRILN) is always associated with the aberrant subclavian artery. Computed Tomography (CT) images can detect this vascular anomaly, which predicts an NRILN. The purpose is to report our procedure to identify the NRILN in patients with the aberrant subclavian artery. Methods: Four of 730 patients undergoing thyroid operation in our hospital, 4 were preoperatively diagnosed with aberrant subclavian artery by CT of the neck. To avoid vocal cord paralysis, we approached the vagal nerve firstly before dissecting the paratracheal region to discover the separation point of the NRILN from the vagal nerve. Results: The NRILN was identified without difficulty in all 4 patients. No patients showed vocal cord paralysis. Conclusions: Approaching the vagal nerve firstly before dissecting the paratracheal region is an efficient, effective and safe procedure to identify an NRILN in patients who are preoperatively diagnosed as having the aberrant subclavian artery. This article is protected by copyright. All rights reserved.
PubMed-ID: 25488277
http://dx.doi.org/10.1002/hed.23932

Traction Injury of the Recurrent Laryngeal Nerve: Results of Continuous Intraoperative Neuromonitoring in a Swine Model.
Head Neck,
Lee HY, Cho YG, You JY, Choi BH, Kim JY, Wu CW, Chiang FY, Kim HY. 2014.
Background Recurrent laryngeal nerve(RLN) palsy is the most serious complication after thyroidectomy. However, little is known about the degree of traction injury that causes loss of signal(LOS). This study aimed to evaluate traction injuries in the swine RLN using continuous intraoperative neuromonitoring(IONM) and determine the traction power that results in LOS. Methods Thirteen pigs underwent traction injury to the RLNs with continuous IONM, and stress-strain curves were determined for eight nerves using the universal material testing machine in an ex vivo model. Results Traction injury at a mean power of 2.83 megapascal(MPa) caused LOS. The mean physiologic limit strain and tensile strength of the swine RLNs were found to be 15.0% and 4.9 MPa, respectively. Histological analysis showed no abnormal structural findings. Conclusion Traction injury of swine RLNs causes LOS at a power of 2.83 MPa. However, all injuered nerves recovered within 7days with no observed structural damage. This article is protected by copyright. All rights reserved.
PubMed-ID: 25488415
http://dx.doi.org/10.1002/hed.23934

Collision Tumours of the Thyroid: An Interesting Case and Review of the Literature.
Head Neck,
Ryan N, Walden G, Lazic D, Tierney P. 2014.
Background: Collision Tumours of the thyroid are a rare pathology that present a diagnostic and treatment challenge. Here we present an interesting case and a review of the current literature as to inform management. Methods and Results: An 88 year old lady presented with acute airway compromise and vocal cord paralysis. Computer topography identified a thyroid mass and wide spread metastasis. Histopathology identified the lesion as a collision tumour consisting of a squamous cell carcinoma and papillary thyroid carcinoma. The patient was managed with surgery and palative radiotherapy however died from complications of a lower respiratory tract infection. Furthermore we present a review of the literature with 33 cases reviewed. Conclusions: Management of collision tumours is complex due to the duality of the pathology. They should be managed in a multidisciplinary team setting and treatment should be patient specific. Generally the most aggressive neoplasm should guide treatment. We recommend surgical management with adjunct therapy This article is protected by copyright. All rights reserved.
PubMed-ID: 25491252
http://dx.doi.org/10.1002/hed.23936

Impact of Postoperative Magnesium Levels on Early Hypocalcaemia and Permanent Hypoparathyroidism After Thyroidectomy.
Head Neck,
Garrahy A, Murphy MS, Sheahan P. 2014.
Background: Postoperative hypocalcaemia is a common complication of thyroidectomy. Magnesium is known to

modulate serum calcium levels and hypomagnesemia may impede correction of hypocalcaemia. Our objective was to investigate whether hypomagnesemia after thyroidectomy has any impact on early hypocalcaemia and / or permanent hypoparathyroidism. Methods: Retrospective review of prospectively maintained database. Inclusion criteria were total or completion total thyroidectomy with postoperative magnesium levels available. The incidence of postoperative hypocalcaemia was correlated with postoperative hypomagnesemia and other risk factors. Results: 201 cases were included. 26 (13%) developed postoperative hypomagnesemia. Hypomagnesemia (p=0.002), cancer diagnosis (p=0.01), central neck dissection (p=0.02), and inadvertent parathyroid resection (p=0.02), were significantly associated with hypocalcaemia. On multivariate analysis, only hypomagnesemia (p=0.005) remained significant. Hypomagnesemia was also a significant predictor of permanent hypoparathyroidism (p=0.0004). Conclusion: Hypomagnesemia is significantly associated with early hypocalcaemia and permanent hypoparathyroidism after thyroidectomy. Magnesium levels should be closely monitored in patients with post-thyroidectomy hypocalcaemia.
PubMed-ID: 25491348
http://dx.doi.org/10.1002/hed.23937

New Endoscopic Thyroidectomy With the Transareola Single-Site Approach: A Comparison With the Bilateral Areolar Approach.
Surg Laparosc Endosc Percutan Tech, 25(2):178-84.
Guo BM, Wu B, Kang J, Deng XZ, Qin HL, Fan YB. 2015.
PURPOSE: We developed the transareola single-site approach (TASSA) for less invasive endoscopic thyroidectomy to avoid scars on exposed areas. Here, we report our experience with the TASSA technique in treatment of benign thyroid tumors and evaluate its feasibility through comparison with the bilateral areolar approach (BAA). METHODS: From September 2009 to December 2011, 129 patients with benign thyroid tumors were enrolled in the study. Of these patients, 51 patients underwent endoscopic thyroidectomy by TASSA and 78 patients by BAA. The TASSA technique was performed using one 10 mm trocar and one 5 mm trocar through circumareolar incisions using conventional endoscopic instruments. The BAA procedure was performed using one 10 mm trocar and two 5 mm trocars through bilateral circumareolar incisions. RESULTS: Comparing TASSA with BAA, there were significant differences in the mean operative time (141.96+/-19.85 vs. 98.14+/-14.15 min) for lobectomy (P<0.05) and in the subcutaneous dissection area (101.00+/-6.33 vs. 132.51+/-5.25 cm, P<0.05). However, there were no significant differences in the duration of hospitalization, amount of drainage, occurrence of postoperative complications, and postoperative pain. All the patients were satisfied with the cosmetic result in the 2 groups. CONCLUSIONS: Endoscopic thyroidectomy using the TASSA procedure is feasible and safe, and affords the advantages of minimal invasiveness and excellent cosmesis results compared with other approaches including BAA. The 2 procedures are technically more challenging procedures, which may become alternative procedures for treatment of patients with benign thyroid tumors, especially those with strong desire for cervical cosmesis.
PubMed-ID: 25503747
http://dx.doi.org/10.1097/SLE.0000000000000119

Lateral Neck Recurrence From Papillary Thyroid Carcinoma: Predictive Factors and Prognostic Significance.
Laryngoscope,
Giordano D, Frasoldati A, Kasperbauer JL, Gabrielli E, Pernice C, Zini M, Pedroni C, Cavuto S, Barbieri V. 2014.
OBJECTIVES/HYPOTHESIS: The aim of this study was to identify any possible predictive factors of lateral neck recurrence in patients with papillary thyroid carcinoma with no ultrasonographic and/or cytological evidence of lymph node metastasis at time of diagnosis. The influence of lateral neck recurrence on survival was also investigated. STUDY DESIGN: Observational retrospective study. METHODS: Retrospective review of clinical records of 610 patients surgically treated for papillary thyroid carcinoma with clinically negative lymph nodes at the Otolaryngology Unit of the Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, from January 1984 to December 2008. RESULTS: Lateral neck recurrences were ipsilateral to the primary tumor in all cases and were associated with the occurrence of more aggressive histological variants and central neck metastasis. Lateral neck recurrences were more frequently observed in patients with distant metastases and were associated with a reduced disease-specific survival. CONCLUSION: Lateral neck compartment ipsilateral to the tumor was the most common site of recurrence, with about half of cases appearing in the first 28 months of follow-up. In patients with papillary thyroid carcinoma, detection of lateral neck metastases prior to first surgery is crucial to surgical planning. Aggressive histological variants and postsurgical evidence of lymph node metastasis from papillary thyroid carcinoma in central neck compartment are associated with a higher risk of lateral neck recurrence. In these patients, a closer postsurgical ultrasound surveillance of the lateral neck compartments

seems worthwhile. LEVEL OF EVIDENCE: 4. Laryngoscope, 2014.
PubMed-ID: 25510637
http://dx.doi.org/10.1002/lary.25094

Ultrasound-Guided Percutaneous Laser Ablation (LA) in Treating Symptomatic Solid Benign Thyroid Nodules: Our Experience in 45 Patients.
Head Neck,
Achille G, Zizzi S, Di SE, Grammatica A, Grammatica L. 2014.
Background: Laser ablation may be useful in debulking of benign thyroid nodules. Methods: To evaluate retrospectively the effectiveness and safety of LA, 45 patients with benign solid thyroid nodules, with a fluid component </=20%, were included in our series between October 2009 and January 2011. All reported pressure and/or cosmetic complaints. Nd:YAG laser at 1064 nm was used, with a fix-power (3W), changing the application time. All patients were evaluated at baseline, 6 and 12 months. Complications were recorded. Results: mean nodule volume reduction decreased from 24.2 mL +/-19.4 to 4.5 +/- 5.2 at 12 months ($p<0.001$). Mean nodule volume reduction was 84% +/- 13. Cosmetic signs were completely resolved in 87%, reduced in 9%, unchanged in 2%; pressure symptoms were resolved in 88%. One patient experienced transient dysphonia. Conclusions: US-guided LA is an effective tool for treatment of symptomatic benign thyroid nodules in patients not eligible for surgery.
PubMed-ID: 25522303
http://dx.doi.org/10.1002/hed.23957

Thyroid Thyrothymic Extension: An Anatomical Study in a Surgical Series.
Head Neck,
Sheahan P, O'Duffy F. 2014.
Introduction: The thyrothymic extension (TTE) is a variable projection from the inferior thyroid pole along the course of the thyrothymic ligament. Awareness of the TTE is critical to ensure complete total thyroidectomy. However, there is little mention of the TTE in the literature. The purpose of the present study was to investigate the frequency of the TTE in our surgical series. Methods: Prospective cohort study of 284 thyroid and parathyroid surgeries performed by a single surgeon. Results: A TTE was present in 138 of 414 evaluable thyroid lobes (33.3%), with no predilection for left or right. The TTE was bilateral in 57% of cases. In 5 cases, there was significant nodular enlargement of the TTE. The inferior parathyroid gland was closely associated with 8% of TTEs. Conclusions: The TTE is a commonly encountered projection from the inferior thyroid pole. Awareness of the TTE is important to ensure complete total thyroidectomy.
PubMed-ID: 25524573
http://dx.doi.org/10.1002/hed.23954

Standard Immunohistochemistry Efficiently Screens for Anaplastic Lymphoma Kinase Rearrangements in Differentiated Thyroid Cancer.
Endocr Relat Cancer, 22(1):55-63.
Park G, Kim TH, Lee HO, Lim JA, Won JK, Min HS, Lee KE, Park dJ, Park YJ, Park WY. 2015.
The anaplastic lymphoma kinase (ALK) gene is frequently rearranged in various types of cancer and is highly responsive to targeted therapeutics. We developed a system to detect rearrangement of ALK in a large group of Korean thyroid cancer patients. We screened 474 malignant or benign thyroid tumor cases to identify ALK fusions. Expression and translocation of the ALK gene were analyzed by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and digital multiplexed gene expression (DMGE) analysis in formalin-fixed paraffin-embedded tissues. Four cases of rearrangement of ALK were detected by IHC, and these cases were validated with FISH on 189 samples. On the other hand, DMGE analysis using Nanostring detected three out of four IHC-positive cases. Two rearrangements of ALK were striatin (STRN)-ALK fusions, which were identified by 5' RACE analysis. Rearrangements of ALK were found exclusively in v-raf murine sarcoma viral oncogene homolog B (BRAF) WT papillary carcinomas. Given the wide availability and accuracy of IHC for detecting ectopic expression of ALK in the thyroid, we suggest that IHC-based screening can be a practical method for identifying patients with ALK rearrangements in differentiated thyroid cancer.
PubMed-ID: 25527510
http://dx.doi.org/10.1530/ERC-14-0467

Postoperative Hypoparathyroidism After Thyroidectomy: Efficient and Cost-Effective Diagnosis and Treatment.
Surgery, 157(2):349-53.

Selberherr A, Scheuba C, Riss P, Niederle B. 2015.
BACKGROUND: To describe a standardized, efficient, and cost-effective protocol for the diagnosis of temporary/persisting postoperative hypoparathyroidism after (total) thyroidectomy. METHODS: We included 237 consecutive patients who underwent (total) thyroidectomy without central neck dissection for various indications. Serum calcium (sCa) and intact parathyroid hormone (iPTH) levels were measured prospectively on the morning of postoperative day 1 to predict the long-term parathyroid metabolism. On the morning of postoperative day 2, measurements were repeated. Follow-up was performed at 1 and 6 months postoperatively. RESULTS: On the morning of postoperative day 1, patients with iPTH >/= 15 pg/mL (178/237; 75%) and sCa > 2.0 mmol/L were normocalcemic, and "normal" parathyroid metabolism was predicted. iPTH levels of <10 pg/mL and sCa levels of </=2.0 mmol/L were present in 33 of the 237 patients ("disturbed" parathyroid metabolism; 14%). A "gray zone" included patients with "uncertain" parathyroid metabolism demonstrating iPTH levels between 10 and 15 pg/mL (26/237; 11%). Patients with "disturbed" and "uncertain" parathyroid metabolism were given oral calcium and vitamin D. On the morning of the second postoperative day, iPTH turned to "normal" in 10 of those 26 (38%) patients, and no further calcium or vitamin D was given. During follow-up, supplemental calcium and vitamin D was able to be stopped in all but 2 patients ("permanent" hypoparathyroidism; 2/237; 0.8%). CONCLUSION: Measurement of iPTH on the morning after operation allows accurate prediction of postoperative parathyroid function in >/=99% of cases. This simple recommendation is practicable in all surgical units, and is an efficient and cost-effective way to recognize patients who require calcium and vitamin D supplementation.
PubMed-ID: 25532435
http://dx.doi.org/10.1016/j.surg.2014.09.007

The Effect of Recombinant Human Thyroid-Stimulating Hormone or Levo-Thyroxine Withdrawal on Salivary Gland Dysfunction After Radioactive Iodine Administration for Thyroid Remnant Ablation.
Head Neck,
Iakovou I, Goulis DG, Tsinaslanidou Z, Giannoula E, Katsikaki G, Konstantinidis I. 2014.
Background. The aim of this study was to examine the incidence of sialadenitis and xerostomia within a year after radioactive iodine (RAI) administration for thyroid remnant ablation after preparation with recombinant human thyroid-stimulating hormone (rhTSH) or levo-thyroxine (LT4) withdrawal. Methods. The study has included 121 patients, divided into four groups: A (rhTSH, 100 mCi), B (rhTSH, 70 mCi), C (LT4 withdrawal, 100 mCi) and D (LT4 withdrawal, 70 mCi). Study outcomes were Summated Xerostomia Inventory score and number of sialadenitis episodes after RAI administration. Results. Salivary gland dysfunction was reported in 31% and 12% of patients, at the end of months 1 and 12, respectively. There was significantly lower incidence in groups A and B in comparison with groups C and D (p=0.002 and 0.021, respectively). Conclusion. The use of rhTSH for preparation of RAI ablation as opposed to LT4 withdrawal reduces the incidence of salivary gland dysfunction.
PubMed-ID: 25537365
http://dx.doi.org/10.1002/hed.23974

Extent of Central Neck Dissection Among Thyroid Cancer Surgeons: A Cross-Sectional Analysis.
Head Neck,
Deutschmann MW, Chin-Lenn L, Au J, Brilz A, Nakoneshny S, Dort JC, Pasieka JL, Chandarana SP. 2014.
Background: It is unclear if surgeons are performing comprehensive central neck dissections (CND) for well-differentiated thyroid cancer. Our objective was to determine mean lymph node (LN) retrieval in CND as well as variability across surgeons and institutions. Methods: A prospectively collected database identified 18 surgeons performing 425 CNDs, 313 unilateral and 112 bilateral. Demographics, peri-operative and pathologic factors were analyzed. Results: Mean LN yield was 7.4 and 11.9 for unilateral and bilateral CND, respectively. While 224 CND were prophylactic, both total and pathologic LN yields were significantly higher in therapeutic CND. There was a significant variation in LN yield across individual surgeons, institutions, and regions. High-volume CND surgeons have significantly lower LN yield compared to low-volume surgeons. Conclusions: CND appears to be performed adequately; however, there is a significant variation in LN yield. Future initiatives should try to standardize the CND performed, with emphasis on obtaining a sufficient yield.
PubMed-ID: 25546489
http://dx.doi.org/10.1002/hed.23996

Incidental Thyroid Nodules in Patients With Primary Hyperparathyroidism.
Head Neck, 36(12):1763-5.
Phillips DJ, Kutler DI, Kuhel WI. 2014.
BACKGROUND: It is desirable to detect neoplastic thyroid disease before proceeding with surgical therapy for

hyperparathyroidism so that both conditions can be treated with a single operation. METHODS: Between March 1998 and June 2009, 227 patients with primary hyperparathyroidism were treated with surgical therapy. Of these, 217 were evaluated preoperatively with a modified 4-dimensional CT and ultrasonography. The medical records of these patients were reviewed in order to document the incidence and significance of thyroid pathology in this cohort of patients. RESULTS: Thyroid nodules were identified in 159 of the 217 patients (73.3%). Nine of 217 patients (4.1%) were treated with either a partial or a total thyroidectomy at the time of parathyroidectomy. Three of these patients had papillary thyroid carcinoma, 1 had a Hurthle cell carcinoma, and 1 had an incidental micropapillary thyroid carcinoma. CONCLUSION: The rate of clinically significant thyroid malignancy in patients undergoing surgical treatment of primary hyperparathyroidism was 1.8%.
PubMed-ID: 25548812

Polymorphisms of Cell Cycle Control Genes Influence the Development of Sporadic Medullary Thyroid Carcinoma.
Eur J Endocrinol, 171(6):761-7.
Barbieri RB, Bufalo NE, Secolin R, Assumpcao LV, Maciel RM, Cerutti JM, Ward LS. 2014.
BACKGROUND: The role of key cell cycle regulation genes such as, CDKN1B, CDKN2A, CDKN2B, and CDKN2C in sporadic medullary thyroid carcinoma (s-MTC) is still largely unknown. METHODS: In order to evaluate the influence of inherited polymorphisms of these genes on the pathogenesis of s-MTC, we used TaqMan SNP genotyping to examine 45 s-MTC patients carefully matched with 98 controls. RESULTS: A multivariate logistic regression analysis demonstrated that CDKN1B and CDKN2A genes were related to s-MTC susceptibility. The rs2066827*GT+GG CDKN1B genotype was more frequent in s-MTC patients (62.22%) than in controls (40.21%), increasing the susceptibility to s-MTC (OR=2.47; 95% CI=1.048-5.833; P=0.038). By contrast, the rs11515*CG+GG of CDKN2A gene was more frequent in the controls (32.65%) than in patients (15.56%), reducing the risk for s-MTC (OR=0.174; 95% CI=0.048-0.627; P=0.0075). A stepwise regression analysis indicated that two genotypes together could explain 11% of the total s-MTC risk. In addition, a relationship was found between disease progression and the presence of alterations in the CDKN1A (rs1801270), CDKN2C (rs12885), and CDKN2B (rs1063192) genes. WT rs1801270 CDKN1A patients presented extrathyroidal tumor extension more frequently (92%) than polymorphic CDKN1A rs1801270 patients (50%; P=0.0376). Patients with the WT CDKN2C gene (rs12885) presented larger tumors (2.9+/-1.8 cm) than polymorphic patients (1.5+/-0.7 cm; P=0.0324). On the other hand, patients with the polymorphic CDKN2B gene (rs1063192) presented distant metastases (36.3%; P=0.0261). CONCLUSION: In summary, we demonstrated that CDKN1B and CDKN2A genes are associated with susceptibility, whereas the inherited genetic profile of CDKN1A, CDKN2B, and CDKN2C is associated with aggressive features of tumors. This study suggests that profiling cell cycle genes may help define the risk and characterize s-MTC aggressiveness.
PubMed-ID: 25565272
http://dx.doi.org/10.1530/EJE-14-0461

