EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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

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

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Journals covered

Journal	IF2013	Journal	IF2013
Acta Cytol	1.562	J Bone Miner Res	6.589
Am J Kidney Dis	5.756	J Clin Endocrinol Metab	6.310
Am J Nephrol	2.646	J Clin Oncol	17.879
Am J Surg	2.406	J Endocrinol	3.586
Am Surgeon	0.918†	J Endocrinol Invest	1.552
Ann Surg	7.188	J Nephrol	1.996
Ann Surg Oncol	3.943	J Nucl Med	5.563
ANZ J Surg	1.098	J Surg Oncol	2.843
Br J Surg	5.210	Lancet	39.207
Cancer	4.901	Langenbecks Arch Surg	2.160
Chirurg	0.516	Laryngoscope	2.032
Clin Endocrinol Oxf	3.353	N Engl J Med	54.420
Clin Nucl Med	2.857	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	12.958
Curr Opin Oncol	3.761	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	15.696
Endocr Relat Cancer	4.907	Nephrol Dial Transplant	3.488
Endocr Rev	19.358	Nephron Clin Pract	1.652†
Eur Arch Otorhinolaryngol	1.608	Neuroendocrinology	4.934
Eur J Endorcrinol	3.686	Oncologist	4.540
Eur J Surg Oncol	2.892	Otolaryngol Head Neck Surg	1.721
Gland Surg	---	Surg Clin North Am	1.932
Head Neck	3.006	Surg Endosc	3.313
Horm Metab Res	2.038	Surg Laparosc Endosc Percutan Tech	0.938
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	1.748	Surg Oncol	2.367
JAMA Surg (*prev:* Arch Surg)	4.297	Surg Oncol Clin N Am	1.674
Int J Cancer	5.007	Surgery	3.105
J Am Coll Surg	4.454	Thyroid	3.843
J Am Soc Nephrol	9.466	Updates In Surgery	---
J Bone Miner Metab	2.114	World J Surg	2.348

Journal names are links to the journal's homepage!, IF2013: Impact factor 2013, †IF 2012, no IF for 2013

Thyroid

Meta-Analyses

Rare metastases of well-differentiated thyroid cancers: a systematic review.
Ann Surg Oncol, 22(2):460-6.
A. Madani, Y. Jozaghi, R. Tabah, J. How and E. Mitmaker. 2015.
BACKGROUND: A minority of metastatic well-differentiated thyroid cancer (WDTC) patients present with end-organ disease other than in the lung, bone or lymph nodes. These metastases tend to be overlooked because of their low incidence, and this results in delayed diagnosis. The purpose of this study was to perform a systematic review of the clinical and histologic features of unusual WDTC metastases. METHODS: A systematic literature search of bibliographic databases, reference lists of articles, and conference proceedings was performed up to 2013. Studies were included if they reported on adult patients with WDTC and pathology-proven metastases to end-organs other than lung, bone, or lymph nodes. A total of 238 studies were included in a qualitative analysis. Data is expressed as N (%) and median [interquartile range]. RESULTS: A total of 492 patients (median age, 62 years [50-70 years]) were identified in 197 case reports and 42 case series. There were 22 different end-organ metastatic sites documented with either papillary [255 (57 %)], follicular [172 (39 %)], or Hurthle-cell [18 (4 %)] histology. A total of 181 (41 %) patients presented with solitary metastasis and 54 (93 %) with elevated serum thyroglobulin. Positron emission tomography and whole-body radioactive iodine scans revealed hypermetabolic foci in 28 (97 %) and 50 (81 %) cases, respectively. Disease-free interval following the initial diagnosis of the primary thyroid cancer was highly variable, ranging from synchronous presentation [66 (33 %)] to metachronous disease after 516 months [mean 86 months (SD 90)]. CONCLUSIONS: WDTC can manifest with highly variable and unusual clinical features. Rare sites of metastases should be considered in the absence of the more common extra-cervical disease recurrence locations.
PubMed-ID: 25192681
http://dx.doi.org/10.1245/s10434-014-4058-y

Risk Factors for Central Compartment Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: A Meta-Analysis.
World J Surg, 39(10):2459-70.
N. Qu, L. Zhang, Q. H. Ji, J. Y. Chen, Y. X. Zhu, Y. M. Cao and Q. Shen. 2015.
BACKGROUND: The surgical management of papillary thyroid microcarcinoma (PTMC), especially regarding the necessity of central lymph node dissection (CLND), remains controversial. This meta-analysis was conducted to investigate the clinicopathologic factors predictive of central compartment lymph node metastasis (CLNM) in patients diagnosed with PTMC. METHODS: PubMed, EMBASE, Ovid, Web of Science, and the Cochrane Library were searched from their inception to September 2013. Published studies that explored the association between clinicopathologic factors and CLNM in PTMC patients were included. From the identified studies, we extracted the number of individuals with or without each risk factor to calculate the CLNM-positive proportions and used fixed/random-effects models for the meta-analyses of overall relative risk (RR). The pooling analysis on the association between CLNM or the different CLNDs and prognosis was also conducted. RESULTS: A total of 19 eligible studies that included 8345 patients were identified. Three studies did therapeutic CLND, while the other 16 studies performed prophylactic CLND in PTMC patients. Meta-analyses revealed that CLNM was associated with male gender (RR = 1.36; 95 % CI 1.22-1.52, p = 0.001), younger age (<45 years; RR = 1.15; 95 % CI 1.04-1.27, p = 0.006), larger tumor size (>5 mm; RR = 1.51 95 % CI 1.32-1.65, p = 0.001), multifocality (RR = 1.40; 95 % CI 1.27-1.54, p = 0.001), and extrathyroidal extension (RR = 1.81; 95 % CI 1.34-2.43, p = 0.001). Meta-regression analysis indicated that a disparity in the proportion of PTMC patients with CLNM in each study was the main factor resulting in heterogeneity among the 19 studies. In addition, the pooling analyses suggested that CLNM did not significantly predict neck recurrences [hazard ratio (HR) = 0.95, 95 % CI 0.67-1.22, p = 0.054], and the prophylactic CLND group did not improve local control significantly compared to the therapeutic group (RR = 0.96, 95 % CI 0.46-2.01, p = 0.544). CONCLUSION: Prophylactic CLND may be performed in PTMC patients with clinically uninvolved central lymph nodes but with high risk factors; multicenter studies with long-term follow-up are recommended to better understand the risk factors and surgical management for central nodes in PTMC.
PubMed-ID: 26099728
http://dx.doi.org/10.1007/s00268-015-3108-3

Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis.
Clin Endocrinol (Oxf), 82(2):280-5.
P. Trimboli, G. Treglia, L. Guidobaldi, F. Romanelli, G. Nigri, S. Valabrega, R. Sadeghi, A. Crescenzi, W. C. Faquin, M. Bongiovanni and L. Giovanella. 2015.
BACKGROUND: The early detection of medullary thyroid carcinoma (MTC) can improve patient prognosis, because histological stage and patient age at diagnosis are highly relevant prognostic factors. As a consequence, delay in the diagnosis and/or incomplete surgical treatment should correlate with a poorer prognosis for patients. Few papers have evaluated the specific capability of fine-needle aspiration cytology (FNAC) to detect MTC, and small series have been reported. This study conducts a meta-analysis of published data on the diagnostic performance of FNAC in MTC to provide more robust estimates. RESEARCH DESIGN AND METHODS: A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted by searching for the terms 'medullary thyroid' AND 'cytology', 'FNA', 'FNAB', 'FNAC', 'fine needle' or 'fine-needle'. The search was updated until 21 March 2014, and no language restrictions were used. RESULTS: Fifteen relevant studies and 641 MTC lesions that had undergone FNAC were included. The detection rate (DR) of FNAC in patients with MTC (diagnosed as 'MTC' or 'suspicious for MTC') on a per lesion-based analysis ranged from 12.5% to 88.2%, with a pooled estimate of 56.4% (95% CI: 52.6-60.1%). The included studies were statistically heterogeneous in their estimates of DR (I-square >50%). Egger's regression intercept for DR pooling was 0.03 (95% CI: -3.1 to 3.2, P = 0.9). The study that reported the largest MTC series had a DR of 45%. Data on immunohistochemistry for calcitonin in diagnosing MTC were inconsistent for the meta-analysis. CONCLUSIONS: The presented meta-analysis demonstrates that FNAC is able to detect approximately one-half of MTC lesions. These findings suggest that other techniques may be needed in combination with FNAC to diagnose MTC and avoid false negative results.
PubMed-ID: 25047365
http://dx.doi.org/10.1111/cen.12563

Randomized controlled trials

Prospective randomized study on injury of the external branch of the superior laryngeal nerve during thyroidectomy comparing intraoperative nerve monitoring and a conventional technique.
Head Neck, 37(10):1456-60.
H. Masuoka, A. Miyauchi, T. Higashiyama, T. Yabuta, M. Fukushima, Y. Ito, M. Kihara, K. Kobayashi, O. Yamada, A. Nakayama and A. Miya. 2015.
BACKGROUND: The external branch of the superior laryngeal nerve (SLN) is susceptible to injuries during thyroidectomy, causing voice impairment. Intraoperative nerve monitoring may facilitate identification of the nerve, reducing voice impairment. METHODS: A total of 252 patients undergoing thyroidectomy were randomly assigned to group N (the NIM-Response 3.0 system was used) or group C (the conventional technique using the Vari-Stim 3 was used) to identify the external branch of the SLNs. The primary endpoint was the identification rate of the external branch of the SLN. The secondary endpoint was the incidence of postoperative voice impairment. RESULTS: The visual and the electrostimulatory identification rates of the external branch of the SLN in group N and group C were 48.8% versus 17.8% ($p < .001$) and 89.2% versus 17.8% ($p < .001$), respectively. The proportion of female patients who had subjective voice impairment was significantly smaller in group N than in group C. CONCLUSION: The use of the NIM-Response 3.0 significantly improved the identification rate of the external branch of the SLN during thyroidectomy, reducing voice impairment.
PubMed-ID: 24844580
http://dx.doi.org/10.1002/hed.23778

Efficacy of a Single Preoperative Dexamethasone Dose to Prevent Nausea and Vomiting After Thyroidectomy (the tPONV Study): A Randomized, Double-blind, Placebo-controlled Clinical Trial.
Ann Surg, 262(6):934-40.
I. Tarantino, R. Warschkow, U. Beutner, W. Kolb, A. Luthi, C. Luthi, B. M. Schmied and T. Clerici. 2015.
OBJECTIVE: Does dexamethasone given before thyroidectomy reduce postoperative nausea and vomiting (PONV) in a randomized controlled trial? BACKGROUND: PONV is an unsettling problem that commonly occurs in patients after thyroidectomy. Various preventive measures have been studied; however, many of these studies have been criticized for their biases (eg, use of opioids, sex selection) or were even retracted. METHODS: This single-institution, randomized, double-blind, placebo-controlled, superiority study was performed between January 1, 2011, and May 30, 2013. Patients undergoing thyroidectomy for benign disease

were allocated by a block randomized list to receive a preoperative single dose of dexamethasone (8 mg) or placebo. Patients and staff were blinded to the treatment assignment. The primary endpoint was the incidence of PONV assessed at 4, 8, 16, 24, 32, and 48 hours after surgery. To observe an incidence reduction of 50%, a total of 152 patients were required for the study. RESULTS: The total incidence of PONV was reported in 65 of 152 patients (43%; 95% confidence interval [CI], 35-51). In the intention-to-treat analysis, PONV occurred in 22 of 76 patients (29%; 95% CI, 20-40) in the treatment arm and in 43 of 76 patients (57%; 95% CI, 45-67) in the control arm (P = 0.001; odds ratio = 0.31; 95% CI, 0.16-0.61; absolute risk reduction = 28%; 95% CI, 12-42). The number needed to treat was 4. No severe dexamethasone-related adverse events were observed during the study. CONCLUSIONS: A single dose of preoperative dexamethasone administration is an effective, safe, and economical measure to reduce PONV incidence after thyroidectomy.
PubMed-ID: 25563879
http://dx.doi.org/10.1097/SLA.0000000000001112

The role of carbon nanoparticles in identifying lymph nodes and preserving parathyroid in total endoscopic surgery of thyroid carcinoma.
Surg Endosc, 29(10):2914-20.
B. Wang, N. C. Qiu, W. Zhang, C. X. Shan, Z. G. Jiang, S. Liu and M. Qiu. 2015.
AIM: To evaluate the efficacy of carbon nanoparticles (CNs) in identifying lymph nodes and preserving parathyroids in endoscopic total thyroidectomy (ETT) with central neck dissection (CND), and to further explore the role of CNs in recovering postoperative parathyroid function. METHOD: Fifty-five patients with papillary thyroid carcinoma were randomized to either CN group (n = 28) or control group (n = 27). The primary outcome measures were pathological results (e.g., amount of incidental removed parathyroids and lymph nodes dissected) and follow-up results [e.g., recovery of serum calcium and parathyroid hormone (PTH) levels]. The secondary end-points were the rates of neuromuscular symptoms, in-hospital postoperative hormonal assay, and lymph node metastases. RESULTS: A total of 193 lymph nodes in the CN group and 123 lymph nodes in the control group were detected. The mean number of detected lymph nodes was significantly higher in the CN group than in the control group (P = 0.009). Parathyroids were present in the thyroid or central nodal specimens of five patients, which were all in the control group. The control group had a relatively higher incidence of incidental parathyroidectomy compared to the CN group (P = 0.023). Compared to the CN group, the incidence of paresthesia was higher in the control group even if not statistically significant. During follow-up, the serum calcium levels were higher in the CN group than in the control group; however, there was no statistically significant difference. For the serum PTH levels, the CN group recovered rapidly to the preoperative levels, whereas the control group climbed steadily to the normal range. The serum PTH levels in the CN group were apparently higher than in the control group at 1 week and 1 month postoperatively. CONCLUSION: CNs play an important role in protecting parathyroid glands, dissecting lymph nodes thoroughly, and promoting rapid recovery of parathyroid in ETT with CND (ChiCTR-TRC-14005042).
PubMed-ID: 25761552
http://dx.doi.org/10.1007/s00464-014-4020-x

Safety and tolerability of sorafenib in patients with radioiodine-refractory thyroid cancer.
Endocr Relat Cancer, 22(6):877-87.
F. Worden, M. Fassnacht, Y. Shi, T. Hadjieva, F. Bonichon, M. Gao, L. Fugazzola, Y. Ando, Y. Hasegawa, J. Park do, Y. K. Shong, J. W. Smit, J. Chung, C. Kappeler, G. Meinhardt, M. Schlumberger and M. S. Brose. 2015.
Effective adverse event (AE) management is critical to maintaining patients on anticancer therapies. The DECISION trial was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial which investigated sorafenib for treatment of progressive, advanced, or metastatic radioactive iodine-refractory, differentiated thyroid carcinoma. Four hundred and seventeen adult patients were randomized (1:1) to receive oral sorafenib (400 mg, twice daily) or placebo, until progression, unacceptable toxicity, noncompliance, or withdrawal. Progression-free survival, the primary endpoint of DECISION, was reported previously. To elucidate the patterns and management of AEs in sorafenib-treated patients in the DECISION trial, this report describes detailed, by-treatment-cycle analyses of the incidence, prevalence, and severity of hand-foot skin reaction (HFSR), rash/desquamation, hypertension, diarrhea, fatigue, weight loss, increased serum thyroid stimulating hormone, and hypocalcemia, as well as the interventions used to manage these AEs. By-cycle incidence of the above-selected AEs with sorafenib was generally highest in cycle 1 or 2 then decreased. AE prevalence generally increased over cycles 2-6 then stabilized or declined. Among these AEs, only weight loss tended to increase in severity (from grade 1 to 2) over time; severity of HFSR and rash/desquamation declined over time. AEs were mostly grade 1 or 2, and were generally managed with dose interruptions/reductions, and concomitant medications (e.g. antidiarrheals, antihypertensives, dermatologic preparations). Most dose interruptions/reductions occurred in early cycles. In conclusion, AEs with sorafenib in DECISION were typically

grade 1 or 2, occurred early during the treatment course, and were manageable over time.
PubMed-ID: 26370187
http://dx.doi.org/10.1530/ERC-15-0252

Consensus Statements/Guidelines

Same thyroid cancer, different national practice guidelines: When discordant American Thyroid Association and National Comprehensive Cancer Network surgery recommendations are associated with compromised patient outcome.
Surgery, 159(1):41-50.
M. A. Adam, P. Goffredo, L. Youngwirth, R. P. Scheri, S. A. Roman and J. A. Sosa. 2015.
BACKGROUND: The American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) guidelines have discordant recommendations for managing patients with differentiated thyroid cancer (DTC). We hypothesized that physician adherence to either of the 2009 extent of surgery guidelines of the ATA or NCCN was associated with improved survival, and that practice is most standardized nationally when guidelines are concordant. METHODS: Adult patients undergoing surgery for DTC were included from the National Cancer Database. Multivariable modeling was used to identify factors associated with nonadherence to the 2009 ATA or NCCN guidelines (2010-2011) and hypothetically examine the association of retrospective adherence to guidelines with survival (1998-2006). RESULTS: A total of 39,687 patients with DTC were included; 2,249 were not treated in accordance with ATA or NCCN guidelines. Factors independently associated with nonadherence were discordance between ATA and NCCN recommendations, black race, and treatment at nonacademic centers ($P < .01$). After adjustment, care not in accordance with either set of guidelines was associated with compromised survival (hazard ratio 1.16, $P = .02$). CONCLUSION: A minority of patients received surgery for DTC not aligned with guidelines; nonadherent care was associated with compromised survival. Discordance in recommendations between guidelines is associated with reduction in adherent care, suggesting that standardizing guidelines could decrease confusion, increase adherence, and thereby may improve outcomes.
PubMed-ID: 26435426
http://dx.doi.org/10.1016/j.surg.2015.04.056

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.
Thyroid, 26(1):1-133.
B. R. Haugen, E. K. Alexander, K. C. Bible, G. M. Doherty, S. J. Mandel, Y. E. Nikiforov, F. Pacini, G. W. Randolph, A. M. Sawka, M. Schlumberger, K. G. Schuff, S. I. Sherman, J. A. Sosa, D. L. Steward, R. M. Tuttle and L. Wartofsky. 2015.
BACKGROUND: Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. Since the American Thyroid Association's (ATA's) guidelines for the management of these disorders were revised in 2009, significant scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer. METHODS: The specific clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on knowledge synthesis methods, including electronic database searching, review and selection of relevant citations, and critical appraisal of selected studies. Published English language articles on adults were eligible for inclusion. The American College of Physicians Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations for therapeutic interventions. We developed a similarly formatted system to appraise the quality of such studies and resultant recommendations. The guideline panel had complete editorial independence from the ATA. Competing interests of guideline task force members were regularly updated, managed, and communicated to the ATA and task force members. RESULTS: The revised guidelines for the management of thyroid nodules include recommendations regarding initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, use of molecular markers, and management of benign thyroid nodules. Recommendations regarding the initial management of thyroid cancer include those relating to screening for thyroid cancer, staging and risk assessment, surgical management, radioiodine remnant ablation and therapy, and thyrotropin suppression

therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using imaging and serum thyroglobulin, thyroid hormone therapy, management of recurrent and metastatic disease, consideration for clinical trials and targeted therapy, as well as directions for future research. CONCLUSIONS: We have developed evidence-based recommendations to inform clinical decision-making in the management of thyroid nodules and differentiated thyroid cancer. They represent, in our opinion, contemporary optimal care for patients with these disorders.
PubMed-ID: 26462967
http://dx.doi.org/10.1089/thy.2015.0020

Other Articles

Significance of allelic percentage of BRAF c.1799T > A (V600E) mutation in papillary thyroid carcinoma.
Ann Surg Oncol, 21 Suppl 4:S619-26.
S. P. Cheng, Y. C. Hsu, C. L. Liu, T. P. Liu, M. N. Chien, T. Y. Wang and J. J. Lee. 2015.
BACKGROUND: Somatic BRAF mutation is frequently observed in papillary thyroid carcinoma (PTC). Recent evidence suggests that PTCs are heterogeneous tumors containing a subclonal or oligoclonal occurrence of BRAF mutation. Conflicting results have been reported concerning the prognostic significance of the mutant allele frequency. Our present aim was to investigate the association between the percentage of BRAF c.1799T > A (p.Val600Glu) alleles and clinicopathological parameters in PTC. METHODS: Genomic DNA was extracted from fresh-frozen specimens obtained from 50 PTC patients undergoing total thyroidectomy. The BRAF mutation status was determined by Sanger sequencing. The percentage of mutant BRAF alleles was quantified by mass spectrometric genotyping, pyrosequencing, and competitive allele-specific TaqMan PCR (castPCR). RESULTS: Positive rate of BRAF mutation was 72 % by Sanger sequencing, 82 % by mass spectrometric genotying, and 84 % by pyrosequencing or castPCR. The average percentage of mutant BRAF alleles was 22.5, 31, and 30.7 %, respectively. There was a good correlation among three quantification methods (Spearman's rho = 0.87-0.97; $p < 0.0001$). The mutant allele frequency was significantly correlated with tumor size (rho = 0.47-0.52; $p < 0.01$) and extrathyroidal invasion. The frequency showed no difference in pathological lymph node metastasis. CONCLUSIONS: The percentage of mutant BRAF alleles is positively associated with tumor burden and extrathyroidal invasion in PTC. Relatively good correlations exist among mass spectrometric genotyping, pyrosequencing, and castPCR in quantification of mutant BRAF allele frequency.
PubMed-ID: 24748129
http://dx.doi.org/10.1245/s10434-014-3723-5

Loss of ERbeta expression in papillary thyroid carcinoma is associated with recurrence in young female.
Clin Endocrinol (Oxf), 82(2):300-6.
H. Y. Ahn, M. S. Kim, M. J. Kim, S. Y. Cho, Y. A. Kim, G. H. Lee, B. C. Lee, Y. J. Park and K. H. Yi. 2015.
OBJECTIVES: We investigated the expression of oestrogen receptors (ERs) in papillary thyroid cancers (PTCs) and evaluated their prognostic role. METHODS: We enrolled 81 female patients who underwent thyroid surgery and had a confirmed diagnosis of PTC between 01 January 1995 and 31 December 1996. Data on clinicopathologic parameters were obtained from patients' medical records. Tissue paraffin blocks of these 81 patients were collected for immunohistochemistry for ERalpha and ERbeta. RESULTS: ERalpha expression was observed in only eight patients (9.9%). In contrast, ERbeta expression was positive in 36 (44.4%) patients. Total thyroidectomy (84.4% vs 61.1%, P = 0.017) and cervical lymph node metastasis (62.2% vs 22.2%, P = 0.000) were more frequent in the ERbeta-negative group than in the ERbeta-positive group. Among younger female patients (<45 years), the ERbeta-negative group showed a tendency towards more frequent recurrent or persistent disease than the ERbeta-positive group (42.3% vs 13.6%, P = 0.029). In contrast, the ERalpha-positive group showed more recurrent or persistent disease than the ERalpha-negative group in older female patients (100% vs 24.1%, P = 0.024). In multivariate analysis, ERbeta negativity, extrathyroidal invasion and radioactive iodine treatment were risk factors for recurrence in young female patients. CONCLUSION: Loss of ERbeta expression was associated with recurrence in young female PTC patients. This finding suggests that oestrogen might play a protective role in the progression of PTC via ERbeta, especially in young female patients.
PubMed-ID: 24801822
http://dx.doi.org/10.1111/cen.12486

Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer.
Head Neck, 37(9):1336-43.
M. H. Wu, W. T. Shen, J. Gosnell and Q. Y. Duh. 2015.
BACKGROUND: The presence and location of regional lymph node metastasis affect the prognosis of patients with thyroid cancer. Lymph node classification of the current TNM system may be inadequate because it insufficiently characterizes the nature and severity of lymph node metastasis that may influence prognosis. METHODS: We retrospectively studied 240 patients with papillary thyroid cancer and node metastases who had undergone total thyroidectomy, lymph node dissection, and postoperative (131) I treatment at the University Cancer Center between 1994 and 2004. We reviewed the status of regional lymph node metastasis, including the location, number, largest size, and extranodal tumor extension and analyzed their effect on the prognosis of the patients. RESULTS: There were 172 women and 68 men, with a median age of 38 years and median tumor size of 1.9 cm. Thirty-five percent had only central compartment (N1a) nodal metastasis and 65% had involvement of both central and lateral compartments (N1b). There were a median of 4 nodes containing metastasis with a median largest diameter of 1.2 cm. Sixty patients (25%) had extranodal extension of cancer. Multivariate analysis showed that patient age ($p = .0017$; hazard ratio [HR], 2.156), >3 lymph node metastasis ($p = .0316$; HR, 1.806), and extranodal extension ($p < .0001$; HR, 4.027) were independent predictors of disease recurrence. Patient age ($p = .0034$; HR, 22.068), vascular invasion ($p = .01$; HR, 8.2), and extranodal extension ($p = .022$; HR, 12.597) were independent predictors of disease-specific survival (DSS). The DSS and recurrence-free survival curve between patients with and without extranodal extension differ significantly ($p < .0001$). For those older than 45 years, the 10-year recurrence was 11 of 43 patients for those without extranodal extension and 24 of 27 patients for those with extranodal extension ($p < .001$). Among patients with stage 4a/4b, those with extranodal extension had a significantly worse DSS and disease-free survival (DFS; $p < .001$) than those without extranodal extension. The prognosis of patients with stage 4a/4b cancer who had no extranodal extension was the same as patients with stage 3 cancer. The status of extranodal extension seems to be a stronger prognostic predictor than the location of metastatic lymph nodes (N1a/1b). CONCLUSION: Presence of extranodal extension of metastatic nodes is a significant adverse independent prognostic factor for patients with lymph node metastasis from papillary cancer. This may need to be considered in future updates of the TNM system for thyroid cancer.
PubMed-ID: 24821456
http://dx.doi.org/10.1002/hed.23747

BRAF mutation in fine-needle aspiration specimens as a potential predictor for persistence/recurrence in patients with classical papillary thyroid carcinoma larger than 10 mm at a BRAF mutation prevalent area.
Head Neck, 37(10):1432-8.
H. J. Moon, E. K. Kim, W. Y. Chung, D. Y. Shin and J. Y. Kwak. 2015.
BACKGROUND: The association between the BRAF mutation and persistence/recurrence was investigated in patients with classical papillary thyroid carcinoma (PTC) at a BRAF mutation prevalent area. METHODS: A total of 282 patients with total thyroidectomy and prophylactic central neck dissection were included in this study. The BRAF mutation was evaluated with cytology specimen using dual priming oligonucleotide (DPO)-based multiplex polymerase chain reaction (PCR) and direct sequencing preoperatively. RESULTS: Thirty-four patients (12%) had persistence/recurrence. In all PTC, the BRAF mutation on both methods was not associated with persistence/recurrence. In PTC >10 mm, the BRAF mutation on DPO-based multiplex PCR was significantly associated with persistence/recurrence and a potential predictor for persistence/recurrence. In PTC </=10 mm, none of the covariates were significantly different between patients with and without persistence/recurrence. CONCLUSION: The BRAF mutation was significantly associated with persistence/recurrence and a potential predictor in patients with classical PTC >10 mm at a BRAF mutation prevalent area.
PubMed-ID: 24838814
http://dx.doi.org/10.1002/hed.23770

Assessing safety and outcomes in outpatient versus inpatient thyroidectomy using the NSQIP: a propensity score matched analysis of 16,370 patients.
Ann Surg Oncol, 22(2):429-36.
N. Khavanin, A. Mlodinow, J. Y. Kim, J. P. Ver Halen, A. K. Antony and S. Samant. 2015.
BACKGROUND: With increasing economic healthcare constraints and an evolving understanding of patient selection criteria and patient safety, outpatient thyroidectomy is now more frequently employed. However, robust statistical analyses evaluating outcomes and safety after outpatient thyroidectomy with matched comparisons to inpatient cohorts are lacking. METHODS: The 2011-2012 NSQIP datasets were queried to identify all patients undergoing thyroidectomy. Inpatient and outpatient procedures cohorts were matched 1:1 using propensity

score analysis to assess outcomes. Outcomes of interest included surgical and medical complications, reoperation, mortality, and readmission. Univariate and multivariate analyses were utilized to identify predictors of these events. Relative risk ratios were calculated for adverse events between inpatient and outpatient cohorts. RESULTS: In total, 21,508 patients were identified to have undergone a thyroidectomy in 2011-2012. Inpatients and outpatients were matched 1:1 with respect to preoperative and operative characteristics, leaving 8,185 patients in each treatment arm. After matching, overall 30-day morbidity was rare with only 250 patients (1.53 %) experiencing any perioperative morbidity. 476 patients (2.91 %) were readmitted within 30-days of the operation. Both pre- and post-matching, inpatient thyroidectomy was associated with increased risks of readmission, reoperation, and any complication. CONCLUSIONS: Based on this comprehensive population-based study, outpatient thyroidectomy appears to be at least as safe as inpatient thyroidectomy. However, there are still differences in outcomes between inpatient and outpatient cohorts, despite statistical matching of preoperative and intraoperative variables. Future research needs to be spent identifying these as-of-yet unknown risk factors to resolve this discrepancy.
PubMed-ID: 24841353
http://dx.doi.org/10.1245/s10434-014-3785-4

Clinical significance of integrin beta6 as a tumor recurrence factor in follicular thyroid carcinoma.
Head Neck, 37(10):1439-47.
Z. N. Zhuang, Z. J. Xu, Q. Zhou, X. Z. Xu, J. Tian, Y. F. Liu, S. Guo, J. Y. Wang and K. S. Xu. 2015.
BACKGROUND: Overexpression of integrin beta6 plays an important role in a variety of malignant tumor invasion and metastasis. METHODS: The expression levels of integrin beta6, matrix metalloproteinase (MMP)-2 and MMP-9 were analyzed by immunohistochemistry with human follicular thyroid carcinomas. Then we investigated their correlation with clinical outcomes parameters, relationship, and the survival time. RESULTS: The integrin beta6 staining was expressed in cellular membrane and cytoplasm of follicular thyroid carcinoma cells. The MMP-2 and MMP-9 expressions were mainly found in cellular cytoplasm. In correlation with the clinical outcome parameters of 60 patients, there were significant statistical differences of integrin beta6, MMP-2, and MMP-9 expression levels in different size of tumor. Integrin beta6 and MMP-9 expressions have significant statistical differences in T classifications. MMP-2 and MMP-9 expressions have significant statistical differences in different M classification. Other clinical outcome parameters had no significant statistical differences. CONCLUSION: Integrin beta6 expression correlated significantly with MMP-9 expression, and may be a valuable recurrence indicator for follicular thyroid carcinomas.
PubMed-ID: 24844802
http://dx.doi.org/10.1002/hed.23780

The impact of locoregional recurrences and distant metastases on the survival of patients with papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 82(2):286-94.
D. H. Su, S. H. Chang and T. C. Chang. 2015.
OBJECTIVE: Some patients with papillary thyroid carcinoma (PTC) would suffer from locoregional recurrences or distant metastases. This study was aimed to elucidate the impacts of locoregional recurrences and distant metastases on these patients' survival. DESIGN: Retrospective hospital-based cohort study. POPULATION: Data were collected from 1636 subjects with PTC at National Taiwan University Hospital between 1985 and 2007. MEASUREMENTS: Overall and disease-specific survival curves were estimated by the Kaplan-Meier method. Time-independent and time-dependent prognostic factors were included simultaneously in multivariate analyses using Cox models. RESULTS: Overall survival (OS) rates at 10- and 20-years were 90% and 76%, respectively. The 10- and 20-year disease-specific survival (DSS) rates were 95% and 90%, respectively. Our multivariate analyses identified that older age, distant metastases (hazard ratio, HR: 6.69, 95% CI: 4.40-10.18), locoregional recurrences (HR: 1.88, 95% CI: 1.22-2.89), lymph node metastases, massive extrathyroid extension, male gender and larger tumour size (>4 cm) were significantly associated with poorer OS. Older age, distant metastases (HR: 15.03, 95% CI: 8.31-27.21), locoregional recurrences (HR: 3.63, 95% CI: 2.03-6.51), massive extrathyroid extension, male gender and larger tumour size (>4 cm) were independently related to worse DSS. The performance of high-dose (131) I ablation had a protective effect on OS and DSS. CONCLUSION: The locoregional recurrences had a moderately harmful impact on OS and DSS, but age and distant metastases were the major decisive factors for OS and DSS. High-dose (131) I ablation had a protective role. However, lymph node dissection did not alter the prognosis whenever lymph node metastases only influenced OS.
PubMed-ID: 24863061
http://dx.doi.org/10.1111/cen.12511

Follicular variant of papillary thyroid carcinoma with B-type Raf(V600E) showing higher frequency of suspicious sonographic features and multifocality.
Head Neck, 37(11):1590-5.
D. Y. Shin, K. J. Kim, S. Chang, H. Kim, S. Hwang, W. Kim, J. Bae, S. Park, S. W. Kang, W. Y. Chung and E. J. Lee. 2015.
BACKGROUND: The purpose of this study was to investigate the correlation between B-type Raf (BRAF) kinase mutation and clinicopathological features of follicular variant of papillary thyroid carcinoma (PTC). METHODS: Eighty-four patients with pathologically confirmed follicular variant of PTC, who underwent a preoperative BRAF(V600E) study, were analyzed. Clinicopathological parameters and ultrasonographic features were compared between the BRAF(V600E) -positive and negative groups. RESULTS: A total of 41.7% of the patients showed BRAF(V600E) . The BRAF(V600E) -positive group showed the smaller tumor size (7.3 +/- 3.6 mm vs 10.7 +/- 8.9 mm; p = .018) and the more frequent multifocality (25.7% vs 8.2%; p = .028). Follicular variant of PTC with BRAF(V600E) showed suspicious ultrasonographic features (88.6% vs 57.1%; p = .002) more frequently. BRAF(V600E) positivity is associated with multifocality after adjusting for age, sex, the presence of suspicious ultrasonographic features, pathological tumor size, and thyrotropin level. CONCLUSION: BRAF(V600E) was correlated with smaller tumor size and suspicious ultrasonographic features in follicular variant of PTC. BRAF(V600E) was a significant parameter for predicting multifocality of follicular variant of PTC.
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http://dx.doi.org/10.1002/hed.23793

Thyroid imaging reporting and data system score combined with Bethesda system for malignancy risk stratification in thyroid nodules with indeterminate results on cytology.
Clin Endocrinol (Oxf), 82(3):439-44.
F. F. Maia, P. S. Matos, E. J. Pavin and D. E. Zantut-Wittmann. 2015.
CONTEXT: The thyroid imaging reporting and data system (TI-RADS) was designed to better select patients who had undergone fine-needle aspiration biopsies (FNABs) with high sensitivity and accuracy. However, the combination of TI-RADS scores and Bethesda system categories in indeterminate thyroid nodules has not been examined extensively. OBJECTIVE: This study aimed to stratify indeterminate thyroid nodules (Bethesda categories III, IV and V) according to risk of malignancy as determined by combining TI-RADS score with Bethesda system classification. DESIGN: Retrospective study. Histopathological, cytological and ultrasound (US) data were available for 242 cases after surgery, including 136 indeterminate nodules. METHODS: All thyroid cytopathological slides and US reports were reviewed and classified according to Bethesda system and TI-RADS categories. The malignancy rate was determined for each Bethesda category, TI-RADS score and both methods combined of indeterminate nodules. RESULTS: The malignancy rates were 8.7%, 51.3% and 67.5% for Bethesda categories III, IV and V, respectively. Based on histopathological comparison, the accuracy was 66.7% for TI-RADS greyscale. TI-RADS 3 and 4A scores were observed in 80% of Bethesda III cases, which led to 80% sensitivity and 90% of negative predictive value (NPV). In contrast, for nodules scored as TI-RADS 4B and 5, the combined cytological results of Bethesda IV and V resulted in a higher risk of malignancy (75% and 76.9%, respectively, P < 0.001). CONCLUSIONS: In view of the high NPV of TI-RADS 3/4A only in Bethesda III category, a surgical approach could be considered for lesions defined as Bethesda III, IV and V when TI-RADS 4B and 5 were concomitant.
PubMed-ID: 24930423
http://dx.doi.org/10.1111/cen.12525