Use of Radioiodine After Thyroid Lobectomy in Patients With Differentiated Thyroid Cancer: Does It Change Outcomes?
J Am Coll Surg, 220(4):617-25.
Kiernan CM, Parikh AA, Parks LL, Solorzano CC. 2015.
BACKGROUND: Radioiodine (RAI) lobe ablation in lieu of completion thyroidectomy is not recommended. This study describes RAI use patterns and outcomes in patients with well-differentiated thyroid cancer (DTC) after thyroid lobectomy (TL). STUDY DESIGN: A total of 170,330 patients diagnosed with DTC between 1998 and 2011 were identified using the National Cancer Database. Demographic, tumor, and treatment variables were analyzed using both univariate and multivariate regression. RESULTS: A total of 32,119 patients (20%) underwent TL as the definitive procedure. Mean age at diagnosis was 48 years, median tumor size was 1 cm, 4% had extrathyroidal extension, 4% had positive lymph nodes, and <1% distant metastases. Radioiodine was administered to 24% of patients in the TL cohort and represented 10% of the overall RAI use. In multivariate analysis, RAI use was associated with age younger than 45 years (odds ratio [OR] = 1.51), community facilities (OR = 1.26), >/=1 cm tumors (OR = 5.67), stage II (OR = 1.54) or III (OR = 2.05), positive lymph nodes (OR = 1.78), and extrathyroidal extension (OR = 1.36). On both univariate and multivariate analysis, RAI after TL was associated with improved survival at both 5 and 10 years follow-up (97% vs 95% and 91% vs 89%, respectively; hazard ratio = 0.53; 95% CI, 0.38-0.72; p < 0.001) CONCLUSIONS: Nearly one quarter of TL patients received RAI. The strongest predictors of RAI use were larger cancers and advanced stage. Use of RAI in these patients was associated with improved overall survival. Future studies and guidelines will need to more clearly address this practice and educate providers about the appropriate use of RAI in TL patients.
PubMed-ID: 25667136
http://dx.doi.org/10.1016/j.jamcollsurg.2014.12.014

The Natural History of the Benign Thyroid Nodule: What Is the Appropriate Follow-Up Strategy?
J Am Coll Surg,
Ajmal S, Rapoport S, Batlle HR, Mazzaglia PJ. 2014.
BACKGROUND: Long-term monitoring of benign thyroid nodules is not addressed in the present American Thyroid Association guidelines. The objective of this study was to determine the appropriate nature and length of follow-up for patients with a benign thyroid nodule. STUDY DESIGN: A retrospective review was performed of all patients referred to single endocrine surgeon for evaluation of thyroid nodules between 2006 and 2012. The review included 263 patients who had benign fine needle aspiration (FNA) cytology and either underwent thyroidectomy or had at least a 1-year follow-up ultrasound. Main outcomes measures were repeat FNA and pathology results. RESULTS: There were 231 women and 32 men. Forty-eight patients underwent immediate thyroidectomy, with pathology showing 2 papillary thyroid cancers (PTC), and 215 patients were followed with annual ultrasounds. During follow-up, 89 (41.3%) nodules underwent repeat FNA after initial biopsy. The repeat FNA cytology showed 91% benign, 7% follicular neoplasm, and 2% PTC. During follow-up, 81 (37.6%) patients underwent thyroidectomy after 3.3 +/- 2.8 years. Reasons for surgery included development of symptoms in 58 (71.6%), a non-benign repeat FNA in 8 (9.8%), or patient preference in 15 (18.5%). Surgical pathology identified 70 (86.4%) benign, 7 (8.6%) PTC, 3 (4%) follicular thyroid cancers, and 1 (1.2%) lymphoma. Median time from initial FNA to thyroidectomy in patients who had malignancy was 4.3 years. The maximum initial nodule size and average increase in nodule size did not differ between benign and malignant nodules ($p = 0.54$ and $p = 0.75$, respectively). CONCLUSIONS: Significant numbers of benign thyroid nodules enlarge more than 5 mm over 3 years, triggering repeat FNA or thyroidectomy. Larger diameter nodules and more rapidly growing nodules were not predictive of malignancy. The practice of annually obtaining ultrasound for benign thyroid nodules should be discouraged.
PubMed-ID: 25667137
http://dx.doi.org/10.1016/j.jamcollsurg.2014.12.010

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

A Randomized, Prospective Trial of Operative Treatments for Hyperparathyroidism in Patients With Multiple Endocrine Neoplasia Type 1.
Surgery, 156(6):1326-34.
Lairmore TC, Govednik CM, Quinn CE, Sigmond BR, Lee CY, Jupiter DC. 2014.
BACKGROUND: Hyperparathyroidism (HPT) in multiple endocrine neoplasia (MEN) type 1 is associated with multiglandular parathyroid disease. Previous retrospective studies comparing subtotal parathyroidectomy (SP) and total parathyroidectomy with autotransplantation (TP/AT) have not established clearly better outcomes with either procedure. METHODS: Patients were assigned randomly to either SP or TP/AT and data were collected prospectively. The rates of persistent HPT, recurrent HPT, and postoperative hypoparathyroidism were compared. RESULTS: The study cohort included 32 patients randomized to receive either SP or TP/AT (mean follow-up, 7.5 +/- 5.7 years). The overall rate of recurrent HPT was 19% (6/32). Recurrent HPT occurred in 4 of 17 patients (24%) treated with SP and 2 of 15 patients (13%) treated with TP/AT (P = .66). Permanent hypoparathyroidism occurred in 3 of 32 patients (9%) overall. The rate of permanent hypoparathyroidism was 12% in the SP group (2/17) and 7% in the TP/AT group (1/15). A second operation was performed in 4 of 17 patients initially treated with SP (24%), compared with 1 of 15 patients undergoing TP/AT (7%; P = .34). CONCLUSION: This randomized trial of SP and TP/AT in patients with MEN 1 failed to show any difference in outcomes when comparing results of SP versus TP/AT. Both procedures are associated with acceptable results, but SP may have advantages in that is involves only 1 surgical incision and avoids an obligate period of transient postoperative hypoparathyroidism.
PubMed-ID: 25262224
http://dx.doi.org/10.1016/j.surg.2014.08.006

Health-Related Quality of Life After Successful Surgery for Primary Hyperparathyroidism: No Additive Effect From Vitamin D Supplementation: Results of a Double-Blind Randomized Study.
Eur J Endocrinol, 172(2):181-7.
Aberg V, Norenstedt S, Zedenius J, Saaf M, Nordenstrom J, Pernow Y, Nilsson IL. 2015.
OBJECTIVE: Vitamin D insufficiency is common in primary hyperparathyroidism (pHPT). Patients with pHPT frequently have a reduced health-related quality of life (HRQoL). Our objectives were to evaluate whether HRQoL in pHPT is associated with vitamin D insufficiency and whether vitamin D supplementation after parathyroidectomy (PTX) could improve HRQoL. DESIGN: A randomized, double-blind study (ClinicalTrials.gov identifier: NCT00982722). METHODS: The study included 150 pHPT patients randomized, 6 weeks after PTX, to daily treatment with either cholecalciferol 1600 IU and calcium carbonate 1000 mg (D+) or calcium carbonate alone (D-). HRQoL was estimated with SF-36 before and after PTX and after 12 months of study medication. RESULTS: Three-quarters (77%) of the pHPT patients had vitamin D insufficiency, defined as 25OHD <50 nmol/l. The pHPT patients scored lower than a reference population in all domains of SF-36. A total of 135 patients completed the entire study period. Improvements in nearly all domains were registered at the follow-up 6 weeks after PTX. At the end of the study medication period, the D+ group had a significantly higher median serum (s-) 25OHD concentration (76 (65; 93) (lower; upper interquartile ranges) vs 48 (40; 62) nmol/l, P<0.001) and a lower plasma (p-) parathyroid hormone concentration (40 (34; 52) vs 49 (38; 66) ng/l, P=0.01) than the D- group. The improvements in HRQoL remained unchanged at the follow-up 1 year after PTX. Postoperative vitamin D supplementation had no obvious effect on HRQoL. CONCLUSION: PTX resulted in significant improvements in HRQoL. Despite a high prevalence of vitamin D insufficiency, 1 year of postoperative vitamin D supplementation had no obvious beneficial effect on HRQoL.
PubMed-ID: 25414430
http://dx.doi.org/10.1530/EJE-14-0757

Harmonic Focus Compared With Classic Hemostasis During Total Parathyroidectomy in Secondary Hyperparathyroidism: a Prospective Randomized Trial.
Am Surg, 80(12):E342-E345.
He Q, Zhuang D, Zheng L, Fan Z, Zhu J, Zhou P, Yu F, Hou L, Li Y, Ge Y. 2014.
PubMed-ID: 25513903

Consensus Statements/Guidelines

- None -

Other Articles

A Novel Technique to Improve the Diagnostic Yield of Negative Sestamibi Scans.
Surgery, 156(3):584-90.
Nagar S, Walker DD, Embia O, Kaplan EL, Grogan RH, Angelos P. 2014.
INTRODUCTION: Minimally invasive parathyroidectomy is successful in achieving cure for most patients with primary hyperparathyroidism. Most surgeons rely on preoperative imaging as part of the workup for localization. Ultrasonography and sestamibi are the 2 most commonly used preoperative imaging studies. When these 2 studies are positive and concordant the preoperative localization is straightforward. However, when >/=1 of these studies is negative, the preoperative localization is suspect. We hypothesize that the yield of useful localizing information from "negative" sestamibi scans can be increased in certain situations. Specifically, in cases where the thyroid lobe length seen on sestamibi is discordant from the lobe length of the ultrasonography, this often represents a "hidden" parathyroid adenoma. If our hypothesis is correct, this could lead to decreased resource utilization in cases of nonlocalized parathyroid adenomas. METHODS: We retrospectively analyzed our database of patients with primary hyperparathyroidism who underwent parathyroidectomy from 2005 to 2011. The anteroposterior views of early phase sestamibi were analyzed for thyroid lobe lengths. A ratio of the length of the right lobe to left lobe was calculated. The thyroid lobe lengths on ultrasonography were measured and similar ratios were calculated. The difference in ratios between sestamibi and ultrasonography was calculated for each patient. A difference in ratios from sestamibi and ultrasonography that corresponded with a "hidden" parathyroid on the side of the additional length on sestamibi at the time of surgery was considered a positive finding. When the difference in ratios from the 2 images did not correspond with a "hidden" parathyroid at the time of operation, it was considered a negative finding. RESULTS: There were 59 patients with single-gland disease, negative sestamibi, and images available for review. There were 32 patients (54%) with the positive finding of a "hidden" parathyroid corresponding with a difference in thyroid lobe length ratios from sestamibi and ultrasonography. The overall mean difference in ratios between sestamibi and ultrasonography was 0.37 +/- 0.32. The mean ratio difference in the group of patients with a negative "hidden" parathyroid was 0.11 +/- 0.02, and the mean ratio difference in the group of patients with a positive "hidden" parathyroid was 0.58 +/- 0.05 (P < .001). When a difference in ratios of >/=0.23 was obtained, this predicted a "hidden" parathyroid with a sensitivity of 93.8% and specificity of 85.2%. There were 39 patients with multigland disease, negative sestamibi, and images available for review. None of these patients had a ratio difference of >/=0.23. The mean ratio difference for patients with multigland disease was significantly lower than that of the single-gland disease (0.08 +/- 0.06 vs 0.37 +/- 0.32; P < .001). CONCLUSION: Discordance between thyroid lobe lengths on the early phase sestamibi compared with ultrasonography has led to successful preoperative identification of parathyroid adenomas, even though the sestamibi was traditionally read as negative. This finding has not been previously described, seems to be reliable, and can lead to improved preoperative localization and decreased resource utilization in this subset patients.
PubMed-ID: 24931283
http://dx.doi.org/10.1016/j.surg.2014.05.020

Denosumab for Management of Refractory Hypercalcaemia in Recurrent Parathyroid Carcinoma.
Eur J Endocrinol, 171(3):L7-L8.
Nadarasa K, Theodoraki A, Kurzawinski TR, Carpenter R, Bull J, Chung TT, Drake WM. 2014.
PubMed-ID: 24939719
http://dx.doi.org/10.1530/EJE-14-0482

Factors Associated With Vertebral Fracture Risk in Patients With Primary Hyperparathyroidism.
Eur J Endocrinol, 171(3):399-406.
Eller-Vainicher C, Battista C, Guarnieri V, Muscarella S, Palmieri S, Salcuni AS, Guglielmi G, Corbetta S, Minisola S, Spada A, Hendy GN, Cole DE, Chiodini I, Scillitani A. 2014.
OBJECTIVE: To examine factors, in addition to bone mineral density (BMD), such as the common calcium-sensing receptor (CASR) gene polymorphisms, associated with vertebral fracture (VFx) risk in primary hyperparathyroidism (PHPT). DESIGN AND METHODS: A cross-sectional analysis of 266 Caucasian PHPT seen as outpatients. Serum calcium (sCa) phosphate metabolism parameters were measured. BMD was assessed by dual-energy X-ray absorptiometry (expressed as Z-score) at lumbar spine (Z-LS) and femoral neck, morphometric VFx by radiograph, and CASR A986S/R990G genotypes by PCR amplification and genomic DNA sequencing. RESULTS: Fractured patients (n=100, 37.6%) had lower sCa (10.8+/-0.7 mg/dl) and Z-LS BMD (-1.0+/-1.44), higher age (61+/-10 years), and prevalence (51%) of >/=1 S alleles of the CASR A986S single-nucleotide polymorphism (SNP; AS/SS), than those not fractured (n=166, 11.2+/-1.0 mg/dl, -0.57+/-0.97, 58+/-13 years, and 38% AS/SS, respectively, P<0.05 for all comparisons). Logistic regression, with VFx as dependent variable, showed independent risks associated with increased age (OR 1.03, 95% CI 1.01-1.06, P=0.006), decreased sCa (OR 1.86, 95% CI 1.28-2.7, P=0.001), and Z-LS BMD (OR 1.4, 95% CI 1.12-1.7, P=0.002) and presence of AS/SS (OR 1.8, 95% CI 1.1-2.9, P=0.05). The presence of two out of three factors (age >/=58 years, sCa <10.8 and Z-LS BMD</=-1.0, and AS/SS genotype) gave an overall OR of 4.2 (95% CI 2.25-7.85, P<0.0001). CONCLUSIONS: In PHPT, VFx is associated positively with age, negatively with sCa and spinal BMD, and presence of at least one copy of the CASR A986S SNP.
PubMed-ID: 24966175
http://dx.doi.org/10.1530/EJE-14-0343

Aluminum Overload Hampers Symptom Improvement Following Parathyroidectomy for Secondary Hyperparathyroidism.
World J Surg, 38(11):2838-44.
Cheng SP, Lee JJ, Liu TP, Chen HH, Wu CJ, Liu CL. 2014.
BACKGROUND: Aluminum overload and accumulation in tissues may lead to skeletal, hematological, and neurological toxicity. The aim of this study was to assess the effects of serum aluminum levels on presentations, postoperative recovery, and symptom improvement in patients undergoing parathyroidectomy for secondary hyperparathyroidism. METHODS: From 2008 to 2013, all patients with end-stage renal disease undergoing initial parathyroidectomy were included in the study. Serum aluminum level was measured preoperatively and/or within 1 week after surgery. Preoperative and postoperative biochemical profile and symptoms were compared between the low and high aluminum groups. RESULTS: A total of 176 patients were included in the study. Of these, 38 (22 %) patients had serum aluminum levels higher than 20 mug/L. A higher percentage of patients in the high aluminum group were on peritoneal dialysis than in the low aluminum group (24 vs. 4 %, p = 0.001). Both groups had similar bone mineral density and changes in biochemical profiles. The preoperative parathyroidectomy assessment of symptoms (PAS) score was not associated with serum aluminum levels (p = 0.349), whereas the postoperative PAS score showed positive association (p = 0.005). There was a negative association between serum aluminum levels and the improvement of total PAS scores (p = 0.001). The high aluminum group had more residual symptoms in three aspects: bone pain (p = 0.038), difficulty getting out of a chair or car (p = 0.045), and pruritus (p = 0.041). CONCLUSIONS: A high serum aluminum level was associated with reduced symptom improvement in patients undergoing parathyroidectomy for secondary hyperparathyroidism.
PubMed-ID: 25002247
http://dx.doi.org/10.1007/s00268-014-2695-8

Surgical Strategy for Primary Hyperparathyreoidism With Thyroid Hemiagenesis.
Langenbecks Arch Surg, 399(8):1077-81.
Ferrari CC, Lorenz K, Dionigi G, Dralle H. 2014.
BACKGROUND: Thyroid hemiagenesis is a rare congenital anomaly, and still more rarely associated with primary hyperparathyroidism (pHPT). Due to the embryologic pathways of the thyroid and parathyroid glands, it remains unclear whether or not thyroid hemiagenesis may be linked to ipsilateral parathyroid agenesis, and consequently, surgical strategy for thyroid hemiagenesis associated pHPT (THAP) does not only depend on preoperative localization but also on the thyroid anomaly. METHODS: Including the present case report, a total of nine cases with THAP retrieved from the literature were reviewed. Seven of nine cases had thyroid hemiagenesis on the left side, three out of nine showed a parathyroid adenoma on the contralateral side to the thyroid hemiagenesis. CONCLUSIONS: Based on these cases, it can be concluded that the embryologic pathways of the thyroid and parathyroid glands are different, and in cases of THAP, parathyroid exploration

should follow standard recommendations for pHPT surgery.
PubMed-ID: 25078534
http://dx.doi.org/10.1007/s00423-014-1228-0

The Biochemical Severity of Primary Hyperparathyroidism Correlates With the Localization Accuracy of Sestamibi and Surgeon-Performed Ultrasound.
J Am Coll Surg, 219(5):1010-9.
Hughes DT, Sorensen MJ, Miller BS, Cohen MS, Gauger PG. 2014.
BACKGROUND: Minimally invasive parathyroidectomy for primary hyperparathyroidism is dependent on preoperative localization, commonly with ultrasound and sestamibi imaging. This study sought to determine if preoperative serum calcium and parathyroid hormone (PTH) levels correlate with localization sensitivity and positive predictive value (PPV). STUDY DESIGN: This is a retrospective analysis of a prospective database of 1,910 patients with primary hyperparathyroidism from 2002 to 2013, who had surgeon-performed ultrasound and/or sestamibi for preoperative localization. The sensitivity and PPV of ultrasound and sestamibi were analyzed by degree of preoperative serum calcium and parathyroid hormone level perturbation. RESULTS: In 1,910 parathyroidectomy patients, ultrasound was localizing in 1,411 of 1,644 (86%) and sestamibi in 802 of 1,165 (69%) ($p < 0.01$). The PPV of ultrasound was 1,135 of 1,411 (80%) and sestamibi was 705 of 802 (88%) ($p < 0.01$). Using logistic regression analysis, there was statistically significant positive correlation between localization and preoperative serum calcium for both sestamibi (odds ratio [OR] 1.21 [95% CI 1.00 to 1.47; $p < 0.05$]) and ultrasound (OR 1.29 [95% CI 1.03 to 1.60; $p < 0.05$]). There was a weak, but statistically significant positive correlation of PTH with sestamibi localization (OR 1.00 [95% CI 1.00 to 1.01; $p < 0.05$]). There was no statistically significant correlation between the PPV and serum calcium or PTH for either study. When patients were divided into quartiles of preoperative serum calcium and PTH levels, localization rates and PPV of both ultrasound and sestamibi increased with higher calcium and PTH levels. Surgeon-performed ultrasound had higher localization rates than sestamibi, with lower calcium and PTH values. Sestamibi demonstrated higher PPV values across all quartiles. CONCLUSIONS: Surgeon-performed ultrasound and sestamibi have higher localization rates and PPV, with increasing preoperative serum calcium and PTH levels. Surgeon-performed ultrasound may be a better initial test for patients with lower calcium (<10.5 mg/dL) and PTH (<90 pg/mL) values due to significantly higher localization rates; however, a localizing sestamibi has higher PPV.
PubMed-ID: 25086814
http://dx.doi.org/10.1016/j.jamcollsurg.2014.06.020

Calcium-Sensing-Related Gene Mutations in Hypercalcaemic Hypocalciuric Patients As Differential Diagnosis From Primary Hyperparathyroidism: Detection of Two Novel Inactivating Mutations in an Italian Population.
Nephrol Dial Transplant, 29(10):1902-9.
Stratta P, Merlotti G, Musetti C, Quaglia M, Pagani A, Izzo C, Radin E, Airoldi A, Baorda F, Palladino T, Leone MP, Guarnieri V. 2014.
BACKGROUND: Inactivating mutations of the calcium-sensing receptor (CaSR), of the G-protein subunit alpha11 (GNA11) and of the adaptor-related protein complex 2, sigma 1 subunit (AP2S1) genes are responsible for familial hypocalciuric hypercalcaemia (FHH). The aim of this study was to analyse prevalence and pathogenicity of CaSR, GNA11 and AP2S1 mutations in patients with an FHH phenotype and to compare them with a sample of patients with primary hyperparathyroidism (PHPT) in order to identify the most useful laboratory parameter for a differential diagnosis. METHODS: Patients with an FHH phenotype were studied with polymerase chain reaction amplification and direct sequencing of the entire CaSR, GNA11 and AP2S1 coding sequences. Novel mutations were introduced in a Myc-tagged human wild-type (WT) CaSR cDNA-expressing vector, and functional assay was performed on human embryonic kidney cells evaluating expression and function of mutated proteins. RESULTS: Among 16 FHH patients, none had an inactivating GNA11 or AP2S1 mutation while 3 (18.8%) carried a CaSR mutation and 10 (62.5%) at least one CaSR polymorphism. Within the latter group, 7 of 10 patients had more than one polymorphism (4.1 +/- 2.1 per patient). Two novel CaSR mutations [c.2120A>T (E707V) and c.2320G>A (G774S)] were identified: the E707V mutation prevented CaSR expression (western blot), whereas the G774S mutation determined a reduced receptor sensitivity to calcium (IP3 assay). PHPT patients showed significantly ($P < 0.001$) higher serum calcium, parathyroid hormone, urinary calcium and calcium-creatinine clearance ratio (CCCR) and significantly lower serum phosphate than FHH ones. CONCLUSIONS: FHH should be clearly differentiated by PHPT to avoid unnecessary surgery: CCCR could be a useful screening tool while genetic analysis should include the two novel CaSR mutations herein described. The role of multiple polymorphisms deserves further investigation in patients with an FHH phenotype.
PubMed-ID: 25104082
http://dx.doi.org/10.1093/ndt/gfu065

Primary Hyperparathyroidism With Negative Imaging: a Significant Clinical Problem.
Ann Surg, 260(3):474-80.
Wachtel H, Bartlett EK, Kelz RR, Cerullo I, Karakousis GC, Fraker DL. 2014.
OBJECTIVE: To compare the outcomes for patients undergoing parathyroidectomy for primary hyperparathyroidism by imaging results. BACKGROUND: Preoperative imaging plays an increasingly important role in the evaluation of primary hyperparathyroidism, and surgical referral may be predicated upon successful imaging. METHODS: We performed a retrospective study of patients undergoing initial parathyroidectomy for primary hyperparathyroidism (2002-2014). Patients were classified as nonlocalized when preoperative imaging failed to identify affected gland(s) and localized if successful. Primary outcome was cure, defined as eucalcemia postoperatively. Intraoperative success, defined by intraoperative parathyroid hormone criteria, and complication rates were also analyzed. Localized and nonlocalized patients were matched (1:1) utilizing a propensity score. Logistic regression determined factors associated with localization in the matched cohort. RESULTS: Of 2185 patients, 38.3% (n = 836) were nonlocalized. Nonlocalized patients had smaller parathyroids by size (1.2 vs 1.6 cm, P < 0.001) and mass (250 vs 537 mg, P < 0.001), higher incidence of hyperplasia (12.8% vs 5.4%, P < 0.001) and lower incidence of single adenoma (73.6 vs 86.0%, P < 0.001) compared with localized patients. There was no difference in intraoperative success (93.9 vs 95.6%, P = 0.073) or cure rates (96.2% vs 97.7%, P = 0.291) between nonlocalized and localized groups. In a propensity-matched cohort of 452 patients, there was no significant difference in cure rates (97.8 vs 97.4%, P = 0.760) between nonlocalized patients and matched localized controls. CONCLUSIONS: Nonlocalization of abnormal glands preoperatively is not associated with a decreased surgical cure rate for primary hyperparathyroidism. Referral for surgical evaluation should be based on biochemical diagnosis rather than localization by imaging.
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http://dx.doi.org/10.1097/SLA.0000000000000875

Fewer Adverse Events After Reoperative Parathyroidectomy Associated With Initial Minimally Invasive Parathyroidectomy.
Am J Surg, 208(5):850-5.
Morris LF, Lee S, Warneke CL, Abadin SS, Suliburk JW, Romero Arenas MA, Lee JE, Grubbs EG, Perrier ND. 2014.
BACKGROUND: This study compared reoperative complication rates after initial minimally invasive parathyroidectomy and standard cervical exploration. METHODS: Records from patients who underwent 1 reoperative parathyroidectomy at a single institution (1998 to 2012) were retrospectively reviewed. RESULTS: Seventy-seven patients were included; 74% underwent initial standard cervical exploration. Preoperative and operative characteristics were similar between groups; 74% underwent focused, unilateral reoperation. A significantly higher rate of postoperative complications occurred in the initial standard cervical exploration group (42% vs 15%, P = .03) that could not be explained by differences in the rates of symptomatic hypocalcemia (P = .5). The type of prior parathyroidectomy was significantly associated with postoperative complications (odds ratio 4.1, 95% confidence interval 1.1 to 15.7, P = .04). In a multivariable logistic regression model that included body mass index, type of operation (for initial and reoperation), and initial operation performed prereferral as covariates, type of prior parathyroidectomy remained a significant predictor of postoperative complications. CONCLUSION: Higher rates of postoperative sequelae after initial standard cervical exploration should be considered before performing routine 4-gland exploration.
PubMed-ID: 25152254
http://dx.doi.org/10.1016/j.amjsurg.2014.05.006

Is Intraoperative Parathyroid Hormone Monitoring Necessary With Ipsilateral Parathyroid Gland Visualization During Anticipated Unilateral Exploration for Primary Hyperparathyroidism: a Two-Institution Analysis of More Than 2,000 Patients.
Surgery, 156(4):760-6.
Rajaei MH, Oltmann SC, Adkisson CD, Elfenbein DM, Chen H, Carty SE, McCoy KL. 2014.
INTRODUCTION: Intraoperative parathyroid hormone (ioPTH) monitoring during focused parathyroidectomy for primary hyperparathyroidism (PHPT) is used commonly, but some argue that ioPTH adds little if a normal ipsilateral parathyroid gland (IPG) is visualized. This hypothesis was tested for validity. METHODS: The prospective databases of consecutive patients with PHPT undergoing initial parathyroidectomy with ioPTH at two academic institutions were queried. Patients with ectopic adenoma, familial PHPT, previous parathyroidectomy, planned bilateral exploration, or <6 months follow-up were excluded. Persistence was defined as hypercalcemia at <6 months. RESULTS: From 1998 to 2013, 2,162 patients met inclusion criteria, and the rate of persistent disease was 1.5%. Most (n = 1,353; 63.5%) underwent single-gland resection with ioPTH and no IPG visualization, with 1% persistence. Among patients with a single adenoma resected and a normal IPG visualized,

15.2% had contralateral disease. Resection based on IPG appearance alone would have resulted in 13% persistent disease. CONCLUSION: In PHPT, the cure rate for initial unilateral exploration guided by ioPTH is 98.5% versus a predicted rate of 87% when decision making is based on IPG appearance alone. Routine visualization of IPG is not necessary during exploration for suspected single adenoma guided by ioPTH. ioPTH remains useful in optimizing outcomes.
PubMed-ID: 25239313
http://dx.doi.org/10.1016/j.surg.2014.06.060

The PRIMARA Study: a Prospective, Descriptive, Observational Study to Review Cinacalcet Use in Patients With Primary Hyperparathyroidism in Clinical Practice.
Eur J Endocrinol, 171(6):727-35.
Schwarz P, Body JJ, Cap J, Hofbauer LC, Farouk M, Gessl A, Kuhn JM, Marcocci C, Mattin C, Munoz TM, Payer J, Van D, V, Yavropoulou M, Selby P. 2014.
OBJECTIVE: Medical management of primary hyperparathyroidism (PHPT) is important in patients for whom surgery is inappropriate. We aimed to describe clinical profiles of adults with PHPT receiving cinacalcet. DESIGN: A descriptive, prospective, observational study in hospital and specialist care centres. METHODS: For patients with PHPT, aged 23-92 years, starting cinacalcet treatment for the first time, information was collected on dosing pattern, biochemistry and adverse drug reactions (ADRs). Initial cinacalcet dosage and subsequent dose changes were at the investigator's discretion. RESULTS: Of 303 evaluable patients with PHPT, 134 (44%) had symptoms at diagnosis (mostly bone pain (58) or renal stones (50)). Mean albumin-corrected serum calcium (ACSC) at baseline was 11.4 mg/dl (2.9 mmol/l). The reasons for prescribing cinacalcet included: surgery deemed inappropriate (35%), patient declined surgery (28%) and surgery failed or contraindicated (22%). Mean cinacalcet dose was 43.9 mg/day (s.d., 15.8) at treatment start and 51.3 mg/day (31.8) at month 12; 219 (72%) patients completed 12 months treatment. The main reason for cinacalcet discontinuation was parathyroidectomy (40; 13%). At 3, 6 and 12 months from the start of treatment, 63, 69 and 71% of patients, respectively, had an ACSC of </=10.3 mg/dl vs 9.9% at baseline. Reductions from baseline in ACSC of >/=1 mg/dl were seen in 56, 63 and 60% of patients respectively. ADRs were reported in 81 patients (27%), most commonly nausea. A total of 7.6% of patients discontinued cinacalcet due to ADRs. CONCLUSIONS: Reductions in calcium levels of >/=1 mg/dl was observed in 60% of patients 12 months after initiation of cinacalcet, without notable safety concerns.
PubMed-ID: 25240499
http://dx.doi.org/10.1530/EJE-14-0355

Multiphase Computed Tomography for Localization of Parathyroid Disease in Patients With Primary Hyperparathyroidism: How Many Phases Do We Really Need?
Surgery, 156(6):1300-6.
Noureldine SI, Aygun N, Walden MJ, Hassoon A, Gujar SK, Tufano RP. 2014.
BACKGROUND: Multiphase computed tomography (CT) involves multiple cervical CT acquisitions to accurately identify hyperfunctional parathyroid glands, thus increasing radiation exposure to the patient. We hypothesized that only 2 cervical acquisitions, instead of the conventional 4, would provide equivalent localization information and halve the radiation exposure. METHODS: We identified 53 consecutive patients with primary hyperparathyroidism who underwent multiphase CT before parathyroidectomy. All scans were reinterpreted first using 2 phases then using all 4 phases. The accuracies of interpretations were determined with surgical findings serving as the standard of reference. RESULTS: Sixty-four hyperfunctional parathyroid glands were resected with a mean weight of 394.3 mg. Two-phase CT lateralized the hyperfunctional glands in 38 patients with a sensitivity, positive predictive value (PPV), and accuracy of 100%, 71.7%, and 71.7%, respectively. Four-phase CT lateralized the hyperfunctional glands in 39 patients with a sensitivity, PPV, and accuracy of 95.1%, 76.5%, and 73.6%, respectively. For quadrant localization, the accuracy of 2-phase and 4-phase CT was 50.9% and 52.8%, respectively. CONCLUSION: Our results suggest that 2-phase and 4-phase CT provide an equivalent diagnostic accuracy in localizing hyperfunctional parathyroid glands. The reduced radiation exposure to the patient may make 2-phase acquisitions a more acceptable alternative for preoperative localization.
PubMed-ID: 25262222
http://dx.doi.org/10.1016/j.surg.2014.08.002

Pedicled Parathyroid Gland Autotransposition in Secondary and Tertiary Hyperparathyroidism.
Laryngoscope, 125(4):894-7.
Shokri T, Lew SQ, Sadeghi N. 2015.
PubMed-ID: 25289604
http://dx.doi.org/10.1002/lary.24962

Localization of Parathyroid Adenoma by (1)(1)C-Choline PET/CT: Preliminary Results.
Clin Nucl Med, 39(12):1033-8.
Orevi M, Freedman N, Mishani E, Bocher M, Jacobson O, Krausz Y. 2014.
PURPOSE: This prospective pilot study was aimed to evaluate (1)(1)C-choline PET/CT (choline) as a tool for localization of parathyroid adenoma (PTA). METHODS: Forty patients with biochemical hyperparathyroidism underwent choline and (9)(9)mTc-MIBI imaging within a median interval of 56 days. Choline and MIBI images were analyzed and correlated with each other, with additional modalities such as ultrasound, CT, MRI, and with surgical findings, when available. RESULTS: Thirty-seven of forty cases were choline-positive, and 3 were choline-negative. Choline uptake on PET was identified with corresponding nodules on CT of the PET/CT, yielding precise localization. Twenty of thirty-seven foci were located in typical sites in the neck, and 17 were ectopic. Clear visualization of PTA was achieved in 33 of 37, whereas findings in 4 cases were suspicious for PTA. MIBI was positive in 33 of 40 cases (22 clearly positive, 11 suspicious). In 29 of 40 cases, choline and MIBI were concordant, but choline findings were clearer in 9 of these 29 studies.At the time of writing, 27 patients had undergone surgery. In 24 cases, there was complete matching of choline with surgical findings of PTA. Overall in 23 cases, both choline and MIBI matched surgical findings of PTA. In 1 case, PTA was correctly localized on choline but not on MIBI, and in 2 cases, neither choline nor MIBI corresponded to the surgical findings. CONCLUSIONS: These preliminary results indicate that the combined functional and anatomical modality of choline PET/CT is a promising tool for PTA localization, providing clearer images than MIBI, equal or better accuracy, and quicker and easier acquisition.
PubMed-ID: 25290292
http://dx.doi.org/10.1097/RLU.0000000000000607

A Novel Mutation in Calcium-Sensing Receptor Gene Associated to Hypercalcemia and Hypercalciuria.
BMC Endocr Disord, 14:81.
Mastromatteo E, Lamacchia O, Campo MR, Conserva A, Baorda F, Cinque L, Guarnieri V, Scillitani A, Cignarelli M. 2014.
BACKGROUND: Familial Hyperparathyroidism (HPT) and Familial benign Hypocalciuric Hypercalcemia (FHH) are the most common causes of hereditary hypercalcemia. FHH has been demonstrated to be caused by inactivating mutations of calcium-sensing receptor (CaSR) gene, involved in PTH regulation as well as in renal calcium excretion. CASE PRESENTATION: In two individuals, father and son, we found a novel heterozygous mutation in CaSR gene. The hypercalcemia was present only in father, which, by contrast to the classic form of FHH showed hypercalciuria (from 300 to 600 mg/24 h in different evaluations) and a Calcium/Creatinine ratio of 0.031, instead of low or normal calciuria (<0.01 typical finding in FHH). His son showed the same mutation in CaSR gene, but no clinical signs or hypercalcemia although serum ionized calcium levels were close to the upper limit of normal values (1.30 mmol/L: normal range: 1.12-1.31 mmol/L). Sequence analysis revealed a point mutation at codon 972 of CaSR gene (chromosome 3q), located within cytoplasmic domain of the CaSR, that changes Threonine with Methionine. The father was treated with Cinacalcet 90 mg/day, with a decrease of total serum calcemia from an average value of 12.2 mg/dl to 10.9 mg/dl. CONCLUSION: This is a case of a novel inactivating point mutation of CaSR gene that determines an atypical clinical presentation of FHH, characterized by hypercalcemia, hypercalciuria and inadequate normal PTH levels. Functional assay demonstrated that the 972 M variant influenced the maturation of the protein, in terms of the post-translational glycosylation. The impairment of the receptor activity is in keeping with the specific localization of the 972 residue in the C-terminal tail, assigned to the intracellular signalling, that on the basis of the our findings appears to be differently modulated in parathyroid gland and in kidney.
PubMed-ID: 25292184
http://dx.doi.org/10.1186/1472-6823-14-81

Maternal Atypical Parathyroid Adenoma As a Cause of Newborn Hypocalcemic Tetany.
Otolaryngol Head Neck Surg, 151(6):1084-5.
Razavi CR, Charitou M, Marzouk M. 2014.
PubMed-ID: 25325666
http://dx.doi.org/10.1177/0194599814555850

Treatment Strategies for Primary Hyperparathyroidism: What Is the Cost?
Am Surg, 80(11):1146-51.
Aliabadi-Wahle S, Kelly TL, Rozenfeld Y, Carlisle JR, Naeole LK, Negreanu FA, Schuman E, Hammill CW. 2014.
Primary hyperparathyroidism (HPT) contributes to the onset of many chronic conditions. Although parathyroidectomy is the only definitive treatment, observation remains a valid option. Over a 3-year span, a major health plan was queried for HPT and benign parathyroid neoplasm. Patients with secondary and tertiary

HPT, Stage III to V kidney disease, and prior renal transplant were excluded. Patients were divided into: observation (Group 1), parathyroidectomy during the study period (Group 2), and parathyroidectomy before the study group (Group 3), and were compared with a control group of 27,092 adult members without HPT using analysis of variance. The 3-year mean total allowed expenditure for Group One (n = 559), Group Two (n = 93), and Group Three (n = 48) were $21,267, $37,043, and $14,702, respectively. Groups One and Two had significantly higher use than the nonparathyroid group (P < 0.0001), whereas that of Group Three was comparable. Group Two had the highest cost, whereas Group Three had a significantly lower cost than Group One (P 0.0001). Primary hyperparathyroidism is associated with a higher use of healthcare resources. Patients observed incurred a higher allowed expenditure than those with prior parathyroidectomy. Surgical treatment may represent a cost-effective strategy for treatment of hyperparathyroidism, although more comprehensive studies are needed to confirm these findings.
PubMed-ID: 25347507