A review of the management and prognosis of thyroid carcinoma with tracheal invasion.
Eur Arch Otorhinolaryngol, 272(8):1833-43.
A. Peng, Y. Li, X. Yang, Z. Xiao, Q. Tang and Q. Wang. 2015.
The objective of the study was to explore the surgical approaches, treatment significance and prognosis of thyroid carcinoma with tracheal invasion. We retrospectively reviewed 48 patients with tracheal invasion by papillary thyroid carcinoma, follicular thyroid carcinoma and medullary thyroid carcinoma by means of clinical data ranging from 1993 to 2011. The patients were classified into three groups in terms of the depth and extent of tracheal invasion by the tumors, i.e., group A of 18 patients with localized tracheal invasion; group B of 21 patients with intraluminal tracheal invasion, and group C of nine patients with extensive invasion of the trachea, larynx, esophagus and/or mediastinum. Of these patients, 18 received radical tumorectomy and segmental resection of the outer layer of the tracheal wall; 21 had radical tumorectomy, circumferential sleeve trachea resection or segmental tracheal resection plus tracheal repair, and the remaining nine patients underwent radical tumorectomy, segmental trachea resection and esophagolaryngectomy. 46 patients took I(131) oral solution and/or had external radiotherapy postoperatively. A survival analysis was done using Kaplan-Meier Estimator for cumulative survival probability together with Log-Rank test, and Cox Regression Model was used for multivariate

analysis. (1) In group A of 18 patients, 10 took I(131)oral solution and 7 received radiotherapy after surgery. The overall 5 and 10-year survival rates were 88.93 and 77.78 %, respectively; (2) In group B of 21 patients, 15 took I(131) oral solution and 7 received radiotherapy after surgery. The overall 5 and 10-year survival rates were 90.47 and 61.87 %, respectively; (3) In group C of 9 patients, 7 received radiotherapy after surgery. The overall 5 and 10-year survival rates were 77.78 and 22.22 %, respectively. Whether they received postsurgical I(131) treatment or radiotherapy, there was a statistical difference between the 5-year survival rates and the 10-year survival rates in all of these three groups (P value in each group is <0.05). In the treatment of thyroid carcinoma with tracheal invasion, radical tumorectomy plus tracheal repair, segmental tracheal resection or circumferential sleeve trachea resection could lengthen the survival time. Radical tumorectomy could enhance the probability of survival of patients with thyroid carcinoma that had extensively invaded the larynx, esophagus and/or mediastinum. Postsurgical I(131) treatment and radiotherapy enhanced the probability of survival.
PubMed-ID: 24972539
http://dx.doi.org/10.1007/s00405-014-3144-x

Robotic thyroidectomy learning curve for beginning surgeons with little or no experience of endoscopic surgery.
Head Neck, 37(12):1705-11.
J. H. Park, J. Lee, N. A. Hakim, H. Y. Kim, S. W. Kang, J. J. Jeong, K. H. Nam, K. S. Bae, S. J. Kang and W. Y. Chung. 2015.
BACKGROUND: This study assessed the results of robotic thyroidectomy by fellowship-trained surgeons in their initial independent practice, and whether standard fellowship training for robotic surgery shortens the learning curve. METHODS: This prospective cohort study evaluated outcomes in 125 patients who underwent robotic thyroidectomy using gasless transaxillary single-incision technique by 2 recently graduated fellowship-trained surgeons. Learning curves were analyzed by operation time, with proficiency defined as the point at which the slope of the time curve became less steep. RESULTS: Of the 125 patients, 113 underwent robotic less-than-total thyroidectomy, 9 underwent robotic total thyroidectomy and 3 underwent robotic total thyroidectomy with modified radical neck dissection. Mean total times for these 3 operations were 100.8 +/- 20.6 minutes, 134.2 +/- 38.7 minutes, and 284.7 +/- 60.4 minutes, respectively. For both surgeons, the operation times gradually decreased, reaching a plateau after 20 robotic less-than-total thyroidectomies. CONCLUSION: The surgical learning curve for robotic thyroidectomy performed by recently graduated fellowship-trained surgeons with little or no experience in endoscopic surgery showed excellent results compared with those in a large series of more experienced surgeons.
PubMed-ID: 24986508
http://dx.doi.org/10.1002/hed.23824

Demographic and socioeconomic factors predictive of compliance with American Thyroid Association guidelines for the treatment for advanced papillary thyroid carcinoma.
Head Neck, 37(12):1776-80.
A. E. Wenaas, C. Z. Nagy, Y. Yiu, L. Xu, K. Horter and J. P. Zevallos. 2015.
BACKGROUND: The American Thyroid Association (ATA) publishes evidence-based guidelines for the treatment of papillary thyroid carcinoma (PTC). We sought to identify factors associated with receiving treatment compliant with the 2006 ATA guidelines for advanced-stage PTC. METHODS: The 2006 ATA guideline compliance was examined in patients with stage III and IV PTC extrapolated from Surveillance, Epidemiology, and End Results (SEER). RESULTS: Sixty percent of patients received ATA-compliant treatment. A stepwise increase in compliance occurred between 2006 and 2009 (p-value trend = .0003). Age 45 to 64 years versus >/=65 (odds ratio [OR] = 0.682; 95% confidence interval [CI] = 0.57-0.81; p < .0001) and higher income (p trend = .012) were associated with an increased likelihood of receiving ATA-compliant care. African Americans (OR = 0.56; 95% CI = 0.42-0.76; p = .0001) and single patients (OR = 0.81; 95% CI = 0.67-0.97; p = .02) were less likely to receive ATA-compliant care. CONCLUSION: This study highlights specific populations at risk for receiving non-ATA-compliant care for PTC and underscores the need to further implement guideline-based practice.
PubMed-ID: 24986680
http://dx.doi.org/10.1002/hed.23831

Utility of BRAF mutation detection in fine-needle aspiration biopsy samples read as "suspicious for papillary thyroid carcinoma".
Head Neck, 37(12):1788-93.
S. M. Jara, R. Bhatnagar, H. Guan, C. D. Gocke, S. Z. Ali and R. P. Tufano. 2015.
BACKGROUND: The purpose of this study was to evaluate the diagnostic utility of BRAF mutation testing on

thyroid nodules "suspicious for papillary thyroid carcinoma" (PTC) cytology. METHODS: A chart review of patients with fine-needle aspiration (FNA) results "suspicious for PTC" with subsequent thyroidectomy was performed. Corresponding archived FNA slides underwent BRAF mutation testing. RESULTS: Sixty-six patients with FNA "suspicious for PTC" underwent thyroidectomy. Forty-two (63.6%) had PTC diagnosed on final histopathology, whereas 21 (31.8%) had benign findings. Thirty-five patients (83%) with histologically proven PTC underwent total thyroidectomy, whereas 7 (17%) underwent hemithyroidectomy. BRAF mutation was detected in 17 of 49 samples (34.6%) available for testing and had 45.5% sensitivity, 87.5% specificity, 88.2% positive predictive value (PPV), and 43.8% negative predictive value (NPV) for diagnosing PTC. Two of 4 patients (50%) who underwent hemithyroidectomy with subsequent completion thyroidectomy had mutated BRAF detected. CONCLUSION: BRAF testing is a useful adjunct to improve PPV for patients with "suspicious for PTC" cytology.
PubMed-ID: 24989827
http://dx.doi.org/10.1002/hed.23829

Lung metastases from differentiated thyroid carcinoma: prognostic factors related to remission and disease-free survival.
Clin Endocrinol (Oxf), 82(3):445-52.
S. Chopra, A. Garg, S. Ballal and C. S. Bal. 2015.
OBJECTIVE: Distant metastases, although rare, account for maximum disease-related mortality in differentiated thyroid cancer (DTC). Lungs and bones are the most frequent sites of metastases. We sought to identify the prognostic factors in adult DTC patients presenting with pulmonary metastases at initial diagnosis. DESIGN: Retrospective cohort study. PATIENTS: From the medical records of 4370 patients, 200 patients aged more than 21 years who were identified to have pulmonary metastases at the time of diagnosis were included in the analysis. RESULTS: The sites of metastases were lungs alone in 133 (67%) patients, and additional sites in remaining 67 (33%) patients were as follows: bones in 59, liver in 4, brain in 2 and both bone and liver in two patients. During the mean follow-up of 61 months (range, 12-312 months), 76 patients achieved remission, 121 (60.5%) patients had biochemically and/or structurally persistent disease and three patients showed disease progression. Multivariate analysis revealed presence of macro-nodular (chest X-ray positive) pulmonary metastases and concomitant skeletal metastases as independent factors decreasing the likelihood of remission. Of the 76 patients with remission, 16 (21%) developed subsequent recurrence. Patient age >45 years and follicular histopathology were independently associated with greater hazards of developing recurrence. CONCLUSION: This study suggests that the patients with macro-nodular lung metastases and/or concomitant skeletal metastases have reduced odds of achieving remission. Moreover, significant number of patients recur even after complete remission with RAI treatment, hence strict surveillance is recommended especially in patients with age >45 years and/or with follicular histology of DTC.
PubMed-ID: 25040494
http://dx.doi.org/10.1111/cen.12558

Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS).
Clin Endocrinol (Oxf), 82(1):136-41.
S. A. Irving, T. Vadiveloo and G. P. Leese. 2015.
OBJECTIVE: The aim of this study was to determine the extent of drug interactions affecting levothyroxine, using study drugs often co-administered to patients on long-term levothyroxine therapy. DESIGN: A retrospective population analysis linking biochemistry and prescription data between 1 January 1993 and 31 December 2012 was used. PATIENTS: The study population was Tayside residents prescribed levothyroxine on at least three occasions, within a six-month period, prior to the start of a study drug. Individuals acted as their own controls pre- and postinitiation of study drug. Overall, 10 999 patients (mean age 58 years, 82% female) being treated with thyroxine were included in the study. MEASUREMENTS: Changes in TSH following initiation of study drug. RESULTS: Iron, calcium, proton pump inhibitors and oestrogen all increased serum TSH concentration: an increase of 0.22 mU/l ($P < 0.001$), 0.27 mU/l ($P < 0.001$), 0.12 mU/l ($P < 0.01$), and 0.08 mU/l ($P < 0.007$), respectively. For these four study drugs, there was a clinically significant increase of over 5 mU/l in serum TSH, in 7.5%, 4.4%, 5.6% and 4.3% patients, respectively. There was a decrease of 0.17 mU/l (P-value 0.01) in the TSH concentration for those patients on statins. The TSH decreased by 5 mU/l in 3.7% of patients. There was no effect with H2 receptor antagonists or glucocorticoids. CONCLUSION: This large population-based study demonstrates significant interaction between levothyroxine and iron, calcium, proton pump inhibitors, statins and oestrogens. These drugs may reduce the effectiveness of levothyroxine, and patients' TSH concentrations should be carefully monitored.

PubMed-ID: 25040647
http://dx.doi.org/10.1111/cen.12559

A cut-off value of basal serum calcitonin for detecting macroscopic medullary thyroid carcinoma.
Clin Endocrinol (Oxf), 82(4):598-603.
H. Kwon, W. G. Kim, Y. M. Choi, E. K. Jang, M. J. Jeon, D. E. Song, J. H. Baek, J. S. Ryu, S. J. Hong, T. Y. Kim, W. B. Kim and Y. K. Shong. 2015.
OBJECTIVE: Serum calcitonin (CT) level is used to detect medullary thyroid carcinoma (MTC), but the cut-off level is unclear. We aimed at identifying the optimal cut-off value of basal serum CT levels for detecting MTC. DESIGN AND PATIENTS: We retrospectively enrolled patients with hypercalcitoninemia (>/=2.9 pmol/l) who had undergone thyroid ultrasonography (US) and subsequent work-up between 2001 and 2013 at Asan Medical Center. We divided patients into four groups: proven MTC (group 1, n = 93), pathologically proven non-MTC after surgery (group 2, n = 57), benign single nodule by cytology (group 3, n = 68) and patients without nodules on US (group 4, n = 24). MEASUREMENT: Basal serum CT levels were evaluated. RESULTS: The median CT level of group 1 (119.5 pmol/l) was significantly higher than those of other groups (4.0, 3.8 and 3.8 pmol/l, P < 0.001). When we adopted 19.0 pmol/l of CT level as a cut-off value, the sensitivity, specificity, and positive and negative predictive values were 77.4%, 98.7%, 97.3% and 87.8%, respectively. When we compared 29.2 pmol/l (100 pg/ml) and 19.0 pmol/l (65 pg/ml) as cut-off values, 19.0 pmol/l was more sensitive and accurate than 29.2 pmol/l. Factors associated with hypercalcitoninemia in non-MTC groups were autoimmune thyroiditis, chronic kidney disease, proton pump inhibitors and other malignancies. Serum CT levels tended to decrease spontaneously in non-MTC groups. CONCLUSION: Basal serum CT levels higher than 19.0 pmol/l can be a useful cut-off value for detecting macroscopic MTC, even though values below 19.0 pmol/l cannot exclude the presence of MTC like small volume MTC or premalignant C-cell hyperplasia.
PubMed-ID: 25041034
http://dx.doi.org/10.1111/cen.12562

Level 7 disease does not confer worse outcome than level 6 disease in differentiated thyroid cancer.
Ann Surg Oncol, 22(2):441-5.
L. Y. Wang, F. L. Palmer, D. Thomas, I. J. Nixon, R. M. Tuttle, J. P. Shah, S. G. Patel, A. R. Shaha and I. Ganly. 2015.
BACKGROUND: Level 7 nodal disease increases patients from N1a to N1b in the American Joint Committee on Cancer (AJCC) TNM classification of differentiated thyroid cancers (DTCs). This results in upstaging of patients older than 45 years of age from stage III to IV. Our objective was to determine if patients with level 7 disease had poorer outcome in comparison to patients with isolated level 6 disease. METHODS: A total of 599 patients with DTC limited to the central neck (level 6 and 7) were identified from an institutional database. Patients with N1b disease due to lateral compartment (level 1-5) involvement or M1 disease were excluded. Fifty-seven patients had positive level 7 disease, and 542 patients had nodal disease limited to level 6. Disease-specific survival (DSS) and recurrence-free survival (RFS) were calculated for each group. RESULTS: Median age was 41 years (range 12-91) and follow-up was 61 months (range 1-330). There were no disease-specific deaths at 5 years. Among patients with level 6 disease at presentation, there were 42 nodal recurrences, and among patients with level 7 disease, there were two recurrences. There were no differences in overall RFS between patients with level 6 or 7 disease (5-year RFS 90.7 vs. 98.2 %, respectively; p = 0.096). CONCLUSIONS: Our results suggest that N1b disease due to level 7 disease does not confer worse DSS or RFS compared with patients with level 6 disease only. Classifying all central neck disease (levels 6 and 7) into the N1a category, and reserving the N1b classification only for patients with lateral neck disease may be more reflective of prognosis.
PubMed-ID: 25190124
http://dx.doi.org/10.1245/s10434-014-4045-3

Long-term outcomes for older patients with papillary thyroid carcinoma: should another age cutoff beyond 45 years be added?
Ann Surg Oncol, 22(2):446-53.
B. H. Lang, C. Y. Lo, K. P. Wong and K. Y. Wan. 2015.
BACKGROUND: Although an age cutoff of 45 years has often been adopted to stratify cancer risk in papillary thyroid carcinoma (PTC), both cancer-specific survival (CSS) and disease-specific survival (DFS) continue to worsen beyond this cutoff. This study aimed to determine whether advanced age (i.e., >60 years) at diagnosis was an independent predictor of CSS and DFS in older (>/=45 years) patients. METHODS: This study analyzed 407 PTC patients with a minimal follow-up period of 7 years. Standard protocol was followed. Both CSS and DFS were estimated using the Kaplan-Meier method and compared with the log-rank test. Variables shown to be significant by the log-rank test were entered into the Cox regression analysis. RESULTS: During a median

follow-up period of 15.1 years, 51 patients (12.5 %) died of PTC, whereas 80 (20.5 %) experienced at least one recurrence. For CSS, age beyond 60 years (hazard ratio [HR], 3.027; 95 % confidence interval [CI] 1.369-6.690; p = 0.006), tumor size greater than 4 cm (HR 2.043; 95 % CI 1.141-4.255; p = 0.049), central nodal metastases (HR 2.726; 95 % CI 1.198-6.200; p = 0.017), lateral nodal metastases (HR 5.247; 95 % CI 2.987-9.216; p < 0.001), and distant metastases (HR 4.297; 95 % CI 1.726-2.506; p = 0.002) were independent predictors. For DFS, only tumor size greater than 4 cm (HR 1.733; 95 % CI 1.030-3.058; p = 0.049), central nodal metastases (HR 2.362; 95 % CI 1.010-5.523; p = 0.047), and lateral nodal metastases (HR 4.383; 95 % CI 2.388-8.042; p < 0.001) were independent predictors. CONCLUSIONS: Advanced age was an independent predictor of CSS, and cancer-related death risk showed a continuing increase beyond the age of 60 years. However, advanced age was not an independent predictor of DFS. Therefore, having another age cutoff appears justifiable for stratifying risk of cancer-related death but less justifiable for disease recurrence. Tumor size as well as central and lateral nodal metastases independently predicted CSS and DFS.
PubMed-ID: 25190130
http://dx.doi.org/10.1245/s10434-014-4055-1

Coupling of prostate and thyroid cancer diagnoses in the United States.
Ann Surg Oncol, 22(3):1043-9.
J. J. Tomaszewski, R. G. Uzzo, B. Egleston, A. T. Corcoran, R. Mehrazin, D. M. Geynisman, J. A. Ridge, C. Veloski, N. Kocher, M. C. Smaldone and A. Kutikov. 2015.
BACKGROUND: Prostate and thyroid cancers represent two of the most overdiagnosed tumors in the US. Hypothesizing that patients diagnosed with one of these malignancies were more likely to be diagnosed with the other, we examined the coupling of diagnoses of prostate and thyroid cancer in a large US administrative dataset. METHODS: The surveillance, epidemiology, and end results (SEER) database was used to identify men diagnosed with clinically localized prostate cancer (CaP) or thyroid cancer between 1995 and 2010. SEER*stat software was used to estimate multivariable-adjusted standardized incidence ratios (SIRs) and investigate the rates of subsequent malignancy diagnosis. Additional non-urologic cancer sites were added as control groups. RESULTS: Patients with thyroid cancer were much more likely to be diagnosed with CaP than patients in the SEER control group (SIR 1.28 [95% CI 1.1-1.5]; p < 0.05). Similarly, the observed incidence of thyroid cancer was significantly higher in patients with CaP when compared with SEER controls (SIR 1.30 [95% CI 1.2-1.4]; p < 0.05). When stratified by follow-up interval, the observed thyroid cancer diagnosis rate among men with CaP was significantly higher than expected at 2-11 (SIR 1.83 [95% CI 1.4-2.4]), 12-59 (SIR 1.24 [95% CI 1.0-1.5]), and 60-119 (SIR 1.25 [95% CI 1.0-1.5]) months of follow-up. There was no increased risk of CaP or thyroid cancer diagnosis among patients with non-urologic malignancies. CONCLUSIONS: There is a significant association of diagnoses with prostate and thyroid cancer in the US. In the absence of a known biological link between these tumors, these data suggest that diagnosis patterns for prostate and thyroid malignancies are linked.
PubMed-ID: 25205302
http://dx.doi.org/10.1245/s10434-014-4066-y

All thyroid ultrasound evaluations are not equal: sonographers specialized in thyroid cancer correctly label clinical N0 disease in well differentiated thyroid cancer.
Ann Surg Oncol, 22(2):422-8.
S. C. Oltmann, D. F. Schneider, H. Chen and R. S. Sippel. 2015.
BACKGROUND: Ultrasound (US) is a standard preoperative study in thyroid cancer. Accurate identification of lymph node (LN) disease in the central neck by US is debated, leading some surgeons to perform prophylactic central dissection. The purpose of this study was to evaluate if US performed by a surgeon with specialization in thyroid sonography correctly determined clinical N0 status. METHODS: Retrospective identification of cN0 thyroid cancer patients from a prospectively maintained database was performed. Exclusion criteria included LN dissection with thyroidectomy or missing preoperative US. Demographics and outcomes were reviewed. Patients were categorized by who performed the thyroid US (surgeon vs. non-surgeon). Additional radioactive iodine (RAI) treatments or subsequent positive pathology defined recurrence. RESULTS: From 2005 to 2012, 177 patients met criteria. Forty-eight patients had surgeon US versus 129 patients with non-surgeon US. Groups were equivalent in age, gender, and tumor size. Forty-six percent had a preoperative diagnosis of cancer, whereas 19 % had benign and 35 % had indeterminate diagnoses. Surgeon US documented LN status more frequently (69 vs. 20 %, p < 0.01). RAI treatment and dose were equivalent. RAI uptake was lower with surgeon US (0.06 % +/- 0.02 vs. 0.20 % +/- 0.03, p < 0.01). Recurrence rates were higher in non-surgeon US (12 vs. 0 %, p = 0.01). Median time to recurrence was 11 months. CONCLUSIONS: Surgeons with thyroid US expertise correctly identify patients as N0, which may eliminate the need for prophylactic LN dissection without increasing risk of early recurrence. Because not all thyroid cancers are diagnosed preoperatively, US examination of the

thyroid should include routine evaluation of the cervical LNs.
PubMed-ID: 25234019
http://dx.doi.org/10.1245/s10434-014-4089-4

Clinical and socioeconomic factors influence treatment decisions in Graves' disease.
Ann Surg Oncol, 22(4):1196-9.
D. M. Elfenbein, D. F. Schneider, J. Havlena, H. Chen and R. S. Sippel. 2015.
BACKGROUND: Definitive treatment of Graves' disease includes radioactive iodine (RAI) and thyroidectomy, but utilization varies. We hypothesize that, in addition to clinical reasons, there are socioeconomic factors that influence whether a patient undergoes thyroidectomy or RAI. METHODS: Patients treated for Graves' disease between August 2007 and September 2013 at our university hospital were included. A comparative analysis of clinical and socioeconomic factors was completed. RESULTS: Of 427 patients, 300 (70 %) underwent RAI, whereas 127 (30 %) underwent surgery. Multiple factors were associated with surgery: younger age (mean 36 vs. 41 years, $p < 0.01$), female gender (33 vs. 19 % males, $p = 0.01$), black race (56 vs. 28 % nonblack, $p < 0.01$), Medicaid or uninsured (43 vs. 27 % private insurance or Medicare, $p < 0.01$), ophthalmopathy (38 vs. 26 %, $p < 0.01$), goiter (35 vs. 23 %, $p < 0.01$), and lowest quartile of median household income (38 vs. 27 % upper three quartiles, $p = 0.03$). Thyroidectomy increased annually, with 52 % undergoing surgery during the final year ($p < 0.01$). Adjusting for confounding, younger age (odds ratio [OR] 1.04; 95 % confidence interval [CI] 1.02, 1.05), female gender (OR 2.06; 95 % CI 1.06, 4.01), ophthalmopathy (OR 2.35; 95 % CI 1.40, 3.96), and later year of treatment (OR 1.66; 95 % CI 1.41, 1.95) remained significantly associated with surgery. CONCLUSIONS: Surgery has now become the primary treatment modality of choice for Graves' disease at our institution. Clinical factors are the main drivers behind treatment choice, but patients with lower SES are more likely to have clinical features best treated with surgery, underlying the importance of improving access to quality surgical care for all patients.
PubMed-ID: 25245130
http://dx.doi.org/10.1245/s10434-014-4095-6

Benign intranodal thyroid tissue mimicking nodal metastasis in a patient with papillary thyroid carcinoma: A case report.
Head Neck, 37(9):E106-8.
Y. J. Lee, D. W. Kim, H. K. Park, T. K. Ha, H. Kim do, S. J. Jung and S. K. Bae. 2015.
BACKGROUND: A case of benign intranodal thyroid tissue mimicking nodal metastasis on ultrasound and CT in a patient with papillary thyroid carcinoma has not been reported. METHODS: The clinical, imaging, and histopathological findings of the patient are presented. A 52-year-old woman who underwent ultrasound-guided fine-needle aspiration for 2 small, suspicious thyroid nodules in both lobes at a local clinic was referred to our hospital for surgical treatment. Ultrasound-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. RESULTS: 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 ultrasound or CT in a patient with papillary thyroid carcinoma.
PubMed-ID: 25270676
http://dx.doi.org/10.1002/hed.23886

Navigating the management of follicular variant papillary thyroid carcinoma subtypes: a classic PTC comparison.
Ann Surg Oncol, 22(4):1200-6.
B. M. Finnerty, D. A. Kleiman, T. Scognamiglio, A. Aronova, T. Beninato, T. J. Fahey, 3rd and R. Zarnegar. 2015.
BACKGROUND: There are three subtypes of follicular variant papillary thyroid carcinoma (fvPTC): completely encapsulated, well circumscribed, and infiltrative. While infiltrative tumors are more aggressive than completely encapsulated, controversy exists regarding management of fvPTC subtypes. We compared the clinicopathologic features of fvPTC subtypes to those of classic PTC (cPTC) to help guide fvPTC management, using cPTC as a reference. METHODS: A retrospective review was performed on 316 patients with PTC treated at a single institution from 2004 to 2011. There were 197 cPTC and 119 fvPTC tumors, including completely encapsulated ($n = 46$), well circumscribed ($n = 46$), and infiltrative ($n = 27$). Clinicopathologic data were compared between groups. RESULTS: fvPTC patients had larger tumors than cPTC patients (1.6 cm vs. 1.2 cm, $p = 0.001$), but age, sex, and family history did not differ. Thirty-one percent of cPTC tumors had extrathyroidal extension compared to 0 % of completely encapsulated, 0 % of well-circumscribed, and 52 % of infiltrative fvPTC tumors (p

< 0.05). Central lymph node metastasis occurred in 50 % of cPTC compared to 0 % in completely encapsulated, 20 % in well-circumscribed, and 72 % in infiltrative fvPTC tumors (p < 0.05). Notably, lymph node metastasis was significantly lower in completely encapsulated than in well-circumscribed tumors, without a difference in the median number of nodes sampled. There were no differences in lymphovascular invasion or extranodal extension. CONCLUSIONS: Like cPTC tumors, infiltrative fvPTC tumors have aggressive clinicopathologic features and thus should be treated similarly. Conversely, completely encapsulated and well-circumscribed tumors have less aggressive features compared to cPTC and are more self-limiting; however, well-circumscribed tumors still have a notable incidence of lymph node metastasis. Clinicians should consider this variability in their management algorithm for fvPTC.
PubMed-ID: 25297901
http://dx.doi.org/10.1245/s10434-014-4126-3

Fewer cancer reoperations for medullary thyroid cancer after initial surgery according to ATA guidelines.
Ann Surg Oncol, 22(4):1207-13.
H. H. Verbeek, J. A. Meijer, W. T. Zandee, K. H. Kramp, W. J. Sluiter, J. W. Smit, J. Kievit, T. P. Links and J. T. Plukker. 2015.
BACKGROUND: Surgery is still the only curative treatment for medullary thyroid cancer (MTC). We evaluated clinical outcome in patients with locoregional MTC with regard to adequacy of treatment following ATA guidelines and number of sessions to first intended curative surgery in different hospitals. METHODS: We reviewed all records of MTC patients (n = 184) treated between 1980 and 2010 in two tertiary referral centers in the Netherlands. Symptomatic MTC (palpable tumor or suspicious lymphadenopathy) patients without distant metastasis were included (n = 86). Patients were compared with regard to adequacy of surgery according to ATA recommendations, tumor characteristics, number of local cancer reoperations, biochemical cure, clinical disease-free survival (DFS), overall survival (OS), and complications. RESULTS: Adherence to ATA guidelines resulted in fewer cancer-related reoperations (0.24 vs. 0.60; P = 0.027) and more biochemical cure (40.9 vs. 20 %; P = 0.038). Surgery according to ATA-guidelines on patients treated in referral centers was significantly more often adequate (59.2 vs. 26.7 %; P = 0.026). Tumor size and LN+ were the most important predictors for clinical recurrence [relative risk (RR) 4.1 (size > 40 mm) 4.1 (LN+) and death (RR 4.2 (size > 40 mm) 8.1 (LN+)]. CONCLUSIONS: ATA-compliant surgery resulted in fewer local reoperations and more biochemical cure. Patients in referral centers more often underwent adequate surgery according to ATA-guidelines. Size and LN+ were the most important predictors for DFS and OS.
PubMed-ID: 25316487
http://dx.doi.org/10.1245/s10434-014-4115-6

Unanticipated thyroid cancer in patients with substernal goiters: are we underestimating the risk?
Ann Surg Oncol, 22(4):1214-8.
M. J. Campbell, L. Candell, C. D. Seib, J. E. Gosnell, Q. Y. Duh, O. H. Clark and W. T. Shen. 2015.
BACKGROUND: The rate of unexpected thyroid cancers found at the time of thyroidectomy is thought to be similar in patients with cervical and substernal multinodular goiters (MNGs). METHODS: The objective of this study was to compare the prevalence of undiagnosed cancer found in patients undergoing a thyroidectomy for a cervical or substernal MNG. We conducted a review of patients with a preoperative diagnosis of an MNG (both cervical and substernal) at a tertiary referral center between 2005 and 2012. RESULTS: We identified 538 patients who underwent thyroidectomy for an MNG (144 with substernal MNGs and 394 with cervical MNGs). Patients with substernal MNGs were older (59.6 vs. 52.3; p < 0.001), more likely to be men (34 vs. 11.1 %; p < 0.001), and less likely to have a history of radiation exposure to the neck (2.1 vs. 12.4 %; p < 0.001). Thyroid cancer (>1 cm) was found in 13.7 % of substernal MNG specimens and in 6.3 % of cervical MNG specimens (p = 0.003). On multivariate analysis, substernal location [odds ratio (OR) = 2.360; confidence interval (CI), 1.201-4.638] was the only variable independently associated with an unexpected thyroid cancer on surgical pathology. CONCLUSION: The rate of postoperatively discovered thyroid cancer is significant in patients with substernal MNGs and is increased when compared to patients with cervical MNGs. Surgeons should counsel their patients regarding the possibility of this unexpected result.
PubMed-ID: 25316492
http://dx.doi.org/10.1245/s10434-014-4143-2

Primary thyroid diffuse large B-cell lymphoma coexistent with papillary thyroid carcinoma: A case report.
Head Neck, 37(9):E109-14.
S. Xie, W. Liu, Y. Xiang, Y. Dai and J. Ren. 2015.
BACKGROUND: Primary thyroid lymphoma (PTL) is uncommon, accounting for 2% to 5% of all thyroid malignancies. Papillary thyroid carcinoma (PTC) is the most frequent thyroid cancer. The coexistence of PTL and PTC is very rare, and the preoperative diagnosis is rather difficult. METHODS: A 41-year-old male patient complaining of fast painless thyroid enlargement for 2 months and a cervical mass for half a month was presented. Imaging demonstrated an enlarged thyroid and a mass in the thyroid. RESULTS: Surgery was conducted, and the final diagnosis of coexistence of PTL and PTC was confirmed by histopathological and immunohistochemical examination. The patient was then treated with cyclophosphamide, hydroxy doxorubicin, oncovin, prednisone (CHOP) chemotherapy and radiotherapy. After 2 months of follow-up, no recurrence or metastasis was noted. CONCLUSION: This rare case highlights the importance for physicians to keep PTL in mind for differential diagnosis in patients with sudden thyroid enlargement and who have clinical history of Hashimoto thyroiditis.
PubMed-ID: 25352071
http://dx.doi.org/10.1002/hed.23917

Collision tumors of the thyroid: A case report and review of the literature.
Head Neck, 37(10):E125-9.
N. Ryan, G. Walkden, D. Lazic and P. Tierney. 2015.
BACKGROUND: Collision tumors of the thyroid are a rare pathology that present a diagnostic and treatment challenge. In this report, we present an interesting case and a review of the current literature as to inform management. METHODS AND RESULTS: An 88-year-old woman presented with acute airway compromise and vocal cord paralysis. CT identified a thyroid mass and widespread metastasis. Histopathology identified the lesion as a collision tumor consisting of a squamous cell carcinoma (SCC) and papillary thyroid carcinoma. The patient was managed with surgery and palliative radiotherapy. However, she died from complications of a lower respiratory tract infection. We also present a review of the literature with 33 cases reviewed. CONCLUSION: Management of collision tumors is complex because of 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.
PubMed-ID: 25491252
http://dx.doi.org/10.1002/hed.23936

Lateral neck recurrence from papillary thyroid carcinoma: Predictive factors and prognostic significance.
Laryngoscope, 125(9):2226-31.
D. Giordano, A. Frasoldati, J. L. Kasperbauer, E. Gabrielli, C. Pernice, M. Zini, C. Pedroni, S. Cavuto and V. Barbieri. 2015.
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.
PubMed-ID: 25510637
http://dx.doi.org/10.1002/lary.25094

Does intraoperative nerve monitoring reliably aid in staging of total thyroidectomies?
Laryngoscope, 125(9):2232-5.
T. E. Fontenot, G. W. Randolph, T. E. Setton, N. Alsaleh and E. Kandil. 2015.
OBJECTIVES/HYPOTHESIS: Demonstrate whether intraoperative nerve monitoring is an effective tool in staging bilateral thyroid and neck surgeries in cases of intraoperative injury to the recurrent laryngeal nerve on the side of initial dissection. We hypothesized that IONM provides reliable and appropriate feedback on the functional status of the RLN on side of initial dissection during total thyroidectomy and central neck surgery. STUDY DESIGN: Case series with planned data collection. METHODS: All patients receiving total thyroidectomies or central neck surgeries were reviewed. The outcomes of patients treated whose procedures were staged based on intraoperative nerve monitoring are described. RESULTS: Ten (4.9%) of 206 procedures were staged based on unfavorable signal change including six patients with thyroid cancers and four with compressive substernal goiters. The overall signal drop in the 10 patients with unfavorable signal change was 63%. Three patients had complete loss of signal. In the other seven patients, the signal dropped by a mean of 48%. In the eight patients with laryngoscopy-proven vocal fold paresis, the signal dropped by a mean of 68%. CONCLUSIONS: Intraoperative nerve monitoring results accurately indicated postoperative ipsilateral vocal cord dysfunction with high reliability. Intraoperative nerve monitoring is a reliable tool in staging thyroid surgery. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25601586
http://dx.doi.org/10.1002/lary.25133