Hyperparathyroidism-Jaw Tumor Syndrome: Results of Operative Management.
Surgery, 156(6):1315-24.
Mehta A, Patel D, Rosenberg A, Boufraqech M, Ellis RJ, Nilubol N, Quezado MM, Marx SJ, Simonds WF, Kebebew E. 2014.
BACKGROUND: Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare, autosomal-dominant disease secondary to germline-inactivating mutations of the tumor suppressor gene HRPT2/CDC73. The aim of the present study was to determine the optimal operative approach to parathyroid disease in patients with HPT-JT. METHODS: A retrospective analysis of clinical and genetic features, parathyroid operative outcomes, and disease outcomes in 7 unrelated HPT-JT families. RESULTS: Seven families had 5 distinct germline HRPT2/CDC73 mutations. Sixteen affected family members (median age, 30.7 years) were diagnosed with primary hyperparathyroidism (PHPT). Fifteen of the 16 patients underwent preoperative tumor localization studies and uncomplicated bilateral neck exploration at initial operation; all were in biochemical remission at most recent follow-up. Of these patients, 31% had multiglandular involvement; 37.5% of the patients developed parathyroid carcinoma (median overall survival, 8.9 years; median follow-up, 7.4 years). Long-term follow-up showed that 20% of patients had recurrent PHPT. CONCLUSION: Given the high risk of malignancy and multiglandular involvement in our cohort, we recommend bilateral neck exploration and en bloc resection of parathyroid tumors suspicious for cancer and life-long postoperative follow-up.
PubMed-ID: 25444225
http://dx.doi.org/10.1016/j.surg.2014.08.004

An Analysis of Whether Surgeon-Performed Neck Ultrasound Can Be Used As the Main Localizing Study in Primary Hyperparathyroidism.
Surgery, 156(5):1127-31.
Aliyev S, Agcaoglu O, Aksoy E, Birsen O, Milas M, Mitchell J, Siperstein A, Berber E. 2014.
BACKGROUND: Tc-99 sestamibi (MIBI) scan is the imaging study most frequently used in primary hyperparathyroidism (PHP). Transcutaneous cervical ultrasonography (US) is the other modality used for preoperative localization. The aim of this study was to determine whether surgeon-performed neck US can be used as the primary localizing study in PHP. METHODS: This was a prospective study of 1,000 consecutive patients with first-time, sporadic PHP who underwent parathyroidectomy at a tertiary academic center. All patients had surgeon-performed neck US and MIBI before bilateral neck exploration. RESULTS: The findings at exploration were 72% single adenoma, 15% double adenoma, and 13% hyperplasia. When US suggested single-gland disease (n = 842), MIBI was concordant in 82.5%, discordant and false in 8%, negative in 7%, and discordant but correct in 2.5%. When US suggested multigland disease (n = 68), MIBI was concordant in 47%, discordant and false in 41%, and negative in 12%. When US was negative (n = 90), MIBI was positive and correct in 43%, negative in 31%, and positive but false in 26%. Surgeon-performed neck US identified unrecognized thyroid nodules in 326 patients (33%), which led to fine-needle aspiration biopsy in 161 (49%) patients and thyroid surgery in 103 (32%) patients, with a final diagnosis of thyroid cancer in 24 (7%) patients. CONCLUSION: Our results show that MIBI provides additional useful information in only a minority of patients with a positive US in PHP. Nevertheless, MIBI benefits about half of patients with a negative US. Because one-third of this patient population has unrecognized thyroid nodules as well, we propose that the most cost-effective algorithm would be to do US first and reserve MIBI for US-negative cases.
PubMed-ID: 25444313
http://dx.doi.org/10.1016/j.surg.2014.05.009

Prognostic Factors and Staging Systems in Parathyroid Cancer: a Multicenter Cohort Study.
Surgery, 156(5):1132-44.

Villar-del-Moral J, Jimenez-Garcia A, Salvador-Egea P, Martos-Martinez JM, Nuno-Vazquez-Garza JM, Serradilla-Martin M, Gomez-Palacios A, Moreno-Llorente P, Ortega-Serrano J, Quintana-Basarrate A. 2014.
BACKGROUND: Parathyroid carcinoma (PC) is an uncommon disease that generally is detected postoperatively and traditionally is associated with a poor prognosis. Our purpose was to evaluate treatment outcomes, prognostic factors, and usefulness of some proposed staging systems for this disease. METHODS: A multicenter review of patients with surgically resected PC was performed, led by the Spanish Association of Surgery. All surgical units affiliated with its endocrine surgery section were invited to answer a questionnaire that collected several hospital-related, clinical, biochemical, operative, pathologic, and follow-up data. Their relationships with prognosis were assessed by both univariate and multivariate analysis, as well as the effectiveness of three staging systems for parathyroid carcinoma. RESULT: Of the 6,863 patients undergoing parathyroidectomy, 62 (0.9%) had PC. Of them, 12 (19.3%) died, in 5 cases (8%) because of disease, and 14 (22.6%) suffered recurrence, after a median follow-up of 55 months. The most predictive independent variables on tumor recurrence were intraoperative tumor rupture (hazard ratio [HR] 6.22; 95% confidence interval [CI] 1.19-32.36; P = .030); the presence of mitotic figures within tumor parenchyma cells (HR 4.76; 95% CI 1.24-18.21; P = .022); and allocation in class III according to Schulte differentiated staging classification (HR 5.23; 95% CI 1.41-19.31; P = .013). As to disease-specific survival, poor outcomes were associated with intraoperative tumor rupture (HR 58.71; 95% CI 2.39-1,439.96; P = .013) and distant recurrence (HR 38.74; 95% CI 3.44-435.62; P = .003). CONCLUSION: In addition to factors associated with tumor histopathology and stage, prognosis of PC is greatly influenced by surgeon's performance, which emphasizes the importance of preoperative diagnosis.
PubMed-ID: 25444314
http://dx.doi.org/10.1016/j.surg.2014.05.014

The Effect of Cinacalcet on Intraoperative Findings in Tertiary Hyperparathyroidism Patients Undergoing Parathyroidectomy.
Surgery, 156(6):1308-13.
Somnay YR, Weinlander E, Schneider DF, Sippel RS, Chen H. 2014.
INTRODUCTION: Tertiary hyperparathyroidism (3HPTH) patients who undergo parathyroidectomy (PTX) are often managed with calcium lowering medications such as cinacalcet (Sensipar) before surgery. Here, we assess how cinacalcet treatment influences intraoperative parathyroid hormone (IOPTH) kinetics and surgical findings in 3HPTH patients undergoing PTX. METHODS: We reviewed retrospectively 113 patients 3HPTH who underwent PTX, 14 of whom were taking cinacalcet and 112 who were not taking the drug. IOPTH levels fitted to linear curves versus time were used to evaluate the role of cinacalcet. RESULTS: Cinacalcet did not correlate with rates of cure (P = .41) or recurrence (P = .54). Patients taking cinacalcet experienced a steeper decrease in IOPTH compared with those not taking the medication (P = .005). Cinacalcet treatment was associated with an increase in rate of hungry bones (P = .04). Weights of the heaviest glands resected (P = .02) and preoperative PTH levels (P = .0004) were greater among patients taking cinacalcet. CONCLUSION: Perioperative cinacalcet treatment in patients with 3HPTH alters IOPTH kinetics by causing a steeper decrease in IOPTH, but does not require modification of the standard IOPTH protocol. Although cinacalcet use does not adversely affect cure rates, it is associated with greater preoperative PTH and an increased incidence of hungry bones, hence serving as an indicator of more severe disease. Cinacalcet does not need to be held before operation.
PubMed-ID: 25456900
http://dx.doi.org/10.1016/j.surg.2014.08.003

Is Central Lymph Node Dissection Necessary for Parathyroid Carcinoma?
Surgery, 156(6):1336-41.
Hsu KT, Sippel RS, Chen H, Schneider DF. 2014.
BACKGROUND: Parathyroid carcinoma is a rare cancer. Unlike other more common malignancies, the importance of lymph node (LN) status remains controversial. The purpose of this study was to determine the relative importance of LN metastases in disease-specific survival (DSS). METHODS: A retrospective review of the Surveillance, Epidemiology, and End Result database was performed on parathyroid carcinoma cases diagnosed between 1988 and 2010. RESULTS: We identified 405 parathyroid carcinoma patients. Among 114 patients with LNs examined at operation, only 12 (10.5%) had positive LNs. Sensitivity analysis found that a tumor size threshold of 3 cm best divided the cohort by DSS. Only tumors >/= 3 cm and distant metastasis but not LN metastases were independent prognostic factors on multivariate analysis. When examining factors associated with LN status, only.
PubMed-ID: 25456903
http://dx.doi.org/10.1016/j.surg.2014.08.005

Fibromyalgia Symptoms and Medication Requirements Respond to Parathyroidectomy.
Surgery, 156(6):1614-20.
Adkisson CD, Yip L, Armstrong MJ, Stang MT, Carty SE, McCoy KL. 2014.
BACKGROUND: Fibromyalgia (FM), an ill-defined symptom complex, is characterized by musculoskeletal pain, headache, depression, fatigue, and cognitive decline, symptoms also seen commonly in primary hyperparathyroidism (PHP). Prevalence of concurrent PHP and FM and response to parathyroidectomy (PTX) of those with both conditions are unknown. METHODS: We reviewed prospective data of 4,000 patients with sporadic PHP who had PTX from 1995 to 2013 examining perioperative symptoms and medication usage for those with diagnosed FM. Cure was defined by normocalcemia at >/= 6 months. RESULTS: Of 2,184 patients, 80 (4%) had a prior diagnosis of FM. Of evaluable FM patients, 97.3% had definitive cure of PHP. After PTX, 89% had improvement in >/= 1 symptom attributed to FM, with improved cognition/memory most common (80%). Improvement in >/= 2, >/= 3, and >/= 4 FM symptoms was appreciated by 71%, 43%, and 25%, respectively. Quality of life and wellness improved in >50%. Postoperative use of drugs prescribed for FM often improved or resolved (narcotics, 77%; anti-inflammatories, 74%; "FM-specific medications," 33%; antidepressants, 30%); 21% discontinued all FM medications postoperatively. CONCLUSION: FM is common in patients operated on for sporadic PHP. Of those with both conditions, after PTX 89% appreciate symptom response and 77% and 21% had a decrease in or discontinuation or medications, respectively. Before diagnosing FM, providers should exclude PHP, which is surgically correctable.
PubMed-ID: 25456962
http://dx.doi.org/10.1016/j.surg.2014.08.063

Parathyroid Carcinoma in More Than 1,000 Patients: A Population-Level Analysis.
Surgery, 156(6):1622-9.
Sadler C, Gow KW, Beierle EA, Doski JJ, Langer M, Nuchtern JG, Vasudevan SA, Goldfarb M. 2014.
BACKGROUND: Parathyroid carcinoma (PC) is a rare malignancy with a moderate prognosis. The staging system, prognostic indicators, and optimal surgical management are still under debate. This large cohort explores prognostic factors for PC. METHODS: 1,022 cases of PC in the 1998-2011 National Cancer Data Base that underwent surgery were examined for predictors of lower overall survival (OS) and relative risk (RR) of death at 5 years. RESULTS: The 5-year OS was 81.1% in 528 patients with >/= 60 months of follow-up. The overall cohort was mainly non-Hispanic (96.5%), white (77.4%), and insured (94.3%), with a median age of 57 years. Mean OS was lower and RR of death greater in older (P < .001), black (P = .007) patients with a secondary malignancy (P = .015) and >/= 2 comorbidities (P = .005), whose surgical specimen had positive surgical margins (P = .026) or positive lymph nodes (P < .001). Multivariate cox regression demonstrated that positive lymph nodes (hazard ratio [HR], 6.47; 95% CI, 1.81-23.11) and older age (HR, 2.35; 95% CI, 1.25-4.43) were associated with lower OS. CONCLUSION: PC is a rare malignancy with a 5-year OS of 81.1%. Positive lymph nodes and older age predict lower OS and an increased risk of death.
PubMed-ID: 25456964
http://dx.doi.org/10.1016/j.surg.2014.08.069

Predictors of Tertiary Hyperparathyroidism: Who Will Benefit From Parathyroidectomy?
Surgery, 156(6):1631-6.
Dewberry LC, Tata S, Graves S, Weber CJ, Sharma J. 2014.
BACKGROUND: Tertiary hyperparathyroidism (3 degrees HPT) is hyperparathyroidism with hypercalcemia after renal transplantation. With unclear guidelines for parathyroidectomy (PTX), this study aims to determine which renal transplant patients develop 3 degrees HPT and would benefit from PTX. METHODS: We performed a retrospective review of patients who received a renal transplant between 1994 and 2013; 105 patients who underwent near total PTX (NTPTX) were compared with 180 renal transplant control patients who did not undergo NTPTX. RESULTS: Calcium and PTH varied significantly between groups (P < .001). One year before transplant, the mean serum calcium was 9.7 +/- 1.1 mg/dL in the NTPTX group versus 9.1 +/- 0.9 mg/dL in the control group (P < .01). One month after transplant, the mean calcium in the NTPTX group was 10.4 +/- 1.1 versus 9.4 +/- 0.6 mg/dL in the control group (P < .001). One year before renal transplant, the median serum PTH level was 723 pg/mL (range, 557-919) in the NTPTX group versus 212 pg/mL (range, 160-439) in the control group (P < .01). One-month post renal transplant, the NTPTX group had a median PTH of 351 pg/mL (range, 199-497) versus 112 pg/mL (range, 73-178) pg/mL in the control group (P < .01). CONCLUSION: Before and after renal transplantation, PTH and calcium levels can serve as predictors of 3 degrees HPT.
PubMed-ID: 25456966
http://dx.doi.org/10.1016/j.surg.2014.08.070

A Novel, Ultrarapid Parathyroid Hormone Assay to Distinguish Parathyroid From Nonparathyroid Tissue.
Surgery, 156(6):1638-43.
James BC, Nagar S, Tracy M, Kaplan EL, Angelos P, Scherberg NH, Grogan RH. 2014.
BACKGROUND: Frozen section is the gold standard for distinguishing parathyroid tissue from lymph nodes, thyroid nodules, or fat during parathyroidectomy and thyroidectomy. Although a very accurate procedure, it can be time-consuming and costly. We hypothesize that the extremely high concentrations of parathyroid hormone (PTH) in parathyroid tissue allow for modification of a standard PTH assay that would distinguish parathyroid from nonparathyroid tissue in substantially less time than frozen section or any currently available PTH assay. METHODS: A prospective, single-institution study using a modified PTH assay protocol and a manual luminometer was undertaken by testing 20 parathyroid adenomas and 9 control tissues. Analyses were performed simultaneously by the modified PTH protocol and the conventional intraoperative PTH assay. RESULTS: PTH luminescence values from parathyroid tissue and control tissue aspirates were significantly different at 60 seconds (P = .015). ROC curve analysis showed the assay to be 100% sensitive and 100% specific in differentiating parathyroid from nonparathyroid tissue. CONCLUSION: Our novel PTH assay accurately and reliably differentiates parathyroid from nonparathyroid tissue within 60 seconds of measurement onset. This assay provides a great advantage in time savings compared with frozen section as well as any currently existing PTH assays.
PubMed-ID: 25456968
http://dx.doi.org/10.1016/j.surg.2014.08.081

Modern Experience With Aggressive Parathyroid Tumors in a High-Volume New England Referral Center.
J Am Coll Surg,
Quinn CE, Healy J, Lebastchi AH, Brown TC, Stein JE, Prasad ML, Callender GG, Carling T, Udelsman R. 2014.
BACKGROUND: Parathyroid carcinoma (PTCA) is an exceptionally rare malignancy, often with a clinical presentation similar to that of benign atypical parathyroid adenoma. Its low incidence portends unclear guidelines for management. Accordingly, thorough examination of clinical and pathologic variables was undertaken to distinguish between PTCA and atypical adenomas. STUDY DESIGN: This was a retrospective analysis of a prospective database at a tertiary academic referral center. Between September 2001 and April 2014, 3,643 patients were referred for surgical treatment of PHPT. Of these, 52 harbored aggressive parathyroid tumors: parathyroid carcinomas (n = 18) and atypical adenomas (n = 34). We analyzed the surgical and clinicopathologic tumor characteristics, and did a statistical analysis. We measured preoperative and intraoperative variables, and postoperative and pathologic outcomes. RESULTS: Parathyroid carcinoma patients present with significantly increased tumor size (3.5 cm vs 2.4 cm, respectively; p = 0.002), mean serum calcium (13.0 vs 11.8 mg/dL, respectively; p = 0.003) and intact parathyroid hormone (iPTH) levels (489 vs 266 pg/mL, respectively; p = 0.04), and a higher incidence of hypercalcemic crisis, compared with patients with atypical adenomas (50% vs 19%, respectively; p = 0.072). Parathyroid carcinoma more frequently lacks a distinct capsule (47.1% vs 12.9%, respectively; p = 0.03) and adheres to adjacent structures (77.8% vs 20.6%, respectively; p = 0.017). Of note, there was no significant difference in loss of parafibromin expression between groups. CONCLUSIONS: Clinical distinction between PTCA and atypical adenomas is of critical importance in determining the appropriate extent of resection and follow-up. Loss of parafibromin has not been shown to distinguish between PTCA and atypical adenoma; clearer definition of clinicopathologic criteria for PTCA is warranted and may lead to improved postoperative management.
PubMed-ID: 25488353
http://dx.doi.org/10.1016/j.jamcollsurg.2014.10.007

Tumour-Associated Fibroblasts Contribute to Neoangiogenesis in Human Parathyroid Neoplasia.
Endocr Relat Cancer, 22(1):87-98.
Verdelli C, Avagliano L, Creo P, Guarnieri V, Scillitani A, Vicentini L, Steffano GB, Beretta E, Soldati L, Costa E, Spada A, Bulfamante GP, Corbetta S. 2015.
Components of the tumour microenvironment initiate and promote cancer development. In this study, we investigated the stromal component of parathyroid neoplasia. Immunohistochemistry for alpha-smooth muscle actin (alpha-SMA) showed an abundant periacinar distribution of alpha-SMA(+) cells in normal parathyroid glands (n=3). This pattern was progressively lost in parathyroid adenomas (PAds; n=6) where alpha-SMA(+)cells were found to surround new microvessels, as observed in foetal parathyroid glands (n=2). Moreover, in atypical adenomas (n=5) and carcinomas (n=4), alpha-SMA(+) cells disappeared from the parenchyma and accumulated in the capsula and fibrous bands. At variance with normal glands, parathyroid tumours (n=37) expressed high levels of fibroblast-activation protein (FAP) transcripts, a marker of tumour-associated fibroblasts. We analysed the ability of PAd-derived cells to activate fibroblasts using human bone-marrow mesenchymal stem cells (hBM-

MSCs). PAd-derived cells induced a significant increase in FAP and vascular endothelial growth factor A (VEGFA) mRNA levels in co-cultured hBM-MSCs. Furthermore, the role of the calcium-sensing receptor (CASR) and of the CXCL12/CXCR4 pathway in the PAd-induced activation of hBM-MSCs was investigated. Treatment of co-cultures of hBM-MSCs and PAd-derived cells with the CXCR4 inhibitor AMD3100 reduced the stimulated VEGFA levels, while CASR activation by the R568 agonist was ineffective. PAd-derived cells co-expressing parathyroid hormone (PTH)/CXCR4 and PTH/CXCL12 were identified by FACS, suggesting a paracrine/autocrine signalling. Finally, CXCR4 blockade by AMD3100 reduced PTH gene expression levels in PAd-derived cells. In conclusion, i) PAd-derived cells activated cells of mesenchymal origin; ii) PAd-associated fibroblasts were involved in tumuor neoangiogenesis and iii) CXCL12/CXCR4 pathway was expressed and active in PAd cells, likely contributing to parathyroid tumour neoangiogenesis and PTH synthesis modulation.
PubMed-ID: 25515730
http://dx.doi.org/10.1530/ERC-14-0161

Parathyroid Carcinoma Presenting With Pathological Fracture: Case Report and Review of the Literature.
Head Neck,
Fortson JK, Su R, Patel VG, Lawrence GE. 2014.
Background Parathyroid carcinoma is a rare neoplasm representing less than 1% of primary hyperparathyroidism cases. It is often not diagnosed until surgical exploration as a preoperative diagnosis is often not possible. Thus preoperative staging for most patients is not feasible and this may compromise the treatment strategy. Method & Result We report a case of a 29 years old male presenting with avulsion fracture of the right elbow after a trivial fall. Neck exploration revealed enlarged left lobe focally adherent to the larynx and trachea. Final pathology revealed parathyroid carcinoma with focally positive margin at the site of tracheal invasion. Conclusion Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. The etiology of parathyroid carcinoma is usually obscured, and the initial operation offers the best chance for cure.
PubMed-ID: 25537741
http://dx.doi.org/10.1002/hed.23965