[Streptococcal mediastinitis after thyroidectomy. A literature review].
Chirurg, 86(12):1145-50.
C. Bures, V. Zielinski, T. Klatte, N. Swietek, F. Kober, E. Tatzgern, R. Bobak-Wieser, E. Gschwandtner, M. Gilhofer, A. Wechsler-Fordos and M. Hermann. 2015.
INTRODUCTION: Surgical site infections after thyroid surgery are mostly superficial and can be well treated. Streptococcal mediastinitis in contrast is a rare but life-threatening complication. CASE REPORT: A 57-year-old female patient experienced septic fever, increase of inflammation parameters and erythema 2 days after thyroid surgery for Graves' disease. This process was triggered by a three-compartment infection by group A Streptococcus (GAS) with involvement of the mediastinum. Therapy over 6 weeks including seven wound revisions with the patient under general anesthesia, pathogen-adapted antibiotic treatment and cervical negative pressure treatment managed to control the infection. A total of 21 cases have been published on this phenomenon, 11 of which had a fatal outcome. CONCLUSION: High fever and surgical site erythema in the early postoperative period after thyroid surgery can be signs of a GAS infection, which might lead to necrotizing, descending, life-threatening mediastinitis. Early diagnosis with support of computed tomography (CT) scans, immediate therapy including wound opening, lavage, intravenous antibiotic treatment with penicillin and clindamycin are vital. If treatment resistance occurs, cervical negative pressure treatment should be considered.
PubMed-ID: 25648436
http://dx.doi.org/10.1007/s00104-014-2972-y

The Learning Curve for Robotic Thyroidectomy Using a Bilateral Axillo-Breast Approach From the 100 Cases.
Surg Laparosc Endosc Percutan Tech, 25(5):412-6.
W. W. Kim, J. H. Jung and H. Y. Park. 2015.
PURPOSE: The purpose of this study was to examine the learning curve for robotic thyroidectomy using a bilateral axillo-breast approach. METHODS: We examined the first 100 robotic thyroidectomies with central lymph node dissection due to papillary thyroid cancer between April 2010 and August 2011. We evaluated the clinical characteristics, operative time, pathologic data, and complications. RESULTS: Operative time was reduced significantly after 40 cases; therefore, the patients were divided into 2 groups: group A (1 to 40 cases) and group B (41 to 100 cases). The mean operative time in group A (232.6+/-10.0 min) was longer than that in group B (188.9+/-6.0 min) with statistical significance (P=0.001). Other data, including characteristics, drainage amount, hospital stay, retrieved lymph nodes, thyroglobulin, and complications, were not different between the 2 groups. The learning curves with lobectomy and total thyroidectomy were reached at the same time. CONCLUSIONS: The learning curve for robotic thyroidectomy with central lymph node dissection using bilateral axillo-breast approach was 40 cases for beginner surgeons. Robotic total thyroidectomy was performed effectively and safely after experience with 40 cases, as with lobectomy.
PubMed-ID: 25730738
http://dx.doi.org/10.1097/SLE.0000000000000121

Papillary Thyroid Carcinoma in Children and Adolescents: Long-Term Follow-Up and Clinical Characteristics.
World J Surg, 39(9):2259-65.
K. Sugino, M. Nagahama, W. Kitagawa, H. Shibuya, K. Ohkuwa, T. Uruno, A. Suzuki, J. Akaishi, C. Masaki, K. Matsuzu and K. Ito. 2015.
BACKGROUND: The aim of this study was to analyze the clinical features and clinical outcomes of papillary thyroid carcinoma (PTC) in the pediatric and adolescent population treated in our institution. METHODS: The subjects were 227 PTC patients 20 years of age or under treated initially between 1979 and 2012. Their mean age at diagnosis was 18-year old (range 7-20 years). Patient characteristics and outcomes in the period before 1999 and the period after 2000 were compared. Cause-specific survival (CSS) rates and disease-free survival (DFS) rates were calculated by the Kaplan-Meier method. RESULTS: Two patients died of their disease and 45 patients had recurrent disease (36 in lymph node, seven in a remnant thyroid, and 11 in the form of distant metastasis). The 10-, 20-, and 30-CSS rates were 99.3, 99.3, and 96.5%, respectively, and the 10-, 20-, and 30-DFS were 83.6, 70.7, and 64.0%, respectively. Gender and preoperative lymph node metastasis were identified as significant factors related to DFS in the multivariate analysis. After the year 2000, there were significantly more patients with a small primary tumor size, significantly more patients without distant metastasis at presentation and significantly more patients without extrathyroidal invasion. CONCLUSION: The number of patients with advanced cancer has been declining in recent years. Lobectomy with prophylactic unilateral central neck dissection is considered acceptable for patients without the risk factors for recurrence.
PubMed-ID: 25802237
http://dx.doi.org/10.1007/s00268-015-3042-4

Stimulating dissecting instruments during neuromonitoring of RLN in thyroid surgery.
Laryngoscope, 125(12):2832-7.
F. Y. Chiang, I. C. Lu, P. Y. Chang, H. Sun, P. Wang, X. B. Lu, H. C. Chen, H. Y. Chen, H. Y. Kim, G. Dionigi and C. W. Wu. 2015.
OBJECTIVES/HYPOTHESIS: During intraoperative neuromonitoring (IONM) of recurrent laryngeal nerve (RLN) in thyroid surgery, the need for frequent shifting between the dissecting instruments and stimulating probe is troublesome and time-consuming. Therefore, use of these two instruments in combination would be a noticeable future direction. This study aimed to investigate the feasibility and safety of using stimulating dissecting instruments (SDIs) that combine the function of surgical dissection and nerve stimulation during IONM. STUDY DESIGN: Prospective outcomes research. METHODS: One hundred consecutive patients with 168 RLNs at risk were enrolled. We developed prototypes of SDIs and applied them to early detect adverse EMG changes during the risky phase of RLN dissection. In the case of substantial EMG change (amplitude decrease > 50%) during dissection, the surgical maneuver was paused and thyroid traction was released immediately. RESULTS: The application of SDIs was feasible in all cases and did not result in any morbidity. Nineteen RLNs were detected with substantial EMG change that was caused by traction stress during dissection with SDIs and that featured progressive gradual EMG recovery after releasing thyroid traction. After thyroid resection, 10 RLNs had a weak point of nerve conduction detected at region of Berry's ligament, but only one nerve with 79% amplitude reduction developed postoperative temporary vocal palsy. CONCLUSION: The application of SDIs is a simple and effective way to monitor the nerve's function instantly during the risky phase of RLN injury in thyroid surgery. It provides surgeons with real-time feedback of EMG response and can be applied as a tool for the early detection of adverse EMG change caused by traction distress. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25809677
http://dx.doi.org/10.1002/lary.25251

Pediatric Thyroid Microcarcinoma.
Ann Surg Oncol, 22(13):4187-92.
J. Lerner and M. Goldfarb. 2015.
BACKGROUND: Thyroid microcarcinomas (TMCs) are increasing in the general population, most commonly in older individuals; however, the incidence, characteristics, and outcomes of TMCs in pediatric patients has not been studied. METHODS: All patients </=19 years of age with differentiated thyroid carcinoma (DTC) were identified from the surveillance, epidemiology, and end results registry from 1988 to 2009. Patients were divided into two groups based on tumor siz e: TMCs (</=1 cm) and tumors >1 cm. Demographic, tumor, and treatment characteristics, as well as overall survival (OS) and disease-specific survival (DSS), were compared between the two groups. The TMC group was analyzed separately for predictors of overall and disease-specific death. RESULTS: Of 1825 pediatric DTC patients, 8.4 % had a TMC, and, over the past decade, the incidence has decreased (6.5 vs 14.5 %; $p < 0.001$). Compared to patients with DTCs >1 cm, TMCs were more likely to have papillary histology, negative lymph nodes, be treated with a partial thyroidectomy [odds ratio (OR) 3.46, CI 2.02-

5.93] and not receive radioiodine (OR 1.77, CI 1.10-2.83). Neither OS (TMC: 253.59 months; DTC >1 cm: 257.97 months) nor DSS (TMC: 256.38 months; DTC >1 cm: 260.77 months) differed between groups. Predictors of decreased OS in the entire cohort included secondary malignancy status (p = 0.001), black race (p = 0.006) and follicular or Hurthle histology (p = 0.001). In patients with primary TMC, only follicular or Hurthle histology (p = 0.001) predicted decreased OS. CONCLUSIONS: TMCs in patients </=19 years of age are declining and comprise <10 % of pediatric thyroid malignancies. TMCs are most commonly treated with a partial thyroidectomy not followed by radioiodine, and have an excellent OS and DSS.
PubMed-ID: 25854844
http://dx.doi.org/10.1245/s10434-015-4546-8

RAI thyroid bed uptake after total thyroidectomy: A novel SPECT-CT anatomic classification system.
Laryngoscope, 125(10):2417-24.
R. Zeuren, A. Biagini, R. K. Grewal, G. W. Randolph, D. Kamani, M. M. Sabra, A. R. Shaha and R. M. Tuttle. 2015.
OBJECTIVE: Recent, more selective use of radioactive iodine (RAI) has led to reevaluation of the clinical importance of achieving complete total thyroidectomy with minimal residual normal thyroid tissue. We utilize the improved localization by post-RAI remnant ablation, single photon emission computerized tomography-computed tomography (SPECT-CT) to define specific anatomic sites of residual RAI-uptake foci after total thyroidectomy for differentiated thyroid cancer (DTC) and to provide a novel classification system relating uptake to thyroid anatomy and preservation of adjacent neural structures. STUDY DESIGN: Retrospective. METHOD: Radioactive iodine-uptake foci in thyroid bed were localized by SPECT/CT imaging at the time of RAI remnant ablation in 141 DTC patients undergoing total thyroidectomy. RESULTS: Minimal residual RAI uptake (median 0.32% at 24 hours) in the thyroid bed was detected by diagnostic planar whole body scans in 93% and by posttherapy SPECT/CT imaging in 99% of subjects. Discrete RAI uptake foci were identified on the SPECT/CT imaging at Berry's ligament (87%), at superior thyroid poles (79%), in paratracheal-lobar regions (67%), in isthmus-region (54%), and in pyramidal lobe (46%). Despite the residual foci, the nonstimulated thyroglobulin (Tg) prior to remnant ablation (with a median thyroid-stimulating hormone of 0.36 m IU/L) was < 0.6 ng/mL in 53% and < 1 ng/mL in 73% of cases. CONCLUSION: After extracapsular total thyroidectomy, highly sensitive detection tools identify microscopic residual RAI avid foci in thyroid bed in the majority of patients. These foci can be classified as 1) neural-related and 2) capsule-related. These common residual foci have no relationship to postoperative Tg, suggesting that attempts at radical removal of thyroid tissue in these locations may not be warranted. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25891354
http://dx.doi.org/10.1002/lary.25295

Undetectable Thyroglobulin Levels in Poorly Differentiated Thyroid Carcinoma Patients Free of Macroscopic Disease After Initial Treatment: Are They Useful?
Ann Surg Oncol, 22(13):4193-7.
T. Ibrahimpasic, R. Ghossein, D. L. Carlson, I. J. Nixon, F. L. Palmer, S. G. Patel, R. M. Tuttle, A. Shaha, J. P. Shah and I. Ganly. 2015.
BACKGROUND: Predictive role of undetectable thyroglobulin (Tg) in patients with poorly differentiated thyroid carcinoma (PDTC) is unclear. Our goal was to report on Tg levels following total thyroidectomy and adjuvant RAI in PDTC patients and to correlate Tg levels with recurrence. METHODS: Forty patients with PDTC with no distant metastases at presentation (M0) and managed by total thyroidectomy and adjuvant RAI were identified from a database of 91 PDTC patients. Of these, 31 patients had Tg values recorded and formed the basis of our analysis. A nonstimulated Tg level <1 ng/ml was used as a cutoff point for undetectable Tg levels. Association of patient and tumor characteristics with Tg levels was examined by chi (2) test. Recurrence-free survival (RFS) stratified by postop Tg level was calculated by Kaplan-Meier method and compared by log-rank test. RESULTS: Twenty patients had undetectable Tg (<1 ng/ml) and 11 had detectable Tg (>/=1 ng/ml; range 2-129 ng/ml) following surgery. After adjuvant RAI, 24 patients had undetectable Tg (<1 ng/ml) and 7 had detectable Tg (>/=1 ng/ml; range 1-57 ng/ml). Patients with undetectable Tg were less likely to have pathologically positive margins compared to those with detectable Tg (33 vs. 72 % respectively; p = 0.03). Patients with undetectable Tg levels had better 5-year regional control and distant control than patients with detectable Tg level (5-year regional recurrence-free survival 96 vs. 69 %; p = 0.03; 5-year distant recurrence-free survival 96 vs. 46 %, p = 0.11). CONCLUSION: Postoperative thyroglobulin levels in subset of patients with PDTC appear to have predictive value for recurrence. Patients with undetectable Tg have a low rate of recurrence.
PubMed-ID: 25893415
http://dx.doi.org/10.1245/s10434-015-4567-3

Thyroid incidentalomas detected on 18F-fluorodeoxyglucose-positron emission tomography/computed tomography: Thyroid Imaging Reporting and Data System (TIRADS) in the diagnosis and management of patients.
Surgery, 158(5):1314-22.
J. H. Yoon, A. Cho, H. S. Lee, E. K. Kim, H. J. Moon and J. Y. Kwak. 2015.
BACKGROUND: Our aim was to evaluate the role of the Thyroid Imaging Reporting and Data System (TIRADS) in the risk stratification of thyroid incidentalomas detected on (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography ((18)F-FDG-PET/CT) scans. METHODS: Eighty-seven thyroid nodules in 84 patients showing incidentally detected increased uptake on (18)F-FDG-PET/CT who also had ultrasonography (US)-guided fine needle aspiration performed were included. On review of the US images, a TIRADS category was assigned to each thyroid nodule based on the number of suspicious US features. The correlation between the TIRADS category and the standard uptake values (SUV) on (18)F-FDG-PET/CT were calculated and compared. RESULTS: Of the 87 thyroid nodules, 47 (54%) were benign, and 40 (46%) were malignant. The malignancy rate of the TIRADS categories were as follows: 9% for category 3, 15% for category 4a, 39% for category 4b, 72% for category 4c, and 100.0% for category 5. Combining the TIRADS with the SUV showed increased specificity and positive predictive value but decreased sensitivity and negative predictive value compared with TIRADS alone (all $P < .05$). The area under the receiver operating characteristics curve value of TIRADS was the greatest, comparable with the combined TIRADS and SUV (0.737 to 0.724, $P = .788$). CONCLUSION: TIRADS may be applied in the risk stratification of thyroid incidentalomas detected on (18)F-FDG-PET/CT. Considering the high malignancy rate of thyroid incidentalomas showing increased (18)F-FDG uptake, ultrasonography-guided fine needle aspiration is mandatory even if there are no suspicious features present on US.
PubMed-ID: 25958065
http://dx.doi.org/10.1016/j.surg.2015.03.017

[Transaxillary robot-assisted thyroidectomy: First experiences with a new operation technique].
Chirurg, 86(10):976-82.
S. Eckhardt, E. Maurer, V. Fendrich and D. K. Bartsch. 2015.
BACKGROUND: The main advantage of transaxillary robotic-assisted thyroid surgery (TRAT) is the avoidance of a scar on the neck. As TRAT is still rarely performed in Germany, there are not yet any German reports on acceptance, operation times and complications. METHODS: In a pilot study all patients with an indication for hemithyroidectomy without preoperative evidence of malignancies or previous neck surgery and a lobe size < 30 ml, a body mass index (BMI) < 30 and age > 18 years were offered transaxillary robotic-assisted hemithyroidectomy (TRAHT) after a detailed explanation of this operation. The acceptance of this new technique, the operation time, complications and patient satisfaction were prospectively recorded and analyzed. RESULTS: Between January 2013 and October 2014 a total of 65 patients were offered the option of a TRAHT and 21 (32%) patients opted for this surgical technique. None of these 21 operations had to be converted and there were no intraoperative complications. The median operation time was 190 min (range 106-300 min) with a significant learning curve (first 5 TRAHT 219 min and last 5 TRAHT 163 min), 10 (48%) patients had a postoperative slight transient skin dysesthesia in the area of the access route, 4 (19%) patients had a transient recurrent laryngeal nerve palsy and 2 patients (9%) had a transient upper brachial plexus palsy. After the first 21 TRAHT operations, 2 Dunhill operations for Grave's disease were also performed via a single axillary incision. The operation times were 320 min and 260 min without complications and 21 out of the 23 patients (91%) were highly satisfied with the cosmetic result and would choose TRAT again. CONCLUSION: The TRAT procedure still has low acceptance by German patients but patient satisfaction after surgery is high due to the cosmetic result. The extended operation time, new complications (e.g. transient plexus palsy) and a potentially increased rate of transient recurrent laryngeal nerve palsy must be critically considered.
PubMed-ID: 25971612
http://dx.doi.org/10.1007/s00104-015-0008-x

Variations in single/two stage thyroidectomies for cancer may be due to differences in thyroid fine needle cytology provision.
Eur J Surg Oncol, 41(8):1033-8.
A. Gandhi, B. Ranganathan, S. A. Thiryayi, M. Rowland and B. K. Yap. 2015.
BACKGROUND & AIMS: Recommended treatment for thyroid cancers >10 mm is single stage total thyroidectomy (SST). Cancers diagnosed by diagnostic lobectomy may need completion surgery resulting in two stage thyroidectomies (TST). We noticed significant variation in numbers of SST and TST between hospitals within our cancer network and explored reasons for this using a prospective database containing all cases from 2004 to 2011 (n = 1030). We therefore conducted a survey of thyroid cytology provision across the network

during 2010-2011. METHODS: A central university hospital with the largest caseload (21.5% of total) was chosen as "benchmark". Of 14 remaining hospitals 3 were excluded from analysis due to low thyroid operation numbers and the remaining compared with benchmark. We used individual chi-squared tests with Bonferroni correction to explore variation in expected and observed numbers of SST/TST. Analysis of variance (ANOVA) was used to examine reasons for observed differences. RESULTS: Significant variance in SST/TST was seen between hospitals ($p < 0.00001$). Three hospitals had frequencies of SST statistically similar to reference hospital; each reported 201-300 thyroid cytology cases during the survey period. The remaining 8 had lower rates of SST, the 2 lowest performing hospitals having SST rates of 11% ($p = 0.0004$) and 9% ($p < 0.0001$). These eight hospitals reported fewer than 200 cytology cases each, shared amongst 4-7 pathologists per site. Differences were unrelated to patient age, gender, tumour histology or stage (ANOVA). Only the reference hospital had specialist cytopathologists. CONCLUSION: Variation in thyroid cytology provision may increase TST rates. Thyroid cytology should be concentrated in high volume centres with specialist thyroid cytopathologists.
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http://dx.doi.org/10.1016/j.ejso.2015.04.010

Identifying the most appropriate age threshold for TNM stage grouping of well-differentiated thyroid cancer.
Eur J Surg Oncol, 41(8):1028-32.
J. Hendrickson-Rebizant, H. Sigvaldason, R. W. Nason and K. A. Pathak. 2015.
OBJECTIVE: Age is integrated in most risk stratification systems for well-differentiated thyroid cancer (WDTC). The most appropriate age threshold for stage grouping of WDTC is debatable. The objective of this study was to evaluate the best age threshold for stage grouping by comparing multivariable models designed to evaluate the independent impact of various prognostic factors, including age based stage grouping, on the disease specific survival (DSS) of our population-based cohort. METHODS: Data from population-based thyroid cancer cohort of 2125 consecutive WDTC, diagnosed during 1970-2010, with a median follow-up of 11.5 years, was used to calculate DSS using the Kaplan Meier method. Multivariable analysis with Cox proportional hazard model was used to assess independent impact of different prognostic factors on DSS. The Akaike information criterion (AIC), a measure of statistical model fit, was used to identify the most appropriate age threshold model. Delta AIC, Akaike weight, and evidence ratios were calculated to compare the relative strength of different models. RESULTS: The mean age of the patients was 47.3 years. DSS of the cohort was 95.6% and 92.8% at 10 and 20 years respectively. A threshold of 55 years, with the lowest AIC, was identified as the best model. Akaike weight indicated an 85% chance that this age threshold is the best among the compared models, and is 16.8 times more likely to be the best model as compared to a threshold of 45 years. CONCLUSION: The age threshold of 55 years was found to be the best for TNM stage grouping.
PubMed-ID: 25986855
http://dx.doi.org/10.1016/j.ejso.2015.04.014

Thyroid swellings in the art of the Italian Renaissance.
Am J Surg, 210(3):591-6.
A. V. Sterpetti, G. De Toma and A. De Cesare. 2015.
BACKGROUND: Thyroid swellings in the art of the Italian Renaissance are sporadically reported in the medical literature. METHODS: Six hundred paintings and sculptures from the Italian Renaissance, randomly selected, were analyzed to determine the prevalence of personages with thyroid swellings and its meaning. RESULTS: The prevalence of personages with thyroid swellings in the art of Italian Renaissance is much higher than previously thought. This phenomenon was probably secondary to iodine deficiency. The presence of personages with thyroid swelling was related to specific meanings the artists wanted to show in their works. CONCLUSIONS: Even if the function and the role of the thyroid were discovered only after thyroidectomy was started to be performed, at the beginning of the 19th century, artists of the Italian Renaissance had the intuition that thyroid swellings were related to specific psychological conditions. Artistic intuition and sensibility often comes before scientific demonstration, and it should be a guide for science development.
PubMed-ID: 26026338
http://dx.doi.org/10.1016/j.amjsurg.2015.01.027

Clinicopathological Significance of Minimal Extrathyroid Extension in Solitary Papillary Thyroid Carcinomas.
Ann Surg Oncol, 22 Suppl 3:S728-33.
C. G. Woo, C. O. Sung, Y. M. Choi, W. G. Kim, T. Y. Kim, Y. K. Shong, W. B. Kim, S. J. Hong and D. E. Song. 2015.
BACKGROUND: The definitive diagnosis of minimal extrathyroid extension (ETE) is subjective because a well-defined true capsule is absent in the thyroid gland. We subclassified the extent of minimal ETE and investigated the clinicopathological significance of the presence of minimal ETE in patients with solitary papillary thyroid carcinomas (PTCs) and solitary papillary thyroid microcarcinomas (PTMCs). METHODS: A series of 546 patients with solitary PTCs, including 144 patients with solitary PTMCs, were retrospectively analyzed. Whether the presence of minimal ETE had an effect on recurrence-free survival (RFS) along with other clinicopathological parameters was investigated. RESULTS: The only independent prognostic factor found to be associated with recurrence was the presence of LN metastasis in solitary PTC ($p = 0.002$) but not in solitary PTMC groups ($p = 0.073$). The presence of minimal ETE had no effect on RFS in both solitary PTC ($p = 0.053$) and solitary PTMC ($p = 0.816$). CONCLUSIONS: The presence of minimal ETE has no significant influence on RFS in solitary PTC and PTMC. There is a risk of overrepresenting the T3 category in solitary PTC and PTMC patients with minimal ETE.
PubMed-ID: 26077913
http://dx.doi.org/10.1245/s10434-015-4659-0

A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma.
Eur J Endocrinol, 173(3):367-75.
B. H. Lang and C. K. Wong. 2015.
BACKGROUND: The issue of whether all incidental papillary thyroid microcarcinoma (PTMC) should be managed by early surgery (ES) has been questioned and there is a growing acceptance that a non-surgical approach (NSA) might be more appropriate. We conducted a cost-effectiveness analysis comparing the two strategies in managing incidental PTMC. METHODS: Our base case was a hypothetical 40-year-old female diagnosed with a unifocal intra-thyroidal 9 mm PTMC. The PTMC was considered suitable for either strategy. A Markov decision tree model was constructed to compare the estimated cost-effectiveness between ES and NSA after 20 years. Outcome probabilities, utilities and costs were derived from the literature. The threshold for cost-effectiveness was set at USD 50,000/quality-adjusted life year (QALY). A further analysis was done for patients < 40 and >/= 40 years. Sensitivity and threshold analyses were used to examine model uncertainty. RESULTS: Each patient who adopted NSA over ES cost an extra USD 682.54 but gained an additional 0.260 QALY. NSA was cost saving (i.e. less costly and more effective) up to 16 years from diagnosis and remained cost-effective from 17 years onward. In the sensitivity analysis, NSA remained cost-effective regardless of patient age (< 40 and >/= 40 years), complications, rates of progression, year cycle and discount rate. In the threshold analysis, none of the scenarios that could have changed the conclusion appeared clinically likely. CONCLUSIONS: For a selected group of incidental PTMC, adopting NSA was not only cost saving in the initial 16 years but also remained cost effective thereafter. This was irrespective of patient age, complication rate or rate of PTMC progression.
PubMed-ID: 26104754
http://dx.doi.org/10.1530/EJE-15-0454

The Impact of Noninvasive Follicular Variant of Papillary Thyroid Carcinoma on Rates of Malignancy for Fine-Needle Aspiration Diagnostic Categories.
Thyroid, 25(9):987-92.
K. C. Strickland, B. E. Howitt, E. Marqusee, E. K. Alexander, E. S. Cibas, J. F. Krane and J. A. Barletta. 2015.
BACKGROUND: Increased recognition of the indolent nature of noninvasive follicular variant of papillary thyroid carcinoma (NFVPTC) along with greater insight into the molecular alterations of these tumors has prompted endocrine pathologists to question whether these tumors warrant a diagnosis of carcinoma. However, a change in terminology would affect the rates of malignancy of fine-needle aspiration (FNA) diagnostic categories. Therefore, the aim of this study was to determine the percentage decrease in associated risk of malignancy for each FNA diagnostic category if NFVPTCs were no longer termed carcinomas. METHODS: We evaluated a cohort of 655 FNAs with subsequent resection specimens over a 22-month time period. The diagnoses of the preceding FNAs were recorded according to the Bethesda System for Reporting Thyroid Cytopathology. For cases with more than one preceding FNA, the FNA diagnosis associated with the highest risk of malignancy was identified. Slides for all resection specimens with a diagnosis of FVPTC were reviewed to identify noninvasive tumors. By definition, all of these tumors were encapsulated, partially encapsulated, or well circumscribed and

lacked any indication of infiltrative growth, capsular penetration, or lymphovascular invasion. RESULTS: Our cohort of 655 FNAs with subsequent resection specimens included 53 (8.1%) nondiagnostic (ND), 167 (25.5%) benign, 97 (14.8%) atypia/follicular lesion of undetermined significance (AUS/FLUS), 88 (13.4%) suspicious for follicular neoplasm (SFN), 94 (14.4%) suspicious for malignancy (SUS), and 156 (23.8%) malignant cases (POS). Surgical resections demonstrated benign findings in 309 (47.2%) and malignant tumors in 346 (52.8%), including 85 NFVPTCs accounting for 24.6% of malignancies. Our rates of malignancy for ND, benign, AUS/FLUS, SFN, SUS, and POS were 18.9%, 13.2%, 39.2%, 45.5%, 87.2%, and 98.7%, respectively. If NFVPTC were no longer termed carcinoma, these rates would drop to 17.0% (10% decrease), 5.4% (59% decrease), 21.6% (45% decrease), 37.5% (18% decrease), 45.7% (48% decrease), and 93.6% (5% decrease), respectively. CONCLUSION: Our findings demonstrate that if terminology were changed and NFVPTCs were not considered carcinomas, the rates of malignancy for FNA diagnostic categories would be substantially decreased, with the most clinically significant decrease seen in the SUS category, which demonstrated a relative decrease of nearly 50%.
PubMed-ID: 26114752
http://dx.doi.org/10.1089/thy.2014.0612

Role of BRAF V600E mutation as an indicator of the extent of thyroidectomy and lymph node dissection in conventional papillary thyroid carcinoma.
Surgery, 158(6):1500-11.
S. K. Kim, J. W. Woo, J. H. Lee, I. Park, J. H. Choe, J. H. Kim and J. S. Kim. 2015.
BACKGROUND: The extent of surgery for papillary thyroid carcinoma (PTC) is associated strongly with disease persistence, recurrence, and mortality. It is difficult, however, to determine the optimal extent for surgery. The BRAF mutation is well known for its diagnostic and prognostic value in PTC. Among the variants of PTC, the clinical importance of the BRAF mutation has been associated particularly with conventional PTC. The goal of this study was to clarify the role of the BRAF mutation as a determinant for the operative extent in conventional PTC. METHODS: Histopathology and BRAF mutation status of 3,019 patients with conventional PTC were analyzed. With regard to the extent of surgery in PTC, focus was given to the factors of tumor bilaterality, central lymph node metastasis (CLNM), and lateral lymph node metastasis. In addition, the prognostic impact of BRAF mutation on loco-regional recurrence was investigated. RESULTS: The BRAF mutation was found to be an independent indicator of tumor bilaterality (odds ratio [OR] 1.484, P = .010); however, it was not an independent indicator of CLNM (OR 1.167, P = .254) or lateral lymph node metastasis (OR 0.647, P = .384). Moreover, it was not an independent indicator of CLNM in either the therapeutic or prophylactic central neck dissection. Finally, BRAF mutation positivity did not increase the risk of loco-regional recurrence (adjusted hazard ratio = 0.829, P = .523). CONCLUSION: The BRAF mutation is a possible indicator for determining the extent of thyroidectomy required but not for the extent of lymph node dissection and prognosis in patients with conventional PTC.
PubMed-ID: 26120069
http://dx.doi.org/10.1016/j.surg.2015.05.016

Implementing the Modified 2009 American Thyroid Association Risk Stratification System in Thyroid Cancer Patients with Low and Intermediate Risk of Recurrence.
Thyroid, 25(11):1235-42.
F. Pitoia, F. Jerkovich, C. Urciuoli, A. Schmidt, E. Abelleira, F. Bueno, G. Cross and R. M. Tuttle. 2015.
OBJECTIVE: The primary purpose of this study was to validate the proposed modified 2009 American Thyroid Association Risk Stratification System (M-2009-RSS) in patients with thyroid cancer and to compare the findings with those of the 2009 ATA Risk of Recurrence (2009 ATA-RR) and the Ongoing Risk of recurrence system. The secondary purpose was to assess which risk stratification system had the best predictive value to foresee the probability of structural incomplete response or the no evidence of disease (NED) status at the end of follow-up. SUBJECTS AND METHODS: This retrospective review included 149 patients with differentiated thyroid cancer who had low and intermediate 2009 ATA-RR and were treated at a single experienced center and followed-up for a median of 6 years (range 3-12 years). Each patient was risk stratified using both the 2009 ATA-RR and the M-2009-RSS. The primary endpoints were 1) the best response to initial therapy defined as either excellent response, biochemical or structural incomplete response, or indeterminate response; 2) clinical status at final follow-up defined as either NED, biochemical incomplete response, structural incomplete response, indeterminate response, or recurrence (biochemical or structural disease identified after a period of NED), and 3) ongoing RR defined as low or high risk according several outcomes after initial treatment. RESULTS: Mean age of included patients was 45.3+/-13 years. Both the ATA 2009-RR and the M-2009-RSS provided clinically meaningful graded estimates with regard to the status of NED at the end of follow-up in low-risk patients (84% for 2009 ATA-RR and 74% for M-2009-RSS) or the likelihood of having persistent structural disease (0% for 2009 ATA RR and 3.6% for the M-2009-RSS). When patients were classified as low risk, the positive predictive

value (PPV) and negative predictive value (NPV) to predict structural disease was 0% and 88.7% for the 2009 ATA-RR, 3.6% and 86.5% for the M-2009-RSS, and 1.6% and 68.2% for the ongoing RR (p=0.022 and 0.055 of chi-square test for PPV and NPV, respectively). CONCLUSIONS: Despite expanding the definition of low risk to include small-volume lymph node metastases, minor extrathyroidal extension, and minimally invasive follicular thyroid cancer, the M-2009-RSS predicts clinical outcomes (structural incomplete response and NED at the end of follow-up) that are very similar to the previously validated 2009 ATA RR classification system.
PubMed-ID: 26132983
http://dx.doi.org/10.1089/thy.2015.0121

Continuous Vagal Nerve Monitoring is Dangerous and Should not Routinely be Done During Thyroid Surgery.
World J Surg, 39(10):2471-6.
D. J. Terris, K. Chaung and W. S. Duke. 2015.
INTRODUCTION: Laryngeal nerve monitoring has been increasingly embraced as a mechanism for mitigating the risk of nerve damage during thyroid and parathyroid surgery. Vagal nerve monitoring has recently been introduced as a potentially increased level of nerve integrity scrutiny. We sought to define the risks and benefits of this technology in a prospective analysis of a series of patients undergoing neck endocrine surgery. SETTING: High-volume academic endocrine surgery practice. METHODS: A prospective, non-controlled trial of continuous vagal nerve monitoring (CVNM) in a projected cohort of 20 non-randomly selected patients undergoing thyroid and parathyroid surgery was planned. A commercially available nerve monitoring system with automatic periodic stimulation was utilized for both laryngeal nerve monitoring and CVNM. Demographic data were obtained, and outcome variables included surgical procedures performed, pathology, complications, incremental time required to achieve CVNM, and benefits of monitoring and stimulation. RESULTS: The patient accrual was aborted after 9 surgeries (12 nerves monitored) because of two serious adverse events (hemodynamic instability and reversible vagal neuropraxia attributable to the monitoring apparatus). No other complications occurred. The time to establish monitoring ranged from 3 to 26 min, with a median of 6 min (representing 2.9-12.2 % of the total surgical procedural time). The stimulation clamp became dislodged 11 times in 5 cases and was replaced in 7 of those instances. Benefits of CVNM included recognition of reduced amplitude and increased nerve latency in two patients. CONCLUSIONS: We report the first evidence that CVNM may cause serious patient harm. This novel approach is invasive and threatens patient safety. Although it may occasionally provide meaningful information, the risk-benefit ratio does not favor widespread adoption.
PubMed-ID: 26138874
http://dx.doi.org/10.1007/s00268-015-3139-9

Transient and permanent hypocalcemia after total thyroidectomy: Early predictive factors and long-term follow-up results.
Surgery, 158(6):1492-9.
S. T. Seo, J. W. Chang, J. Jin, Y. C. Lim, K. S. Rha and B. S. Koo. 2015.
BACKGROUND: Post-thyroidectomy hypocalcemia is among the most common complications of total thyroidectomy. The purpose of this study was to evaluate early predictive factors and long-term changes in intact parathyroid hormone (iPTH) levels in patients with transient and permanent hypocalcemia after total thyroidectomy. PATIENTS AND METHODS: A total of 349 consecutive patients who underwent total thyroidectomy with or without neck dissection between 2009 and 2011 were reviewed. PTH, total calcium (Ca), and ionized Ca (iCa) levels were evaluated at 1 hour, and 1, 3, 5, and 7 days, and 1, 3, 6, and 12 months postoperatively. Biochemical profiles at 1 hour after total thyroidectomy in patients with transient and permanent hypocalcemia were compared. Patients with postoperative hypocalcemia were followed for 12 months. RESULTS: Lesser preoperative serum levels of Ca and more extensive surgery were significantly associated with postoperative hypocalcemia ($P < .05$). The absolute level and relative decline (%) in iPTH at 1 hour were the most reliable predictors of postoperative hypocalcemia according to the receiver operating characteristics curve, with a threshold of 10.42 pg/mL and 70%. Sensitivity and specificity of the predictors were 83.4% (95% CI, 76.4-89.1), 100% (95% CI, 84.6-100.0), 84.1 (95% CI, 77.2-89.7), and 95.5% (95% CI, 77.2-99.9), respectively. Parathyroid function recovered in the first month after total thyroidectomy in 78 of 99 patients (79%) with transient hypocalcemia. However, 46 of 61 patients (74%) with a subnormal iPTH level at 3 months after surgery had permanent hypocalcemia. CONCLUSION: Mean postoperative PTH level and the mean relative decline in PTH measured 1 hour postoperatively were the most reliable predictors of postoperative or permanent hypocalcemia.
PubMed-ID: 26144879
http://dx.doi.org/10.1016/j.surg.2015.04.041

Voice outcomes following reoperative central neck dissection for recurrent/persistent thyroid cancer.
Laryngoscope, 125(11):2621-5.
H. Starmer, S. I. Noureldine, O. B. Ozgursoy and R. P. Tufano. 2015.
OBJECTIVES/HYPOTHESIS: We aimed to assess voice outcomes following reoperative central neck dissection (RCND) to characterize postoperative voice difficulties experienced, determine the natural progression of vocal recovery, and identify risk factors for the development of voice disorders postoperatively. STUDY DESIGN: Prospective cohort study. METHODS: Consecutive patients with recurrent/persistent thyroid cancer who were deemed appropriate candidates for RCND were eligible for participation in this study. A battery of voice evaluation measures was administered both preoperatively and 2 to 4 weeks postoperatively. RESULTS: Twenty consecutive patients were included. Postoperatively, six (30%) new incidents of vocal fold motion impairment (VFMI) were identified, with two (10%) being due to intentional recurrent laryngeal nerve (RLN) transection. On 1-year follow-up, two patients had full restoration of vocal fold mobility and four had persistent VFMI. No preoperative voice/laryngeal exam factors were predictive of postoperative VFMI. Clinically relevant change in postoperative Voice Handicap Index score was absent in all patients without VFMI and present in five of six patients with VFMI (P=.0004). Patients with VFMI had significantly poorer overall dysphonia grade, less glottic closure, and elevated jitter in contrast to those individuals without VFMI. Patients with malignant tissue in the remnant thyroid were four times more likely to develop VFMI than those with central neck lymph node metastases alone (P=.06). CONCLUSION: Patients undergoing RCND are at risk for postoperative VFMI, even when the RLN is anatomically preserved, with subsequent impact on quality of life. Presence of malignant disease in the remnant thyroid appears to be the best predictor for postoperative VFMI. LEVEL OF EVIDENCE: 2b.
PubMed-ID: 26153252
http://dx.doi.org/10.1002/lary.25427

Long-Term Outcomes Following Therapy in Differentiated Thyroid Carcinoma: NTCTCS Registry Analysis 1987-2012.
J Clin Endocrinol Metab, 100(9):3270-9.
A. A. Carhill, D. R. Litofsky, D. S. Ross, J. Jonklaas, D. S. Cooper, J. D. Brierley, P. W. Ladenson, K. B. Ain, H. G. Fein, B. R. Haugen, J. Magner, M. C. Skarulis, D. L. Steward, M. Xing, H. R. Maxon and S. I. Sherman. 2015.
CONTEXT: Initial treatments for patients with differentiated thyroid cancer are supported primarily by single-institution, retrospective studies, with limited follow-up and low event rates. We report updated analyses of long-term outcomes after treatment in patients with differentiated thyroid cancer. OBJECTIVE: The objective was to examine effects of initial therapies on outcomes. DESIGN/SETTING: This was a prospective multi-institutional registry. PATIENTS: A total of 4941 patients, median follow-up, 6 years, participated. INTERVENTION: Interventions included total/near-total thyroidectomy (T/NTT), postoperative radioiodine (RAI), and thyroid hormone suppression therapy (THST). MAIN OUTCOME MEASURE: Main outcome measures were overall survival (OS) and disease-free survival using product limit and proportional hazards analyses. RESULTS: Improved OS was noted in NTCTCS stage III patients who received RAI (risk ratio [RR], 0.66; P = .04) and stage IV patients who received both T/NTT and RAI (RR, 0.66 and 0.70; combined P = .049). In all stages, moderate THST (TSH maintained subnormal-normal) was associated with significantly improved OS (RR stages I-IV: 0.13, 0.09, 0.13, 0.33) and disease-free survival (RR stages I-III: 0.52, 0.40, 0.18); no additional survival benefit was achieved with more aggressive THST (TSH maintained undetectable-subnormal). This remained true, even when distant metastatic disease was diagnosed during follow-up. Lower initial stage and moderate THST were independent predictors of improved OS during follow-up years 1-3. CONCLUSIONS: We confirm previous findings that T/NTT followed by RAI is associated with benefit in high-risk patients, but not in low-risk patients. In contrast with earlier reports, moderate THST is associated with better outcomes across all stages, and aggressive THST may not be warranted even in patients diagnosed with distant metastatic disease during follow-up. Moderate THST continued at least 3 years after diagnosis may be indicated in high-risk patients.
PubMed-ID: 26171797
http://dx.doi.org/10.1210/JC.2015-1346

The Value of Repeat Thyroid Fine-Needle Aspiration Biopsy in Patients with a Previously Benign Result: How Often Does It Alter Management?
Thyroid, 25(10):1121-6.
N. Singh Ospina, T. J. Sebo, J. C. Morris and M. R. Castro. 2015.
BACKGROUND: Thyroid nodules are prevalent and mostly benign, being present in up to 67% of the population when assessed by ultrasound. Due to the variable diagnostic performance of ultrasound-guided fine-needle aspiration biopsy (USFNA) of the thyroid and the possibility of a false-negative result, current clinical guidelines recommend ultrasonographic follow-up of benign thyroid nodules. The objective of this study was to evaluate the

clinical relevance of a repeat fine-needle aspiration (rFNA) in patients with an initial benign fine-needle aspiration biopsy (iFNA). METHODS: A retrospective review was conducted of medical records of patients seen at the Mayo Clinic between January of 2003 and December of 2013 who had undergone rFNA of a nodule with benign iFNA. The outcome measured was the result of the rFNA and histopathological correlation, when available. RESULTS: Three hundred and thirty-four nodules with benign iFNA underwent rFNA during the 10-year study period. The rFNA was most commonly reported as benign (85.3%), followed by suspicious (7.2%), nondiagnostic (5.7%), and malignant (1.8%). The rFNA changed clinical management in 9.5% of the cases. The prevalence of thyroid malignancy ranged from 4.1% to 1.2% based on the gold standard used (histology vs. long-term follow-up, 4.0 +/- 2.3 years). CONCLUSION: In the majority of patients with a benign iFNA, results of the rFNA were unchanged. However, in a small group of patients, the rFNA may differ from the initial results, and alter management. Even so, the prevalence of malignancy remains very low, ranging from 1.2% to 4.1% depending on the gold standard.
PubMed-ID: 26177342
http://dx.doi.org/10.1089/thy.2015.0146

Institutional experience with lateral neck dissections for thyroid cancer.
Surgery, 158(4):972-8; discussion 8-80.
J. A. Glenn, T. W. Yen, G. G. Fareau, A. A. Carr, D. B. Evans and T. S. Wang. 2015.
INTRODUCTION: Compartment-oriented neck dissection is recommended for patients with evidence of thyroid cancer metastases to lateral compartment lymph nodes. This study reviews the outcomes of patients who underwent lateral neck dissections (LND) at a high-volume institution. METHODS: This is a retrospective review of patients who underwent LND for metastatic thyroid cancer from January 2009 to June 2014. Preoperative evaluation, operative findings, and postoperative outcomes were analyzed. RESULTS: Ninety-six patients underwent 127 LNDs. Fine-needle aspiration (FNA) confirmed metastases in 82 lateral necks (65%). The remaining 45 LNDs (35%) were performed based on clinical suspicion of metastases; 29 (64%) had metastases on final pathology. Twenty patients had 26 complications, which included chyle leak (7 [6%]), spinal accessory nerve dysfunction (7 [6%]), neck seroma requiring drainage (2 [2%]), and surgical site infection (10 [8%]). CONCLUSION: LND is associated with a risk of early postoperative morbidity, but long-term complications are uncommon in the hands of experienced surgeons. In patients with thyroid cancer, a comprehensive preoperative evaluation of the lateral neck with physical examination, ultrasonography, and possible FNA should be performed. For those with suspicion of metastases, LND can be an important therapeutic option, but discussion with the patient regarding potential risks and benefits is essential.
PubMed-ID: 26187683
http://dx.doi.org/10.1016/j.surg.2015.03.066

Serum Immunoproteomics Combined With Pathological Reassessment of Surgical Specimens Identifies TCP-1zeta Autoantibody as a Potential Biomarker in Thyroid Neoplasia.
J Clin Endocrinol Metab, 100(9):E1206-15.
P. V. Belousov, A. V. Bogolyubova, Y. S. Kim, A. Y. Abrosimov, A. T. Kopylov, A. A. Tvardovskiy, K. V. Lanshchakov, A. Y. Sazykin, N. Y. Dvinskikh, Y. I. Bobrovskaya, L. S. Selivanova, E. S. Shilov, A. M. Schwartz, Y. V. Shebzukhov, N. V. Severskaia, V. E. Vanushko, S. A. Moshkovskii, S. A. Nedospasov and D. V. Kuprash. 2015.
CONTEXT: Current methods of preoperative diagnostics frequently fail to discriminate between benign and malignant thyroid neoplasms. In encapsulated follicular-patterned tumors (EnFPT), this discrimination is challenging even using histopathological analysis. Autoantibody response against tumor-associated antigens is a well-documented phenomenon with prominent diagnostic potential; however, autoantigenicity of thyroid tumors remains poorly explored. OBJECTIVES: Objectives were exploration of tumor-associated antigen repertoire of thyroid tumors and identification of candidate autoantibody biomarkers capable of discrimination between benign and malignant thyroid neoplasms. DESIGN, SETTING, AND PATIENTS: Proteins isolated from FTC-133 cells were subjected to two-dimensional Western blotting using pooled serum samples of patients originally diagnosed with either papillary thyroid carcinoma (PTC) or EnFPT represented by apparently benign follicular thyroid adenomas, as well as healthy individuals. Immunoreactive proteins were identified using liquid chromatography-tandem mass-spectrometry. Pathological reassessment of EnFPT was performed applying nonconservative criteria for capsular invasion and significance of focal PTC nuclear changes (PTC-NCs). Recombinant T-complex protein 1 subunitzeta (TCP-1zeta) was used to examine an expanded serum sample set of patients with various thyroid neoplasms (n = 89) for TCP-1zeta autoantibodies. All patients were included in tertiary referral centers. RESULTS: A protein demonstrating a distinct pattern of EnFPT-specific seroreactivity was identified as TCP-1zeta protein. A subsequent search for clinicopathological correlates of TCP-1zeta seroreactivity revealed nonclassical capsular invasion or focal PTC-NC in all TCP-1zeta antibody-positive cases.

Further studies in an expanded sample set confirmed the specificity of TCP-1zeta autoantibodies to malignant EnFPT. CONCLUSIONS: We identified TCP-1zeta autoantibodies as a potential biomarker for presurgical discrimination between benign and malignant encapsulated follicular-patterned thyroid tumors. Our results suggest the use of nonconservative morphological criteria for diagnosis of malignant EnFPT in biomarker identification studies and provide a peculiar example of uncovering the diagnostic potential of a candidate biomarker using incorporation of pathological reassessment in the pipeline of immunoproteomic research.
PubMed-ID: 26196948
http://dx.doi.org/10.1210/jc.2014-4260

Recurrent laryngeal nerve safety parameters of the Harmonic Focus during thyroid surgery: Porcine model using continuous monitoring.
Laryngoscope, 125(12):2838-45.
C. W. Wu, Y. J. Chai, G. Dionigi, F. Y. Chiang, X. Liu, H. Sun, G. W. Randolph, R. P. Tufano and H. Y. Kim. 2015.
OBJECTIVES/HYPOTHESIS: The Harmonic Focus (HF) is one of the most popular energy-based devices. The aim of this study was to provide recurrent laryngeal nerve (RLN) functional data that define the safety parameters of the HF during thyroidectomy. STUDY DESIGN: Prospective porcine model using continuous electrophysiologic monitoring. METHODS: Ten piglets were used. At varying distances from the RLN, the HF was activated (activation study). The HF was also applied directly on the RLN after activation on sternocleidomastoid muscle for 10 seconds with different cooling times (cooling study). RESULTS: In the activation study, there was no adverse electromyography (EMG) event at more than 1 mm distance. In the cooling study, there was no adverse EMG event after a 10-second cooling period. When the HF was cooled on the sternocleidomastoid muscle, there was no adverse EMG event after 2 seconds cooling time. CONCLUSIONS: The safe distance of the HF was 1 mm, and it should be cooled for more than 10 seconds or 2 seconds after cooling on muscle. The HF should be used in a standardized manner to avoid RLN injury. LEVEL OF EVIDENCE: NA.
PubMed-ID: 26198968
http://dx.doi.org/10.1002/lary.25412

4-IPP, a selective MIF inhibitor, causes mitotic catastrophe in thyroid carcinomas.
Endocr Relat Cancer, 22(5):759-75.
L. Varinelli, D. Caccia, C. C. Volpi, C. Caccia, M. De Bortoli, E. Taverna, A. V. Gualeni, V. Leoni, A. Gloghini, G. Manenti and I. Bongarzone. 2015.
Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that is over-expressed in several human neoplastic cells. When MIF binds its receptor (CD74) and co-receptor (CD44), it initiates signaling cascades that orchestrate cell proliferation and survival, and it can directly modulate the activity of AMPK. These activities indicate that MIF potentially regulates cell survival and metabolism. We found that MIF was primarily co-expressed with CD74 in 16 out of 23 papillary thyroid carcinoma (PTC) and in all the 27 available anaplastic thyroid carcinoma (ATC) biopsy samples. MIF and CD74 were co-expressed in TPC-1 and HTC-C3 cell lines. The selective MIF inhibitor, 4-iodo-6-phenylpyrimidine (4-IPP), blocked MIF/CD74 internalization, activated JNK, and dose-dependently inhibited proliferation inducing apoptosis and mitotic cell death. In two CD74-negative cell lines, NIM-1 and K1, 4-IPP treatment partially reduced proliferation. Coordinated MIF and CD74 expression appeared to confer in tumor cells the plasticity necessary to escape cell cycle regulation, metabolic changes, and stress conditions. MIF/CD74 signaling removal made cells susceptible to apoptosis and mitotic cell death. This finding suggests a possible avenue for targeting DNA endoreduplication, thus preventing the proliferation of therapy-resistant cell subpopulations. This study highlights MIF/CD74 axis as an important player in the biology of aggressive thyroid neoplasms.
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http://dx.doi.org/10.1530/ERC-15-0299

Comparison of Intraoperative versus Postoperative Parathyroid Hormone Levels to Predict Hypocalcemia Earlier after Total Thyroidectomy.
Otolaryngol Head Neck Surg, 153(3):343-9.
D. R. Lee, A. M. Hinson, E. R. Siegel, S. C. Steelman, D. L. Bodenner and B. C. Stack, Jr. 2015.
OBJECTIVE: To determine differences in the mean parathyroid hormone (PTH) levels for normocalcemic and hypocalcemic total thyroidectomy patients who were tested for PTH during the intraoperative or early postoperative period. DATA SOURCES: MEDLINE, the Cochrane Database, and other databases from 1960 to 2014 in the English language and specific to humans for relevant articles. REVIEW METHODS: Studies were included if PTH was obtained within 24 hours of thyroidectomy. Studies were excluded (1) if only a

hemithyroidectomy was performed, (2) if means of studied PTH values were not reported in the article, or (3) if the time of the PTH draw fell outside of defined "intraoperative" or "early postoperative" windows. PTH values were divided into 3 groups: preoperative (control group), intraoperative (ie, discharge decisions were based on PTH values drawn in the operating room), and early postoperative (ie, PTH values at 1 to 4 hours after surgery were used as a guide). RESULTS: The reported means of perioperative PTH levels and percentage of patients who developed hypocalcemia were collected from 14 studies. PTH evaluated at both the intraoperative and early postoperative periods was significantly lower in patients who became hypocalcemic versus patients who remained normocalcemic. There was no significant difference when PTH was measured intraoperatively or early postoperatively. CONCLUSION: Intraoperative PTH has no significant disadvantage versus early postoperative PTH when used as a clinical guide for discharge after thyroidectomy.
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http://dx.doi.org/10.1177/0194599815596341

Anaplastic Thyroid Cancer: Large Database, Cautious Interpretations.
Ann Surg Oncol, 22(13):4113-4.
A. R. Shaha. 2015.
PubMed-ID: 26219238
http://dx.doi.org/10.1245/s10434-015-4744-4

The impact of CLAUDIN-1 on follicular thyroid carcinoma aggressiveness.
Endocr Relat Cancer, 22(5):819-30.
D. Zwanziger, J. Badziong, S. Ting, L. C. Moeller, S. Kurt Werner, U. Siebolts, C. Wickenhauser, H. Dralle and D. Fuehrer. 2015.
CLAUDIN-1 belongs to the family of transmembrane tight junction proteins tightening the paracellular cleft of epithelial cells. In human malignancies, CLAUDIN-1 is often dysregulated and located in subcellular compartments, particularly in the nucleus where it may influence cellular behaviour. Here, we studied CLAUDIN-1 in relation to the biological characteristics of follicular thyroid carcinoma (FTC). CLAUDIN-1 immuno-staining showed loss of membrane expression and increased nuclear CLAUDIN-1 localization in FTC metastases. CLAUDIN-1 function was further investigated in two different follicular thyroid carcinoma cell lines: FTC-133 isolated from a regional lymph node metastasis and FTC-238 derived from a lung metastasis. In both cell lines CLAUDIN-1 expression was demonstrated in the cell nuclei with a significantly higher protein expression in FTC-238 compared to FTC-133 cells. Interestingly, in vitro scratch assay revealed enriched nuclear CLAUDIN-1 expression near the scratch. Furthermore, the increase of the pathogenic character of FTC-133 cells by RASV12 transfection was associated with elevated CLAUDIN-1 expression and enhanced cell migration, invasion and proliferation. Likewise over-expression of nuclear CLAUDIN-1 in FTC-133 cells resulted in increased cell migration and invasion. Conversely, CLAUDIN-1 downregulation in FTC-238 cells by siRNA resulted in decreased cell migration and invasion and was accompanied by reduced phosphoPKC expression. Moreover, activation and inhibition of PKC resulted in CLAUDIN-1 up- and downregulation in FTC cells respectively. These data suggest an impact of CLAUDIN-1 on follicular thyroid carcinoma aggressiveness, which could potentially be influenced by PKC activity.
PubMed-ID: 26219679
http://dx.doi.org/10.1530/ERC-14-0502

Is There Justification for Total Thyroidectomy in Low-Risk Papillary Thyroid Carcinoma? A Decision-Analysis Model.
World J Surg, 39(11):2707-17.
S. Stern, O. Hilly, E. Horowitz, M. Leshno and R. Feinmesser. 2015.
BACKGROUND: Low-risk papillary thyroid carcinoma is commonly treated surgically. However, uncertainties exist in regard to the optimal extent of surgery. We approached this question using a decision-analysis model. METHODS: A Markov model was used to compare outcome between patients with small (1-2 cm) low-risk PTC treated by hemithyroidectomy or total thyroidectomy. Probabilities and utilities were derived from the literature. The model was evaluated with Monte Carlo simulation. Sensitivity analysis was used to determine which variables most affected the model. RESULTS: Hemithyroidectomy was associated with a minor increase in mortality risk. After incorporation of mortality risk, complications, and quality-of-life measures, hemithyroidectomy was found to be superior to total thyroidectomy, with an increasing benefit over time. Quality-of-life measures, especially disutility of disease recurrence and undergoing surgery, had the greatest effect on the incremental benefit of hemithyroidectomy. CONCLUSION: Based on our decision-analysis model, hemithyroidectomy is the preferred option in low-risk PTC.

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http://dx.doi.org/10.1007/s00268-015-3167-5

Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients.
Ann Surg, 262(3):519-25; discussion 24-5.
L. Yip, M. N. Nikiforova, J. Y. Yoo, K. L. McCoy, M. T. Stang, M. J. Armstrong, K. J. Nicholson, N. P. Ohori, C. Coyne, S. P. Hodak, R. L. Ferris, S. O. LeBeau, Y. E. Nikiforov and S. E. Carty. 2015.
OBJECTIVES: To correlate thyroid cancer genotype with histology and outcomes. BACKGROUND: The prognostic significance of molecular signature in thyroid cancer (TC) is undefined but can potentially change surgical management. METHODS: We reviewed a consecutive series of 1510 patients who had initial thyroidectomy for TC with routine testing for BRAF, RAS, RET/PTC, and PAX8/PPARG alterations. Histologic metastatic or recurrent TC was tracked for 6 or more months after oncologic thyroidectomy. RESULTS: Papillary thyroid cancer (PTC) was diagnosed in 97% of patients and poorly differentiated/anaplastic TC in 1.1%. Genetic alterations were detected in 1039 (70%); the most common mutations were BRAFV600E (644/1039, 62%), and RAS isoforms (323/1039, 31%). BRAFV600E-positive PTC was often conventional or tall cell variant (58%), with frequent extrathyroidal extension (51%) and lymph node metastasis (46%). Conversely, RAS-positive PTC was commonly follicular variant (87%), with infrequent extrathyroidal extension (4.6%) and lymph node metastasis (5.6%). BRAFV600E and RET/PTC-positive PTCs were histologically similar. Analogously, RAS and PAX8/PPARG-positive PTCs were histologically similar. Compared with RAS or PAX8/PPARG-positive TCs, BRAFV600E or RET/PTC-positive TCs were more often associated with stage III/IV disease (40% vs 15%, P < 0.001) and recurrence (10% vs 0.7%, P < 0.001; mean follow-up 33 +/- 21 mo). Distant metastasis was highest in patients with RET/PTC-positive TC (10.8%, P = 0.02). CONCLUSIONS: In this large study of prospective mutation testing in unselected patients with TC, molecular signature was associated with distinctive phenotypes including cancers, with higher risks of both distant metastasis and early recurrence. Preoperative genotype provides valuable prognostic data to appropriately inform surgery.
PubMed-ID: 26258321
http://dx.doi.org/10.1097/SLA.0000000000001420

Factors Predictive of Emergency Department Visits and Hospitalization Following Thyroidectomy and Parathyroidectomy.
Ann Surg Oncol, 22 Suppl 3:S707-13.
R. A. FitzGerald, A. R. Sehgal, J. A. Nichols and C. R. McHenry. 2015.
BACKGROUND: This study aimed to determine the incidence and risk factors for emergency department (ED) visits and unplanned hospitalization after thyroid and parathyroid surgery. METHODS: A retrospective study of all patients who underwent thyroidectomy or parathyroidectomy from 2007 to 2014 was conducted to assess for ED visits or unplanned hospitalization within 30 days after surgery. Uni- and multivariate analyses were used to identify risk factors for ED visits and hospitalization. RESULTS: Of 864 patients who underwent thyroidectomy (n = 673) or parathyroidectomy (n = 191), 96 (11.1 %) had an ED visit and 41 (4.7 %) were hospitalized within 30 days after surgery. Univariate analysis showed hypocalcemia (p = 0.001), younger age (p = 0.02), total thyroidectomy (p = 0.01), and lack of private health insurance (p = 0.005) to be predictive of an ED visit and hypocalcemia (p = 0.0001), Hashimoto's thyroiditis (p = 0.049), total thyroidectomy (p = 0.005), and African American race (p = 0.03) were predictive of hospitalization after thyroidectomy. Multivariate analysis showed younger age (odds ratio [OR] 1.5 per 10-year decrease in age; p = 0.002; 95 % confidence interval [CI] 1.1-1.8) and Medicare insurance (OR 2.7; p = 0.01; 95 % CI 1.3-5.7) to be independently associated with an ED visit, and hypocalcemia (OR 4.7; p < 0.001; 95 % CI 2.2-11.0) was the only independent factor associated with hospitalization after thyroidectomy. Univariate analysis showed hypocalcemia, renal hyperparathyroidism, and multiglandular disease to be predictive of an ED visit and hospitalization after parathyroidectomy. The sample size for parathyroidectomy was too small for multivariate analysis. CONCLUSIONS: Targeted strategies for transitions of care for patients with postoperative hypocalcemia may help to reduce ED visits and hospitalization after thyroidectomy and parathyroidectomy.
PubMed-ID: 26259757
http://dx.doi.org/10.1245/s10434-015-4797-4

Cancer Incidence and Mortality in Patients Treated Either With RAI or Thyroidectomy for Hyperthyroidism.
J Clin Endocrinol Metab, 100(10):3710-7.
E. Ryodi, S. Metso, P. Jaatinen, H. Huhtala, R. Saaristo, M. Valimaki and A. Auvinen. 2015.
CONTEXT: Some previous studies have suggested increased cancer risk in hyperthyroid patients treated with

radioactive iodine (RAI). It is unclear whether the excess cancer risk is attributable to hyperthyroidism, its treatment, or the shared risk factors of the two diseases. OBJECTIVE: The objective was to assess cancer morbidity and mortality in hyperthyroid patients treated with either RAI or surgery. PATIENTS: We identified 4334 patients treated surgically for hyperthyroidism in Finland during 1986-2007 from the Hospital Discharge Registry and 1814 patients treated with RAI for hyperthyroidism at Tampere University Hospital. For each patient, three age- and gender-matched controls were chosen. Information on cancer diagnoses was obtained from the Cancer Registry. The follow-up began 3 months after the treatment and ended at cancer diagnosis, death, emigration, or the common closing date (December 31, 2009). RESULTS: The overall cancer incidence was not increased among the hyperthyroid patients compared to their controls (rate ratio [RR], 1.05; 95% confidence interval [CI], 0.96-1.15). However, the risk of cancers of the respiratory tract (RR, 1.46; 95% CI, 1.05-2.02) and the stomach (RR, 1.64; 95% CI, 1.01-2.68) was increased among the patients. The overall cancer mortality did not differ between the patients and the controls (RR, 1.08; 95% CI, 0.94-1.25). The type of treatment did not affect the overall risk of cancer (hazard ratio for RAI vs thyroidectomy, 1.03; 95% CI, 0.86-1.23) or cancer mortality (hazard ratio, 1.04; 95% CI, 0.91-1.21). CONCLUSIONS: In this cohort of Finnish patients with hyperthyroidism treated with thyroidectomy or RAI, the overall risk of cancer was not increased, although an increased risk of gastric and respiratory tract cancers was seen in hyperthyroid patients. Based on this large-scale, long-term follow-up study, the increased cancer risk in hyperthyroid patients is attributable to hyperthyroidism and shared risk factors, not the treatment modality.
PubMed-ID: 26262435
http://dx.doi.org/10.1210/jc.2015-1874

In-Depth Survey of Scarring and Distress in Patients Undergoing Bilateral Axillo-Breast Approach Robotic Thyroidectomy or Conventional Open Thyroidectomy.
Surg Laparosc Endosc Percutan Tech, 25(5):436-9.
H. Koo do, M. Kim da, J. Y. Choi, K. E. Lee, S. H. Cho and Y. K. Youn. 2015.
PURPOSE: Oncologic and surgical outcomes of bilateral axillo-breast approach (BABA) robotic thyroidectomy (RoT) are comparable with those of open thyroidectomy (OT). We compared degree of scarring and psychological/physical distress between OT and BABA RoT. MATERIALS AND METHODS: Study included 129 cases of thyroidectomy (78 OT, 51 BABA RoT). Patients were evaluated by psychology consultant using 5-point scale questionnaire. RESULTS: BABA RoT was associated with lower degree of scarring than OT (7.8 vs. 11.7, P<0.001). Psychological distress immediately after operation and during surveillance period was higher in OT than in BABA RoT (3.1 vs. 2.6, P=0.009 and 2.4 vs. 1.9, P<0.001). Physical distress (pain and exercise limitation) did not differ between groups (2.5 vs. 2.6, P=0.321 and 2.0 vs. 1.9, P=0.0175). CONCLUSIONS: BABA RoT was associated with less scarring and psychological distress than OT. BABA RoT might be alternative for patients who are concerned about neck scar.
PubMed-ID: 26271022
http://dx.doi.org/10.1097/SLE.0000000000000187

Impact of Timeliness of Resection and Thyroidectomy Margin Status on Survival for Patients with Anaplastic Thyroid Cancer: An Analysis of 335 Cases.
Ann Surg Oncol, 22(13):4166-74.
P. Goffredo, S. M. Thomas, M. A. Adam, J. A. Sosa and S. A. Roman. 2015.
BACKGROUND: Controversies regarding anaplastic thyroid cancer (ATC) surround aggressiveness of tumor resection in the presence of extrathyroidal extension and the impact of delayed surgery on patient survival. Our goal was to analyze the survival implications of complete and timely resections. METHODS: Adult patients with ATC were culled from the National Cancer Data Base for the years 2003-2006. Kaplan-Meier curves and Cox proportional hazard regression analyses were used for univariate and multivariate survival analyses, respectively. RESULTS: A total of 680 ATC patients were identified. In the surgical cohort (n = 335), the female-to-male ratio was 1.6:1; mean age was 68.6 years. Patients with ATCs were staged as IVA in 42.7 % of cases, IVB in 32.2 %, and IVC in 25.1 %. Median time from diagnosis to surgery was 15 days. Negative margin status was more often achieved in patients diagnosed with stage IVA disease ($p < 0.001$). Compared to surgical patients, those who did not receive thyroid resections were older and had a more advanced stage of disease (both $p < 0.001$). In multivariable analyses, positive margin status was associated with increased mortality in stage IVA ATC ($p = 0.017$) but had no survival impact in stages IVB and IVC ($p > 0.05$). After adjustment for possible confounders, increasing time from diagnosis to surgery was not found to be associated with compromised survival outcomes for any disease stage. CONCLUSIONS: Timely and aggressive surgical management should be pursued in patients with intrathyroidal disease; however, aggressive resections may not be recommended for patients with stage IVB and IVC disease when morbidity and operative risks outweigh the limited benefits of surgery.

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

Administration of Radioactive Iodine Therapy Within 1 Year After Total Thyroidectomy Does Not Affect Vocal Function.
J Nucl Med, 56(10):1480-6.
C. H. Ryu, J. Ryu, Y. M. Ryu, Y. J. Lee, E. K. Lee, S. K. Kim, T. S. Kim, T. H. Kim, C. Y. Lee, S. Y. Park, K. W. Chung and Y. S. Jung. 2015.
The purpose of this study was to evaluate the impact of radioactive iodine therapy (RIT) on vocal function during the early follow-up period after total thyroidectomy (TT) using perceptive and objective measurements, questionnaires regarding subjective symptoms, and data on vocal function in a prospectively enrolled and serially followed thyroid cancer cohort. METHODS: Of 212 patients who underwent TT and were screened between January and December 2010 at our hospital, 160 were included in the final analysis. Patients with the following histories were excluded: lateral neck dissection, organic vocal fold disease, external radiotherapy, and voice evaluation during thyroxine withdrawal. Patients were stratified into 3 groups: TT, TT with low-dose RIT (1.1-2.2 GBq), and TT with high-dose RIT (>/=3.7 GBq). Voice evaluations were performed before surgery and at 1, 6, and 12 mo after TT. RESULTS: Vocal characteristics were altered after TT, including changes on the grade, roughness, and strain scale; increased amplitude perturbation; decreased fundamental frequency; narrowed pitch range; and global disturbances in subjective functional parameters on the voice handicap index. However, the degree of vocal changes among the 3 groups did not significantly differ within the 1-y postoperative follow-up period. According to the results of subgroup analyses of patients who demonstrated good voice outcomes after TT, there were no significant functional differences among the 3 groups. CONCLUSION: RIT at any dose does not affect vocal function within 1 y of TT.
PubMed-ID: 26272814
http://dx.doi.org/10.2967/jnumed.115.161463

Outcomes and Risk Factors for Complications of Laser Ablation for Thyroid Nodules: A Multicenter Study on 1531 Patients.
J Clin Endocrinol Metab, 100(10):3903-10.
C. M. Pacella, G. Mauri, G. Achille, D. Barbaro, G. Bizzarri, P. De Feo, E. Di Stasio, R. Esposito, G. Gambelunghe, I. Misischi, B. Raggiunti, T. Rago, G. L. Patelli, S. D'Este, P. Vitti and E. Papini. 2015.
BACKGROUND: Image-guided laser ablation therapy (LAT) of benign thyroid nodules demonstrated favorable results in randomized trials with fixed modalities of treatment. The aim of this retrospective multicenter study was to assess the effectiveness, tolerability, and complications of LAT in a large consecutive series of patients from centers using this technique in their routine clinical activity. PATIENTS: Clinical records of 1534 consecutive laser-treated nodules in 1531 patients from eight Italian thyroid referral centers were assessed. Inclusion criteria were as follows: solid or mixed nodules with fluid component up to 40%; benign cytological findings; and normal thyroid function. METHODS: LAT was performed with a fixed-power protocol, whereas the number of applicators and illumination times were different according to target size. From one to three illuminations with pullback technique and with a total energy delivery based on the nodule volume were performed during the same session. Patients were evaluated during LAT, within 30 days, and 12 months after the procedure. RESULTS: Total number of treatments was 1837; 1280 (83%) of nodules had a single LAT session. Mean nodule volume decreased from 27 +/- 24 mL at baseline to 8 +/- 8 mL 12 months after treatment (P < .001). Mean nodule volume reduction was 72% +/- 11% (range 48%-96%). This figure was significantly greater in mixed nodules (79% +/- 7%; range 70%-92%) because they were drained immediately before laser illumination. Symptoms improved from 49% to 10% of cases (P < .001) and evidence of cosmetic signs from 86% to 8% of cases (P < .001). Seventeen complications (0.9%) were registered. Eight patients (0.5%) experienced transitory voice changes that completely resolved at the ear-nose-throat examination within 2-84 days. Nine minor complications (0.5%) were reported. No changes in thyroid function or autoimmunity were observed. CONCLUSIONS: Real practice confirmed LAT as a clinically effective, reproducible, and rapid outpatient procedure. Treatments were well tolerated and risk of major complications was very low.
PubMed-ID: 26274342
http://dx.doi.org/10.1210/jc.2015-1964

PTCSC3 Is Involved in Papillary Thyroid Carcinoma Development by Modulating S100A4 Gene Expression.
J Clin Endocrinol Metab, 100(10):E1370-7.
J. Jendrzejewski, A. Thomas, S. Liyanarachchi, A. Eiterman, J. Tomsic, H. He, H. S. Radomska, W. Li, R. Nagy, K. Sworczak and A. de la Chapelle. 2015.