A Long-Term Prospective Evaluation Comparing Robotic Parathyroidectomy With Minimally Invasive Open Parathyroidectomy for Primary Hyperparathyroidism.
Head Neck,
Tolley N, Garas G, Palazzo F, Prichard A, Chaidas K, Cox J, Darzi A, Arora A. 2014.
Background. Targeted parathyroidectomy is a popular technique for localized pathology. No single technique is established as superior. The objective was to compare robotic-assisted parathyroidectomy (RAP) with the most common approach. Methods. Prospective, non-randomised study. Fifteen consecutive RAP patients compared to 15 matched controls undergoing focused lateral parathyroidectomy (FLP). Results. Biochemical cure occurred in 29/30 patients (97%). No major complications occurred although there was one robotic conversion. RAP demonstrated a significant time reduction (R2 =0.436, p=0.01) but took much longer to perform than FLP (119 min vs. 34min, p=0.001). RAP was associated with less initial postoperative pain (p=0.036) and higher satisfaction with scar cosmesis (p=0.002) until 6 months. Quality of life improved in both groups (p=0.007). Conclusions. RAP provides superior early cosmesis with equivalent global health improvement compared to FLP. The high cost and learning curve may preclude widespread adoption. Further evaluation is necessary to establish its clinical efficacy regarding scar cosmesis.
PubMed-ID: 25545792
http://dx.doi.org/10.1002/hed.23990

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

- None -

Other Articles

Development of a Novel Nomogram to Predict Hypertension Cure After Laparoscopic Adrenalectomy in Patients With Primary Aldosteronism.
World J Surg, 38(10):2640-4.
Utsumi T, Kamiya N, Endo T, Yano M, Kamijima S, Kawamura K, Imamoto T, Naya Y, Ichikawa T, Suzuki H. 2014.
BACKGROUND: Primary aldosteronism is the most common curable cause of secondary hypertension. Despite resection, however, many patients with primary aldosteronism continue to require antihypertensive drugs to control their blood pressure. Although many patients with primary aldosteronism want to know the postoperative probability of hypertension cure before surgery, there are no predictive models calculating its probability. We therefore developed a nomogram to predict hypertension cure in patients with primary aldosteronism after laparoscopic adrenalectomy. METHODS: We retrospectively surveyed 132 Japanese patients with primary aldosteronism who were treated by unilateral laparoscopic adrenalectomy. Hypertension cure was defined as normal blood pressure (<140/90 mmHg) without antihypertensive drugs 6 months postoperatively. We developed a novel nomogram that postoperatively predicted cured hypertension in 105 (80 %) randomly selected patients and validated it with the remaining 27 (20 %). RESULTS: At 6 months, blood pressure had normalized in 42 % of patients without antihypertensive drugs. Duration of hypertension, preoperative number of antihypertensive drug classes, age, and sex were incorporated into a novel nomogram as independent predictors of hypertension cure. The value of the area under the receiver operating characteristics curve for this nomogram was 0.83-which was significantly higher than that of the Aldosteronoma Resolution Score-on internal validation. CONCLUSIONS: We developed the first nomogram that can accurately predict postoperative hypertension cure in patients with primary aldosteronism. This nomogram can help clinicians calculate the probability of postoperative hypertension cure in patients with primary aldosteronism and objectively inform them of their hypertension outcome before laparoscopic adrenalectomy.
PubMed-ID: 24831672
http://dx.doi.org/10.1007/s00268-014-2612-1

Laparoendoscopic Single-Site Adrenalectomy Versus Conventional Laparoscopic Adrenalectomy: a Comparison of Surgical Outcomes and an Analysis of a Single Surgeon's Learning Curve.
Surg Endosc, 28(10):2911-9.
Hirasawa Y, Miyajima A, Hattori S, Miyashita K, Kurihara I, Shibata H, Kikuchi E, Nakagawa K, Oya M. 2014.
BACKGROUND: Conventional laparoscopic adrenalectomy (LA) is the gold standard procedure for benign adrenal tumors. Laparoendoscopic single-site adrenalectomy (LESS-A) has been developed as an extension of standard laparoscopic minimally invasive procedures. METHODS: This retrospective study compared the first experience of one surgeon with 70 LESS-A to 140 LA cases with respect to evaluating the influence of the inexperience on surgical outcomes and to assess this surgeon's learning curve for LESS-A. RESULTS: Age, gender, BMI, percentage of patients with prior abdominal surgery, tumor laterality, and tumor size were all

comparable between the two groups. There were no statistically significant differences in any surgical outcomes, including mean operative time, pneumoperitoneum time, estimated blood loss, transfusion requirements, hemoglobin decrease at postoperative day 1, analgesic requirements, postoperative day of oral intake, conversion rate, or morbidity between the two groups. The one exception was hospital stay. There were no mortalities or reoperations in either group. The morbidity rates in the LESS-A group and LA group were 4.2 and 6.4%, respectively (p = 0.528). LESS-A appears to have a steep learning curve and the operative time of the initial 70 cases decreased markedly and remained stable when the experience level exceeded 12 cases. There was no morbidity or conversion in these first 12 LESS-A cases. Multiple regression analysis revealed that surgeon experience (p = 0.008) and tumor size (p = 0.001) were independent predictors of prolonged operative time. CONCLUSIONS: Surgical outcomes of LESS-A were equivalent to those of LA without compromising safety. The introduction of LESS-A at our hospital was smooth and safe. While the indication for LESS-A has been controversial, LESS-A was a useful procedure, especially for cases in which cosmesis is of paramount importance.
PubMed-ID: 24853845
http://dx.doi.org/10.1007/s00464-014-3553-3

Despite Limited Specificity, Computed Tomography Predicts Lateralization and Clinical Outcome in Primary Aldosteronism.
World J Surg, 38(11):2855-62.
Kline GA, Dias VC, So B, Harvey A, Pasieka JL. 2014.
BACKGROUND: Computed tomography (CT) of the adrenals is a common first step for investigation of primary aldosteronism (PA). However, prior studies report poor specificity, necessitating adrenal vein sampling (AVS) prior to surgical consideration. METHODS: We examined our AVS database to determine whether CT adrenal findings could help select patients with a high likelihood of lateralization by AVS or high-value blood pressure (BP) outcomes. Subjects (N = 113) with validated outcomes were divided into groups of CT 'positive' or CT 'negative' according to the presence or absence of an adrenal mass and compared for the outcomes of lateralization by AVS or proportions achieving normotension off medications following surgery. RESULTS: For patients with CT adrenal masses, there was a significantly higher odds ratio (OR) for both outcomes (6.3 and 9.7, p < 0.01). In subgroup analysis, age <40 years carried particularly high odds for lateralization and cure when a CT mass was present (ORs 45 and 26, p < 0.01). Young individuals with normal CT adrenals rarely lateralized (10 %) and, in such patients, even factors like hypokalemia, body mass index (BMI), and plasma aldosterone level did not change the result on regression analysis. CONCLUSIONS: CT-imaged adrenal masses strongly predicted lateralization by AVS and normotension with surgical treatment of lateralized PA. In PA, CT-positive patients should indeed be offered AVS and/or surgery given the high chance of good outcomes; younger CT-negative patients should be advised of a low chance of finding surgical disease by AVS.
PubMed-ID: 25002246
http://dx.doi.org/10.1007/s00268-014-2694-9

(11)C-Hydroxyephedrine Positron Emission Tomography in the Postoperative Management of Pheochromocytoma and Paraganglioma.
Neuroendocrinology, 100(1):60-70.
Yamamoto S, Wassberg C, Hellman P, Sundin A. 2014.
AIM: Accurate detection of recurrent disease and restaging are essential in the postoperative surveillance of many patients with pheochromocytomas (PHEOs) and paragangliomas (PGLs). In this study, the impact of positron emission tomography (PET) and PET/computed tomography (CT) with (11)C-hydroxyephedrine (HED) was evaluated for the postoperative surveillance and diagnosis of recurrent disease and for functional monitoring of locoregional and systemic therapy. METHODS: One hundred and eleven HED-PET and PET/CT examinations performed in 48 patients after surgical intervention for PHEO/PGL were analyzed retrospectively. In a subgroup of 16 patients who underwent systemic and locoregional therapies, the tracer uptake in tumors was also measured as the functional volume (FV), maximum standardized uptake value (SUVmax), mean SUV (SUVmean) and as the total catecholamine transporter tumor volume (TCTTV) calculated as TCTTV = FV x SUVmean. The PET imaging results were correlated with CT/magnetic resonance imaging findings and biochemical and clinical follow-up data. RESULTS: In the first postoperative examination, HED-PET was positive in 24/48 and negative in 24/48 patients with no false-positive results, yielding 92.3% sensitivity and 100% specificity. For the 16 patients, there was a significant correlation between FV and SUVmax and SUVmax and TCTTV. TCTTV correlated significantly with plasma and urinary catecholamines. In 11/16 patients, SUVmax and TCTTV increased/decreased in parallel but not in the remaining 5 patients. CONCLUSION: HED-PET and PET/CT were found to be valuable in the postoperative follow-up in detecting recurrent and metastatic disease. In a subgroup of patients, functional monitoring of systemic and locoregional therapies was feasible by

assessing the changes of the TCTTV, and therefore warrants further prospective evaluation.
PubMed-ID: 25012453
http://dx.doi.org/10.1159/000365516

Genetics and the Clinical Approach to Paragangliomas.
Horm Metab Res, 46(13):964-73.
Schulte KM, Talat N, Galata G, Aylwin S, Izatt L, Eisenhofer G, Barthel A, Bornstein SR. 2014.
This study analyses new information on gene mutations in paragangliomas and puts them into a clinical context. A suspicion of malignancy is critical to determine the workup and surgical approach in adrenal (A-PGL) and extra-adrenal (E-PGL) paragangliomas (PGLs). Malignancy rates vary with location, family history, and gene tests results. Currently there is no algorithm incorporating the above information for clinical use. A sum of 1,821 articles were retrieved from PubMed using the search terms "paraganglioma genetics". Thirty-seven articles were selected of which 9 were analyzed. It was found that 599/2,487 (24%) patients affected with paragangliomas had a germline mutation. Of these 30.2% were mutations in SDHB, 25% VHL, 19.4% RET, 18.4% SDHD, 5.0% NF1, and 2.0% SDHC genes. A family history was positive in 18.1-64.3% of patients. Adrenal PGLs accounted for 55.1% in mutation (+) and 81.0% in mutation (-) patients (RR 1.2, $p < 0.0001$). Bilateral A-PGLs accounted for 56.4% in mutation (+) and 3.2% in mutation (-) patients (RR 8.7, $p < 0.0001$). E-PGL were found in 33.6% of mut+ and 17.3% of mut- (RR 1.7, $p < 0.0001$). In mutation (+) patients PGLs malignancy varied with location, adrenal (6.4%) thoraco-abdominal E-PGL (38%), H & N E-PGL (10%). Malignancy rates were 8.2% in mutation (-) and lower in mutation (+) PGLs except for SDHB 36.5% and SDHC 8.3%. Exclusion of a mutation lowered the probability of malignancy significantly in E-PGL (RR 0.03 (95% CI 0.1-0.6); $p < 0.001$). Mutation analysis provides valuable preoperative information to assess the risk of malignancy in A-PG and E-PGLs and should be considered in the work up of all E-PGL lesions.
PubMed-ID: 25014332
http://dx.doi.org/10.1055/s-0034-1383581

Influence of Adrenal Pathology on Perioperative Outcomes: a Multi-Institutional Analysis.
Am J Surg, 208(4):619-25.
Kiernan CM, Shinall MC, Jr., Mendez W, Peters MF, Broome JT, Solorzano CC. 2014.
BACKGROUND: Endoscopic or open adrenalectomies are performed for variable pathologies. We investigated if adrenal pathology affects perioperative outcomes independent of operative approach. METHODS: A multi-institutional retrospective review of 345 adrenalectomies was performed. A multivariate analysis was utilized. RESULTS: Pathology groups included benign non-pheochromocytoma tumors (50.4%), pheochromocytomas (41%), adrenocortical carcinomas (5.2%), and metastatic tumors (3.4%). Controlling for age, body mass index, tumor size, procedure type, and pathology, pheochromocytomas exhibited greater blood loss (92 mL more, $P = .007$) and operative times (33 min more, $P < .001$) than benign non-pheochromocytoma tumors. Metastatic tumors demonstrated longer operative times (53 min more, $P = .013$). Open adrenalectomy was associated with greater blood loss (396 mL more, $P = .001$), transfusion requirement ($P = .021$), operative times (79 min more, $P < .001$), hospital stay (6.6 days more, $P < .001$) and complications ($P < .001$) when compared with endoscopic adrenalectomy. CONCLUSIONS: The type of adrenal pathology appears to influence blood loss and operative time but not complications in patients undergoing adrenalectomy. Open adrenalectomy remains a major driver of adverse perioperative outcomes.
PubMed-ID: 25129428
http://dx.doi.org/10.1016/j.amjsurg.2014.06.002

Treatment of Cushing's Disease: a Mechanistic Update.
J Endocrinol, 223(2):R19-R39.
Cuevas-Ramos D, Fleseriu M. 2014.
Cushing's disease (CD) is characterized by an ACTH-producing anterior corticotrope pituitary adenoma. If hypothalamus-pituitary-adrenal (HPA) axis physiology is disrupted, ACTH secretion increases, which in turn stimulates adrenocortical steroidogenesis and cortisol production. Medical treatment plays an important role for patients with persistent disease after surgery, for those in whom surgery is not feasible, or while awaiting effects of radiation. Multiple drugs, with different mechanisms of action and variable efficacy and tolerability for controlling the deleterious effects of chronic glucocorticoid excess, are available. The molecular basis and clinical data for centrally acting drugs, adrenal steroidogenesis inhibitors, and glucocorticoid receptor antagonists are reviewed, as are potential novel molecules and future possible targets for CD treatment. Although progress has been made in the understanding of specific corticotrope adenoma receptor physiology and recent clinical studies have detected improved effects with a combined medical therapy approach, there is a clear need for a more efficacious and better-tolerated medical therapy for patients with CD. A better understanding of the

molecular mechanisms in CD and of HPA axis physiology should advance the development of new drugs in the future.
PubMed-ID: 25134660
http://dx.doi.org/10.1530/JOE-14-0300

A New Risk Stratification Algorithm for the Management of Patients With Adrenal Incidentalomas.
Surgery, 156(4):959-65.
Birsen O, Akyuz M, Dural C, Aksoy E, Aliyev S, Mitchell J, Siperstein A, Berber E. 2014.
BACKGROUND: Although adrenal incidentalomas (AI) are detected in </=5% of patients undergoing chest and abdominal computed tomography (CT), their management is challenging. The current guidelines include recommendations from the National Institutes of Health, the American Association of Endocrine Surgeons (AAES), and the American Association for Cancer Education (AACE). The aim of this study was to develop a new risk stratification model and compare its performance against the existing guidelines for managing AI. METHODS: A risk stratification model was designed by assigning points for adrenal size (1, 2, or 3 points for tumors <4, 4-6, or >6 cm, respectively) and Hounsfield unit (HU) density on noncontrast CT (1, 2, or 3 points for HU <10, 10-20, or >20, respectively). This model was applied retrospectively to 157 patients with AI managed in an endocrine surgery clinic to assign a score to each tumor. The utility of this model versus the AAES/AACE guidelines was assessed. RESULTS: Of the 157 patients, 54 (34%), had tumors <4 cm with HU <10 (a score of 2). One third of these were hormonally active on biochemical workup and underwent adrenalectomy. The remaining two thirds were nonsecretory lesions and have been followed conservatively with annual testing. In 103 patients (66%), the adrenal mass was >4 cm and/or had indeterminate features on noncontrast CT (HU >10, irregular borders, heterogeneity), and adrenalectomy was performed after hormonal evaluation was completed (10 were hormonally active on biochemical testing). Seven of these patients (7%) had adrenocortical cancer on final pathology with tumor size <4 cm in 0, 4-6 cm in 1, and >6 cm in 5 patients. Of the hormonally inactive patients, 32% had a score of 3, 38% 4, and 30% 5 or 6. The incidence of adrenocortical cancer in these subgroups was 0, 0, and 25%, respectively. CONCLUSION: This study shows that an algorithm that utilizes the hormonal activity at the first decision step followed by a consolidated risk stratification, based on tumor size and HU density, has a potential to spare a substantial number of patients from unnecessary "diagnostic" surgery for AI.
PubMed-ID: 25239353
http://dx.doi.org/10.1016/j.surg.2014.06.042

Adrenalectomy for Adrenal-Mediated Hypertension: National Surgical Quality Improvement Program Analysis of an Institutional Experience.
Am Surg, 80(11):1152-8.
Shada AL, Stokes JB, Turrentine FE, Simpson VB, Padia SH, Carey RM, Hanks JB, Smith PW. 2014.
Adrenal-mediated hypertension (AMH) has been increasingly treated by laparoscopic adrenalectomy (LA). Metabolic derangements in patients with AMH could result in perioperative complications and mortality. Long-term operative and clinical outcomes after laparoscopic treatment of AMH have not been evaluated using large clinical databases. The institutional National Surgical Quality Improvement Program (NSQIP) data for patients undergoing adrenalectomy for AMH between 2002 and 2012 were reviewed. Patient demographics, perioperative variables, and outcomes were analyzed and compared with national NSQIP adrenalectomy data. Improvement in AMH was recorded when discontinuation or reduction of antihypertensive medication occurred or with a decrease of blood pressure on the preoperative antihypertensive regimen. Ninety-four patients underwent adrenalectomy. There were 48 patients with pheochromocytoma (PHE) and 46 patients with aldosterone-producing adenoma (APA). Eighty-five patients (90%) were taking antihypertensive medications preoperatively compared with 36 patients (38%) postoperatively ($P < 0.0001$). Patients with PHE were more likely to discontinue all medications compared with the patients with APA (80 vs 20%, respectively, $P < 0.0001$). Patients with PHE and APA, respectively, took an average of 2.0 and 3.2 antihypertensive medications preoperatively compared with 0.3 and 1.2 postoperatively. There were no conversions to open procedures or 30-day mortality. Our results were 0 per cent for cerebral vascular accident, 0 per cent for myocardial infarction, and 0.5 per cent for transfusions compared with the national NSQIP data of 0.2, 0, and 6.7 per cent, respectively. Patients presenting with significant AMH including PHE and APA can be effectively and safely treated with LA with minimal complications and with a significant number of patients eliminating or decreasing their need for antihypertensive medications.
PubMed-ID: 25347508

A Novel Staging System for Adrenocortical Carcinoma Better Predicts Survival in Patients With Stage I/II Disease.