CONTEXT: We previously showed that a long noncoding RNA gene, PTCSC3, located close to the variant rs944289 that predisposes to papillary thyroid carcinoma (PTC) might target the S100A4 gene. OBJECTIVE: The aim was to investigate the impact of PTCSC3 on S100A4 expression and its role in cancer development. DESIGN: S100A4 abundance was analyzed by quantitative PCR (qPCR) in unaffected and tumor tissue from n = 73 PTC patients. The expression of PTCSC3 and S100A4 was studied in BCPAP and TPC-1 cell lines with forced expression of PTCSC3 by qPCR. Expression of S100A4 target genes (VEGF and MMP-9) was studied in the BCPAP cell line with forced expression of PTCSC3 by qPCR, reverse transcriptase PCR, and Western blot. The impact of PTCSC3 on BCPAP motility and invasiveness was analyzed by the Transwell and Matrigel assays, respectively. SETTING: This was a laboratory-based study using cells from clinical samples and thyroid cancer cell lines. MAIN OUTCOME AND MEASURE: We aimed to find evidence for a link between the expression of PTCSC3 and thyroid carcinogenesis. RESULTS: Expression data from PTC cell lines pinpointed S100A4 as the most significantly downregulated gene in the presence of PTCSC3. S100A4 was upregulated in tumor tissue (P = 9.33 x 10(-7)) while PTCSC3 was strongly downregulated (P = 2.2 x 10(-16)). S100A4 transcription was moderately correlated with PTCSC3 expression in unaffected thyroid tissue (r = 0.429, P = .0001), and strongly in unaffected tissue of patients with the risk allele of rs944289 (r = 0.685, P = 7.88 x 10(-5)). S100A4, VEGF, and MMP-9 were suppressed in the presence of PTCSC3 (P = .0051, P = .0090, and P =.0037, respectively). PTC cells expressing PTCSC3 showed reduction in motility and invasiveness (P = 4.52 x 10(-5) and P = 1.0 x 10(-4), respectively). CONCLUSIONS: PTCSC3 downregulates S100A4, leading to a reduction in cell motility and invasiveness. We propose that PTCSC3 impacts PTC predisposition and carcinogenesis through the S100A4 pathway.
PubMed-ID: 26274343
http://dx.doi.org/10.1210/jc.2015-2247

RAS proto-oncogene in medullary thyroid carcinoma.
Endocr Relat Cancer, 22(5):R235-52.
M. M. Moura, B. M. Cavaco and V. Leite. 2015.
Medullary thyroid carcinoma (MTC) is a rare malignancy originating from the calcitonin-secreting parafollicular thyroid C cells. Approximately 75% of cases are sporadic. Rearranged during transfection (RET) proto-oncogene plays a crucial role in MTC development. Besides RET, other oncogenes commonly involved in the pathogenesis of human cancers have also been investigated in MTC. The family of human RAS genes includes the highly homologous HRAS, KRAS, and NRAS genes that encode three distinct proteins. Activating mutations in specific hotspots of the RAS genes are found in about 30% of all human cancers. In thyroid neoplasias, RAS gene point mutations, mainly in NRAS, are detected in benign and malignant tumors arising from the follicular epithelium. However, recent reports have also described RAS mutations in MTC, namely in HRAS and KRAS. Overall, the prevalence of RAS mutations in sporadic MTC varies between 0-43.3%, occurring usually in tumors with WT RET and rarely in those harboring a RET mutation, suggesting that activation of these proto-oncogenes represents alternative genetic events in sporadic MTC tumorigenesis. Thus, the assessment of RAS mutation status can be useful to define therapeutic strategies in RET WT MTC. MTC patients with RAS mutations have an intermediate risk for aggressive cancer, between those with RET mutations in exons 15 and 16, which are associated with the worst prognosis, and cases with other RET mutations, which have the most indolent course of the disease. Recent results from exome sequencing indicate that, besides mutations in RET, HRAS, and KRAS, no other recurrent driver mutations are present in MTC.
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http://dx.doi.org/10.1530/ERC-15-0070

Chyle Fistula After Neck Dissection: An 8-Year, Single-Center, Prospective Study of Incidence, Clinical Features, and Treatment.
Ann Surg Oncol, 22 Suppl 3:S1000-6.
D. Ahn, J. H. Sohn and J. Y. Jeong. 2015.
BACKGROUND: Chyle fistula is a relatively rare complication of neck dissection, and there is a lack of consensus regarding its incidence, risk factors, and management. METHODS: Between 2007 and 2014, a total of 472 cases of neck dissection involving the level IV compartment were included in the study. The incidence, risk factors, and clinical course of chyle fistula were investigated, as well as the outcomes of conventional management and the use of octreotide injection in high-output chyle fistula. RESULTS: The overall incidence of chyle fistula was 4.7 % (22/472), with an incidence of 3.0 % and 6.2 % after right and left neck dissection, respectively. The presence of a metastatic lesion around the junction of the internal jugular vein and subclavian vein was the only factor significantly associated with the development of chyle fistula (approximately fourfold higher risk) in univariate and multivariate analyses. In 22 cases of chyle fistula, the mean total drainage volume was 3226 mL during a mean 15.4 days of drain placement. Total parental nutrition for the management of chyle

fistula was required in 16 cases. Nine (40.9 %) of 22 cases experienced additional complications related to chyle fistula. Of the six high-output cases, four were managed with conservative methods plus octreotide injection, and three did not require surgery. CONCLUSIONS: The incidence of chyle fistula after neck dissection was higher than expected, especially on the right side. Surgeons should pay greater attention to chyle fistula from preoperative evaluation to postoperative management.
PubMed-ID: 26286200
http://dx.doi.org/10.1245/s10434-015-4822-7

The 8q24 rs6983267G variant is associated with increased thyroid cancer risk.
Endocr Relat Cancer, 22(5):841-9.
R. Sahasrabudhe, A. Estrada, P. Lott, L. Martin, G. Polanco Echeverry, A. Velez, G. Neta, M. Takahasi, V. Saenko, N. Mitsutake, E. Jaeguer, C. S. Duque, A. Rios, M. Bohorquez, R. Prieto, A. Criollo, M. Echeverry, I. Tomlinson and L. G. Carmona. 2015.
The G allele of the rs6983267 single-nucleotide polymorphism, located on chromosome 8q24, has been associated with increased risk of several cancer types. The association between rs6983267G and thyroid cancer (TC) has been tested in different populations, mostly of European ancestry, and has led to inconclusive results. While significant associations have been reported in the British and Polish populations, no association has been detected in populations from Spain, Italy and the USA. To further investigate the role of rs6983267G in TC susceptibility, we evaluated rs6983267 genotypes in three populations of different continental ancestry (British Isles, Colombia and Japan), providing a total of 3067 cases and 8575 controls. We detected significant associations between rs6983267G and TC in the British Isles (odds ratio (OR)=1.19, 95% CI: 1.11-1.27, P=4.03x10(-7)), Japan (OR=1.20, 95% CI: 1.03-1.41, P=0.022) and a borderline significant association of similar effect direction and size in Colombia (OR=1.19, 95% CI: 0.99-1.44, P=0.069). A meta-analysis of our multi-ethnic study and previously published non-overlapping datasets, which included a total of 5484 cases and 12 594 controls, confirmed the association between rs6983267G and TC (P=1.23x10(-7), OR=1.13, 95% CI: 1.08-1.18). Our results therefore support the notion that rs6983267G is a bona fide TC risk variant that increases the risk of disease by approximately 13%.
PubMed-ID: 26290501
http://dx.doi.org/10.1530/ERC-15-0081

Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease.
J Clin Endocrinol Metab, 100(11):4037-47.
Q. Wu, M. P. Rayman, H. Lv, L. Schomburg, B. Cui, C. Gao, P. Chen, G. Zhuang, Z. Zhang, X. Peng, H. Li, Y. Zhao, X. He, G. Zeng, F. Qin, P. Hou and B. Shi. 2015.
CONTEXT: Epidemiological studies have supported the premise that an adequate selenium intake is essential for thyroid gland function. OBJECTIVE: The objective was to investigate whether the prevalence of thyroid disease differed in two areas that were similar, except for very different soil/crop selenium concentrations. DESIGN: Cross-sectional observational study. SETTING: The setting was two counties of Shaanxi Province, China, here defined as adequate- and low-selenium. PARTICIPANTS: A total of 6152 participants were selected by stratified cluster-sampling. MAIN OUTCOME MEASURES: Participants completed demographic and dietary questionnaires and underwent physical and thyroid ultrasound examinations. Serum samples were analyzed for thyroid function parameters and selenium concentration. Serum selenium was compared between different demographic, dietary, and lifestyle categories in the two counties. The relationship between selenium status, dietary factors, and pathological thyroid conditions was explored by logistic regression. RESULTS: Complete data sets were available from 3038 adequate-selenium participants and 3114 low-selenium participants in whom median (interquartile range) selenium concentrations differed almost 2-fold (103.6 [79.7, 135.9] vs 57.4 [39.4, 82.1] mug/L; P = .001). The prevalence of pathological thyroid conditions (hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, and enlarged thyroid) was significantly lower in the adequate-selenium county than in the low-selenium county (18.0 vs 30.5%; P < .001). Higher serum selenium was associated with lower odds ratio (95% confidence interval) of autoimmune thyroiditis (0.47; 0.35, 0.65), subclinical hypothyroidism (0.68; 0.58, 0.93), hypothyroidism (0.75; 0.63, 0.90), and enlarged thyroid (0.75; 0.59, 0.97). CONCLUSIONS: Low selenium status is associated with increased risk of thyroid disease. Increased selenium intake may reduce the risk in areas of low selenium intake that exist not only in China but also in many other parts of the world.
PubMed-ID: 26305620
http://dx.doi.org/10.1210/jc.2015-2222

A new appraisal of iodine refractory thyroid cancer.
Endocr Relat Cancer, 22(6):R301-10.
F. Vaisman, D. P. Carvalho and M. Vaisman. 2015.
Thyroid cancer incidence is increasing all over the world - mostly due to an increase in the detection of small tumors that were previously undetected. A small percentage of these tumors lose the ability to uptake and/or to respond to radioiodine (RAI) therapy, especially in metastatic patients. There are several new therapeutic options that have emerged in the last 5 years to treat RAI refractory thyroid cancer patients, however, it is very important to properly identify RAI refractory patients and to clarify those appropriate for these treatments. In this review, we discuss the RAI refractory definitions and the criteria that have been suggested based on RAI uptake in the post therapy scan, as well as the response after RAI therapy and the possible molecular mechanisms involved in this process. We offer a review of the therapeutic options available at the moment and the therapeutic considerations based on a patient's individualized personal characteristics, primary tumor histology, tumor burden and location and velocity of lesion growth.
PubMed-ID: 26307020
http://dx.doi.org/10.1530/ERC-15-0300

Are we really at the dawn of understanding sporadic pediatric thyroid carcinoma?
Endocr Relat Cancer, 22(6):R311-24.
M. I. Cordioli, L. Moraes, A. N. Cury and J. M. Cerutti. 2015.
Data from the National Cancer Institute and from the literature have disclosed an increasing incidence of thyroid cancer in children, adolescents and adults. Although children and adolescents with thyroid cancer tend to present with more advanced disease than adults, their overall survival rate is excellent; however, there is no clear explanation for the differences observed in the clinicopathological outcomes in these age groups. There has been an ongoing debate regarding whether the clinicopathological differences may be due to the existence of distinct genetic alterations. Efforts have been made to identify these acquired genetic abnormalities that will determine the tumor's biological behavior and ultimately allow molecular prognostication. However, most of the studies have been performed in radiation-exposed pediatric thyroid carcinoma. Therefore, our understanding of the role of these driver mutations in sporadic pediatric differentiated thyroid cancer development is far from complete, and additionally, there is a strong need for studies in both children and adolescents. The aim of this review is to present an extensive literature review with emphasis on the molecular differences between pediatric sporadic and radiation-exposed differentiated thyroid carcinomas and adult population.
PubMed-ID: 26307021
http://dx.doi.org/10.1530/ERC-15-0381

Thyroid hormones and tetrac: new regulators of tumour stroma formation via integrin alphavbeta3.
Endocr Relat Cancer, 22(6):941-52.
K. A. Schmohl, A. M. Muller, A. Wechselberger, S. Ruhland, N. Salb, N. Schwenk, H. Heuer, J. Carlsen, B. Goke, P. J. Nelson and C. Spitzweg. 2015.
To improve our understanding of non-genomic, integrin alphavbeta3-mediated thyroid hormone action in tumour stroma formation, we examined the effects of triiodo-l-thyronine (T3), l-thyroxine (T4) and integrin-specific inhibitor tetrac on differentiation, migration and invasion of mesenchymal stem cells (MSCs) that are an integral part of the tumour's fibrovascular network. Primary human bone marrow-derived MSCs were treated with T3 or T4 in the presence of hepatocellular carcinoma (HCC) cell-conditioned medium (CM), which resulted in stimulation of the expression of genes associated with cancer-associated fibroblast-like differentiation as determined by qPCR and ELISA. In addition, T3 and T4 increased migration of MSCs towards HCC cell-CM and invasion into the centre of three-dimensional HCC cell spheroids. All these effects were tetrac-dependent and therefore integrin alphavbeta3-mediated. In a subcutaneous HCC xenograft model, MSCs showed significantly increased recruitment and invasion into tumours of hyperthyroid mice compared to euthyroid and, in particular, hypothyroid mice, while treatment with tetrac almost completely eliminated MSC recruitment. These studies significantly improve our understanding of the anti-tumour activity of tetrac, as well as the mechanisms that regulate MSC differentiation and recruitment in the context of tumour stroma formation, as an important prerequisite for the utilisation of MSCs as gene delivery vehicles.
PubMed-ID: 26307023
http://dx.doi.org/10.1530/ERC-15-0245

Shear Wave Elastography in the Diagnosis of Thyroid Nodules with Coexistent Chronic Autoimmune Hashimoto's Thyroiditis.
Otolaryngol Head Neck Surg, 153(5):779-85.
B. Liu, J. Liang, L. Zhou, Y. Lu, Y. Zheng, W. Tian and X. Xie. 2015.
OBJECTIVE: To evaluate the diagnostic performance of shear wave elastography (SWE) in the differentiation of malignant and benign thyroid nodules with coexistent Hashimoto's thyroiditis (HT). STUDY DESIGN: Case series with chart review. SETTING: Tertiary general hospital. SUBJECTS AND METHODS: From September 2012 to January 2014, conventional ultrasound and SWE were performed on 243 patients with 286 thyroid nodules with histologic results. The HT group consisted of 93 patients with 117 nodules. The non-HT group consisted of 140 patients with 169 nodules. RESULTS: In the benign and malignant nodules, there were no significant differences of the mean, minimum, or maximum SWE values between HT and non-HT groups (P = .158-.945). However, SWE values of extranodular tissue were significantly higher in the HT group (P = .000-.011). In the HT group, the maximum SWE value showed the highest area under the receiver operating characteristic curve (0.817; 95% confidence interval, .735-.900), and there were no significant differences when compared with other SWE parameters (P = .669-.848). In the multivariate analysis, hypoechogenicity (odds ratio = 9.855, P = .002), microcalcification (odds ratio = 3.977, P = .046), and maximum SWE value (odds ratio = 40.712, P < .001) were independent predictors of thyroid malignancy. CONCLUSIONS: SWE could be performed to obtain a differential diagnosis between malignant and benign thyroid nodules, including nodules with coexistent HT. Although all the SWE parameters within a 2-mm region of interest that was placed on the stiffest region could be applied, we suggest that the maximum value of nodules harbored within a Hashimoto's gland be used.
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http://dx.doi.org/10.1177/0194599815600149

A Bedside Risk Calculator to Preoperatively Distinguish Follicular Thyroid Carcinoma from Follicular Variant of Papillary Thyroid Carcinoma.
World J Surg, 39(12):2928-34.
B. R. Englum, J. Pura, S. D. Reed, S. A. Roman, J. A. Sosa and R. P. Scheri. 2015.
BACKGROUND: Follicular thyroid carcinoma (FTC) and follicular variant of papillary thyroid carcinoma (FV-PTC) are difficult entities to distinguish based on cytology prior to pathologic evaluation of surgical specimens but may have different treatment algorithms. The current study describes trends in rates of FTC versus FV-PTC in the U.S. and develops a risk assessment tool to aid clinicians in predicting final diagnosis and shaping treatment plans. METHODS: Relative rates of FTC and FV-PTC in the surveillance, epidemiology, and end results (SEER) database were evaluated for temporal trends from 1988 to 2011. Using multivariable logistic regression, a simplified scoring system was developed to estimate the risk of FTC versus FV-PTC using patient and tumor characteristics. The National Cancer Data Base was used for model validation. RESULTS AND DISCUSSION: Of 115,091 thyroid cancer cases in the SEER database from 1988 to 2011, 23,980 involved FTC (n = 5056; 21 %) or FV-PTC (n = 18,924; 79 %). In 1988, half of follicular cases were FV-PTC; however, FV-PTC accounted for over 85 % of these lesions by 2010. Increasing age >45 years, male gender, black race, increasing tumor size, and distant metastases were strongly associated with increased risk of FTC, while lymph node disease and extrathyroidal extension were associated with FV-PTC. A bedside risk assessment nomogram using these preoperative variables classified patient risk of FTC from 2 to 70 %. FV-PTC has become the dominant malignancy with follicular cytology, accounting for >85 % of these cases. A simple bedside risk assessment tool can risk stratify patients with follicular lesions and inform patient and clinician discussions and decision making.
PubMed-ID: 26324158
http://dx.doi.org/10.1007/s00268-015-3192-4

Thyroid Radiation Dose and Other Risk Factors of Thyroid Carcinoma Following Childhood Cancer.
J Clin Endocrinol Metab, 100(11):4282-90.
F. de Vathaire, N. Haddy, R. S. Allodji, M. Hawkins, C. Guibout, C. El-Fayech, C. Teinturier, O. Oberlin, H. Pacquement, F. Diop, A. Kalhouche, M. Benadjaoud, D. Winter, A. Jackson, G. Bezin Mai-Quynh, A. Benabdennebi, D. Llanas, C. Veres, M. Munzer, T. D. Nguyen, P. Y. Bondiau, D. Berchery, A. Laprie, E. Deutsch, D. Lefkopoulos, M. Schlumberger, I. Diallo and C. Rubino. 2015.
CONTEXT: Thyroid carcinoma is a frequent complication of childhood cancer radiotherapy. The dose response to thyroid radiation dose is now well established, but the potential modifier effect of other factors requires additional investigation. OBJECTIVE: This study aimed to investigate the role of potential modifiers of the dose response. DESIGN: We followed a cohort of 4338 5-year survivors of solid childhood cancer treated before 1986 over an average of 27 years. The dose received by the thyroid gland and some other anatomical sites during radiotherapy was estimated after reconstruction of the actual conditions in which irradiation was delivered.

RESULTS: Fifty-five patients developed thyroid carcinoma. The risk of thyroid carcinoma increased with a radiation dose to the thyroid of up to two tenths of Gy, then leveled off for higher doses. When taking into account the thyroid radiation dose, a surgical or radiological splenectomy (>20 Gy to the spleen) increased thyroid cancer risk (relative risk [RR] = 2.3; 95% confidence interval [CI], 1.3-4.0), high radiation doses (>5 Gy) to pituitary gland lowered this risk (RR = 0.2; 95% CI, 0.1-0.6). Patients who received nitrosourea chemotherapy had a 6.6-fold (95% CI, 2.5-15.7) higher risk than those who did not. The excess RR per Gy of radiation to the thyroid was 4.7 (95% CI, 1.7-22.6). It was 7.6 (95% CI, 1.6-33.3) if body mass index at time of interview was equal or higher than 25 kg/m(2), and 4.1 (95% CI, 0.9-17.7) if not (P for interaction = .1). CONCLUSION: Predicting thyroid cancer risk following childhood cancer radiation therapy probably requires the assessment of more than just the radiation dose to the thyroid. Chemotherapy, splenectomy, radiation dose to pituitary gland, and obesity also play a role.
PubMed-ID: 26327481
http://dx.doi.org/10.1210/jc.2015-1690

Postoperative vocal fold palsy in patients undergoing thyroid surgery with continuous or intermittent nerve monitoring.
Br J Surg, 102(11):1380-7.
R. Schneider, C. Sekulla, A. Machens, K. Lorenz, P. Nguyen Thanh and H. Dralle. 2015.
BACKGROUND: Continuous monitoring of electromyographic (EMG) amplitudes of the vocal muscles detects impending injury of the recurrent laryngeal nerve (RLN) during thyroid operations earlier than intermittent EMG monitoring. This may alert the surgeon to stop a manoeuvre causing stretching or pressure on the RLN, with better recovery of nerve function. METHODS: Patients with intact preoperative RLN function who underwent thyroid surgery for benign disease between January 2011 and September 2014 under continuous intraoperative nerve monitoring (CIONM) or intermittent intraoperative nerve monitoring (IIONM) were included in this observational study conducted at a tertiary surgical centre. For CIONM, combined EMG events indicative of imminent nerve injury were defined as an EMG amplitude decrease of 50 per cent or more and a latency increase of 10 per cent relative to baseline values. The rates of early and permanent palsy for the two groups of patients were compared. RESULTS: There were 1526 patients, 788 of whom (1314 nerves at risk) underwent thyroid surgery using CIONM and 738 (965 nerves at risk) had IIONM. With the use of CIONM, 63 (82 per cent) of 77 combined events were reversible during the operation. No permanent vocal fold palsy occurred with CIONM, whereas four unilateral permanent vocal fold palsies (0.4 per cent) were diagnosed after IIONM (P = 0.019). CONCLUSION: Operation with CIONM resulted in fewer permanent vocal fold palsies compared with IIONM after thyroid surgery in patients with benign disease.
PubMed-ID: 26333134
http://dx.doi.org/10.1002/bjs.9889

BRAF V600E and decreased NIS and TPO expression are associated with aggressiveness of a subgroup of papillary thyroid microcarcinoma.
Eur J Endocrinol, 173(4):525-40.
A. U. Bastos, G. Oler, B. H. Nozima, R. A. Moyses and J. M. Cerutti. 2015.
BACKGROUND: Thyroid cancer incidence has dramatically increased worldwide over the last two decades. The rise is mostly due to an increased detection of small papillary thyroid carcinomas (PTCs) (</=20 mm), predominantly microPTC (</=10 mm). Although small tumors generally have an excellent outcome, a considerable percentage may have a more aggressive disease and worse prognosis. The clinical challenge is to preoperatively identify those tumors that are more likely to recur. AIM: To improve risk stratification and patient management, we sought to determine the prognostic value of BRAF V600E, NRAS or RET/PTC mutations in patients with PTC measuring <20 mm, mainly microPTC. METHODS: The prevalence of RET/PTC fusion genes was examined by quantitative RT-PCR. BRAF V600E and NRAS Q61 mutations were determined by PCR sequencing. To further elucidate why some small PTC are less responsive to radioactive iodine treatment therapy, we explored if these genetic alterations may modulate the expression of iodine metabolism genes (NIS, TPO, TG, TSHR and PDS) and correlated with clinico-pathological findings that are predictors of recurrence. RESULTS: This study shows that tumors measuring </=20 mm exhibited higher prevalence of BRAF V600E mutation, which correlated with aggressive histopathological parameters, higher risk of recurrence, and lower expression of NIS and TPO. Although this correlation was not found when microPTC were evaluated, we show that tumors measuring 7-10 mm, which were positive for BRAF mutation, presented more aggressive features and lower expression of NIS and TPO. CONCLUSION: We believe that our findings will help to decide the realistic usefulness of BRAF V600E mutation as a preoperative marker of poor prognosis in small PTC, primarily in microPTC.

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http://dx.doi.org/10.1530/EJE-15-0254

Inverse Agonist of Estrogen-Related Receptor gamma Enhances Sodium Iodide Symporter Function Through Mitogen-Activated Protein Kinase Signaling in Anaplastic Thyroid Cancer Cells.
J Nucl Med, 56(11):1690-6.
T. D. Singh, S. Y. Jeong, S. W. Lee, J. H. Ha, I. K. Lee, S. H. Kim, J. Kim, S. J. Cho, B. C. Ahn, J. Lee and Y. H. Jeon. 2015.
Anaplastic thyroid cancer (ATC), a rare thyroid cancer with poor prognosis, is associated with insufficient function of the sodium iodide symporter (NIS). Estrogen-related receptor gamma (ERRgamma) is a member of the orphan nuclear receptors with important functions in cell development and homeostasis. However, there are no reports that demonstrate whether ERRgamma is related to NIS function. Here, we evaluated the role of ERRgamma in the regulation of NIS function in ATC cells using GSK5182, an inverse agonist of ERRgamma. METHODS: Two ATC cell lines, BHT-101 and CAL62, were incubated with GSK5182 at various time points and doses. The NIS function in the ATC cells was serially assessed by their uptake of radioiodine. The effects of GSK5182 on ERRgamma and the mitogen-activated protein (MAP) kinase pathway, as well as on NIS protein, were evaluated by immunoblot assay. To examine whether the GSK5182-induced NIS functional activity can be affected by inhibition of the MAP kinase pathway, the MAP kinase activity and levels of radioiodine uptake were determined after application of a mitogen-activated protein kinase kinase (MEK) inhibitor to GSK5182-treated cells. Finally, the cytotoxic effect of (131)I was determined by clonogenic assay. RESULTS: Treatment with GSK5182 resulted in dose- and time-dependent increases in iodide uptake in ATC cells, which were accompanied by both the downregulation of ERRgamma protein and the activation of extracellular signal-regulated kinase (ERK) 1/2. Both the increased radioiodine uptake and ERK1/2 activation of ATC cells were completely inhibited by the specific MEK inhibitor. GSK5182 treatment enhanced the membrane localization of NIS in both ATC cell lines. Accordingly, preexposure to GSK5182 enhanced the cytotoxic effects of (131)I treatment in ATC cells. CONCLUSION: These findings suggest that the inverse agonist of ERRgamma enhances the responsiveness of radioiodine therapy by modulating NIS function in ATC cells via the regulation of ERRgamma and the MAP kinase signaling pathway.
PubMed-ID: 26338896
http://dx.doi.org/10.2967/jnumed.115.160366

Thyroid: Laser ablation of thyroid nodules is rapid, safe and effective.
Nat Rev Endocrinol, 11(11):631.
T. Geach. 2015.
PubMed-ID: 26346955
http://dx.doi.org/10.1038/nrendo.2015.153

TERT promoter mutations in thyroid cancer: a report from a Middle Eastern population.
Endocr Relat Cancer, 22(6):901-8.
E. Qasem, A. K. Murugan, H. Al-Hindi, M. Xing, M. Almohanna, M. Alswailem and A. S. Alzahrani. 2015.
Telomerase reverse transcriptase (TERT) promoter mutations C228T and C250T have recently been described in follicular cell-derived thyroid cancer (TC) in patients from North America and Europe. In this study, we explored whether these findings could be replicated in patients from a different ethnic group. We screened 17 benign thyroid adenomas and 265 TC samples from patients in the Middle East for these mutations by PCR and direct sequencing using DNA isolated from paraffin-embedded tumor tissues. None of the 17 benign adenomas harbored TERT promoter mutations. Of 265 TC, 34 (12.8%) harbored TERT promoter mutations, including 10/153 (6.5%) conventional papillary TC (CPTC), 8/57 (14.0%) follicular variant PTC, 9/30 (30%) tall cell variant PTC, 1/3 (30%) Hurthle cell thyroid cancer (HTC), 1/5 (20%) follicular TC, and 5/13 (38.5%) poorly differentiated TC. C250T mutation was present in only 6/265 (2.3%) cases, while C228T mutation was present in a total of 28/265 (10.6%) cases. These two mutations were mutually exclusive. TERT promoter mutations were significantly more common in older (>/=45 years) than younger patients and were associated with larger tumour size, vascular invasion, higher TNM stage (stage III and IV), BRAF(V600E) mutation and persistent/recurrent disease at 6-12 months after initial treatment and at the last follow up. These associations were stronger in non-CPTC. Thus, this study on a large cohort of TC patients from Middle East demonstrates that TERT promoter mutations are relatively common, especially in the non-CPTC, and are associated with more aggressive histopathological features, BRAF(V600E) mutation, and disease persistence/recurrence than the WT TERT.
PubMed-ID: 26354077
http://dx.doi.org/10.1530/ERC-15-0396

Analysis of an institutional protocol for thyroid lobectomy: Utility of routine intraoperative frozen section and expedited (overnight) pathology.
Surgery, 159(2):512-7.
R. W. Berg, T. W. Yen, D. B. Evans, B. Hunt, F. A. Quiroz, S. D. Wilson and T. S. Wang. 2015.
BACKGROUND: Intraoperative frozen section (FS) often is performed in patients who undergo thyroid lobectomy to determine the need for completion thyroidectomy. At our institution, if FS pathology is benign, final pathology is expedited overnight. The aim of this study was to determine the utility of FS and to identify a cost-effective management algorithm for thyroid lobectomy. METHODS: A retrospective review was performed of patients who underwent thyroid lobectomy between January 2009 and May 2013. Preoperative cytology ranged from "benign" to "suspicious for malignancy." Clinically significant cancers were defined as >1 cm in size, or multifocal microcarcinomas. RESULTS: Of the 192 patients who underwent thyroid lobectomy with FS, FS was suspicious for malignancy in 5 (3%) patients; 1 (0.5%) underwent immediate completion thyroidectomy. On final pathology, 9 (5%) patients had clinically significant cancers and underwent completion thyroidectomy. FS had a sensitivity and positive predictive value of 22% and 40%, respectively, in identifying clinically significant thyroid cancer. Cost of thyroid lobectomy at varying rates of same-day discharge favored thyroid lobectomy without FS but with expedited pathology for all scenarios. CONCLUSION: At our institution, there appears to be limited utility of FS at the time of thyroid lobectomy given the low predictive value for diagnosing a clinically significant thyroid cancer. In patients who are admitted overnight, expedited pathology is slightly less costly and may improve patient quality-of-life and decrease costs by avoiding delayed completion thyroidectomy. Overnight pathology for patients who undergo thyroid lobectomy may achieve modest cost-savings depending on institutional FS results and rates of malignancy.
PubMed-ID: 26361834
http://dx.doi.org/10.1016/j.surg.2015.07.031

Algorithm for early discharge after total thyroidectomy using PTH to predict hypocalcemia: prospective study.
Langenbecks Arch Surg, 400(7):831-6.
F. Schlottmann, A. L. Arbulu, E. E. Sadava, P. Mendez, L. Pereyra, J. M. Fernandez Vila and N. A. Mezzadri. 2015.
PURPOSE: Hypocalcemia is the most common complication after total thyroidectomy. The aim of this study was to determine whether postoperative parathyroid hormone (PTH) levels predict hypocalcemia in order to design an algorithm for early discharge. METHODS: We present a prospective study including patients who underwent total thyroidectomy. Hypocalcemia was defined as serum ionized calcium < 1.09 mmol/L or clinical evidence of hypocalcemia. PTH measurement was performed preoperatively and at 1, 3, and 6 h postoperatively. The percent decline of preoperative values was calculated for each time point. RESULTS: One hundred and six patients were included. Thirty-six (33.9%) patients presented hypocalcemia. A 50% decline in PTH levels at 3 h postoperatively showed the highest sensitivity and specificity to predict hypocalcemia (91 and 73%, respectively). No patients with a decrease <35% developed hypocalcemia (100% sensitivity), and all patients with a decrease >80% had hypocalcemia (100% specificity). CONCLUSIONS: PTH determination at 3 h postoperatively is a reliable predictor of hypocalcemia. According to the proposed algorithm, patients with less than 80% drop in PTH levels can be safely discharged the day of the surgery.
PubMed-ID: 26362424
http://dx.doi.org/10.1007/s00423-015-1341-8

Glucose-deprivation increases thyroid cancer cells sensitivity to metformin.
Endocr Relat Cancer, 22(6):919-32.
A. Bikas, K. Jensen, A. Patel, J. Costello, Jr., D. McDaniel, J. Klubo-Gwiezdzinska, O. Larin, V. Hoperia, K. D. Burman, L. Boyle, L. Wartofsky and V. Vasko. 2015.
Metformin inhibits thyroid cancer cell growth. We sought to determine if variable glucose concentrations in medium alter the anti-cancer efficacy of metformin. Thyroid cancer cells (FTC133 and BCPAP) were cultured in high-glucose (20 mM) and low-glucose (5 mM) medium before treatment with metformin. Cell viability and apoptosis assays were performed. Expression of glycolytic genes was examined by real-time PCR, western blot, and immunostaining. Metformin inhibited cellular proliferation in high-glucose medium and induced cell death in low-glucose medium. In low-, but not in high-glucose medium, metformin induced endoplasmic reticulum stress, autophagy, and oncosis. At micromolar concentrations, metformin induced phosphorylation of AMP-activated protein kinase and blocked p-pS6 in low-glucose medium. Metformin increased the rate of glucose consumption from the medium and prompted medium acidification. Medium supplementation with glucose reversed metformin-inducible morphological changes. Treatment with an inhibitor of glycolysis (2-deoxy-d-glucose (2-DG)) increased thyroid cancer cell sensitivity to metformin. The combination of 2-DG with metformin led to cell death.

Thyroid cancer cell lines were characterized by over-expression of glycolytic genes, and metformin decreased the protein level of pyruvate kinase muscle 2 (PKM2). PKM2 expression was detected in recurrent thyroid cancer tissue samples. In conclusion, we have demonstrated that the glucose concentration in the cellular milieu is a factor modulating metformin's anti-cancer activity. These data suggest that the combination of metformin with inhibitors of glycolysis could represent a new strategy for the treatment of thyroid cancer.
PubMed-ID: 26362676
http://dx.doi.org/10.1530/ERC-15-0402

Comparison of transaxillary approach, retroauricular approach, and conventional open hemithyroidectomy: A prospective study at single institution.
Surgery, 159(2):524-31.
D. Y. Lee, K. J. Lee, W. G. Han, K. H. Oh, J. G. Cho, S. K. Baek, S. Y. Kwon, J. S. Woo and K. Y. Jung. 2015.
BACKGROUND: The aims of this study were to evaluate and compare the operative outcomes and postoperative subjective functional parameters of transaxillary (TA) and retroauricular (RA) approach thyroidectomy, with those of conventional hemithyroidectomy. METHODS: From May 2011 through December 2013, 153 patients who underwent hemithyroidectomy were categorized prospectively into 3 groups according to the surgical approach used (TA, RA, and conventional hemithyroidectomy groups). All patients underwent prospective acoustic and functional evaluation, using a comprehensive battery of functional assessments, preoperatively and postoperatively at 1 week, 1 month, 3 months, 6 months, and 12 months. RESULTS: Age at diagnosis was significantly lower in the TA (n = 50) and RA groups (n = 42) than in the conventional group (n = 61; P < .001). The frequency of occurrence of vocal cord paralysis, inadvertently excised parathyroid, and hematoma did not differ among the groups (P = .447, .519, and .069, respectively). Three months postoperatively, maximal vocal pitch was significantly higher in the RA group than in the conventional and TA groups (P = .021). Although the overall pain score was not different, the Dysphagia Handicap Index of the RA group at 1 month postoperatively was significantly higher (P < .001) than in the other groups. Chest paresthesia was significantly more severe in the TA group, especially at 3 months postoperative (P = .035). The cosmetic satisfaction score was significantly higher in the RA and TA groups than in the conventional group (P = .001 and 0.035, respectively) at 3 and 6 months postoperatively. CONCLUSION: Both TA and RA hemithyroidectomy were followed by excellent surgical outcomes, especially with regard to cosmesis. However, delayed recovery of swallowing in RA and chest paresthesia in TA may be mitigating factors.
PubMed-ID: 26385538
http://dx.doi.org/10.1016/j.surg.2015.08.010

Patients Treated at Low-Volume Centers have Higher Rates of Incomplete Resection and Compromised Outcomes: Analysis of 31,129 Patients with Papillary Thyroid Cancer.
Ann Surg Oncol, 23(2):403-9.
L. M. Youngwirth, M. A. Adam, R. P. Scheri, S. A. Roman and J. A. Sosa. 2015.
BACKGROUND: Data on the importance of margin status after total thyroidectomy for papillary thyroid cancer (PTC) remain limited. This study sought to identify factors associated with positive margins and to determine the impact of positive margins on survival for patients with PTC. METHODS: The National Cancer Data Base (1998-2006) was queried for patients with PTC who had undergone total thyroidectomy. The patients were divided into three groups based on margin status (negative, microscopically positive, and macroscopically positive). Patient demographic, clinical, and pathologic features were evaluated. A binary logistic regression model was developed to identify factors associated with positive margins. A Cox proportional hazards model was developed to identify factors associated with survival. RESULTS: Of the 31,129 patients enrolled in the study, 91.3 % had negative margins, 8.1 % had microscopically positive margins, and 0.6 % had macroscopically positive margins. The patients with negative margins were younger and more likely to be female, white, covered by private insurance, and treated at an academic or high-volume center ($p < 0.05$). They had smaller tumors and were less likely to have advanced-stage disease. After multivariable adjustment, increasing patient age [odds ratio (OR) = 1.02; $p < 0.01$], government insurance (OR = 1.20; $p < 0.01$), and no insurance (OR = 1.34; $p = 0.01$) were associated with positive margins. Reception of surgery at a high-volume facility (OR = 0.72; $p < 0.01$) was protective. After multivariable adjustment, both microscopically [hazard ratio (HR), 1.49; $p < 0.01$] and macroscopically positive margins (HR = 2.38; $p < 0.01$) were associated with compromised survival. CONCLUSIONS: Several vulnerable patient populations have a higher risk of incomplete resection after thyroidectomy for PTC. High-risk thyroid cancer patients should be referred to high-volume centers to optimize outcomes.
PubMed-ID: 26416710
http://dx.doi.org/10.1245/s10434-015-4867-7

Postoperative Pain After Robotic Thyroidectomy by a Gasless Unilateral Axillo-Breast or Axillary Approach.
Surg Laparosc Endosc Percutan Tech, 25(6):478-82.
C. M. Song, Y. B. Ji, H. S. Bang, K. R. Kim, H. Kim and K. Tae. 2015.
The aim of this study was to compare postoperative pain after robotic thyroidectomy with that after conventional open thyroidectomy. We analyzed 123 patients who underwent robotic thyroidectomy and 170 patients who underwent conventional open thyroidectomy. Postoperative pain was evaluated on a visual analogue scale rating of 0 to 10, 1 day to 1 month after surgery. Mean pain visual analogue scale scores for the robotic and open groups were 3.33 and 3.57 (P=0.476) on day 1, 2.29 and 2.58 (P=0.285) on day 3, 2.19 and 1.74 (P=0.057) after 1 week, and 0.98 and 1.01 (P=0.843) after 1 month, respectively. There was no difference between the 2 groups in the doses of parenteral analgesic medication administered (robotic vs. open, mean 174 vs. 194 mg, P=0.189). In conclusion, postoperative pain and the dose of analgesic medication in both groups are similar.
PubMed-ID: 26422088
http://dx.doi.org/10.1097/SLE.0000000000000204

Preoperative High-Resolution Ultrasound for the Assessment of Malignant Central Compartment Lymph Nodes in Papillary Thyroid Cancer.
Thyroid, 25(12):1351-4.
M. T. Khokhar, K. M. Day, R. B. Sangal, N. N. Ahmedli, L. R. Pisharodi, M. D. Beland and J. M. Monchik. 2015.
BACKGROUND: The identification and removal of malignant central compartment lymph nodes (MCLN) is important to minimize the risk of persistent or recurrent local disease in patients with papillary thyroid cancer (PTC). While the diagnostic accuracy of preoperative ultrasound for the assessment of lateral compartment node metastases is well recognized, its role in the identification of central compartment node metastases in patients with PTC is less established. This study delineates the utility of high-resolution ultrasound (HUS) for the assessment of MCLN in patients with PTC. METHODS: A retrospective chart review was performed of 227 consecutive patients who underwent total thyroidectomy for biopsy-proven PTC by a single endocrine surgeon in an academic tertiary care center between 2004 and 2014. Preoperative sonographic results were compared to postoperative pathology reports to determine the accuracy of HUS for the assessment of MCLN. Statistical analysis also included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). RESULTS: HUS identified abnormal central compartment nodes in 51 (22.5%) patients. All 227 patients underwent a careful central compartment node exploration. One hundred and four (45.8%) patients had MCLN identified by surgery, of whom 65 (62.5%) had a negative preoperative central compartment HUS. The sensitivity and specificity of preoperative HUS for the assessment of MCLN were 0.38 and 0.90, respectively. The PPV and NPV were 0.76 and 0.63, with an accuracy of 0.66. CONCLUSION: Preoperative HUS is quite specific for the identification of MCLN in patients with PTC. The present findings emphasize, however, that a negative HUS does not obviate the need for careful exploration of the central compartment to minimize the risk of persistent or recurrent local disease.
PubMed-ID: 26431908
http://dx.doi.org/10.1089/thy.2015.0176

Recurrence of papillary thyroid carcinoma with lateral cervical node metastases: Predictive factors and operative management.
Surgery, 159(3):755-62.
N. Chereau, C. Buffet, C. Tresallet, F. Tissier, L. Leenhardt and F. Menegaux. 2015.
BACKGROUND: Lateral neck lymph node (LN) metastases (N1b) have been identified as independent risk factors of recurrence in patients with papillary thyroid carcinoma (PTC). OBJECTIVE: This study aimed to determine the predictive factors of recurrence in N1b PTC patients and to clarify the postoperative event patterns. METHODS: All patients who underwent operation for N1b PTC between 1978 and 2012 were reviewed. The median follow-up period was 6.5 years. RESULTS: In total, 344 N1b patients were included. Twenty-four patients (7%) were lost to long-term follow-up. Among the remaining 320 patients, the mean (+/-SD) follow-up time was 8.9 +/- 8.8 years (median, 6.5; range, 2-36.4). Eighty-two patients (26%) presented with lymph node recurrence (LR). Multivariate analyses showed that LN metastases with extracapsular extension and the LN ratio (ratio between the number of N1 and number of resected LN) in the lateral compartment were independent predictors of recurrent disease. The median time to reoperation was 19 months (range, 3-173), with 79% of reoperations occurring within 2 years after the initial thyroidectomy. Reoperations for LR (75 patients) were performed in 76% of the patients with a focused minimal access approach or selective LN dissection. After curative reoperative surgery for recurrence, complications occurred in 6 patients (8%), including a 1% permanent complication rate. CONCLUSION: Extranodal extension of LN metastases and the LN ratio in the lateral

compartment are prognostic factors for recurrence. In most cases, reoperation for LR can be performed with a focused minimal access approach, with a low morbidity rate.
PubMed-ID: 26435440
http://dx.doi.org/10.1016/j.surg.2015.08.033

Decade in review-thyroid disease: The endocrinology of thyroid disease from 2005 to 2015.
Nat Rev Endocrinol, 11(11):634-6.
P. R. Larsen. 2015.
PubMed-ID: 26437622
http://dx.doi.org/10.1038/nrendo.2015.169

DIAGNOSIS OF ENDOCRINE DISEASE: High-yield thyroid fine-needle aspiration cytology: an update focused on ancillary techniques improving its accuracy.
Eur J Endocrinol, 174(2):R53-63.
M. Bongiovanni, P. Trimboli, E. D. Rossi, G. Fadda, A. Nobile and L. Giovanella. 2015.
Thyroid fine-needle aspiration (FNA) cytology is a fast growing field. One of the most developing areas is represented by molecular tests applied to cytological material. Patients that could benefit the most from these tests are those that have been diagnosed as 'indeterminate' on FNA. They could be better stratified in terms of malignancy risk and thus oriented with more confidence to the appropriate management. Taking in to consideration the need to improve and keep high the yield of thyroid FNA, professionals from various fields (i.e. molecular biologists, endocrinologists, nuclear medicine physicians and radiologists) are refining and fine-tuning their diagnostic instruments. In particular, all these developments aim at increasing the negative predictive value of FNA to improve the selection of patients for diagnostic surgery. These advances involve terminology, the application of next-generation sequencing to thyroid FNA, the use of immunocyto- and histo-chemistry, the development of new sampling techniques and the increasing use of nuclear medicine as well as molecular imaging in the management of patients with a thyroid nodule. Herein, we review the recent advances in thyroid FNA cytology that could be of interest to the 'thyroid-care' community, with particular focus on the indeterminate diagnostic category.
PubMed-ID: 26450171
http://dx.doi.org/10.1530/EJE-15-0817

Diagnostic accuracy of circulating thyrotropin receptor messenger RNA combined with neck ultrasonography in patients with Bethesda III-V thyroid cytology.
Surgery, 159(1):113-7.
A. Aliyev, J. Patel, J. Brainard, M. Gupta, C. Nasr, B. Hatipoglu, A. Siperstein and E. Berber. 2015.
BACKGROUND: The aim of this study was to analyze the usefulness of thyrotropin receptor messenger RNA (TSHR-mRNA) combined with neck ultrasonography (US) in the management of thyroid nodules with Bethesda III-V cytology. METHODS: Cytology slides of patients with a preoperative fine needle aspiration (FNA) and TSHR-mRNA who underwent thyroidectomy between 2002 and 2011 were recategorized based on the Bethesda classification. Results of thyroid FNA, TSHR-mRNA, and US were compared with the final pathology. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. RESULTS: There were 12 patients with Bethesda III, 112 with Bethesda IV, and 58 with Bethesda V cytology. The sensitivity of TSHR-mRNA in predicting cancer was 33%, 65%, and 79 %, and specificity was 67%, 66%, and 71%, for Bethesda III, IV, and V categories, respectively. For the same categories, the PPV of TSHR-mRNA was 25%, 33%, and 79%, respectively; whereas the NPV was 75%, 88%, and 71%, respectively. The addition of neck US to TSHR-mRNA increased the NPV to 100% for Bethesda III, and 86%, for Bethesda IV, and 82% for Bethesda V disease. CONCLUSION: This study documents the potential usefulness of TSHR-mRNA for thyroid nodules with Bethesda III-V FNA categories. TSHR-mRNA may be used to exclude Bethesda IV disease. A large sample analysis is needed to determine its accuracy for Bethesda category III nodules.
PubMed-ID: 26454673
http://dx.doi.org/10.1016/j.surg.2015.06.063

Intraoperative high-dose calcium stimulation test in patients with sporadic medullary thyroid carcinoma is highly accurate in predicting lateral neck metastases.
Surgery, 159(1):70-6.
C. De Crea, M. Raffaelli, V. Milano, C. Carrozza, C. Zuppi, R. Bellantone and C. P. Lombardi. 2015.
BACKGROUND: Intraoperative measurement of calcitonin is not highly accurate in predicting the completeness of the operative resection after total thyroidectomy combined with central neck dissection (TT-CND) in patients with medullary thyroid carcinoma (MTC). We evaluated whether an intraoperative, high-dose calcium stimulation

test (IO-CST) after TT-CND can predict lateral neck involvement. METHODS: Eleven patients who underwent primary operation for sporadic MTC were included. High-dose (25 mg/kg) calcium gluconate was administered after TT-CND with calcitonin measured at 2, 5, and 10 minutes after the calcium gluconate infusion. RESULTS: There were 2 males and 9 females (mean age, 51 years; range, 18-88). Three patients showed lateral neck metastases. At a mean follow-up of 7.0 months (range, 2-10), 1 patient showed distant metastases and 1 a slightly increased calcitonin level. After IO-CST, serum calcitonin increased in all the 3 patients with lateral neck metastases, and it remained unchanged or decreased in the other patients without lateral neck metastases. Percent variation of serum calcitonin after IO-CST was 92% in patients with lateral neck metastases and -3.1 +/- 4.9% in patients without lateral neck metastases. CONCLUSION: Calcitonin measurement after IO-CST in patients with sporadic MTC can be highly accurate in predicting lateral neck nodes involvement. These results could represent a stimulus toward the development of a quick calcitonin assay.
PubMed-ID: 26456123
http://dx.doi.org/10.1016/j.surg.2015.08.022

Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma.
J Clin Endocrinol Metab, 100(12):4563-9.
E. N. Klein Hesselink, J. D. Lefrandt, E. P. Schuurmans, J. G. Burgerhof, B. Groen, R. T. Gansevoort, A. N. van der Horst-Schrivers, R. P. Dullaart, I. C. Van Gelder, A. H. Brouwers, M. Rienstra and T. P. Links. 2015.
BACKGROUND: Patients with differentiated thyroid carcinoma (DTC) have a favorable prognosis after treatment with thyroidectomy, radioiodine, and TSH suppression. However, treatment is associated with long-term cardiovascular toxicity. The aim of this study was to evaluate whether there is an increased risk of atrial fibrillation (AF) in DTC patients and whether AF occurrence is related to DTC treatment. PATIENTS AND METHODS: Incident AF was compared between 518 DTC patients and 1563 matched controls. A cumulative incidence curve was plotted, and competing risk regression analyses with adjustment for all-cause mortality were performed. Within the DTC cohort, associations between time-varying DTC treatment variables and incident AF were analyzed. RESULTS: For both cohorts, the mean age was 48.6 years (75% of subjects were women). The AF incidence rate was 6.2/1000 person-years for DTC patients and 2.7/1000 person-years for controls. DTC patients had a 2.25-fold (95% confidence interval [CI], 1.40-3.63) and 2.47-fold (95% CI, 1.55-3.95) increased AF risk in crude and fully adjusted analyses, respectively. Within the DTC cohort, the TSH level (which was suppressed in 85.7% of patients) was not associated with AF, whereas a higher cumulative radioiodine dose slightly increased AF risk: subdistribution hazard ratio, 1.04 (95% CI, 1.01-1.08) per 50 mCi (1.85 GBq) increase, after adjustment. CONCLUSION: Patients with DTC have an increased AF risk, independent from established AF risk factors. We could not demonstrate a relation between TSH and AF, whereas a higher cumulative radioiodine dose was associated with a slightly increased AF risk. Electrocardiogram screening for AF may be warranted during follow-up of DTC patients to allow early diagnosis and treatment of AF and to prevent its complications.
PubMed-ID: 26480284
http://dx.doi.org/10.1210/jc.2015-2782

Outcomes of thyroidectomy from a large California state database.
Am J Surg, 210(6):1170-6; discussion 6-7.
A. Weiss, R. P. Parina, J. A. Tang, K. T. Brumund, D. C. Chang and M. Bouvet. 2015.
BACKGROUND: Thyroidectomy is an operation with infrequent but potentially significant complications. This study aimed to determine risk factors for complication after thyroidectomy in California. METHODS: The California Office of Statewide Health Planning and Development database was retrospectively analyzed from 1995 to 2010. Main outcome measures were complications including death. Logistic regression identified risk factors for complications. RESULTS: There were 106,773 patients; 61% were women and 44% Caucasian; 16,287 (15%) thyroidectomies were performed at high-volume centers. Complication rates included voice change (.5%), vocal cord dysfunction (1.1%), hypocalcemia (4.5%), tracheostomy (1.62%), hematoma (1.75%), and death (.3%). There was significantly increased risk of complications for patients older than 65 compared with those younger than 40 years (odds ratio, 2.0; 95% confidence interval, 1.8 to 2.3; $P < .01$). High-volume hospitals were protective against complication (odds ratio, .8; 95% confidence interval, .6 to .97; $P = .026$). CONCLUSIONS: Older age was a significant risk factor for complication after thyroidectomy. High-volume hospitals had lower risk. This information is useful in counseling patients about the risks of thyroid surgery.
PubMed-ID: 26482517
http://dx.doi.org/10.1016/j.amjsurg.2015.08.011

Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence.
Surgery, 159(1):11-9.
I. D. Hay, T. R. Johnson, G. B. Thompson, T. J. Sebo and M. S. Reinalda. 2015.
BACKGROUND: This study assessed the influence of extrathyroid extension (EE) on cause-specific mortality (CSM) and tumor recurrence (TR) in patients treated for papillary thyroid carcinoma (PTC). METHODS: We studied outcome in 3,524 patients with PTC without distant metastases at diagnosis. CSM and TR were investigated in 422 patients with gross EE (GEE) or microscopic EE (MEE). RESULTS: The 30-year CSM rate for GEE of 25% was 12-fold greater (P < .001) than 2% seen with surgically intra-thyroid tumors (SIT); no patient who underwent MEE died of PTC. No difference (P = .36) existed in CSM rates between 127 MEE and 3,102 microscopically intra-thyroid tumors (MITs). The 20-year TR rate for GEE was 43% versus 12% with SIT (P < .001). Analyzing only 2,067 pN0 tumors, we found that GEE patients had greater TR rates (all sites), compared with SIT or MEE (P < .001). When 44 MEE were compared with 1,941 MIT cases, TR (all sites) rates were not different (P = .74). In patients aged >45 with tumors <41 mm, 20-year TR rates for MIT (stages I/II) and MEE (stage III) were not different at 4.7% and 3.8% (P = .71). CONCLUSION: MEE without concomitant GEE did not increase rates of either CSM or TR in PTC. Accordingly, these results raise concerns regarding current AJCC staging recommendations.
PubMed-ID: 26514317
http://dx.doi.org/10.1016/j.surg.2015.05.046

HABP2 Mutation and Nonmedullary Thyroid Cancer.
N Engl J Med, 373(21):2086-7.
S. K. Gara and E. Kebebew. 2015.
PubMed-ID: 26581001
http://dx.doi.org/10.1056/NEJMc1511631

A "safe and effective" protocol for management of post-thyroidectomy hypocalcemia.
Am J Surg, 210(6):1162-8; discussion 8-9.
M. B. Albuja-Cruz, N. Pozdeyev, S. Robbins, R. Chandramouli, C. D. Raeburn, J. Klopper, B. R. Haugen and R. McIntyre, Jr. 2015.
BACKGROUND: This study evaluates the outcomes of a protocol to manage hypocalcemia after thyroidectomy (TTX). METHODS: A review of prospectively collected data was performed in 130 patients who underwent TTX after the introduction of a specific protocol. These patients were compared with a control group of 195 patients who underwent TTX the year prior when routine calcium supplementation was utilized and no specific protocol was used. RESULTS: Of the 120 patients in whom the protocol was followed, 44 (37%) patients were classified as high risk, 15 (13%) intermediate risk, and 61 (51%) low risk. The protocol had a sensitivity of 85% and a negative predictive value of 92% for predicting subsequent hypocalcemia. With the implementation of the protocol, there was significant reduction in temporary hypocalcemia events (P = .008) and intravenous calcium drip (P = .49). Also, calcium supplementation was significantly lower in the protocol group (P </= .001). CONCLUSIONS: This hypocalcemia protocol identifies patients who do not require additional supplementation and additional monitoring. At the same time, it identifies those who will benefit from supplementation after TTX.
PubMed-ID: 26601651
http://dx.doi.org/10.1016/j.amjsurg.2015.07.010

Impact of vocal cord ultrasonography on endocrine surgery practices.
Surgery, 159(1):58-63.
D. Carneiro-Pla, C. C. Solorzano and S. M. Wilhelm. 2015.
BACKGROUND: It is common practice to perform flexible laryngoscopy (FL) to ensure true vocal cord (TVC) mobility in patients with previous neck operations or patients with suspected VC dysfunction. Vocal cord ultrasonography (VCUS) is accurate in identifying TVC paralysis. The goal of this study is to evaluate the impact of VCUS as the initial study to confirm TVC mobility in patients requiring preoperative FL. METHODS: A total of 194 consecutive patients with indications for preoperative FL underwent VCUS. In group 1, 52 patients had FL regardless of the results of VCUS, whereas in group 2, 142 patients had VCUS followed by FL only when VCUS was unsatisfactory. RESULTS: VCUS visualized TVC/arytenoids in 164 of 194 (85%) patients. TVC visualization was more common in women (95%) and in patients without thyroid cartilage calcification (92%) (P < .0005). VCUS predicted all paralyzed TVC. In group 2, 76% of patients had adequate VCUS and avoided preoperative FL. Among 24% of patients in whom VCUS was inadequate, 16 had preoperative FL attributable to a lack of TVC visualization, 6 had abnormal TVC mobility, 11 needed additional confirmations, and 2 had previous FL for another reason. CONCLUSION: VCUS changed surgeon practices by avoiding the need for preoperative FL in

the majority of patients. This noninvasive and sensitive method demonstrates TVC mobility and safely precludes preoperative FL in most patients.
PubMed-ID: 26603853
http://dx.doi.org/10.1016/j.surg.2015.06.067

Critical Points Regarding Hypocalcemia after Total Thyroidectomy.
Otolaryngol Head Neck Surg, 153(6):1080.
A. K. Coskun. 2015.
PubMed-ID: 26621931
http://dx.doi.org/10.1177/0194599815610120

An Evaluation of Postoperative Complications and Cost After Short-Stay Thyroid Operations.
Ann Surg Oncol, 23(5):1440-5.
S. Narayanan, D. Arumugam, S. Mennona, M. Wang, T. Davidov and S. Z. Trooskin. 2015.
BACKGROUND: Concern for postoperative complications causing airway compromise has limited widespread acceptance of ambulatory thyroid surgery. We evaluated differences in outcomes and hospital costs in those monitored for a short stay of 6 h (SS), inpatient observation of 6-23 h (IO), or inpatient admission of >23 h (IA). METHODS: We retrospectively reviewed all patients undergoing thyroidectomy from 2006 to 2012. The incidence of postoperative hemorrhage, nerve dysfunction, and hypocalcemia were evaluated, as well as cost data comparing the SS and IO groups. RESULTS: Of 1447 thyroidectomies, 880 (60.8 %) were performed as SS, 401 (27.7 %) as IO, and 166 (11.5 %) as IA. Fewer patients in the SS group (59 %) underwent total thyroidectomy than IO (73 %) and IA (71 %; $p < 0.01$), and SS patients had smaller thyroid weights (27.9 g) compared with IO and IA (47.2 and 98.9 g, respectively; $p < 0.01$). Ten (0.69 %) patients developed hematomas requiring reoperation, five of the ten patients received antiplatelet or anticoagulant therapy perioperatively. Only one patient in the IA group bled within the 6- to 23-h period, and no patients with bleeding who were discharged at 6 h would have benefitted from 23-h observation. Twenty-four (1.66 %) recurrent laryngeal nerve injuries were identified, 16 with temporary neuropraxias. In addition, 24 (1.66 %) patients had symptomatic hypocalcemia, which was transient in 17 individuals. Financial data showed higher payments and lower costs associated with SS compared with IO. CONCLUSIONS: Selective SS thyroidectomy can be safe and cost effective, with few overall complications in patients undergoing more complex operations involving larger thyroids who were admitted to hospital.
PubMed-ID: 26628433
http://dx.doi.org/10.1245/s10434-015-5004-3

Macrocalcitonin Is a Novel Pitfall in the Routine of Serum Calcitonin Immunoassay.
J Clin Endocrinol Metab, 101(2):653-8.
T. G. Alves, T. S. Kasamatsu, J. H. Yang, M. C. Meneghetti, A. Mendes, I. S. Kunii, S. C. Lindsey, C. P. Camacho, M. R. Dias da Silva, R. M. Maciel, J. G. Vieira and J. R. Martins. 2015.
CONTEXT: Calcitonin (CT) is a sensitive marker of medullary thyroid carcinoma (MTC) and is used for primary diagnosis and follow-up after thyroidectomy. However, persistently elevated CT is observed even after complete surgical removal without evidence of a recurrent or persistent tumor. OBJECTIVE: To investigate the presence of assay interference in the serum CT of MTC patients who are apparently without a structural disease. PATIENTS AND METHODS: We studied three index MTC cases for CT assay interference and 14 patients with metastatic MTC. The CT level was measured using an immunofluorometric assay. Screening for assay interference was performed by determination of CT levels before and after serum treatment with polyethylene glycol. Additionally, samples were analyzed by chromatography on ultra-performance liquid chromatography and protein A-Sepharose. RESULTS: Patients with biochemical and structural disease showed CT mean recovery of 84.1% after polyethylene glycol treatment, whereas patients suspected of interference showed recovery from 2-7%. The elution profile on UPLC showed that the immunometric CT from these three patients behaved like a high molecular mass aggregate (>300 kDa). Additionally, when these samples were applied to the protein A-Sepharose, CT immunoreactivity was retained on the column and was only released after lowering the pH. CONCLUSIONS: For the first time, our results show the presence of a novel pitfall in the CT immunoassay: "macrocalcitonin." Its etiology, frequency, and meaning remain to be defined, but its recognition is of interest and can help clinicians avoid unnecessary diagnostic investigations and treatment during the follow-up of MTC.
PubMed-ID: 26647152
http://dx.doi.org/10.1210/jc.2015-3137

Sorafenib for the Treatment of Progressive Metastatic Medullary Thyroid Cancer: Efficacy and Safety Analysis.

Thyroid, 26(3):414-9.
L. A. de Castroneves, M. V. Negrao, R. M. de Freitas, C. Papadia, J. V. Lima, Jr., J. T. Fukushima, E. F. Simao, M. A. Kulcsar, M. R. Tavares, A. A. Jorge, G. de Castro, Jr., P. M. Hoff and A. O. Hoff. 2015.
BACKGROUND: Treatment of advanced medullary thyroid carcinoma (MTC) was recently improved with the approval of vandetanib and cabozantinib. However, there is still a need to explore sequential therapy with more than one tyrosine kinase inhibitor (TKI) and to explore alternative therapies when vandetanib and cabozantinib are not available. This study reports the authors' experience with sorafenib as a treatment for advanced MTC. METHODS: This is a retrospective longitudinal study of 13 patients with progressive metastatic MTC treated with sorafenib 400 mg twice daily between December 2011 and January 2015. The primary endpoints were to evaluate response and progression-free survival (PFS) in patients treated with sorafenib outside a clinical trial. The secondary endpoint was an assessment of the toxicity profile. One patient was excluded because of a serious allergic skin rash one week after starting sorafenib. RESULTS: The analysis included 12 patients with metastatic MTC (median age 48 years), 10 with sporadic and 2 with hereditary disease. The median duration of treatment was 11 months, and the median follow-up was 15.5 months. At data cutoff, 2/12 (16%) patients were still on treatment for 16 and 34 months. According to Response Evaluation Criteria in Solid Tumors analysis, 10 (83.3%) patients showed stable disease, and two (16.6%) had progression of disease; no partial response was observed. The median PFS was nine months. However, three patients with extensive and rapidly progressive disease died within three months of sorafenib treatment. The median PFS excluding these three patients was 12 months. Adverse events (AE) occurred in nine (75%) patients. The main AEs were skin toxicity, weight loss, and fatigue. Five (41.6%) patients needed dose reduction, and one patient discontinued treatment because of toxicity. CONCLUSIONS: Treatment with sorafenib in progressive metastatic MTC is well tolerated and resulted in disease control and durable clinical benefit in 75% of patients. Sorafenib treatment could be considered when vandetanib and cabozantinib are not available or after failing these drugs.
PubMed-ID: 26701095
http://dx.doi.org/10.1089/thy.2015.0334

Parathyroids

Meta-Analyses

Effect of Parathyroidectomy Upon Left Ventricular Mass in Primary Hyperparathyroidism: A Meta-Analysis.
J Clin Endocrinol Metab, 100(12):4399-407.
D. J. McMahon, A. Carrelli, N. Palmeri, C. Zhang, M. DiTullio, S. J. Silverberg and M. D. Walker. 2015.
CONTEXT: Primary hyperparathyroidism (PHPT) has been associated with increased left ventricular mass (LVM) in many studies. Most studies have been inadequately powered to assess the effect of parathyroidectomy (PTX) on LVM. OBJECTIVE: The objective was to evaluate whether PTX has a benefit on LVM in patients with PHPT. DATA SOURCES: Sources included PubMed, Medline, Cochrane Library, clinicaltrials.gov, review articles, and abstracts from meetings. STUDY SELECTION: Eligible studies included prospective studies of PTX vs observation or PTX alone in patients with PHPT who had LVM measured by echocardiography. DATA EXTRACTION: Two investigators independently identified eligible studies and extracted data. Random-effects models were used to obtain final pooled estimates. DATA SYNTHESIS: Fifteen studies (four randomized controlled trials and 11 observational) of 457 participants undergoing PTX were included. PTX was associated with a reduction in LVM (crude Hedges gu -0.290 +/- 0.070, 95% confidence interval [CI] -0.423 to -0.157) of 11.6 g/m(2) (12.5%) on average. Effect size estimates differed by study duration (P < .001), with improvements seen in shorter (</= 6 mo) but not longer studies. There was a trend toward greater improvement in observational studies vs randomized controlled trials (P = .07), and both serum calcium and PTH were higher in the former. Using random-effects models, the estimated effect size remained significant (Hedges gu -0.250, 95% CI -0.450 to -0.050). Higher preoperative PTH but not calcium was associated with a greater decline in LVM (beta = -.039, 95% CI -0.075 to -0.004). CONCLUSION: PTX reduced LVM in PHPT, and higher preoperative PTH levels were associated with greater improvements. Because the benefit was limited to short-term studies and PHPT disease severity was not independent of study design, further work is needed to clarify the factors that influence the change in LVM and whether the benefit persists beyond 6 months after PTX. Although the clinical significance of the LVM improvement is unclear, these data indicate that PTH may underlie increased LVM in PHPT.
PubMed-ID: 26445115
http://dx.doi.org/10.1210/jc.2015-3202

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Development of hypoparathyroidism animal model and the feasibility of small intestinal submucosa application on the parathyroid autotransplantation.
Eur Arch Otorhinolaryngol, 272(10):2969-77.
H. S. Park, S. Y. Jung, H. Y. Kim, Y. Kim da, M. S. Kim, S. M. Chung, Y. S. Rho and H. S. Kim. 2015.
The purpose of this study is to evaluate the feasibility of small intestinal submucosa (SIS) application on the parathyroid autotransplantation in a rat model of hypoparathyroidism. The rats were divided into four groups: NC (no procedure, n = 5), PTX (total parathyroidectomy, n = 6), PT (total parathyroidectomy and parathyroid autotransplantation, n = 10) and PT + SIS group (total parathyroidectomy and parathyroid autotransplantation with SIS, n = 10). The levels of parathyroid hormone (PTH), calcium, and phosphorous were measured on 0, 3,

7, 21, 56 and 84 days after surgery. PTH level was expressed as median (interquartile range) and histological and immunohistochemical examinations were performed. PTH levels were significantly decreased to "not detectable level" from day 3 in PTX group. PTH was not detected in both PT and PT + SIS groups on the 21st day. On the 56th day, PTH levels were increased in both groups: 3 out of 8 rats (37.5%) in the PT group, 6 out of 9 rats (66.7%) in the PT + SIS group. The PTH level was fully recovered to its preoperative range on the day 84 as 6 of 8 rats (75%) of the PT group and 7 of 9 rats (77.8%) of the PT + SIS group were recovered; the PTH levels were 117.84 and 178.36 pg/ml, respectively. The neo-vascularization was well observed around the parathyroid tissue, and the number of new vessels formed was higher in the PT + SIS group (15 vessels/high power field) as compared to the PT group (10 vessels/high power field). This study showed the feasibility and the treatment effect of SIS as the success rate of autotransplantation of parathyroid tissue was significantly increased without severe inflammatory response in hypothyroidism animal model.
PubMed-ID: 25182391
http://dx.doi.org/10.1007/s00405-014-3262-5

Justified follow-up: a final intraoperative parathyroid hormone (ioPTH) Over 40 pg/mL is associated with an increased risk of persistence and recurrence in primary hyperparathyroidism.
Ann Surg Oncol, 22(2):454-9.
M. H. Rajaei, A. M. Bentz, D. F. Schneider, R. S. Sippel, H. Chen and S. C. Oltmann. 2015.
INTRODUCTION: After parathyroidectomy for sporadic primary hyperparathyroidism (PHPT), overall rates of persistence/recurrence are extremely low. A marker of increased risk for persistence/recurrence is needed. We hypothesized that final intraoperative parathyroid hormone (FioPTH) >/=40 pg/mL is indicative of increased risk for disease persistence/recurrence, and can be used to selectively determine the degree of follow-up. METHOD: A retrospective review of PHPT patients undergoing parathyroidectomy with ioPTH monitoring was performed. An ioPTH decline of 50 % was the only criteria for operation termination. Patients were grouped based on FioPTH of <40, 40-59, and >60 pg/mL. RESULTS: Between 2001 and 2012, 1,371 patients were included. Mean age was 61 +/- 0.4 years, and 78 degrees % were female. Overall persistence rate was 1.4 degrees %, with a 2.9 degrees % recurrence rate. Overall, 976 (71 degrees %) patients had FioPTH < 40, 228 (16.6 degrees %) had FioPTH 40-59, and 167 (12.2 degrees %) had FioPTH >/=60. Mean follow-up was 21 +/- 0.6 months. Patients with FioPTH <40 were younger, with lower preoperative serum calcium, PTH, and creatinine (all p </= 0.001). Patients with FioPTH <40 had the lowest persistence rate (0.2 %) versus patients with FioPTH 40-59 (3.5 %) or FioPTH >/=60 (5.4 %; p < 0.001). Recurrence rate was also lowest in patients with FioPTH <40 (1.3 vs. 5.9 vs. 8.2 %, respectively; p < 0.001). Disease-free status was greatest in patients with FioPTH <40 at 2 years (98.5 vs. 96.8 vs. 90.5 %, respectively) and 5 years (95.7 vs. 72.3 vs. 74.8 %, respectively; p < 0.01). CONCLUSIONS: Patients with FioPTH < 40 pg/mL had lower rates of persistence and recurrence, than patients with FioPTH 40-59, or >/=60. Differences became more apparent after 2 years of follow-up. Patients with FioPTH >/=40 pg/mL warrant close and prolonged follow-up.
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http://dx.doi.org/10.1245/s10434-014-4006-x