Surgery, 156(6):1378-85.
Asare EA, Wang TS, Winchester DP, Mallin K, Kebebew E, Sturgeon C. 2014.
BACKGROUND: Current American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) and European Network for the Study of Adrenal Tumors staging for adrenocortical carcinoma (ACC) have not shown a survival difference between patients with stage I/II disease. This study evaluates current staging systems for survival prediction using a larger cohort and assesses whether incorporating age into ACC staging improves survival predictions. METHODS: Patients in the National Cancer Data Base (1985-2006) with a diagnosis of ACC were identified and staged using a novel TNM-A staging system: Stage I (T1/T2N0M0, age </= 55), stage II (T1/T2N0M0, age >55), stage III (T1/T2N1M0 or T3/T4N0-N1M0, any age), or stage IV (any T any NM1, any age). Differences in overall survival (OS) by stage were compared using a Cox proportional hazards model. RESULTS: Staging was derived for 1,579 of 3,262 patients. Median age was 54 years; mean tumor size was 11.6 cm. Using current staging, differences in 5-year OS was observed only between patients with stages II/III and III/IV ACC. With TNM-A staging, differences in 5-year OS between all stages was significant (I/II [P < .003], II/III [P < .0001], III/IV [P < .0001]). CONCLUSION: A staging system that incorporates patient age better predicts 5-year OS among patients with stages I/II ACC. Consideration should be given to including age in staging for ACC, because it may better inform providers about treatment and prognosis.
PubMed-ID: 25456914
http://dx.doi.org/10.1016/j.surg.2014.08.018

Long-Term Blood Pressure Control in Patients Undergoing Adrenalectomy for Primary Hyperaldosteronism.
Surgery , 156(6):1394-402.
Wachtel H, Cerullo I, Bartlett EK, Kelz RR, Cohen DL, Karakousis GC, Roses RE, Fraker DL. 2014.
BACKGROUND: Data on long-term blood pressure (BP) control after adrenalectomy for primary hyperaldosteronism are limited. We analyzed long-term outcomes to identify factors predictive of cure. METHODS: We performed a retrospective cohort study of patients undergoing adrenalectomy for primary hyperaldosteronism (1997-2013). BP and antihypertensive medications were assessed at long-term follow-up (>/= 12 months). Primary outcome was cure, defined as normotension off antihypertensives. RESULTS: Of 85 patients, 15.3% (n = 13) were cured, 54.1% (n = 46) were normotensive while remaining on anti-hypertensives, and 30.6% (n = 26) were hypertensive. Younger age (P = .011), female sex (P < .001), lesser body mass index (P = .018), shorter duration of hypertension (P = .002), lower creatinine (P = .001), and fewer preoperative antihypertensive medications (P < .001) were associated with cure. Female sex, body mass index </= 25 kg/m(2), hypertension <5 years, creatinine </= 0.8 mg/dL, and <2 antihypertensives were incorporated into a scoring system. For a score of 0-1 (n = 61) the cure rate was 3%; 100% of patients with a score of 4-5 (n = 3) were cured. This scoring system performed comparably to the Aldosterone Resolution Score, which has been used to evaluate short-term postoperative outcomes. CONCLUSION: This is the largest study to identify factors associated with long-term BP control after adrenalectomy and incorporate these into a scoring system. These data provide a potential tool to guide preoperative patient counseling.
PubMed-ID: 25456918
http://dx.doi.org/10.1016/j.surg.2014.08.021

Surgery Is Associated With Improved Survival for Adrenocortical Cancer, Even in Metastatic Disease.
Surgery, 156(6):1531-40.
Livhits M, Li N, Yeh MW, Harari A. 2014.
BACKGROUND: Adrenocortical carcinoma (ACC) is a rare but lethal tumor. Predictors of survival include earlier stage at presentation and complete operative resection. We assessed effect of treatment and demographic variables on survival. METHODS: ACC cases were abstracted from the California Cancer Registry and Office of Statewide Health Planning and Development (1999-2008). Predictors included patient demographics, comorbidities, tumor size, stage, and treatment (none, surgery, chemotherapy and/or radiation [CRT], and surgery plus CRT). RESULTS: We studied 367 patients with median tumor size of 10 cm. At presentation, 37% had localized, 17% had regional, and 46% had metastatic disease. Median survival was 1.7 years (7.4 years local, 2.6 years regional, and 0.3 years metastatic, P < .0001). One-year and 5-year survival was: 92%/62% (local); 73%/39% (regional); and 24%/7% (metastatic). Increased age (hazard ratio [HR] 1.16) and Cushing's syndrome (HR 1.66) worsened survival (P < .05). Low socioeconomic status worsened survival in local and regional disease (P < .05). In multivariable regression, both surgery (regional HR 0.13; metastatic HR 0.52) and surgery plus CRT (regional HR 0.15; metastatic HR 0.31) improved survival compared with no treatment (P < .02). CONCLUSION: In ACC, surgery is associated with improved survival, even in metastatic disease. Surgery should be considered for select patients as part of multimodality treatment.

PubMed-ID: 25456949
http://dx.doi.org/10.1016/j.surg.2014.08.047

From First Symptoms to Final Diagnosis of Cushing's Disease: Experiences of 176 Patients.
Eur J Endocrinol, 172(3):285-9.
Kreitschmann-Andermahr I, Psaras T, Tsiogka M, Starz D, Kleist B, Siegel S, Milian M, Kohlmann J, Menzel C, Fuhrer-Sakel D, Honegger J, Sure U, Muller O, Buchfelder M. 2015.
OBJECTIVE: To obtain structured information on the diagnostic delay in patients with Cushing's disease (CD) from the patients perspective to provide leverage points for earlier diagnosis. DESIGN: The study includes 176 patients with ACTH-dependent CD who had received pituitary surgery completed a self-developed questionnaire on their symptomatology before the illness was diagnosed, the course and length of the diagnostic process, and the role of the involved health care professionals. METHODS: Data were analyzed statistically. Answers in free text options were categorized and counted. RESULTS: The overall diagnostic process took 3.8+/-4.8 years (median 2 years), during which 4.6+/-3.8 (1-30) physicians were consulted, most frequently the family physician (FP; 83.0%). The presented symptoms were various and often vague, e.g. 'poor general condition' (at FPs), or very common in the field of the visited specialist (i.e. 'skin changes' at dermatologists). Women recognized the first CD symptoms themselves significantly more frequently than men, whereas physicians recognized CD symptoms significantly more frequently in males. CONCLUSION: A clear difficulty of diagnosing CD seems that patients describe isolated symptoms to the FP or the respective specialists according to their fields of specialization. As FPs are contacted most frequently, they should be trained to recognize the broad spectrum of CD symptoms, especially in female patients with weight gain, and initiate endocrinological referral.
PubMed-ID: 25501963
http://dx.doi.org/10.1530/EJE-14-0766

PROGRESS IN ALDOSTERONISM: A Review of the Prevalence of Primary Aldosteronism in Pre-Hypertension and Hypertension.
Eur J Endocrinol, 172(5):R191-R203.
Piaditis G, Markou A, Papanastasiou L, Androulakis II, Kaltsas G. 2015.
Primary aldosteronism (PA) secondary to excessive and/or autonomous aldosterone secretion from the renin-angiotensin system accounts for approximately 10% of cases of hypertension and is primarily caused by bilateral adrenal hyperplasia (BAH) or aldosterone-producing adenomas (APAs). Although the diagnosis has traditionally been supported by low serum potassium levels, normokalaemic and even normotensive forms of PA have been identified expanding further the clinical phenotype. Moreover, recent evidence has shown that serum aldosterone correlates with increased blood pressure (BP) in the general population and even moderately raised aldosterone levels are linked to increased cardiovascular morbidity and mortality. In addition, aldosterone antagonists are effective in BP control even in patients without evidence of dysregulated aldosterone secretion. These findings indicate a higher prevalence of aldosterone excess among hypertensive patients than previously considered that could be attributed to disease heterogeneity, aldosterone level fluctuations related to an ACTH effect or inadequate sensitivity of current diagnostic means to identify apparent aldosterone excess. In addition, functioning aberrant receptors expressed in the adrenal tissue have been found in a subset of PA cases that could also be related to its pathogenesis. Recently a number of specific genetic alterations, mainly involving ion homeostasis across the membrane of zona glomerulosa, have been detected in approximately 50% of patients with APAs. Although specific genotype/phenotype correlations have not been clearly identified, differential expression of these genetic alterations could also account for the wide clinical phenotype, variations in disease prevalence and performance of diagnostic tests. In the present review, we critically analyse the current means used to diagnose PA along with the role that ACTH, aberrant receptor expression and genetic alterations may exert, and provide evidence for an increased prevalence of aldosterone dysregulation in patients with essential hypertension and pre-hypertension.
PubMed-ID: 25538205
http://dx.doi.org/10.1530/EJE-14-0537

NET

Meta-Analyses

Curative Versus Palliative Surgical Resection of Liver Metastases in Patients With Neuroendocrine Tumors: a Meta-Analysis of Observational Studies.
Gland Surg, 3(4):243-51.
Bacchetti S, Pasqual EM, Bertozzi S, Londero AP, Risaliti A. 2014.
BACKGROUND: The role of surgical therapy in patients with liver metastases from neuroendocrine tumors (NETs) is unclear. In this study, the results obtained with curative or palliative resection, by reviewing recent literature and performing a meta-analysis, were examined. MATERIALS AND METHODS: A systematic review and meta-analysis of observational studies published between January 1990 and October 2013 were performed. Studies that evaluated the different survival between patients treated by curative or palliative surgical resection of hepatic metastases from NETs were considered. The collected studies were evaluated for heterogeneity, publication bias, and quality. To calculate the pooled hazard ratio (HR) estimate and the 95% confidence interval (95% CI), a fixed-effects model was applied. RESULTS: After the literature search, 2,546 studies were found and, among 38 potentially eligible studies, 3 were considered. We did not find a significant longer survival in patients treated with curative surgical resection of hepatic metastases when compared to palliative hepatic resection HR 0.40 (95% CI: 0.14-1.11). In one study, palliative resection of hepatic metastases significantly increased survival when compared to embolization. CONCLUSIONS: Curative and also palliative surgery of NETs liver metastases may improve survival outcome. However, further randomized clinical trials are needed to elucidate this argument.
PubMed-ID: 25493256
http://dx.doi.org/10.3978/j.issn.2227-684X.2014.02.05

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

A Tailored Approach for Endoscopic Treatment of Small Rectal Neuroendocrine Tumor.
Surg Endosc, 28(10):2931-8.
Heo J, Jeon SW, Jung MK, Kim SK, Shin GY, Park SM, Ahn SY, Yoon WK, Kim M, Kwon YH. 2014.
INTRODUCTION: Resection of rectal neuroendocrine tumors (NETs) less than 1 cm in diameter can be performed using various endoscopic techniques. Endoscopic mucosal resection (EMR) traditionally had suboptimal complete resection rate compared to endoscopic submucosal resection with band ligation (ESMR-L). However, the previous studies did not consider the characteristics of rectal NETs. The aim of our study is to compare the efficacy of ESMR-L and EMR using tailored approach according to the characteristics of rectal NETs. METHODS: 82 rectal NETs in 77 patients treated by ESMR-L (n = 48) or EMR (n = 34) between September 2007 and October 2012 were retrospectively analyzed. ESMR-L was used for flat-type tumors or tumors with non-lifting sign after submucosal injection. Conventional EMR was used for elevated-type tumors or tumors with well-lifting sign after submucosal injection. RESULTS: The pathological complete resection rate was higher in the ESMR-L group (45 lesions, 93.8%) compared with the EMR group (30 lesions, 88.2%); however, this difference was not significant (p = 0.441). Overall complication did not differ significantly between the ESMR-L group and the EMR group (p = 0.774). There was one case of a remnant lesion in the ESMR-L group, which was managed by EMR after circumferential pre-cutting (EMR-P), and no recurrence has been detected in either the ESMR-L or EMR group. CONCLUSIONS: ESMR-L and EMR procedures could have a similar excellent

complete resection rate, if we select the endoscopic resection technique according to the characteristics of the small rectal NETs.
PubMed-ID: 24853847
http://dx.doi.org/10.1007/s00464-014-3555-1

Therapy of Endocrine Disease: Treatment of Malignant Pheochromocytoma and Paraganglioma.
Eur J Endocrinol, 171(3):R111-R122.
Baudin E, Habra MA, Deschamps F, Cote G, Dumont F, Cabanillas M, Arfi-Roufe J, Berdelou A, Moon B, Al GA, Patel S, Leboulleux S, Jimenez C. 2014.
Metastatic pheochromocytomas and paragangliomas (MPPs) present clinicians with three major challenges: scarcity, complexity of characterization, and heterogeneous behavior and prognosis. As with the treatment for all neuroendocrine tumors, the control of hormonal symptoms and tumor growth is the main therapeutic objective in MPP patients. A significant number of MPP patients still die from uncontrolled hormone secretion. In addition, the management of MPPs remains palliative. Steps forward include proper characterization of MPP patients at large cancer referral centers with multidisciplinary teams; improved strategies to stratify patients prognostically; and implementation of trials within national and international networks. Progress in the molecular characterization and staging of MPPs constitutes the basis for significant treatment breakthroughs.
PubMed-ID: 24891137
http://dx.doi.org/10.1530/EJE-14-0113

GEP-NETS Update: a Review on Surgery of Gastro-Entero-Pancreatic Neuroendocrine Tumors.
Eur J Endocrinol, 171(4):R153-R162.
Partelli S, Maurizi A, Tamburrino D, Baldoni A, Polenta V, Crippa S, Falconi M. 2014.
The incidence of neuroendocrine tumors (NETs) has increased in the last decades. Surgical treatment encompasses a panel of approaches ranging from conservative procedures to extended surgical resection. Tumor size and localization usually represent the main drivers in the choice of the most appropriate surgical resection. In the presence of small (<2 cm) and asymptomatic nonfunctioning NETs, a conservative treatment is usually recommended. For localized NETs measuring above 2 cm, surgical resection represents the cornerstone in the management of these tumors. As they are relatively biologically indolent, an extended resection is often justified also in the presence of advanced NETs. Surgical options for NET liver metastases range from limited resection up to liver transplantation. Surgical choices for metastatic NETs need to consider the extent of disease, the grade of tumor, and the presence of extra-abdominal disease. Any surgical procedures should always be balanced with the benefit of survival or relieving symptoms and patients' comorbidities.
PubMed-ID: 24920289
http://dx.doi.org/10.1530/EJE-14-0173

Predictors of Lymph Node Metastases and Impact on Survival in Resected Pancreatic Neuroendocrine Tumors: a Single-Center Experience.
Am J Surg, 208(5):775-80.
Wong J, Fulp WJ, Strosberg JR, Kvols LK, Centeno BA, Hodul PJ. 2014.
BACKGROUND: Staging for pancreatic neuroendocrine tumors (PNET) considers tumor size and lymph node (LN) status; however, correlation with survival remains unclear. METHODS: A single-institution database of patients with resected PNET was analyzed. RESULTS: Of the 150 patients, incidentally discovered PNET was the most common presentation (42%). One hundred thirteen patients (75%) had LN data, 32 (28%) with positive LN (LN+). Procedure and tumor size did not predict LN+. Perineural invasion (P = .016) and lymphovascular (P < .001) invasion, however, were more common in LN+. Multivariate analysis showed poor/moderate differentiation predicted LN+. Median follow-up was 52 months and median overall survival was 225 months. Fifty-two patients (35%) developed recurrence and median disease-free survival (DFS) was 74 months. Only poor/moderate differentiation affected DFS. CONCLUSIONS: PNET has an unclear prognosis based on variables factored into stage. In this study, tumor size did not predict LN+; furthermore, LN+ did not impact overall survival or DFS. Tumor differentiation appears to be more important in determining prognosis.
PubMed-ID: 24997491
http://dx.doi.org/10.1016/j.amjsurg.2014.04.003

Clinical Management of Paragangliomas.
Eur J Endocrinol, 171(6):R231-R243.
Corssmit EP, Romijn JA. 2014.
Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia, which are associated with either sympathetic tissue in adrenal (pheochromocytomas (PCCs)) and extraadrenal (sympathetic

paraganglioma (sPGLs)) locations or parasympathetic tissue of the head and neck paragangliomas (HNPGLs). As HNPGLs are usually benign and most tumors grow slowly, a wait-and-scan policy is often advised. However, their location in the close proximity to cranial nerves and vasculature may result in considerable morbidity due to compression or infiltration of the adjacent structures, necessitating balanced decisions between a wait-and-see policy and active treatment. The main treatment options for HNPGL are surgery and radiotherapy. In contrast to HNPGLs, the majority of sPGL/PCCs produces catecholamines, in advanced cases resulting in typical symptoms and signs such as palpitations, headache, diaphoresis, and hypertension. The state-of-the-art diagnosis and localization of sPGL/PCCs are based on measurement of plasma and/or 24-h urinary excretion of (fractionated) metanephrines and methoxytyramine (MT). sPGL/PCCs can subsequently be localized by anatomical (computed tomography and/or magnetic resonance imaging) and functional imaging studies (123I-metaiodobenzylguanidine-scintigraphy, 111In-pentetreotide scintigraphy, or positron emission tomography with radiolabeled dopamine or dihydroxyphenylalanine). Although most PGL/PCCs are benign, factors such as genetic background, tumor size, tumor location, and high MT levels are associated with higher rates of metastatic disease. Surgery is the only curative treatment. Treatment options for patients with metastatic disease are limited. PGL/PCCs have a strong genetic background, with at least one-third of all cases linked with germline mutations in 11 susceptibility genes. As genetic testing becomes more widely available, the diagnosis of PGL/PCCs will be made earlier due to routine screening of at-risk patients. Early detection of a familial PGL allows early detection of potentially malignant PGLs and early surgical treatment, reducing the complication rates of this operation.
PubMed-ID: 25063320
http://dx.doi.org/10.1530/EJE-14-0396

Outcome of Surgery for Pancreatic Neuroendocrine Neoplasms.
Br J Surg, 101(11):1405-12.
Fischer L, Bergmann F, Schimmack S, Hinz U, Priess S, Muller-Stich BP, Werner J, Hackert T, Buchler MW. 2014.
BACKGROUND: The incidence of pancreatic neuroendocrine neoplasms (pNEN) is increasing. This study aimed to evaluate predictors of overall survival and the indication for surgery. METHODS: Data collected between October 2001 and December 2012 were analysed. Histological grading and staging was based on the classifications of the World Health Organization, the International Union Against Cancer and the European Neuroendocrine Tumour Society. RESULTS: Some 310 patients (150 female, 48.4 per cent) underwent surgical resection. The final survival analysis included 291 patients. Five-year overall survival differed according to tumour grade (G): 91.0 per cent among 156 patients with pancreatic neuroendocrine tumours (pNET) G1, 70.8 per cent in 111 patients with pNET G2, and 20 per cent in 24 patients with pancreatic neuroendocrine carcinomas (pNEC) G3 (P < 0.001). Tumours graded G3 (hazard ratio (HR) 6.96, 95 per cent confidence interval 3.67 to 13.21), the presence of distant metastasis (HR 2.41, 1.32 to 4.42) and lymph node metastasis (HR 2.10, 1.07 to 4.16) were independent predictors of worse survival (P < 0.001, P = 0.004 and P = 0.032 respectively). Eight of 61 asymptomatic patients with pNEN smaller than 2 cm had tumours graded G2 or G3, and six of 51 patients had lymph node metastasis. Among patients with pNEC G3, the presence of distant metastasis had a significant impact on the 5-year overall survival rate: 0 per cent versus 43 per cent in those without distant metastasis (P = 0.036). CONCLUSION: Neuroendocrine tumours graded G3, lymph node and distant metastasis are independent predictors of worse overall survival in patients with pNEN.
PubMed-ID: 25132004
http://dx.doi.org/10.1002/bjs.9603