Outcomes after subtotal parathyroidectomy for primary hyperparathyroidism due to hyperplasia: significance of whole vs. partial gland remnant.
Ann Surg Oncol, 22(3):966-71.
M. H. Rajaei, S. C. Oltmann, D. F. Schneider, R. S. Sippel and H. Chen. 2015.
INTRODUCTION: Primary hyperparathyroidism (PHPT) due to multigland hyperplasia is managed by subtotal parathyroidectomy (sPTX), with a partial gland left in situ. However, smaller, hyperplastic glands may be encountered intraoperatively, and it is unclear if leaving an intact gland is an equivalent alternative. This study evaluates the rates of permanent hypoparathyroidism and cure of PHPT patients with four-gland hyperplasia that were left with either a whole gland remnant (WGR) or a partial gland remnant (PGR) after sPTX. METHODS: We reviewed the outcomes of PHPT patients with hyperplasia who underwent sPTX at an academic institution. Surgeon intraoperative judgment determined remnant size (a WGR vs. a PGR). RESULTS: Between 2002 and 2013, 172 patients underwent sPTX for PHPT. There were 108 patients (62.8%) who had a WGR. Another 64 patients (37.2%) had a PGR. Mean age was 60 +/- 14 years. There were 82.6% female patients. Cases with positive family history for PHPT were more likely to have a PGR (12.5 vs. 3.7%; p = 0.03). Patients had similar preoperative and postoperative laboratories. Individuals with a PGR tended to have larger glands encountered by surgeons intraoperatively (525 +/- 1,308 vs. 280 +/- 341 mg; p = 0.02). One patient with a WGR developed permanent hypocalcemia. Overall, the cure rate was 97.1%. A mean of 29 +/- 28.7 months follow-up revealed a recurrence rate of 5.2%. Disease persistence and recurrence rates were similar in patients. CONCLUSION: PHPT due to hyperplasia is managed by sPTX, leaving WGR without increased rates of disease persistence/recurrence. Patients without family history for hyperparathyroidism and those with smaller glands

may be the best candidates for this approach.
PubMed-ID: 25245126
http://dx.doi.org/10.1245/s10434-014-4022-x

Transoral robotic-assisted surgical excision of a retropharyngeal parathyroid adenoma: a case report.
Head Neck, 37(11):E150-2.
S. Bearelly, B. L. Prendes, S. J. Wang, C. Glastonbury and L. A. Orloff. 2015.
BACKGROUND: Transoral robotic surgery has been used with increasing frequency for oropharyngeal malignancies. We present the first known case of a transoral robotic-assisted parathyroidectomy. METHODS/RESULTS: A 77-year-old woman with primary hyperparathyroidism was suspected of having a parathyroid adenoma. After several nonlocalizing single photon emission CT/CT sestamibi scans, a neck ultrasound revealed a suspicious low level 6 nodule. Surgical excision of this nodule proved to be a reactive lymph node. She then had a dynamic parathyroid protocol MRI and CT, which revealed a small retropharyngeal adenoma candidate. A transoral robotic-assisted surgical approach was utilized to bluntly dissect the retropharyngeal space just above the arytenoids to excise the nodule. After excision, the intraoperative parathyroid hormone (PTH) normalized and surgical pathology confirmed parathyroid adenoma. CONCLUSION: Transoral robotic-assisted surgery is a novel technique that can be utilized for resection of a parathyroid adenoma in the retropharyngeal space.
PubMed-ID: 25809987
http://dx.doi.org/10.1002/hed.24010

Real-Time Super Selective Venous Sampling in Remedial Parathyroid Surgery.
J Am Coll Surg, 220(6):994-1000.
A. H. Lebastchi, J. E. Aruny, P. I. Donovan, C. E. Quinn, G. G. Callender, T. Carling and R. Udelsman. 2015.
BACKGROUND: Remedial cervical exploration for persistent or recurrent primary hyperparathyroidism can be technically difficult, but is expedited by accurate preoperative localization. We investigated the use of real-time super selective venous sampling (sSVS) in the setting of negative noninvasive imaging modalities. STUDY DESIGN: We performed a retrospective analysis of a prospective database incorporating real-time sSVS in a tertiary academic medical center. Between September 2001 and April 2014, 3,643 patients were referred for surgical treatment of primary hyperparathyroidism. Of these, 31 represented remedial patients who had undergone one (n=28) or more (n=3) earlier cervical explorations and had noninformative, noninvasive preoperative localization studies. RESULTS: We extended the use of the rapid parathyroid hormone assay in the interventional radiology suite, generating near real-time data facilitating onsite venous localization by a dedicated interventional radiologist. The predictive value of real-time sSVS localization was investigated. Overall, sSVS correctly predicted the localization of the affected gland in 89% of cases. Of 31 patients who underwent sSVS, a significant rapid parathyroid hormone gradient was identified in 28 (90%), localizing specific venous drainage of a culprit gland. All patients underwent subsequent surgery and were biochemically cured, with the exception of one who had metastatic parathyroid carcinoma. Three patients with negative sSVS were also explored and cured. CONCLUSIONS: Preoperative parathyroid localization is of paramount importance in remedial cervical explorations. Real-time sSVS is a sensitive localization technique for patients with persistent or recurrent primary hyperparathyroidism, when traditional noninvasive imaging studies fail. These results validate the utility and benefit of real-time sSVS in guiding remedial parathyroid surgery.
PubMed-ID: 25868412
http://dx.doi.org/10.1016/j.jamcollsurg.2015.01.004

Parathyroid Carcinoma: An Update on Treatment Outcomes and Prognostic Factors from the National Cancer Data Base (NCDB).
Ann Surg Oncol, 22(12):3990-5.
E. A. Asare, C. Sturgeon, D. J. Winchester, L. Liu, B. Palis, N. D. Perrier, D. B. Evans, D. P. Winchester and T. S. Wang. 2015.
BACKGROUND: Parathyroid carcinoma is a rare disease. Conflicting results on prognostic factors and extent of surgical resection for patients with parathyroid carcinoma have been made based on small sample sizes. A large, robust dataset is needed to help address some of the controversies. METHODS: A retrospective review of patients with parathyroid carcinoma in the National Cancer Data Base from 1985 to 2006 was performed. Characteristics of the cohort and type of treatment were evaluated. Prognostic factors were assessed with Cox proportional hazards regression models and 5- and 10-year OS rates were determined. RESULTS: There were 733 evaluable patients with a mean age of 56.1 +/- 15.3 years (median 57, range 15-89) and mean tumor size of 29.6 +/- 18.4 mm (median 25.0 mm, range 10.0-150.0). Tumor size, age at diagnosis, male sex, positive nodal status, and complete tumor resection had hazard ratios for death of 1.02 (1.01-1.02, $p < 0.0001$), 1.06 (1.05-

1.07, p < 0.0001), 1.67 (1.24-2.25, p = 0.0008), 1.25 (0.57-2.76, p = 0.6), and 0.42 (0.22-0.81, p = 0.01), respectively, on multivariable analysis. Patients who had removal of the parathyroid tumor with concomitant resection of adjacent organs had HR for death of 0.70 (0.35-1.41, p = 0.3). The 5- and 10-year OS rates were 82.3 and 66 % respectively. CONCLUSIONS: Patient age, tumor size, and sex have modest effects on survival in patients with parathyroid carcinoma. A staging system with prognostic value for parathyroid carcinoma should include at least these pertinent prognostic factors.
PubMed-ID: 26077914
http://dx.doi.org/10.1245/s10434-015-4672-3

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

Parathyroidectomy Halts the Deterioration of Renal Function in Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 100(8):3069-73.
F. Tassone, A. Guarnieri, E. Castellano, C. Baffoni, R. Attanasio and G. Borretta. 2015.
OBJECTIVE: Decreased renal function has been consistently included among factors prompting recommendation for surgery in primary hyperparathyroidism (PHPT). However, most retrospective studies addressing this issue did not show an improvement in renal function after parathyroidectomy (PTX). The aim of this study was to investigate changes in renal function after PTX in PHPT patients subdivided according to renal function at diagnosis. DESIGN: This was a retrospective cross-sectional study. PATIENTS AND METHODS: We studied 109 consecutive PHPT patients before and after PTX. Biochemical evaluation included fasting total and ionized serum calcium, phosphate, creatinine, immunoreactive intact PTH, and 25-hydroxyvitamin D3 levels. Glomerular filtration rate (GFR) was assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. RESULTS: Mean (+/- SD) CKD-EPI estimated GFR (eGFR) at diagnosis was 82.4 +/- 19.3 mL/min/1.73 m(2) (median, 84.8 mL/min/1.73 m(2); interquartile range, 68.5-94.2 mL/min/1.73 m(2)). Patients with eGFR equal to or higher than 60 mL/min/1.73 m(2) (group 1, n = 95) were significantly younger than patients with eGFR lower than 60 mL/min/1.73 m(2) (group 2, n = 14; P < .0003). After PTX, eGFR did not change in patients of group 2 (P = .509), whereas it was significantly reduced in patients of group 1 (P < .0002). The difference in eGFR between baseline and post-PTX values was correlated negatively with baseline serum creatinine (R = -0.27; P = .0052) and positively with baseline CKD-EPI eGFR (R = 0.32; P = .00062). At multiple regression analysis, only systolic blood pressure and baseline CKD-EPI eGFR were independent predictors of GFR variation. CONCLUSION: Surgical cure of PHPT halts renal function deterioration in patients with coexisting renal disease. Our study thus supports the indication for surgery in patients with eGFR less than 60 mL/min/1.73 m(2), as recommended by current guidelines. Moreover, our data show that presurgical renal function is a relevant predictor of renal function after PTX.

PubMed-ID: 26079781
http://dx.doi.org/10.1210/jc.2015-2132

Parathyroid Carcinoma: Is It Time for Change?
Ann Surg Oncol, 22(12):3772-3.
D. F. Schneider. 2015.
PubMed-ID: 26100817
http://dx.doi.org/10.1245/s10434-015-4673-2

Immunohistochemical Expression of E-Cadherin in Atypical Parathyroid Adenoma.
World J Surg, 39(10):2477-83.
R. Schneider, S. Bartsch-Herzog, A. Ramaswamy, D. K. Bartsch and E. Karakas. 2015.
BACKGROUND: Atypical parathyroid adenoma (APA) is a rare entity, sharing clinical symptoms like solid palpable mass in the neck, laboratory changes with very high serum calcium and parathyroid hormone levels, and some histopathological features with parathyroid carcinomas (PC). However, clinical behavior of APA seems to comply with benign parathyroid tumors (PA). There is some evidence that loss of the membranous staining pattern of E-Cadherin (E-Cad) suggests a key role of epithelial mesenchymal transition in the tumorigenesis of PC. Thus, the aim of this study was to compare clinical and surgical characteristics and immunohistochemical expression of E-Cad in APA, PC, and PA. METHODS: Data of patients who underwent surgery for primary hyperparathyroidism (pHPT) between 1985 and 2010 were retrospectively evaluated. All data were analyzed with special regard to distinctive criteria of APA, including trabecular growth, broad fibrous bands, nuclear atypia, mitosis, pseudocapsular invasion or strong adherence to the surrounding tissue, and potential invasive growth of a grossly altered and enlarged parathyroid gland. In addition, laboratory and clinical data were evaluated and additional immunohistochemical staining with E-Cad was performed in suspicious APA patients with available tissue. RESULTS: In 68 patients (39 female, 29 male), the parathyroid tumor was suspicious for APA. In 46 patients, a bilateral cervical exploration was performed. 15 patients underwent an en bloc resection including a hemithyroidectomy and lymphonodular dissection of the ipsilateral central compartment due to the malignant macroscopic aspect of the parathyroid. In seven patients, a focused parathyroid resection was done. The available parathyroid tissue of 38 APA patients was immunopositive for membranous E-Cad staining. During follow-up, only one patient with a successful initial surgery suffered from recurrent pHPT due to another solitary PA 10 years after initial surgery but without evidence of malignancy. CONCLUSIONS: In contrast to PC, parathyroid tumors suspicious for APA are characterized by a strong membranous E-Cad staining and, like PA, by a benign clinical course.
PubMed-ID: 26154578
http://dx.doi.org/10.1007/s00268-015-3149-7

PTH(1-34) for Surgical Hypoparathyroidism: A Prospective, Open-Label Investigation of Efficacy and Quality of Life.
J Clin Endocrinol Metab, 100(9):3590-7.
A. Santonati, A. Palermo, E. Maddaloni, D. Bosco, A. Spada, F. Grimaldi, B. Raggiunti, R. Volpe, S. Manfrini and F. Vescini. 2015.
CONTEXT: Conventional therapy for hypoparathyroidism consists of calcium and calcitriol, but sometimes normal serum calcium cannot be maintained, and/or this approach might lead to nephrocalcinosis, nephrolithiasis, or renal insufficiency. OBJECTIVE: The objective of the study was to investigate the effects of 6 months of PTH(1-34) treatment in adult subjects with postoperative hypoparathyroidism and to evaluate quality-of-life changes. DESIGN: This was a 2-year prospective, open-label study. At baseline and after 6 months of PTH(1-34) treatment, calcium and vitamin D supplementation requirements, serum calcium, phosphate, creatinine, alkaline phosphatase, uric acid, and 24-hour urinary calcium excretion were evaluated. Quality of life was evaluated by the Rand 36-Item Short Form Health Survey covering eight domains of physical and mental health. SETTING: This was an Italian multicentric study. PARTICIPANTS: Participants included 42 subjects with surgical hypoparathyroidism (90% females, age range 34-77 y). INTERVENTION: The intervention included a twice-daily PTH(1-34) 20 mug sc injection. RESULTS: The mean serum calcium levels significantly increased from baseline to 15 days (7.6 +/- 0.6 vs 9.1 +/- 0.9 mg/dL, P < .001) and remained stable until the end of the observational period, despite a significant reduction in calcium and vitamin D supplementation. Phosphate levels gradually decreased from baseline to the sixth month (P = .005 for the trend), whereas the alkaline phosphatase increased (P < .001). Data from the Rand 36-Item Short Form Health Survey showed a significant improvement in the mean scores of all eight domains (P < .001). CONCLUSION: This is the largest study that demonstrates the effectiveness of PTH(1-34) in the treatment of adult patients with postsurgical hypoparathyroidism, and it shows that PTH(1-34) may improve the mental and physical health in hypoparathyroid subjects.

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http://dx.doi.org/10.1210/jc.2015-1855

Preoperative 4D CT Localization of Nonlocalizing Parathyroid Adenomas by Ultrasound and SPECT-CT.
Otolaryngol Head Neck Surg, 153(5):775-8.
A. M. Hinson, D. R. Lee, B. A. Hobbs, R. T. Fitzgerald, D. L. Bodenner and B. C. Stack, Jr. 2015.
OBJECTIVE: To evaluate 4-dimensional (4D) computed tomography (CT) for the localization of parathyroid adenomas previously considered nonlocalizing on ultrasound and single-photon emission CT with CT scanning (SPECT-CT). To measure radiation exposure associated with 4D-CT and compared it with SPECT-CT. STUDY DESIGN: Case series with chart review. SETTING: University tertiary hospital. SUBJECTS AND METHODS: Nineteen adults with primary hyperparathyroidism who underwent preoperative 4D CT from November 2013 through July 2014 after nonlocalizing preoperative ultrasound and technetium-99m SPECT-CT scans. Sensitivity, specificity, predictive values, and accuracy of 4D CT were evaluated. RESULTS: Nineteen patients (16 women and 3 men) were included with a mean age of 66 years (range, 39-80 years). Mean preoperative parathyroid hormone level was 108.5 pg/mL (range, 59.3-220.9 pg/mL), and mean weight of the excised gland was 350 mg (range, 83-797 mg). 4D CT sensitivity and specificity for localization to the patient's correct side of the neck were 84.2% and 81.8%, respectively; accuracy was 82.9%. The sensitivity for localizing adenomas to the correct quadrant was 76.5% and 91.5%, respectively; accuracy was 88.2%. 4D CT radiation exposure was significantly less than the radiation associated with SPECT-CT (13.8 vs 18.4 mSv, P = 0.04). CONCLUSION: 4D CT localizes parathyroid adenomas with relatively high sensitivity and specificity and allows for the localization of some adenomas not observed on other sestamibi-based scans. 4D CT was also associated with less radiation exposure when compared with SPECT-CT based on our study protocol. 4D CT may be considered as first- or second-line imaging for localizing parathyroid adenomas in the setting of primary hyperparathyroidism.
PubMed-ID: 26248963
http://dx.doi.org/10.1177/0194599815599372

Letter to the Editor: Ceasing in Renal Function Deterioration After Parathyroidectomy: The Possible Hypotheses.
J Clin Endocrinol Metab, 100(9):L76.
M. Kizilgul, S. Kan, B. Ucan, E. Cakal and T. Delibasi. 2015.
PubMed-ID: 26339741
http://dx.doi.org/10.1210/JC.2015-2683

Intraoperative Parathormone Monitoring Mitigates Age-Related Variability in Targeted Parathyroidectomy for Patients with Primary Hyperparathyroidism.
Ann Surg Oncol, 22 Suppl 3:S655-61.
B. Bishop, B. Wang, P. P. Parikh and J. I. Lew. 2015.
BACKGROUND: Preoperative parathyroid localization studies, namely, sestamibi (MIBI) and surgeon-performed ultrasound (SUS), are commonly used for targeted parathyroidectomy (PTX) with intraoperative parathormone monitoring (IPM) in patients with primary hyperparathyroidism (pHPT). This study examined age-related variability in abnormal parathyroid gland localization for targeted PTX and the value of IPM across age groups. METHODS: A retrospective review examined prospectively collected data of 833 patients who underwent targeted PTX guided by IPM. The patients were stratified into three age groups as follows: younger [<47 years; mean -1 standard deviation (SD)], typical (47-73 years), and older (>73 years; mean +1 SD) based on an age distribution curve for pHPT. The accuracy, sensitivity, and positive predictive value (PPV) for MIBI, SUS, and IPM were analyzed and compared among age groups. Operative success was defined as eucalcemia for 6 months or longer after PTX, and operative failure was defined as elevated calcium and PTH levels within 6 months after PTX. RESULTS: Of the 833 patients, the youngest group had the highest accuracy and sensitivity for MIBI, SUS, and IPM compared with the older groups ($p < 0.05$). The accuracy and sensitivity of MIBI and SUS also decreased significantly with increased age ($p < 0.05$). Within all three age groups, IPM was consistently more accurate and sensitive than SUS or MIBI ($p < 0.05$). CONCLUSIONS: Age can significantly affect the accuracy and sensitivity of MIBI and SUS in targeted PTX for patients with pHPT. Across all age groups, IPM remains more accurate than preoperative localization studies. For the elderly, in whom multiglandular disease appears increased, surgeons should have a lower threshold for conversion to bilateral neck exploration.
PubMed-ID: 26353763
http://dx.doi.org/10.1245/s10434-015-4843-2

Value of Prophylactic Cervical Thymectomy in Parathyroid Hyperplasia.
Ann Surg Oncol, 22 Suppl 3:S662-8.
M. M. Boltz, N. Zhang, C. Zhao, S. Thiruvengadam, A. E. Siperstein and J. Jin. 2015.
BACKGROUND: In parathyroid hyperplasia (HPT), parathyroid glands within the cervical thymus are a cause for recurrence. As a result of differences in pathophysiology, variable practice patterns exist regarding performing bilateral cervical thymectomy (BCT) in primary hyperplasia versus hyperplasia from renal failure or familial disease. The objective of this study was to capture patients where thymic tissue was found with subtotal parathyroidectomy (PTX) and intended BCT, identify number of thymic supernumerary glands (SNGs), and determine overall cure rate. METHODS: Retrospective review of patients with four-gland exploration and intended BCT for HPT from 2000 to 2013 was performed. Identification of thymic tissue and SNGs were determined by operative/pathology reports. Univariate analysis identified differences in cure rate for patients undergoing subtotal PTX with or without BCT. RESULTS: Thymic tissue was found in 52 % of 328 primary HPT (19 % unilateral, 33 % bilateral), 77 % of 128 renal HPT (28 % unilateral, 49 % bilateral), and 100 % of familial HPT (24 % unilateral, 76 % bilateral) patients. Nine percent of primary, 18 % of renal, and 10 % of familial HPT patients had SNGs within thymectomy specimens. Cure rates of primary HPT patients with BCT were 99 % compared to 94 % in subtotal PTX alone. Renal HPT cure rates were 94 % with BCT compared to 89 % without BCT. CONCLUSIONS: Renal HPT patients benefited most in cure when thymectomy was performed. Although the rate of SNGs found in primary HPT was lower than renal HPT, the cure rate mimicked the pattern in renal disease. Furthermore, the incidences of SNGs in primary and familial HPT were similar. On the basis of these data, we advocate that BCT be considered in primary HPT when thymic tissue is readily identified.
PubMed-ID: 26353764
http://dx.doi.org/10.1245/s10434-015-4859-7

Management of the Parathyroid Glands During Preventive Thyroidectomy in Patients With Multiple Endocrine Neoplasia Type 2.
Ann Surg, 262(4):641-6.
J. F. Moley, M. Skinner, W. E. Gillanders, T. C. Lairmore, K. J. Rowland, A. L. Traugott, L. X. Jin and S. A. Wells, Jr. 2015.
OBJECTIVES: Patients with multiple endocrine neoplasia type 2 (MEN2) have mutations in the RET protooncogene and virtually all of them will develop medullary thyroid carcinoma. Family members identified by genetic testing are candidates for preventive thyroidectomy. Management of the parathyroids during thyroidectomy is controversial. Some experts advocate total parathyroidectomy with autotransplantation, whereas others recommend preserving the parathyroids in situ. METHODS: Between 1993 and 2000, we performed preventive thyroidectomies on 50 patients with MEN2A (group A). All patients had a central neck dissection (CND) combined with total parathyroidectomy and autotransplantation of parathyroid slivers to the nondominant forearm or to the neck. Between 2003 and the present, we performed 102 preventive thyroidectomies attempting to preserve the parathyroid glands in situ with an intact vascular pedicle (group B). Individual parathyroids were autotransplanted only if they appeared nonviable or could not be preserved intact. Central neck dissection was done only if the serum calcitonin was greater than 40 pg/mL. RESULTS: Permanent hypoparathyroidism occurred in 3 (6%) of 50 patients in group A, compared with 1 (1%) of 102 patients in group B (P = 0.1). After total thyroidectomy, no patient in either group developed permanent recurrent laryngeal nerve injury or hyperparathyroidism. Immediate postoperative serum calcitonin levels were in the normal range (<5 pg/mL) in 100 of 102 patients in group B. No patients in either group have died. Oncologic follow-up of patients in group B is in progress. CONCLUSIONS: In patients with MEN2A treated by preventive total thyroidectomy routine total parathyroidectomy with autotransplantation and CND gives excellent long-term results. However, preservation of the parathyroids in situ during preventive thyroidectomy combined with selective CND based on preoperative basal serum calcitonin levels is an effective and safe alternative that results in a very low incidence of hypoparathyroidism.
PubMed-ID: 26366543
http://dx.doi.org/10.1097/SLA.0000000000001464

How Well Does Renal Transplantation Cure Hyperparathyroidism?
Ann Surg, 262(4):653-9.
I. Lou, D. Foley, S. K. Odorico, G. Leverson, D. F. Schneider, R. Sippel and H. Chen. 2015.
BACKGROUND: Most patients with end-stage renal disease will develop hyperparathyroidism (HPT). Transplantation reportedly resolves HPT in most cases. Currently, guidelines recommend a watchful waiting approach to HPT for the first 12 months after the transplantation to allow maximal allograft function. The purpose of our study is to examine the incidence and impact of HPT, defined as an elevated parathyroid hormone (PTH) level, after renal transplantation in a contemporary cohort. METHODS: Primary kidney transplantation was

performed on 1609 patients from January 1, 2004, to June 6, 2012. Patients were stratified by timing of achieving normal serum PTH levels, and a multivariate logistic regression was constructed to determine predictive variables. Kaplan-Meier analysis was then performed on overall graft survival based on PTH normalization. RESULTS: Four hundred eighty-eight (30.3%) patients achieved normal PTH within 1 year posttransplant. Four hundred twenty-seven (26.6%) attained normal PTH between 1 and 2 years, with the remaining 694 (43.1%) categorized as having HPT. Patients achieving normal PTH within 12 months of transplantation had a significantly longer median graft survival (7.33 years) compared with those patients who normalized between 12 and 24 months (4.92 years, P < 0.001), and those with HPT (5.13 years, P < 0.001). Comparing normalization of PTH by 2 years to HPT patients, obesity (P < 0.001), months on dialysis (P < 0.001), and delayed graft failure (P = 0.006) were predictive of nonnormalization. Overall, allograft survival analysis revealed a survival advantage for patients who normalize PTH within 24 months of transplantation (P = 0.038). CONCLUSIONS: Renal transplant resolves HPT in 56.9% of patients at 2 years. Resolution within the first year portends longer graft survival. Therefore, earlier intervention for HPT should be considered.
PubMed-ID: 26366545
http://dx.doi.org/10.1097/SLA.0000000000001431

The effect of parathyroidectomy on patient survival in secondary hyperparathyroidism.
Nephrol Dial Transplant, 30(12):2027-33.
K. M. Ivarsson, S. Akaberi, E. Isaksson, E. Reihner, R. Rylance, K. G. Prutz, N. Clyne and M. Almquist. 2015.
BACKGROUND: Secondary hyperparathyroidism is a common condition in patients with end-stage renal disease and is associated with osteoporosis and cardiovascular disease. Despite improved medical treatment, parathyroidectomy (PTX) is still necessary for many patients on renal replacement therapy. The aim of this study was to evaluate the effect of PTX on patient survival. METHODS: A nested index-referent study was performed within the Swedish Renal Registry (SRR). Patients on maintenance dialysis and transplantation at the time of PTX were analysed separately. The PTX patients in each of these strata were matched for age, sex and underlying renal diseases with up to five referent patients who had not undergone PTX. To calculate survival time and hazard ratios, indexes and referents were assigned the calendar date (d) of the PTX of the index patient. The risk of death after PTX was calculated using crude and adjusted Cox proportional hazards regressions. RESULTS: There were 20 056 patients in the SRR between 1991 and 2009. Of these, 579 (423 on dialysis and 156 with a renal transplant at d) incident patients with PTX were matched with 1234/892 non-PTX patients. The adjusted relative risk of death was a hazard ratio (HR) of 0.80 [95% confidence interval (CI) 0.65-0.99] for dialysis patients at d who had undergone PTX compared with matched patients who had not. Corresponding results for the patients with a renal allograft at d were an HR of 1.10 (95% CI 0.71-1.70). CONCLUSIONS: PTX was associated with improved survival in patients on maintenance dialysis but not in patients with renal allograft.
PubMed-ID: 26374600
http://dx.doi.org/10.1093/ndt/gfv334

Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation.
Surgery, 159(1):172-9.
I. Lou, D. F. Schneider, G. Leverson, D. Foley, R. Sippel and H. Chen. 2015.
BACKGROUND: Parathyroidectomy (PTX) is the only curative treatment for tertiary hyperparathyroidism (3HPT). With the introduction of calcimimetics (cinacalcet), PTX can sometimes be delayed or avoided. The purpose of this study was to determine the current incidence of utilization of PTX in patients with posttransplant 3HPT with the advent of cinacalcet. METHODS: We evaluated renal transplant patients between January 1, 2004, and June 30, 2012, with a minimum of 24 months follow-up who had persistent allograft function. Patients with an increased serum level of parathyroid hormone (PTH) at 1 year after successful renal transplantation with normocalcemia or hypercalcemia were defined as having 3HPT. A multivariate logistic regression model was constructed to determine factors associated with undergoing PTX. RESULTS: We identified 618 patients with 3HPT, only 41 (6.6%) of whom underwent PTX. Patients with higher levels of serum calcium (P < .001) and PTH (P = .002) posttransplant were more likely to be referred for PTX. Importantly, those who underwent PTX had serum calcium and PTH values distributed more closely to the normal range on most recent follow-up. PTX was not associated with rejection (P = .400) or with worsened allograft function (P = .163). CONCLUSION: PTX seems to be underused in patients with 3HPT at our institution. PTX is associated with high cure rates, improved serum calcium and PTH levels, and is not associated with rejection.
PubMed-ID: 26603850
http://dx.doi.org/10.1016/j.surg.2015.08.039

Adrenals

Meta-Analyses

Open Versus Laparoscopic Adrenalectomy for Adrenocortical Carcinoma: A Meta-analysis of Surgical and Oncological Outcomes.
Ann Surg Oncol, 23(4):1195-202.
R. Autorino, P. Bove, M. De Sio, R. Miano, S. Micali, L. Cindolo, F. Greco, J. Nicholas, C. Fiori, G. Bianchi, F. J. Kim and F. Porpiglia. 2015.
PURPOSE: This study was designed to determine the role of laparoscopic adrenalectomy (LA) in the surgical management of adrenocortical carcinoma (ACC). METHODS: A systematic literature review was performed on January 2, 2015 using PubMed. Article selection proceeded according to PRISMA criteria. Studies comparing open adrenalectomy (OA) to LA for ACC and including at least 10 cases per each surgical approach were included. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. Pooled estimates were calculated with the fixed-effect model, if no significant heterogeneity was identified; alternatively, the random-effect model was used when significant heterogeneity was detected. Main demographics, surgical outcomes, and oncological outcomes were analyzed. RESULTS: Nine studies published between 2010 and 2014 were deemed eligible and included in the analysis, all of them being retrospective case-control studies. Overall, they included 240 LA and 557 OA cases. Tumors treated with laparoscopy were significantly smaller in size (WMD -3.41 cm; confidence interval [CI] -4.91, -1.91; $p < 0.001$), and a higher proportion of them (80.8 %) more at a localized (I-II) stage compared with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2; $p < 0.001$). Hospitalization time was in favor of laparoscopy, with a WMD of -2.5 days (CI -3.3, -1.7; $p < 0.001$). There was no difference in the overall recurrence rate between LA and OA (relative risk [RR] 1.09; CI 0.83, 1.43; $p = 0.53$), whereas development of peritoneal carcinomatosis was higher for LA (RR 2.39; CI 1.41, 4.04; $p = 0.001$). No difference could be found for time to recurrence (WMD -8.2 months; CI -18.2, 1.7; $p = 0.11$), as well as for cancer specific mortality (OR 0.68; CI 0.44, 1.05; $p = 0.08$). CONCLUSIONS: OA should still be considered the standard surgical management of ACC. LA can offer a shorter hospital stay and possibly a faster recovery. Therefore, this minimally invasive approach can certainly play a role in this setting, but it should be only offered in carefully selected cases to avoid jeopardizing the oncological outcome.
PubMed-ID: 26480850
http://dx.doi.org/10.1245/s10434-015-4900-x

Randomized controlled trials

- None –

Consensus Statements/Guidelines

- None -

Other Articles

Treatment of malignant phaeochromocytoma with a combination of cyclophosphamide, vincristine and dacarbazine: own experience and overview of the contemporary literature.
Clin Endocrinol (Oxf), 82(1):84-90.
T. Deutschbein, M. Fassnacht, D. Weismann, M. Reincke, K. Mann and S. Petersenn. 2015.
OBJECTIVE: Malignant phaeochromocytomas are rare and highly aggressive tumours. This retrospective study evaluated the outcome of combined chemotherapy with cyclophosphamide, vincristine and dacarbazine (also known as CVD regimen). METHODS: Patients with histologically and radiologically confirmed malignant phaeochromocytoma who were treated with the CVD regimen for progressive disease were retrospectively

identified from chart review. Treatment cycles were usually repeated at 21-day intervals, with cyclophosphamide (750 mg/m(2)), vincristine (1.4 mg/m(2)) and dacarbazine (600 mg/m(2)) on day 1, and dacarbazine only (600 mg/m(2)) on day 2. The main outcome measures were best response during treatment and progression-free survival. RESULTS: Eight patients (4 males; median age 55.5 (range 31-77) years) with progressive disease underwent a median of 6 (range 3-11) cycles. Best treatment responses were as follows: partial response, n = 2 (25%); stable disease, n = 3 (38%); and progressive disease, n = 3 (38%). The median progression-free survival was 5.4 (range 2.5-26.8) months. After the initial administration of 6 cycles, two patients received a second course of chemotherapy with another 6 cycles after new progressive disease had been detected. Subsequently, these patients were progression-free for another 6.0 and 6.4 months. Mild gastrointestinal symptoms and fatigue were the most common adverse events. CONCLUSION: Although objective tumour response rates were lower than previously reported in small series, the CVD regimen allowed disease stabilization for a substantial period of time and may therefore be considered as a treatment option in advanced stages. To improve disease outcome, however, new therapeutic approaches and larger multicentre studies are needed.
PubMed-ID: 25143180
http://dx.doi.org/10.1111/cen.12590

Expression of LIN28 and its regulatory microRNAs in adult adrenocortical cancer.
Clin Endocrinol (Oxf), 82(4):481-8.
A. M. Faria, S. Sbiera, T. C. Ribeiro, I. C. Soares, B. M. Mariani, D. S. Freire, G. R. de Sousa, A. M. Lerario, C. L. Ronchi, T. Deutschbein, A. Wakamatsu, V. A. Alves, M. C. Zerbini, B. B. Mendonca, M. C. Fragoso, A. C. Latronico, M. Fassnacht and M. Q. Almeida. 2015.
OBJECTIVE: LIN28 control cells reprogramming and pluripotency mainly through miRNA regulation and has been overexpressed in many advanced cancers. In this study, we evaluated the prognostic role of LIN28 and its regulatory miRNAs in a large cohort of adrenocortical tumours (ACTs). PATIENTS AND METHODS: LIN28 protein expression was assessed in 266 adults ACTs (78 adenomas and 188 carcinomas) from Brazil and Germany. LIN28A and LIN28B gene expression was analysed in 59 ACTs (31 adenomas and 28 carcinomas) and copy number variation in 39 ACTs. In addition, we determined the expression of let-7 family, mir-9, mir-30 and mir-125 in 28 carcinomas. RESULTS: LIN28A gene was overexpressed in aggressive ACCs when compared with adenomas and nonaggressive ACCs, but no LIN28A copy number variation was found in ACTs. Unexpectedly, weak LIN28 protein expression was significantly associated with reduced disease-free survival in ACC patients (P = 0.01), but for overall survival only a trend was detectable (P = 0.117). In the multivariate analysis, only Ki67 index >/=10% (HR 4.6, P = 0.000) and weak LIN28 protein expression (HR 2.0, P = 0.03) were independent predictors of recurrence in ACC patients. Interestingly, mir-9 expression, a negative LIN28A/B regulator, was significantly higher in aggressive than in nonaggressive ACCs [2076 (from 36 to 9307) vs 133.4 (from 2.4 to 5193); P = 0.011] and was highly associated with reduced overall (P = 0.01) and disease-free survival (P = 0.01). However, mir-9 prognostic role should be further evaluated in a larger cohort. CONCLUSION: Weak LIN28 protein expression was associated with recurrence in ACCs. Additionally, overexpression of mir-9, a negative LIN28A regulator, was associated with poor outcome.
PubMed-ID: 25200669
http://dx.doi.org/10.1111/cen.12607

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

the functional characteristics of these tumors and new imaging-based treatment options. Finally, due to the use of new targeting moieties, gene-targeted radiotherapeutics and nanobodies-based theranostic approaches are expected to become a reality in the near future.
PubMed-ID: 26045470
http://dx.doi.org/10.1530/ERC-15-0175