Long-Term Prognosis of Resected Pancreatic Neuroendocrine Tumors in Von Hippel-Lindau Disease Is Favorable and Not Influenced by Small Tumors Left in Place.
Ann Surg,
de ML, Gaujoux S, Cros J, Hentic O, Vullierme MP, Couvelard A, Cadiot G, Sauvanet A, Ruszniewski P, Richard S, Hammel P. 2014.
BACKGROUND:: Management of pancreatic neuroendocrine tumors (PNETs) associated with von Hippel-Lindau disease (VHL) is challenging because of the malignant potential and difficulty in predicting prognosis. OBJECTIVE:: Compare the long-term outcome of resected VHL-PNET and sporadic PNET. METHODS:: Data of all patients with VHL (n = 23) operated on for nonmetastatic PNET were reviewed. Patient characteristics and recurrence-free survival rates were compared with those in patients operated on for sporadic PNET, matched for tumor size, stage, and Ki-67 index. RESULTS:: Patients in both groups had similar demographic characteristics, except that patients with VHL were younger (36 vs 56 years, P < 0.0001). Median tumor size was 30 mm. Median Ki-67 index was 3% and 4% in the VHL and sporadic groups (P = 0.95), respectively, and lymph node metastases were present in 43% and 30% of cases, respectively (P = 0.45). Sixteen (70%) patients with VHL

had multiple PNET; lesions less than 15 mm were left in place in 11 patients. Median postoperative follow-up was 107 months (interquartile range, 57-124 months) and 71 months (interquartile range, 58-131 months) in the VHL and control groups, respectively. Median recurrence-free survival could not have been.
PubMed-ID: 25185468
http://dx.doi.org/10.1097/SLA.0000000000000856

Diagnostic Imaging in Neuroendocrine Tumors.
J Nucl Med, 55(10):1576-7.
Mansi L, Cuccurullo V. 2014.
PubMed-ID: 25236352
http://dx.doi.org/10.2967/jnumed.114.147082

CUX1: a Modulator of Tumour Aggressiveness in Pancreatic Neuroendocrine Neoplasms.
Endocr Relat Cancer, 21(6):879-90.
Krug S, Kuhnemuth B, Griesmann H, Neesse A, Muhlberg L, Boch M, Kortenhaus J, Fendrich V, Wiese D, Sipos B, Friemel J, Gress TM, Michl P. 2014.
Pancreatic neuroendocrine neoplasms (PNENs) constitute a rare tumour entity, and prognosis and treatment options depend on tumour-mediating hallmarks such as angiogenesis, proliferation rate and resistance to apoptosis. The molecular pathways that determine the malignant phenotype are still insufficiently understood and this has limited the use of effective combination therapies in the past. In this study, we aimed to characterise the effect of the oncogenic transcription factor Cut homeobox 1 (CUX1) on proliferation, resistance to apoptosis and angiogenesis in murine and human PNENs. The expression and function of CUX1 were analysed using knockdown and overexpression strategies in Ins-1 and Bon-1 cells, xenograft models and a genetically engineered mouse model of insulinoma (RIP1Tag2). Regulation of angiogenesis was assessed using RNA profiling and functional tube-formation assays in HMEC-1 cells. Finally, CUX1 expression was assessed in a tissue microarray of 59 human insulinomas and correlated with clinicopathological data. CUX1 expression was upregulated during tumour progression in a time- and stage-dependent manner in the RIP1Tag2 model, and associated with pro-invasive and metastatic features of human insulinomas. Endogenous and recombinant CUX1 expression increased tumour cell proliferation, tumour growth, resistance to apoptosis, and angiogenesis in vitro and in vivo. Mechanistically, the pro-angiogenic effect of CUX1 was mediated via upregulation of effectors such as HIF1alpha and MMP9. CUX1 mediates an invasive pro-angiogenic phenotype and is associated with malignant behaviour in human insulinomas.
PubMed-ID: 25248790
http://dx.doi.org/10.1530/ERC-14-0152

High Prognostic Value of 18F-FDG PET for Metastatic Gastroenteropancreatic Neuroendocrine Tumors: a Long-Term Evaluation.
J Nucl Med, 55(11):1786-90.
Bahri H, Laurence L, Edeline J, Leghzali H, Devillers A, Raoul JL, Cuggia M, Mesbah H, Clement B, Boucher E, Garin E. 2014.
This study aimed to evaluate the long-term prognostic usefulness of (18)F-FDG PET for patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEPNETs). METHODS: Thirty-eight patients with metastatic GEPNETs were prospectively enrolled. Initial check-up comprised CT scan, (111)In-pentetreotide scintigraphy (SRS), and (18)F-FDG PET. Only (18)F-FDG PET-positive lesions with a maximum standardized uptake value (SUVmax) greater than 4.5 or an SUV ratio (SUVmax tumor to SUVmax nontumoral liver tissue, or T/NT ratio) of 2.5 or greater were considered positive for prognosis-that is, indicating a poor prognosis. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Factors associated with survival were assessed with univariate and multivariate analyses, using the Cox regression model. RESULTS: Median PFS and OS were significantly higher for patients with a negative (18)F-FDG PET finding, with an OS of 119.5 mo (95% confidence interval [CI], 72-infinity), than for patients with a positive (18)F-FDG PET finding (only 15 mo [95% CI, 4-27]) ($P < 10(-3)$). Median PFS and OS were significantly higher for the patient group that had a positive SRS than the group with a negative SRS ($P = 0.0002$). For patients with a positive SRS, PFS and OS were significantly shorter when the (18)F-FDG PET finding was positive: 19.5 mo (95% CI, 4-37) for PFS and 119.5 mo (95% CI, 81-infinity) for OS ($P < 10(-3)$). In the patient group with a low-grade GEPNET and a positive SRS, PFS and OS were also significantly lower for patients with a positive (18)F-FDG PET. At 48-mo follow-up, 100% of patients who had a positive (18)F-FDG PET for disease progression (of which 47% were also SRS-positive) were deceased, and 87% of patients with a negative (18)F-FDG PET were alive ($P < 0.0001$). The T/NT ratio was the only parameter associated with OS on multivariate analysis. CONCLUSION: Overall, (18)F-FDG PET appears to be of major importance in the prognostic evaluation of metastatic GEPNET. A positive (18)F-

FDG PET with an SUV ratio (T/NT) of 2.5 or greater was a poor prognostic factor, with a 4-y survival rate of 0%. A positive SRS does not eliminate the need for performing (18)F-FDG PET, which is of greater prognostic utility.
PubMed-ID: 25286923
http://dx.doi.org/10.2967/jnumed.114.144386

Hallmarks of Gastrointestinal Neuroendocrine Tumours: Implications for Treatment.
Endocr Relat Cancer, 21(6):R445-R460.
Walenkamp A, Crespo G, Fierro MF, Fossmark R, Igaz P, Rinke A, Tamagno G, Vitale G, Oberg K, Meyer T. 2014.
In the past few years, there have been advances in the treatment of neuroendocrine tumours (NETs) and improvements in our understanding of NET biology. However, the benefits to patients have been relatively modest and much remains yet to be done. The 'Hallmarks of Cancer', as defined by Hanahan and Weinberg, provide a conceptual framework for understanding the aberrations that underlie tumourigenesis and to help identify potential targets for therapy. In this study, our objective is to review the major molecular characteristics of NETs, based on the recently modified 'Hallmarks of Cancer', and highlight areas that require further research.
PubMed-ID: 25296914
http://dx.doi.org/10.1530/ERC-14-0106

Can Complementary 68Ga-DOTATATE and 18F-FDG PET/CT Establish the Missing Link Between Histopathology and Therapeutic Approach in Gastroenteropancreatic Neuroendocrine Tumors?
J Nucl Med, 55(11):1811-7.
Has SD, Kuyumcu S, Turkmen C, Sanli Y, Aykan F, Unal S, Adalet I. 2014.
Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are indolent neoplasms presenting unpredictable and unusual biologic behavior that causes many clinical challenges. Tumor size, existence of metastasis, and histopathologic classification remain incapable in terms of treatment decision and prognosis estimation. This study aimed to compare (68)Ga-DOTATATE and (18)F-FDG PET/CT in GEPNETs and to investigate the relation between the complementary PET/CT results and histopathologic findings in the management of therapy, particularly in intermediate-grade patients. METHODS: The relation between complementary (68)Ga-DOTATATE and (18)F-FDG PET/CT results of 27 GEPNET patients (mean age, 56 y; age range, 33-79 y) and histopathologic findings was evaluated according to grade and localization using standardized maximum uptake values and Ki67 indices. Grade 2 (G2) patients were further evaluated in 2 groups as G2a (3%-9%) and G2b (10%-20%) according to Ki67 indices. RESULTS: The sensitivity of (68)Ga-DOTATATE and (18)F-FDG PET/CT was 95% and 37%, respectively, and the positive predictive values were 93.8% and 36.2%, respectively. The sensitivity in detecting liver metastasis, lymph nodes, bone metastasis, and primary lesion was 95%, 95%, 90%, and 93% for (68)Ga-DOTATATE and 40%, 28%, 28%, and 75% for (18)F-FDG, respectively. Statistically significant differences were found between grades 1-2, 2a-2b, and 1-2b with respect to (68)Ga-DOTATATE PET/CT as well as between 1-2a and 1-2b with respect to (18)F-FDG PET/CT. However, no statistical differences were found between 1 and 2a ($P > 0.05$) for (68)Ga-DOTATATE and 2a and 2b ($P = 0.484$) for (18)F-FDG. The impact of the combined (18)F-FDG and (68)Ga-DOTATATE PET/CT on the therapeutic decision was 59%. CONCLUSION: Combined (68)Ga-DOTATATE and (18)F-FDG PET/CT is helpful in the individual therapeutic approach of GEPNETs and can overcome the shortcomings of histopathologic grading especially in intermediate-grade GEPNETs.
PubMed-ID: 25315243
http://dx.doi.org/10.2967/jnumed.114.142224

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors.
N Engl J Med, 371(16):1556-7.
Caplin ME, Pavel M, Ruszniewski P. 2014.
PubMed-ID: 25317881
http://dx.doi.org/10.1056/NEJMc1409757

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors.
N Engl J Med, 371(16):1555-6.
Ozdemir N, Yazici O, Zengin N. 2014.
PubMed-ID: 25317882
http://dx.doi.org/10.1056/NEJMc1409757#SA1

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors.
N Engl J Med, 371(16):1556.

Yang F, Jin C, Fu D. 2014.
PubMed-ID: 25317883
http://dx.doi.org/10.1056/NEJMc1409757#SA2

Can PET/CT Guide the Personalized Treatment of Patients With Gastroenteropancreatic Neuroendocrine Neoplasms?
J Nucl Med, 55(11):1757-8.
Schillaci O. 2014.
PubMed-ID: 25342386
http://dx.doi.org/10.2967/jnumed.114.147538

GEP-NETS Update: Interventional Radiology: Role in the Treatment of Liver Metastases From GEP-NETs.
Eur J Endocrinol, 172(4):R151-R166.
de BT, Deschamps F, Tselikas L, Ducreux M, Planchard D, Pearson E, Berdelou A, Leboulleux S, Elias D, Baudin E. 2015.
Neuroendocrine tumors from gastro-pancreatic origin (GEP-NET) can be responsible for liver metastases. Such metastases can be the dominant part of the disease as well due to the tumor burden itself or the symptoms related to such liver metastases. Intra-arterial therapies are commonly used in liver only or liver-dominant disease and encompass trans-arterial chemoembolization (TACE), trans-arterial embolization (TAE), and radioembolization (RE). TACE performed with drug emulsified in Lipiodol has been used for the past 20 years with reported overall survival in the range of 3-4 years, with objective response up to 75%. Response to TACE is higher when treatment is used as a first-line therapy and degree of liver involvement is lower. Benefit of TACE over TAE is unproven in randomized study, but reported in retrospective studies namely in pancreatic NETs. RE provides early interesting results that need to be further evaluated in terms of benefit and toxicity. Radiofrequency ablation allows control of small size and numbered liver metastases, with low invasiveness. Ideal metastases to target are one metastasis <5 cm, or three metastases <3 cm, or a sum of diameter of all metastases below 8 cm. Ablation therapies can be applied in the lung or in the bones when needed, and more invasive surgery should be probably saved for large-size metastases. Even if the indication of image-guided therapy in the treatment of GEP-NET liver metastases needs to be refined, such therapies allow for manageable invasive set of treatments able to address oligometastatic patients in liver, lung, and bones. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stage of the disease.
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Tumor-Associated Macrophages Are a Useful Biomarker to Predict Recurrence After Surgical Resection of Nonfunctional Pancreatic Neuroendocrine Tumors.
Ann Surg, 260(6):1088-94.
Wei IH, Harmon CM, Arcerito M, Cheng DF, Minter RM, Simeone DM. 2014.
OBJECTIVE: Patients with nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) have poorer survival than those with functional PNETs. Our objective was to identify risk factors for recurrence after resection to better define surveillance parameters to improve long-term outcomes. METHODS: A retrospective analysis was performed for NF-PNET patients who underwent resection at the University of Michigan from 1995 to 2012. Immunohistochemical staining of tissues from patients with and without disease recurrence was performed for Ki-67 and the macrophage marker CD68, as tumor-associated macrophages are important for PNET development and progression. Clinicopathological factors and patient outcomes were measured. RESULTS: Ninety-seven NF-PNET patients underwent surgical resection. There was a recurrence rate of 14.4% (14/97). The median time to recurrence was 0.61 years, with 10 (71%) patients recurring within the first 2 years. Six of 7 patients (86%) monitored at 6-month surveillance intervals were diagnosed with recurrence on their first computed tomographic scan or during the intervening intervals. By Cox proportional hazards analysis, the most significant independent risk factors for recurrence were higher grade, stage, and intraoperative blood loss. High CD68 score and Ki-67 index correlated with recurrence risk, and Ki-67 index inversely correlated with time to recurrence. In patients who otherwise had few risk factors, a high CD68 score was a significant prognostic factor for recurrence. CONCLUSIONS: In patients with NF-PNETs, risk factors associated with recurrence were high EBL, grade, stage, CD68 score, and Ki-67 index. The CD68 score was an important prognostic factor in patients who otherwise had few clinicopathological risk factors; therefore, the CD68 score should be considered when planning surveillance strategies. We recommend that NF-PNET patients at high risk of recurrence undergo initial surveillance every 3 months for 2 years after surgery.
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Measurements of Plasma Metanephrines by Immunoassay Vs Liquid Chromatography With Tandem Mass Spectrometry for Diagnosis of Pheochromocytoma.
Eur J Endocrinol, 172(3):251-60.
Weismann D, Peitzsch M, Raida A, Prejbisz A, Gosk M, Riester A, Willenberg HS, Klemm R, Manz G, Deutschbein T, Kroiss M, Darr R, Bidlingmaier M, Januszewicz A, Eisenhofer G, Fassnacht M. 2015.
BACKGROUND: Reports conflict concerning measurements of plasma metanephrines (MNs) for diagnosis of pheochromocytomas/paragangliomas (PPGLs) by immunoassays compared with other methods. We aimed to compare the performance of a commercially available enzyme-linked immunoassay (EIA) kit with liquid chromatography-tandem mass spectrometric (LC-MS/MS) measurements of MNs to diagnose PPGLs. METHODS: In a substudy of a prospective, multicenter trial to study the biochemical profiles of monoamine-producing tumors, we included 341 patients (174 males and 167 females) with suspected PPGLs (median age 54 years), of whom 54 had confirmed PPGLs. Plasma MNs were measured by EIA and LC-MS/MS, each in a specialized laboratory. RESULTS: Plasma normetanephrine (NMN) and MN were measured 60 and 39% lower by EIA than by LC-MS/MS. Using upper cut-offs stipulated for the EIA, diagnostic sensitivity was only 74.1% at a specificity of 99.3%. In contrast, use of similar cut-offs for MN and overall lower age-adjusted cut-offs for NMN measured by LC-MS/MS returned a diagnostic sensitivity and specificity of 98.1 and 99.7%. Areas under receiver-operating characteristic curves, nevertheless, indicated comparable diagnostic performance of the EIA (0.993) and LC-MS/MS (0.985). Diagnostic sensitivity for the EIA increased to 96.2% with a minimal loss in specificity (95.1%) following use of cut-offs for the EIA adapted to correct for the negative bias. CONCLUSIONS: The EIA underestimates plasma MNs and diagnostic sensitivity is poor using commonly stipulated cut-offs, resulting in a high risk for missing patients with PPGLs. Correction of this shortcoming can be achieved by appropriately determined cut-offs resulting in comparable diagnostic performance of EIA and LC-MS/MS assays.
PubMed-ID: 25452465
http://dx.doi.org/10.1530/EJE-14-0730

A Practical Method to Determine the Site of Unknown Primary in Metastatic Neuroendocrine Tumors.
Surgery, 156(6):1359-65.
Maxwell JE, Sherman SK, Stashek KM, O'Dorisio TM, Bellizzi AM, Howe JR. 2014.
INTRODUCTION: The site of a primary neuroendocrine tumor (NET) tumor is unknown before treatment in approximately 20% of small bowel (SBNET) and pancreatic (PNET) cases despite extensive workup. It can be difficult to discern a PNET from an SBNET on hematoxylin and eosin stains, and thus, more focused diagnostic tests are required. Immunohistochemistry (IHC) and gene expression profiling are two methods used to identify the tissue of origin from biopsied metastases. METHODS: Tissue microarrays were created from operative specimens and stained with up to seven antibodies used in the NET-specific IHC algorithm. Expression of four genes for differentiating between PNETs and SBNETs was determined by quantitative polymerase chain reaction and then used in a previously validated gene expression classifier (GEC) algorithm designed to determine the primary site from gastrointestinal NET metastases. RESULTS: The accuracy of the IHC algorithm in identifying the primary tumor site from a set of 37 metastases was 89%, with only one incorrect call. Three other samples were indeterminate as the result of pan-negative staining. The GEC's accuracy in a set of 136 metastases was 94%. The algorithm identified the primary tumor site in all cases in which IHC failed. CONCLUSION: Performing IHC, followed by GEC for indeterminate cases, identifies accurately the primary site in SBNET and PNET metastases in virtually all patients.
PubMed-ID: 25456909
http://dx.doi.org/10.1016/j.surg.2014.08.008

Hypoglycemia After Resection of Pheochromocytoma.
Surgery, 156(6):1404-8.
Chen Y, Hodin RA, Pandolfi C, Ruan DT, McKenzie TJ. 2014.
BACKGROUND: Hypoglycemia after resection of pheochromocytoma is a rare and poorly understood complication thought to be secondary to rebound hyperinsulinemia and increased peripheral glucose uptake. We examined the incidence of this complication and aimed to identify predisposing risk factors. METHODS: Patients who underwent pheochromocytoma resection between 1993 and 2013 at 2 large academic medical centers were identified retrospectively from a research patient data registry. The primary end point was postoperative hypoglycemia defined as blood glucose <55 mg/dL. RESULTS: A total of 213 patients underwent resection of pheochromocytoma for a total of 215 operations. Nine patients (4.2%) experienced postoperative hypoglycemia, with 8 of 9 episodes occurring in the first 24 hours. Patients who developed hypoglycemia were more likely to have greater preoperative 24-hour urinary metanephrine (4,726 vs 2,461 mug/24 h, P = .05) and experienced.
PubMed-ID: 25456920
http://dx.doi.org/10.1016/j.surg.2014.08.020

Reappraisal of Lymphatic Mapping for Midgut Neuroendocrine Patients Undergoing Cytoreductive Surgery.
Surgery , 156(6):1498-502.
Wang YZ, Carrasquillo JP, McCord E, Vidrine R, Lobo ML, Zamin SA, Boudreaux P, Woltering E. 2014.
BACKGROUND: We previously reported that midgut neuroendocrine tumors (NETs) often develop alternative lymphatic drainage owing to lymphatic obstructions from extensive mesenteric lymphadenopathy, making intraoperative lymphatic mapping mandatory. We hypothesize that this innovative approach needs a longer term validation. METHODS: We updated our results by reviewing 303 patients who underwent cytoreduction from November 2006 to October 2011. Of these patients, 112 had lymphatic mappings and 98 were for midgut NET primaries. Among them, 77 mappings were for the initial cytoreduction and 35 were for reexploration and further cytoreduction. The operative findings, pathology reports, and long-term surgical outcomes were reviewed. RESULTS: Lymphatic mapping changed traditional resection margins in 92% of patients. Of the 35 patients who underwent reexploration without initial mapping, 19 (54%) showed a recurrence at or near the anastomotic sites. In contrast, none of the 112 mapped patients had shown signs of recurrence in a 1- to 5-year follow-up. Additionally, 20 of 45 ileocecal valves (44.4%) were spared in patients whose tumors were at the terminal ileum that, traditionally, would call for a right hemicolectomy. CONCLUSION: With a longer follow-up, lymphatic mapping has proven to be a safe and effective way to prevent local recurrences and preserve the ileocecal valve for selected patients.
PubMed-ID: 25456941
http://dx.doi.org/10.1016/j.surg.2014.05.028

Comparison of Tumor Markers for Predicting Outcomes After Resection of Nonfunctioning Pancreatic Neuroendocrine Tumors.
Surgery, 156(6):1504-10.
Cherenfant J, Talamonti MS, Hall CR, Thurow TA, Gage MK, Stocker SJ, Lapin B, Wang E, Silverstein JC, Mangold K, Odeleye M, Kaul KL, Lamzabi I, Gattuso P, Winchester DJ, Marsh RW, Roggin KK, Bentrem DJ, Baker MS, Prinz RA. 2014.
BACKGROUND: This study compares the predictability of 5 tumor markers for distant metastasis and mortality in pancreatic neuroendocrine tumors (PNETs). METHODS: A total of 128 patients who underwent pancreatectomy for nonfunctioning PNETs between 1998 and 2011 were evaluated. Tumor specimens were stained via immunochemistry for cytoplasmic and nuclear survivin, cytokeratin 19 (CK19), c-KIT, and Ki67. Univariate and multivariate regression analyses and receiver operating characteristics curve were used to evaluate the predictive value of these markers. RESULTS: A total of 116 tumors (91%) were positive for cytoplasmic survivin, 95 (74%) for nuclear survivin, 85 (66.4%) for CK19, 3 for c-KIT, and 41 (32%) for Ki67 >3%. Twelve (9%) tumors expressed none of the markers. Survivin, CK19, and c-KIT had no substantial effect on distant metastasis or mortality. Age >55 years, grade 3 histology, distant metastasis, and Ki67 >3% were associated with mortality ($P < .05$). A cut-off of Ki67 >3% was the best predictor (83%) of mortality with an area under the curve of 0.85. Ki67 >3% also predicted occurrence of distant metastases with odds ratio of 9.22 and 95% confidence interval of 1.55-54.55 ($P < .015$). CONCLUSION: Of the 5 markers studied, only Ki67 >3% was greatly associated with distant metastasis and death. Survivin, CK19, and c-KIT had no prognostic value in nonfunctioning PNETs.
PubMed-ID: 25456943
http://dx.doi.org/10.1016/j.surg.2014.08.043

Predictors of Recurrence in Pheochromocytoma.
Surgery, 156(6):1523-7.
Press D, Akyuz M, Dural C, Aliyev S, Monteiro R, Mino J, Mitchell J, Hamrahian A, Siperstein A, Berber E. 2014.
BACKGROUND: The recurrence rate of pheochromocytoma after adrenalectomy is 6.5-16.5%. This study aims to identify predictors of recurrence and optimal biochemical testing and imaging for detecting the recurrence of pheochromocytoma. METHODS: In this retrospective study we reviewed all patients who underwent adrenalectomy for pheochromocytoma during a 14-year period at a single institution. RESULTS: One hundred thirty-five patients had adrenalectomy for pheochromocytoma. Eight patients (6%) developed recurrent disease. The median time from initial operation to diagnosis of recurrence was 35 months. On multivariate analysis, tumor size >5 cm was an independent predictor of recurrence. One patient with recurrence died, 4 had stable disease, 2 had progression of disease, and 1 was cured. Recurrence was diagnosed by increases in plasma and/or urinary metanephrines and positive imaging in 6 patients (75%), and by positive imaging and normal biochemical levels in 2 patients (25%). CONCLUSION: Patients with large tumors (>5 cm) should be followed vigilantly for recurrence. Because 25% of patients with recurrence had normal biochemical levels, we recommend routine imaging and testing of plasma or urinary metanephrines for prompt diagnosis of recurrence.

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http://dx.doi.org/10.1016/j.surg.2014.08.044

Cytological Ki-67 in Pancreatic Endocrine Tumors: a New "Must"?
Gland Surg, 3(4):219-21.
Franchi G, Manzoni MF. 2014.
In the last decades, the incidence of neuroendocrine tumors (NETs) has been rising and this might be due to more awareness, improved diagnostic tools and a change in definition. The histopathological type of the tumor, its Ki-67 or MIB-1 proliferation index, size and location, as well as the age of the patient, seems to be the most important factor that affects prognosis and survival. In 2008, in one of our studies, we concluded that the cytological Ki-67 may improve the preoperative assessment of pancreatic NETs (pNETs), helping the clinician choosing the optimal therapeutical approach". Although the literature reports discordant opinions on the value of tumor proliferation markers in predicting a patient's prognosis, many studies have then reinforced the idea that Ki-67 expression in histological sections obtained from pNETs is an important predictor of their biological behaviour. The WHO classification of pNETs includes Ki-67.
PubMed-ID: 25493251
http://dx.doi.org/10.3978/j.issn.2227-684X.2014.08.02

Grading of EUS-FNA Cytologic Specimens From Patients With Pancreatic Neuroendocrine Neoplasms: It Is Time Move to Tissue Core Biopsy?
Gland Surg, 3(4):222-5.
Vinayek R, Capurso G, Larghi A. 2014.
Pancreatic neuroendocrine neoplasms (p-NENs) are rare and characterized by an indolent course, with a much better prognosis than non-neuroendocrine tumors of the pancreas. In the non-functional class of p-NENS, surgery remains the only curative treatment for early localized disease, but there are few therapeutic options for advanced disease. The prognosis of non-functional p-NENs is determined by many clinical criteria. In 2010, however, the World Health Organization (WHO) introduced a grading system in which determination of the Ki-67 proliferative index has become essential with key role in determining therapeutic decision in both advanced and early diseases. Conventionally, Ki-67 has been assessed on surgical specimens. In last decade, however, the availability of EUS-guided fine needle aspiration (EUS-FNA) has provided the opportunity to sample pancreatic lesions and to assess the value of this parameter pre-operatively. The few studies reporting the use of EUS-FNA cytological specimens for Ki-67 measurement showed promising results. As shown by Weynand and colleagues FNA-cytology may underestimate the staging and caution in using this method to classify tumors as low-grade (G1) should be adopted. Thus, Ki-67 expression on cytological specimens remains unsatisfactory and the need for tissue biopsy specimens has been strongly advocated. Based on a recent study that has reported a high concordance of EUS-guided core biopsy for histologic examination and surgical specimens, especially when a cut-off of 5% is used to differentiate G1 and G2 tumors, EUS tissue acquisition by core biopsy is ready for prime time and should be adopted as a standard of practice.
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Impact of 68Ga-DOTATATE PET/CT on the Management of Neuroendocrine Tumors: the Referring Physician's Perspective.
J Nucl Med, 56(1):70-5.
Herrmann K, Czernin J, Wolin EM, Gupta P, Barrio M, Gutierrez A, Schiepers C, Mosessian S, Phelps ME, Allen-Auerbach MS. 2015.
Somatostatin receptor imaging with (68)Ga-DOTATATE PET/CT (DOTATATE) is increasingly used for managing patients with neuroendocrine tumors. The objective of this study was to determine referring physicians' perspectives on the impact of DOTATATE on the management of neuroendocrine tumors. METHODS: A set of 2 questionnaires (pre-PET and post-PET) was sent to the referring physicians of 100 consecutive patients with known or suspected neuroendocrine tumors, who were evaluated with DOTATATE. Questionnaires on 88 patients were returned (response rate, 88%). Referring physicians categorized the DOTATATE findings on the basis of the written PET reports as negative, positive, or equivocal for disease. The likelihood for metastatic disease was scored as low, moderate, or high. The intended management before and changes as a consequence of the PET study were indicated. RESULTS: The indications for PET/CT were initial and subsequent treatment strategy assessments in 14% and 86% of patients, respectively. Referring physicians reported that DOTATATE led to a change in suspicion for metastatic disease in 21 patients (24%; increased and decreased suspicion in 9 [10%] and 12 [14%] patients, respectively). Intended management changes were reported in 53 of 88 (60%) patients. Twenty patients (23%) scheduled to undergo chemotherapy were switched

to treatments without chemotherapy, and 6 (7%) were switched from watch-and-wait to other treatment strategies. Conversely, 5 patients (6%) were switched from their initial treatment strategy to watch-and-wait. CONCLUSION: This survey of referring physicians demonstrates a substantial impact of DOTATATE on the intended management of patients with neuroendocrine tumors.
PubMed-ID: 25500825
http://dx.doi.org/10.2967/jnumed.114.148247

Long-Term Results of the Surgical Management of Insulinoma Patients With MEN1: a Groupe D'Etude Des Tumeurs Endocrines (GTE) Retrospective Study.
Eur J Endocrinol, 172(3):309-19.
Vezzosi D, Cardot-Bauters C, Bouscaren N, Lebras M, Bertholon-Gregoire M, Niccoli P, Levy-Bohbot N, Groussin L, Bouchard P, Tabarin A, Chanson P, Lecomte P, Guilhem I, Carrere N, Mirallie E, Pattou F, Peix JL, Goere D, Borson-Chazot F, Caron P, Bongard V, Carnaille B, Goudet P, Baudin E. 2015.
OBJECTIVE: Management of insulinomas in the context of MEN1 remains poorly studied. The aim of this study was to evaluate long-term results of various surgical approaches in a large cohort of insulinoma-MEN1 patients. DESIGN AND METHODS: Consecutive insulinoma-MEN1 patients operated on for a nonmetastatic insulinoma between 1957 and 2010 were retrospectively selected from the MEN1 database of the French Endocrine Tumor Group. The type of surgery was categorized as distal pancreatectomy (DP), total pancreatectomy/cephalic duodenopancreatectomy (TP/CDP), or enucleation (E). Primary endpoint was time until recurrence of hypoglycemia after initial surgery. Secondary endpoints were post-operative complications. RESULTS: The study included 73 patients (median age=28 years). Surgical procedures were DP (n=46), TP/CDP (n=9), or E (n=18). After a median post-operative follow-up of 9.0 years (inter-quartile range (IQR): 2.5-16.5 years), 60/73 patients (82.2%) remained hypoglycemia free. E and TP/CDP were associated with a higher risk of recurrent hypoglycemia episodes (unadjusted hazard ratio: 6.18 ((95% CI: 1.54-24.8); P=0.010) for E vs DP and 9.51 ((95% CI: 1.85-48.8); P=0.007) for TP/CDP vs DP. After adjustment for International Union against Cancer pTNM classification, enucleation remained significantly associated with a higher probability of recurrence. Long-term complications had occurred in 20 (43.5%) patients with DP, five (55.6%) with TP/CDP, but in none of the patients who have undergone E (P=0.002). CONCLUSION: In the French Endocrine database, DP is associated with a lower risk for recurrent hypoglycemia episodes. Due to lower morbidity, E alone might be considered as an alternative.
PubMed-ID: 25538206
http://dx.doi.org/10.1530/EJE-14-0878

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

The Profile of Successful Applicants for Endocrine Surgery Fellowships: Results of a National Survey.
Am J Surg, 208(4):685-9.
Kulaylat AN, Kenning EM, Chesnut CH, III, James BC, Schubart JR, Saunders BD. 2014.
BACKGROUND: The American Association of Endocrine Surgeons initiated a fellowship match in 2007. The profile of applicants who successfully match into an endocrine surgery (ES) fellowship has not previously been characterized. METHODS: An institutional review board-approved, web-based survey was distributed to recent and current ES fellows. RESULTS: The survey response rate was 62% (56/90). The overall mean age was 33 years (standard deviation +/-3), 54% were female, and 37% self-identified as non-white. Only 5% entered their surgical training with the aim of specializing in ES. During residency, respondents were exposed to high volumes of index ES cases. Sixty-two percent had dedicated research time. At the time of fellowship application, the median number of publications was 5 (range, 0 to 25), and 30% of respondents had additional advanced degrees. CONCLUSION: Entering ES fellows has diverse backgrounds, with strong academic credentials. These data help inform the career mentoring of aspiring ES applicants.
PubMed-ID: 25048570
http://dx.doi.org/10.1016/j.amjsurg.2014.03.013

Exome Sequencing Reveals Mutant Genes With Low Penetrance Involved in MEN2A-Associated Tumorigenesis.
Endocr Relat Cancer, 22(1):23-33.
Cai J, Li L, Ye L, Jiang X, Shen L, Gao Z, Fang W, Huang F, Su T, Zhou Y, Wang W, Ning G. 2015.
Activating rearranged during transfection (RET) mutations function as the initiating causative mutation for multiple endocrine neoplasia type 2A (MEN2A). However, no conclusive findings regarding the non-RET genetic events have been reported. This is the first study, to our knowledge, examining genomic alterations in matched MEN2A-associated tumors. We performed exome sequencing and SNP array analysis of matched MEN2A tumors and germline DNA. Somatic alterations were validated in an independent set of patients using Sanger sequencing. Genes of functional interest were further evaluated. The germline RET mutation was found in all MEN2A-component tumors. Thirty-two somatic mutations were identified in the nine MEN2A-associated tumors, of which 28 (87.5%) were point mutations and 4 (12.5%) were small insertions, duplications, or deletions. We sequenced all the mutations as well as coding sequence regions of the 12 genes in an independent sample set including 35 medullary thyroid cancers (20 MEN2A) and 34 PCCs (22 MEN2A), but found no recurrent mutations. Recurrent alterations were found in 13 genes with either mutations or alterations in copy number, including an EIF4G1 mutation (p. E1147V). Mutation of EIF4G1 led to increased cell proliferation and RET/MAPK phosphorylation, while knockdown of EIF4G1 led to reduced cell proliferation and RET/MAPK phosphorylation in TT, MZ-CRC1, and PC-12 cells. We found fewer somatic mutations in endocrine tumors compared with non-endocrine tumors. RET was the primary driver in MEN2A-associated tumors. However, low-frequency alterations such as EIF4G1 might participate in MEN2A-associated tumorigenesis, possibly by

regulating the activity of the RET pathway.
PubMed-ID: 25404689
http://dx.doi.org/10.1530/ERC-14-0225

2014 American Association of Endocrine Surgeons Presidential Address: Evolution.
Surgery, 156(6):1289-96.
Carty SE. 2014.
PubMed-ID: 25456898
http://dx.doi.org/10.1016/j.surg.2014.08.072

Readmission After Thyroidectomy and Parathyroidectomy: What Can We Learn From NSQIP?
Surgery, 156(6):1419-22.
Wang TS, Yen TW. 2014.
PubMed-ID: 25456924
http://dx.doi.org/10.1016/j.surg.2014.08.084

Risk Factors for 30-Day Hospital Readmission After Thyroidectomy and Parathyroidectomy in the United States: An Analysis of National Surgical Quality Improvement Program Outcomes.
Surgery, 156(6):1423-30.
Mullen MG, LaPar DJ, Daniel SK, Turrentine FE, Hanks JB, Smith PW. 2014.
BACKGROUND: The 30-day readmission rate is a quality metric under the Affordable Care Act. Readmission rates after thyroidectomy and parathyroidectomy and associated factors remain ill-defined. We evaluated patient and perioperative factors for association with readmission after thyroidectomy and parathyroidectomy. METHODS: The American College of Surgeons National Surgical Quality Improvement Program Participant Use File (2011) data for thyroid (n = 3,711) and parathyroid (n = 3,358) resections were analyzed. Patient- and operation-related factors were assessed by univariate and multivariate analyses. RESULTS: Among 7,069 patients, 30-day readmission rate was 4.0%: 4.1% after thyroidectomy and 3.8% after parathyroidectomy. Significant associations for 30-day readmission included declining functional status (odds ratio [OR], 6.4-10.1), preoperative hemodialysis (OR, 2.6; 95% CI, 1.5-4.7), malnutrition (OR, 3.4; 95% CI, 1.2-10.1), increasing American Society of Anesthesiologists class (OR 1.3-4.7), unplanned reoperation (OR, 61.6), and length of stay (LOS) <24 hours (OR, 0.61; 95% CI, 0.45-0.85; all P < .05). Readmission was associated with greater total and postoperative LOS and major postoperative complications, including renal insufficiency (all P < .01). CONCLUSION: Thirty-day readmission after cervical endocrine resection occurs in 4% of patients. Discharge within 24 hours of operation does not affect the likelihood of readmission. Risk factors for readmission are multifactorial and driven by preoperative conditions. Decreasing the index hospital stay and preventing major postoperative complications may decrease readmissions and improve quality metrics.
PubMed-ID: 25456925
http://dx.doi.org/10.1016/j.surg.2014.08.074

Risk Scoring Can Predict Readmission After Endocrine Surgery.
Surgery, 156(6):1432-8.
Iannuzzi JC, Fleming FJ, Kelly KN, Ruan DT, Monson JR, Moalem J. 2014.
BACKGROUND: Hospitals and surgeons simultaneously are pressured to decrease readmissions and duration of stay. We hypothesized that readmissions after endocrine surgery could be predicted by using a novel risk-score. METHODS: The National Surgical Quality Improvement Program database was queried for cervical endocrine operations performed during 2011 and 2012. The primary end point was unplanned readmission within 30 days. Multivariable logistic regression was used to create and validate a scoring system to predict unplanned readmissions. RESULTS: Overall, 34,046 cases were included with a readmission rate of 2.8% (n = 947). The most frequent reasons for readmission were hypocalcemia (32.4%) surgical-site infection (8.4%), and hematoma (8.0%) (2012 data only). The readmission risk score was created using the following factors: thyroid malignancy, hypoalbuminemia, renal insufficiency, American Society of Anesthesiologists class, and duration of stay >1 day. Predicted readmission rate by number of risk factors was 1.7 % for 0 risk factors, 3.2% for 1 risk factor (5-11 points), 5.8% for 2 risk factors, 10.5% for 3 risk factors, and 18.0% for 4 risk factors. The model had good predictive ability with c = 0.646. CONCLUSION: Readmissions after cervical endocrine operations can be predicted. This risk score could be used to direct resource use for preoperative, inpatient, and outpatient care delivery to reduce readmissions.
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http://dx.doi.org/10.1016/j.surg.2014.08.023

Endocrine Surgery in Present-Day Academia.
Surgery, 156(6):1461-9.
Kuo JH, Pasieka JL, Parrack KM, Chabot JA, Lee JA. 2014.
BACKGROUND: Endocrine surgery is a specialty that is evolving constantly. In this study, we sought to delineate the practice patterns of surgeons taking care of endocrine diseases in present-day academic centers. METHODS: A review of the Faculty Practice Solutions Center database was conducted for the years 2005, 2009, and 2013. Practice patterns were determined by International Classification of Diseases, 9th Revision and Current Procedural Terminology codes, and analyzed for practice composition, regional variability, and volume of endocrine operations. RESULTS: Of 97 national academic centers, 52 were identified to have 120 practicing American Association of Endocrine Surgeons (AAES) surgeons in the study. On average, endocrine operations comprise approximately 65% of the AAES surgeon's practice, and 51% are considered high-volume surgeons for thyroidectomy, parathyroidectomy, and adrenalectomy. Most non-AAES surgeons who perform endocrine operations are otolaryngologists (24.5%) and other general surgeons (18.5%). Overall, non-AAES surgeons perform the majority of endocrine operations at academic institutions (61.6%), and low-volume surgeons perform most of these operations (55.6%). CONCLUSION: Research has shown that high-volume surgeons have improved outcomes. Even in academia, however, the majority of endocrine operations are performed by low-volume surgeons, suggesting that there is an opportunity for expanding the number of surgeons with expertise in endocrine surgery in present-day academic centers.
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http://dx.doi.org/10.1016/j.surg.2014.08.025