Bilateral Pheochromocytomas in MEN2A Syndrome: A Two-Institution Experience.
World J Surg, 39(10):2484-91.
B. H. Lang, H. W. Yu, C. Y. Lo, K. E. Lee, M. M. Garcia-Barcelo, Y. C. Woo, P. C. Lee, K. P. Wong, P. K. Tam and K. S. Lam. 2015.
BACKGROUND: Bilateral pheochromocytoma (PHEO) is more frequently found in patients with multiple endocrine neoplasia 2A carrying a RET germline mutation located in codon 634 (C634). However, it is unclear whether different amino acid substitutions within C634 cause differences in bilateral PHEOs expression. We aimed to answer this by pooling data from two Asian institutions. METHODS: Sixty-seven patients had confirmed C634 germline mutation. Age-dependent penetrance of bilateral PHEO was calculated from date of birth to the date when bilateral PHEO was first diagnosed or when the contralateral gland became a PHEO (if the patient already had one adrenal gland removed). Age-dependent penetrance was estimated by the Kaplan-Meier method and compared by log-rank test. RESULTS: The 4 different amino acid substitutions included C634R (arginine) (n = 19, 28.4 %), C634Y (tyrosine) (n = 36, 38.8 %), C634G (glycine) (n = 4, 6.0 %), and C634W (tryptophan) (n = 8, 11.9 %). The age-related penetrance of PHEO was similar between C634R, C634Y, C634G, and C634W (by age 40, 69.8, 55.2, 25.0, and 56.2 %, respectively) (p = 0.529). However, the age-related penetrance of bilateral PHEO in C634R was significantly higher than C634Y (by age of 40, 59.3 % vs. 25.2 %, p = 0.046) or C634Y, C634G, and C634W combined (59.3 % vs. 21.5 %, p = 0.024). Nevertheless, the accumulative risk of bilateral PHEOs across all four C634 mutations almost approached 100 % over time. CONCLUSION: The accumulative risk of bilateral PHEOs almost reached 100 % but its onset was significantly earlier in C634R mutation. These findings implied that those with C634R mutation might benefit from earlier screening of contralateral PHEO than other C634 mutations after an unilateral adrenalectomy.
PubMed-ID: 26071011
http://dx.doi.org/10.1007/s00268-015-3117-2

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

15 YEARS OF PARAGANGLIOMA: Metabolism and pheochromocytoma/paraganglioma.
Endocr Relat Cancer, 22(4):T83-90.
M. Mannelli, E. Rapizzi, R. Fucci, L. Canu, T. Ercolino, M. Luconi and W. F. Young, Jr. 2015.
The discovery of SDHD as a pheochromocytoma/paraganglioma susceptibility gene was the prismatic event that led to all of the subsequent work highlighting the key roles played by mitochondria in the pathogenesis of these tumors and other solid cancers. Alterations in the function of tricarboxylic acid cycle enzymes can cause accumulation of intermediate substrates and subsequent changes in cell metabolism, activation of the angiogenic pathway, increased reactive oxygen species production, DNA hypermethylation, and modification of the tumor microenvironment favoring tumor growth and aggressiveness. The elucidation of these tumorigenic mechanisms should lead to novel therapeutic targets for the treatment of the most aggressive forms of pheochromocytoma/paraganglioma.
PubMed-ID: 26113605
http://dx.doi.org/10.1530/ERC-15-0215

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

The ARMC5 gene shows extensive genetic variance in primary macronodular adrenocortical hyperplasia.
Eur J Endocrinol, 173(4):435-40.
R. Correa, M. Zilbermint, A. Berthon, S. Espiard, M. Batsis, G. Z. Papadakis, P. Xekouki, M. B. Lodish, J. Bertherat, F. R. Faucz and C. A. Stratakis. 2015.
OBJECTIVE: Primary macronodular adrenal hyperplasia (PMAH) is a rare type of Cushing's syndrome (CS) that results in increased cortisol production and bilateral enlargement of the adrenal glands. Recent work showed that the disease may be caused by germline and somatic mutations in the ARMC5 gene, a likely tumor suppressor gene (TSG). We investigated 20 different adrenal nodules from one patient with PMAH for ARMC5 somatic sequence changes. DESIGN: All of the nodules were obtained from a single patient who underwent bilateral adrenalectomy. DNA was extracted by standard protocol and the ARMC5 sequence was determined by the Sanger method. RESULTS: Sixteen of 20 adrenocortical nodules harbored, in addition to what appeared to be the germline mutation, a second somatic variant. The p.Trp476* sequence change was present in all 20 nodules, as well as in normal tissue from the adrenal capsule, identifying it as the germline defect; each of the 16 other variants were found in different nodules: six were frame shift, four were missense, three were nonsense, and one was a splice site variation. Allelic losses were confirmed in two of the nodules. CONCLUSION: This is the most genetic variance of the ARMC5 gene ever described in a single patient with PMAH: each of 16 adrenocortical nodules had a second new, 'private,' and--in most cases--completely inactivating ARMC5 defect, in addition to the germline mutation. The data support the notion that ARMC5 is a TSG that needs a second, somatic hit, to mediate tumorigenesis leading to polyclonal nodularity; however, the driver of this extensive genetic variance of the second ARMC5 allele in adrenocortical tissue in the context of a germline defect and PMAH remains a mystery.
PubMed-ID: 26162405
http://dx.doi.org/10.1530/EJE-15-0205

Is there a role for segmental adrenal venous sampling and adrenal sparing surgery in patients with primary aldosteronism?
Eur J Endocrinol, 173(4):465-77.
F. Satoh, R. Morimoto, K. Seiji, N. Satani, H. Ota, Y. Iwakura, Y. Ono, M. Kudo, M. Nezu, K. Omata, Y. Tezuka, Y. Kawasaki, S. Ishidoya, Y. Arai, K. Takase, Y. Nakamura, K. McNamara, H. Sasano and S. Ito. 2015.
OBJECTIVE AND DESIGN: Adrenal venous sampling (AVS) is critical to determine the subtype of primary aldosteronism (PA). Central AVS (C-AVS)--that is, the collection of effluents from bilateral adrenal central veins (CV)--sometimes does not allow differentiation between bilateral aldosterone-producing adenomas (APA) and idiopathic hyperaldosteronism. To establish the best treatment course, we have developed segmental AVS (S-AVS); that is, we collect effluents from the tributaries of CV to determine the intra-adrenal sources of aldosterone overproduction. We then evaluated the clinical utility of this novel approach in the diagnosis and treatment of PA. METHODS: We performed C-AVS and/or S-AVS in 297 PA patients and assessed the accuracy of diagnosis based on the results of C-AVS (n=138, 46.5%) and S-AVS (n=159, 53.5%) by comparison with those of clinicopathological evaluation of resected specimens. RESULTS: S-AVS demonstrated both elevated and attenuated secretion of aldosterone from APA and non-tumorous segments, respectively, in patients with bilateral APA and recurrent APA. These findings were completely confirmed by detailed histopathological

examination after surgery. S-AVS, but not C-AVS, also served to identify APA located distal from the CV. CONCLUSIONS: Compared to C-AVS, S-AVS served to identify APA in some patients, and its use should expand the pool of patients eligible for adrenal sparing surgery through the identification of unaffected segments, despite the fact that S-AVS requires more expertise and time. Especially, this new technique could enormously benefit patients with bilateral or recurrent APA because of the preservation of non-tumorous glandular tissue.
PubMed-ID: 26194502
http://dx.doi.org/10.1530/EJE-14-1161

[Adrenocortical tumors > 8 cm should be treated by open surgery].
Chirurg, 86(9):897.
H. Dralle. 2015.
PubMed-ID: 26223672
http://dx.doi.org/10.1007/s00104-015-0069-x

15 YEARS OF PARAGANGLIOMA: Pheochromocytoma, paraganglioma and genetic syndromes: a historical perspective.
Endocr Relat Cancer, 22(4):T147-59.
T. Else. 2015.
The last decades have elucidated the genetic basis of pheochromocytoma (PC) and paraganglioma (PGL) (PCPGL)-associated hereditary syndromes. However, the history of these syndromes dates back at least another 150 years. Detailed descriptions by clinicians and pathologists in the 19th and 20th centuries led to the recognition of the PCPGL-associated syndromes von Hippel-Lindau disease, neurofibromatosis type 1, and multiple endocrine neoplasia type 2. In the beginning of the current millennium the molecular basis of the hereditary PGL syndrome was elucidated by the discovery of mutations in genes encoding enzymes of the Krebs cycle, such as succinate dehydrogenase genes (SDHx) and other mutations, causing 'pseudo-hypoxia' signaling. These recent developments also marked a paradigm shift. It reversed the traditional order of genetic research that historically aimed to define the genetic basis of a known hereditary syndrome but now is challenged with defining the full clinical phenotype associated with a newly defined genetic basis. This challenge underscores the importance to learn from medical history, continue providing support for clinical research, and train physicians with regards to their skills to identify patients with PCPGL-associated syndromes to extend our knowledge of the associated phenotype. This historical overview provides details on the history of the paraganglial system and PCPGL-associated syndromes. As such, it hopefully will not only be an interesting reading for the physician with a historical interest but also emphasize the necessity of ongoing astute individual clinical observations and clinical registries to increase our knowledge regarding the full phenotypic spectrum of these conditions.
PubMed-ID: 26273101
http://dx.doi.org/10.1530/ERC-15-0221

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

PubMed-ID: 26273102
http://dx.doi.org/10.1530/ERC-15-0268

Biochemical and clinical benefits of unilateral adrenalectomy in patients with subclinical hypercortisolism and bilateral adrenal incidentalomas.
Eur J Endocrinol, 173(6):719-25.
I. Perogamvros, D. A. Vassiliadi, O. Karapanou, E. Botoula, M. Tzanela and S. Tsagarakis. 2015.
OBJECTIVE: The treatment of subclinical hypercortisolism in patients with bilateral adrenal incidentalomas (AI) is debatable. We aimed to compare the biochemical and clinical outcome of unilateral adrenalectomy vs a conservative approach in these patients. DESIGN: Retrospective study. METHODS: The study included 33 patients with bilateral AI; 14 patients underwent unilateral adrenalectomy of the largest lesion (surgical group), whereas 19 patients were followed up (follow-up group). At baseline and at each follow-up visit, we measured 0800 h plasma ACTH, midnight serum cortisol (MSF), 24-h urinary-free cortisol (UFC) and serum cortisol following a standard 2-day low-dose-dexamethasone-suppression test (LDDST). We evaluated the following comorbidities: arterial hypertension, impaired glucose tolerance or diabetes mellitus, dyslipidemia and osteoporosis. RESULTS: Baseline demographic, clinical characteristics and the duration of follow-up (53.9+/-21.3 vs 51.8+/-20.1 months, for the surgical vs the follow-up group) were similar between groups. At the last follow-up visit the surgical group had a significant reduction in post-LDDST cortisol (2.4+/-1.6 vs 6.7+/-3.9 mug/dl, P=0.002), MSF (4.3+/-2 vs 8.8+/-4.6 mug/dl, P=0.006) and 24-h UFC (50.1+/-21.1 vs 117.9+/-42.4 mug/24 h, P=0.0007) and a significant rise in mean+/-s.d. morning plasma ACTH levels (22.2+/-9.6 vs 6.9+/-4.8 pg/ml, P=0.002). Improvement in co-morbidities was seen only in the surgical group, whereas no changes were noted in the follow-up group. CONCLUSIONS: Our early results show that removal of the largest lesion offers significant improvement both to cortisol excess and its metabolic consequences, without the debilitating effects of bilateral adrenalectomy. A larger number of patients, as well as a longer follow-up, are required before drawing solid conclusions.
PubMed-ID: 26330465
http://dx.doi.org/10.1530/EJE-15-0566

18F-FDG PET/CT in the post-operative monitoring of patients with adrenocortical carcinoma.
Eur J Endocrinol, 173(6):749-56.
A. Ardito, C. Massaglia, E. Pelosi, B. Zaggia, V. Basile, R. Brambilla, F. Vigna-Taglianti, E. Duregon, V. Arena, P. Perotti, D. Penna and M. Terzolo. 2015.
CONTEXT: The role of (18)F-labeled 2-fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the post-operative monitoring of patients with adrenocortical carcinoma (ACC) is still unclear. OBJECTIVE: To assess the accuracy of FDG PET/CT to diagnose ACC recurrence in a real world setting. DESIGN AND METHODS: Retrospective evaluation of data of 57 patients with presumed ACC recurrence at CT scan who underwent FDG PET/CT within a median time of 20 days. We compared the results of either FDG PET/CT or CT with a gold standard confirmation of recurrence (positive histopathology report of removed/biopsied lesions or radiological progression of target lesions at follow-up) to assess their diagnostic performance at different body sites to correctly categorize target lesions. We also assessed whether FDG PET/CT findings may be useful to inform the management strategy. RESULTS: In 48 patients with confirmed ACC recurrence, we found that FDG PET/CT had lower sensitivity than CT in diagnosing liver and lung recurrences of ACC. FDG PET/CT had higher specificity than CT in categorizing liver lesions. FDG PET/CT had a greater positive likelihood ratio than CT to identify liver and abdominal ACC recurrences. The management strategy was changed based on FDG PET/CT findings in 12 patients (21.1%). CONCLUSIONS: The greater sensitivity of CT may be partly expected due the specific inclusion criteria of the study; however, the greater specificity of FDG PET/CT was particularly useful in ruling out suspected ACC recurrences found by CT. Thus, use of FDG PET/CT as a second-line test in the post-operative surveillance of ACC patients following CT finding of a potential recurrence may have a significant impact on patient management.
PubMed-ID: 26346137
http://dx.doi.org/10.1530/EJE-15-0707

Pheochromocytoma diagnosed pathologically with previous negative serum markers.
J Surg Oncol, 112(5):492-5.
M. G. Heavner, L. S. Krane, S. M. Winters and M. Mirzazadeh. 2015.
BACKGROUND AND OBJECTIVES: Patients presenting with adrenal masses require workup with catecholamine or metabolite measurements to rule out pheochromocytoma. There is a select portion of patients with marker negative pheochromocytoma. The aim of this study is to compare patient characteristics and presentations between marker positive and marker negative tumors. METHODS: We performed an IRB-

approved retrospective chart review of 88 cases of pheochromocytoma excised at our institution from 1995 to 2013. We considered any abnormal elevation in diagnostic test to be marker-positive. RESULTS: Seventy-eight cases had laboratory results available. Among these, seven had no elevations in laboratory testing. There was no difference in age or tumor size, but marker-negative patients had higher BMI than marker-positive patients. Marker negative patients were more likely to present with vertigo/dizziness (P = 0.003). Neither was more likely to have a genetic syndrome associated with risk of pheochromocytoma. CONCLUSIONS: Marker-negative pheochromocytoma is uncommon, representing 9% of cases in our series. Of patients with adrenal masses or presentation suggesting catecholamine excess with normal labs, those with vertigo/dizziness may warrant a metaiodobenzylguanidine scan or repeat testing to avoid missing pheochromocytoma. Clinicians may need a high degree of suspicion for pheochromocytoma in patients with negative testing and elevated BMI.
PubMed-ID: 26384104
http://dx.doi.org/10.1002/jso.24031

Indocyanine green (ICG) fluorescence-guided laparoscopic adrenalectomy.
J Surg Oncol, 112(6):650-3.
J. C. DeLong, J. M. Chakedis, A. Hosseini, K. J. Kelly, S. Horgan and M. Bouvet. 2015.
OBJECTIVE: Laparoscopic adrenalectomy has become the standard of care for many adrenal tumors. However, the success of the operation hinges on identifying the adrenal vein and complete tumor resection. We demonstrate the use of a commercially available near infrared fluorescent imaging system to clearly delineate the vascular anatomy of adrenal neoplasms and enhance the border between tumor and normal tissue. We hypothesize that this will increase the safety of laparoscopic adrenalectomy. MATERIALS AND METHODS: We performed laparoscopic adrenalectomy utilizing indocyanine green (ICG) and a specialized laparoscopic fluorescence imaging system on four consecutive patients undergoing laparoscopic adrenalectomy over a 4-month period. RESULTS: The adrenal arteries and vein were vividly enhanced with ICG fluorescence guidance, and the border between tumor and adjacent tissue was clearly demarcated. The operations were performed safely with minimal blood loss and short operative times. There were no complications. CONCLUSIONS: Adrenal neoplasms can be resected laparoscopically under ICG fluorescence guidance and can be used to clearly identify vascular structures and enhance the borders of the tumor. This technique allows for clear identification of the adrenal vein and has the potential to improve the safety of laparoscopic adrenalectomy.
PubMed-ID: 26420733
http://dx.doi.org/10.1002/jso.24057

Selective strategy for intensive monitoring after pheochromocytoma resection.
Surgery, 159(1):275-82.
C. E. Benay, M. Tahiri, L. Lee, E. Theodosopoulos, A. Madani, L. S. Feldman and E. J. Mitmaker. 2015.
BACKGROUND: Guidelines recommend 24-48 hours of intensive monitoring after resection of pheochromocytoma. However, many patients do not require it. The objective of this study is to identify preoperative risk factors associated with postoperative hemodynamic instability (HDI) so as to select patients who may not require intensive postoperative monitoring. METHODS: Medical records of patients undergoing pheochromocytoma resection over a 12-year period were reviewed. Postoperative HDI was defined as systolic blood pressure of >200 or <90, heart rate >110 or <50 or needing active resuscitation. RESULTS: We included 41 patients; 49% had postoperative HDI but only 34% had HDI > 6 hours. Risk factors for HDI were preoperative mean arterial pressure (MAP) > 100 mm Hg (14% vs 45%), norepinephrine/normetanephrine levels >3x normal (44 vs 82%), and resection of another solid organ (0 vs 20%). Avoidance of planned postoperative monitoring for low-risk patients would have reduced estimated costs by 34%. CONCLUSION: Fewer than one-half of patients undergoing resection for pheochromocytoma benefit from intensive monitoring. High preoperative MAP, high norepinephrine/normetanephrine levels, and concomitant resection of another organ are risk factors for postoperative HDI. After a 6-hour interval of postoperative stability, selective rather than routine use of intensive monitoring may be an efficient strategy for monitoring lower risk patients.
PubMed-ID: 26435433
http://dx.doi.org/10.1016/j.surg.2015.06.045

Should specific patient clinical characteristics discourage adrenal surgeons from performing laparoscopic transperitoneal adrenalectomy?
Surgery, 159(1):240-8.
K. P. Economopoulos, R. Phitayakorn, C. C. Lubitz, P. M. Sadow, S. Parangi, A. E. Stephen and R. A. Hodin. 2015.
BACKGROUND: Although laparoscopic transperitoneal adrenalectomy (LTA) has become a standard operative approach to patients with benign adrenal masses, some authors have suggested that LTA should be avoided in

obese patients, patients who have had previous abdominal surgery, and in cases of bilateral adrenalectomy. We sought to determine whether LTA in these clinical situations is associated with worse outcomes. METHODS: Consecutive patients who underwent LTA at a tertiary care center (1/2002-8/2014) were reviewed retrospectively. Study endpoints included operative time, duration of stay, conversion to open procedure, and postoperative complications. Statistical analyses were performed by use of Wilcoxon rank sum test, Kruskal-Wallis test, Fisher exact test, chi(2) test, and binary logistic regression analyses. RESULTS: A total of 365 patients had a planned LTA, 6 of whom were converted to an open adrenalectomy. Obesity, history of previous abdominal surgery, and bilateral adrenalectomy were not associated with greater conversion rates or postoperative complications. Male sex, tumor size >/= 4 cm and obesity (body mass index >/= 30 kg/m(2)) were significant factors associated with increased operative time. Bilateral adrenalectomy, age, and pheochromocytomas were associated with increased hospital stays. CONCLUSION: Obesity, history of prior abdominal surgery and bilateral adrenalectomy should not be used to discourage experienced adrenal surgeons from performing LTA.
PubMed-ID: 26453136
http://dx.doi.org/10.1016/j.surg.2015.07.045

DNA copy amplification and overexpression of SLC12A7 in adrenocortical carcinoma.
Surgery, 159(1):250-7.
T. C. Brown, C. C. Juhlin, J. M. Healy, A. Stenman, J. C. Rubinstein, R. Korah and T. Carling. 2015.
BACKGROUND: Overexpression of Solute carrier family 12 member 7 (SLC12A7) promotes tumor aggressiveness in various cancers. Previous studies have identified the 5p15.33 region, containing the SLC12A7 locus, as being amplified frequently in adrenocortical carcinoma (ACC). Copy number amplifications (CNAs) may alter gene expression levels and occur frequently in ACC; however, SLC12A7 gene amplifications or expression levels have not been studied in ACC. METHODS: Fifty-five cases of clinically well-characterized ACCs were recruited for this study. Whole-exome sequencing was used to predict CNAs in 19 samples. CNA analysis was performed on an expanded cohort of 26 samples with the use of TaqMan Copy Number Assays. SLC12A7 mRNA expression was analyzed in 32 samples with real-time quantitative polymerase chain reaction and protein expression was assessed by immunohistochemistry. SLC12A7 CNAs and expression patterns were evaluated for correlation with patient and tumor characteristics. RESULTS: Whole-exome sequencing and TaqMan Copy Number Assays demonstrated SLC12A7 amplifications in 68.4% and 65.4% of ACCs tested, respectively. Furthermore, SLC12A7 copy gains were associated with increased gene expression ($P < .05$) and non-functional tumors ($P < .05$). SLC12A7 gene expression levels were increased in ACCs compared with normal adrenal tissue ($P < .05$). CONCLUSION: SLC12A7 gene amplification and overexpression occurs frequently in ACCs and may represent a novel molecular event associated with ACC.
PubMed-ID: 26454676
http://dx.doi.org/10.1016/j.surg.2015.08.038

Clinical course and prognostic factors in patients with malignant pheochromocytoma and paraganglioma: A single institution experience.
J Surg Oncol, 112(8):815-21.
Y. M. Choi, T. Y. Sung, W. G. Kim, J. J. Lee, J. S. Ryu, T. Y. Kim, W. B. Kim, S. J. Hong, D. E. Song and Y. K. Shong. 2015.
OBJECTIVES: Malignant pheochromocytoma (PCC)/paraganglioma (PG) are rare neuroendocrine malignancies, and their clinical courses and prognoses are not well understood. This study aimed to evaluate prognostic factors associated with the survival of malignant PCC/PG. METHODS: This retrospective study reviewed 299 patients with PCC and 46 with PG treated between 1997 and 2013 at our single tertiary hospital. Malignant PCC/PG was defined as the presence of distant metastasis or recurrence at sites where neuroendocrine tissue is normally not present. RESULTS: Twenty-seven patients (9%) were confirmed with malignant PCC and six patients (13%) with malignant PG. Twenty-seven patients (82%) had distant metastases, nine patients (27%) presented with a metastasis at the initial diagnosis, whilst 24 patients (73%) were diagnosed with malignant PCC/PG during follow-up (median, 4.3 year). The median survival was 7.2 years, and the 5 year survival rate was 75.4%. Older age (>45 years), larger tumor size (>6 cm), synchronous metastasis, and absence of surgical excision were associated with poor survival by univariate analysis. By multivariate analysis, older age (HR = 4.3, P = 0.02) and synchronous metastasis (HR = 4.3, P = 0.01) were significantly associated with a poor prognosis. CONCLUSIONS: Patients with malignant PCC/PG have diverse clinical courses. Poor survival was independently associated with older age and synchronous metastasis.
PubMed-ID: 26464058
http://dx.doi.org/10.1002/jso.24063

NET

Meta-Analyses

- None -

Randomized controlled trials

Efficacy of octreotide long-acting repeatable in neuroendocrine tumors: RADIANT-2 placebo arm post hoc analysis.
Endocr Relat Cancer, 22(6):933-40.
J. R. Strosberg, J. C. Yao, E. Bajetta, M. Aout, B. Bakker, J. D. Hainsworth, P. B. Ruszniewski, E. Van Cutsem, K. Oberg and M. E. Pavel. 2015.
Somatostatin analogues (SSA) have demonstrated antiproliferative activity in addition to efficacy for carcinoid symptom control in functional neuroendocrine tumors (NET). A post hoc analysis of the placebo arm of the RAD001 In Advanced Neuroendocrine Tumors-2 (RADIANT-2) study was conducted to assess the efficacy of octreotide long-acting repeatable (LAR) on progression-free survival (PFS) and overall survival (OS) estimated using the Kaplan-Meier method. Out of 213 patients randomized to placebo plus octreotide LAR in RADIANT-2, 196 patients with foregut, midgut, or hindgut NET were considered for present analysis. Of these, 41 patients were SSA-treatment naive and 155 had received SSA therapy before study entry. For SSA-naive patients, median PFS by adjudicated central review was 13.6 (95% CI 8.2-22.7) months. For SSA-naive patients with midgut NET (n=24), median PFS was 22.2 (95% CI 8.3-29.5) months. For patients who had received SSA previously, the median PFS was 11.1 (95% CI 8.4-14.3) months. Among the SSA-pretreated patients who had midgut NET (n=119), the median PFS was 12.0 (95% CI 8.4-19.3) months. Median OS was 35.8 (95% CI 32.5-48.9) months for patients in the placebo plus octreotide LAR arm; 50.6 (36.4 - not reached) months for SSA-naive patients and 33.5 (95% CI 27.5-44.7) months for those who had received prior SSA. This post hoc analysis of the placebo arm of the large phase 3 RADIANT-2 study provides data on PFS and OS among patients with progressive NET treated with octreotide therapy.
PubMed-ID: 26373569
http://dx.doi.org/10.1530/ERC-15-0314

Consensus Statements/Guidelines

- None -

Other Articles

Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study.
Ann Surg Oncol, 22(3):1000-7.
D. J. Birnbaum, O. Turrini, L. Vigano, N. Russolillo, A. Autret, V. Moutardier, L. Capussotti, Y. P. Le Treut, J. R. Delpero and J. Hardwigsen. 2015.
BACKGROUND: The role of extended resections in the management of advanced pancreatic neuroendocrine tumors (PNETs) is not well defined. METHODS: Between 1995 and 2012, 134 patients with PNET underwent isolated (isoPNET group: 91 patients) or extended pancreatic resection (synchronous liver metastases and/or adjacent organs) (advPNET group: 43 patients). RESULTS: The associated resections included 27 hepatectomies, 9 vascular resections, 12 colectomies, 10 gastrectomies, 4 nephrectomies, 4 adrenalectomies, and 3 duodenojejunal resections. R0 was achieved in 41 patients (95%) in the advPNET. The rates of T3-T4 (73 vs 16%; p < .0001) and N+ (35 vs 13%; p = .007) were higher in the advPNET group. Mortality (5 vs 2%) and major morbidity (21 vs 19%) rates were similar between the 2 groups. The 5-year overall survival (OS) of the series was 87% in the isoPNET group and 66% in the advPNET group (p = .006). Only patients with both locally

advanced disease and liver metastases showed worse survival (p = .0003). The advPNET group developed recurrence earlier [disease-free survival (DFS) at 5 years: 26 vs 81%; p < .001]. In univariate analysis, negative prognostic factors of survival were: poor degree of differentiation (p < .001), liver metastasis (p = .011), NE carcinoma (p < .001), and resection of adjacent organs (p = .013). The multivariate analysis did not highlight any factor that influenced OS. In multivariate analysis independent DFS factors were a poor degree of differentiation (p = .03) and the European Neuroendocrine Tumor Society stage (p = .01). CONCLUSIONS: An aggressive surgical approach for locally advanced or metastatic tumors is safe and offers long-term survival.
PubMed-ID: 25190116
http://dx.doi.org/10.1245/s10434-014-4016-8

Incidence of Second Primary Malignancies in Patients with Neuroendocrine Tumours.
Neuroendocrinology, 102(1-2):26-32.
A. K. Clift, P. Drymousis, A. Al-Nahhas, H. Wasan, J. Martin, S. Holm and A. Frilling. 2015.
BACKGROUND: An association between neuroendocrine tumours (NET) and increased risk of developing second primary malignancies (SPM) has been recognised. METHODS: This was a retrospective review of our institutional prospectively maintained database of NET patients. We identified patients who had been diagnosed with both neuroendocrine and any additional malignancies via examination of patient notes. RESULTS: Clinical data for 169 patients were analysed. After exclusion of patients known to have hereditary tumour predisposition syndromes, 29 SPM were identified in 26 patients (15.38%), the commonest being colorectal (n = 6), breast and renal carcinomas (both n = 5). SPM were classified as previous, synchronous or subsequent relative to NET diagnosis. Rates of SPM in pancreatic and small-bowel NET patients were comparable (15.7 vs. 19.6%, p = 0.78). A person-year methodology was used to compare observed numbers of SPM against expected values generated from age- and sex-specific incidence tables, with standardised incidence ratios (SIR) and 95% confidence intervals (CI) calculated. SPM incidence was significantly elevated in the synchronous subset (SIR 2.732, CI 1.177-5.382) whilst significantly fewer NET patients had a cancer history compared to the general population (SIR 0.4, CI 0.241-0.624). No overall differences were evident between observed and expected incidences of subsequent SPM (SIR 0.36, CI 0.044-1.051). The incidence of synchronous colorectal cancers was markedly elevated (SIR 13.079, CI 4.238-30.474). CONCLUSIONS: Our data support the use of colonoscopy in the diagnostic work-up of NET patients in anticipation of a colorectal SPM. The mechanistic underpinnings of this clinical phenomenon require further genetic investigation, and consideration of this knowledge in patient management pathways is warranted.
PubMed-ID: 25824138
http://dx.doi.org/10.1159/000381716

Long-Term Outcomes of Surgical Management of Pancreatic Neuroendocrine Tumors with Synchronous Liver Metastases.
Neuroendocrinology, 102(1-2):68-76.
S. Partelli, M. Inama, A. Rinke, N. Begum, R. Valente, V. Fendrich, D. Tamburrino, T. Keck, M. E. Caplin, D. Bartsch, C. Thirlwell, G. Fusai and M. Falconi. 2015.
BACKGROUND: The value of surgical resection in the management of pancreatic neuroendocrine tumors (PNET) with liver metastases (LM) is still debated. The aim of this study was to evaluate the outcomes of surgery of PNET with LM. METHODS: Patients with PNET with synchronous LM between 2000 and 2011 from 4 high-volume institutions were included. The patients were divided into 3 groups: curative resection, palliative resection, and no resection. RESULTS: Overall, 166 patients were included. Eighteen patients (11%) underwent curative resection, 73 patients (43%) underwent palliative resection, and 75 patients (46%) underwent conservative treatment. The median overall survival (OS) from the time of diagnosis was 73 months. Patients who underwent curative resection had a significantly better median OS from the initial diagnosis compared with those who underwent palliative resection and those who were conservatively treated (97 vs. 89 vs. 36 months, p = 0.0001). The median OS from the time of diagnosis in those patients who underwent radical or palliative resection was 97 months, with a 5-year survival rate of 76%. On multivariate analysis, factors associated with OS from the time of diagnosis were the presence of bilobar metastases, tumor grading, and curative resection in a first model. On a second model, curative or palliative surgery was an independent predictor of OS. Among 91 patients who underwent surgery, the presence of pancreatic neuroendocrine carcinoma G3 was the only factor independently associated with a poorer survival after surgery (median OS: 35 vs. 97 months, p < 0.0001). CONCLUSIONS: Patients with LM from PNET benefit from surgical resection, although surgery should be reserved to well- or moderately differentiated forms.
PubMed-ID: 26043944
http://dx.doi.org/10.1159/000431379

Ki-67 Index and Solid Growth Pattern as Prognostic Markers in Small Intestinal Neuroendocrine Tumors.
Neuroendocrinology, 102(4):327-34.
K. Landerholm and S. E. Falkmer. 2015.
BACKGROUND/AIMS: The prognostic value of histopathological grading and the growth pattern of small intestinal neuroendocrine tumors (SI-NET) is unclear. In particular, the cutoff level between grades G1 and G2 at Ki-67 index above 2% is an open issue, and both lower and higher cutoffs have been proposed. The morphological solid growth pattern (SGP) in SI-NET has been reported to be associated with worse survival. The present study investigates whether a Ki-67 index cutoff of 1% has a higher predictive power than one of 2% for disease-specific survival in SI-NET, and whether an SGP is associated with survival. PATIENTS AND METHODS: From a population-based cohort, 127 SI-NET patients with available tumor specimens were included. Medical records and pathology reports were reviewed. Tumor specimens were reexamined to confirm the diagnosis, recalculate the Ki-67 index, and assess the presence of an SGP, introducing an SGP score from 0 to 3+. RESULTS: The current grading system with a G1/G2 cutoff of 2% was more discriminative (HR 2.30; 95% CI 1.20-4.38, p = 0.012) than one with a lower cutoff of 1% (HR 1.65; 95% CI 0.95-2.87, p = 0.078) after adjustment for patient age and clinical stage. SGP score was strongly associated with clinical stage (p = 0.004) and histopathological grade (p < 0.001) but was not an independent prognostic factor for disease-specific survival in SI-NET (p = 0.122) after adjusting for age, stage, and grade. CONCLUSIONS: The present grading system of SI-NET is supported by our results. The SGP is not an independent prognostic factor for disease-specific survival in SI-NET.
PubMed-ID: 26065631
http://dx.doi.org/10.1159/000434724

Biochemical Testing After Pheochromocytoma Removal: How Early?
Horm Metab Res, 47(9):633-6.
T. Zelinka, O. Petrak, B. Hamplova, H. Turkova, P. Waldauf, J. Rosa, Z. Somloova, R. Holaj, B. Strauch, T. Indra, M. Krsek, A. Brabcova Vrankova, Z. Musil, J. Duskova, J. Kubinyi, D. Michalsky, K. Novak and J. Widimsky, Jr. 2015.
Pheochromocytomas are catecholamine-producing tumors with typical clinical presentation. Tumor resection is considered as an appropriate treatment strategy. Due to its unpredictable clinical behavior, biochemical testing is mandatory to confirm the success of tumor removal after surgery. The aim of the study was to investigate the feasibility of a shorter interval of postoperative testing (earlier than the recommended 2-4 weeks according to recently published Guidelines). We investigated 81 patients with pheochromocytoma before and after surgery. Postoperative examination was performed of stable subjects after their transport from the surgical to the internal ward (7.1+/-2.2 days after surgery). Plasma metanephrines were used for the diagnosis of pheochromocytoma and confirmation of successful tumor removal. All subjects with pheochromocytoma had markedly elevated plasma metanephrines before surgery. No correlation between postoperative interval (the shortest being 3 days) and plasma metanephrine levels was found. Postoperative plasma metanephrine levels did not differ significantly from those taken at the one-year follow-up. In conclusion, we have shown that early postoperative diagnostic workup of subjects with pheochromocytoma is possible and may thus simplify early postoperative management of this clinical condition.
PubMed-ID: 26177121
http://dx.doi.org/10.1055/s-0035-1555900

Laryngeal Neuroendocrine Carcinoma: A Population-Based Analysis of Incidence and Survival.
Otolaryngol Head Neck Surg, 153(6):966-72.
R. Ghosh, R. Dutta, P. M. Dubal, R. C. Park, S. Baredes and J. A. Eloy. 2015.
OBJECTIVE: Laryngeal neuroendocrine carcinoma (LNEC) is a rare malignancy with various subtypes, each with different characteristics. Classification of these subtypes is used to delineate treatment and management, as most are clinically aggressive with poor prognosis. This study analyzes the characteristics and survival outcomes of LNEC using population-based data. STUDY DESIGN: Analysis of a population-based tumor registry. SETTING: Academic medical center. SUBJECTS AND METHODS: The Surveillance, Epidemiology, and End Results (SEER) database (1973-2011) was queried for LNEC cases. Data analyzed included patient demographics, incidence, treatment modality, and survival. RESULTS: In total, 257 LNEC cases were extracted from the SEER database. Sixty-three percent were male, and the mean age of diagnosis was 61.9 years. Most cases were located in the supraglottis (62.6%), were of the small cell carcinoma (52.9%) histologic subtype, and were grade IV (40.9%) and American Joint Committee on Cancer (AJCC) stage IV (59.4%). Surgery and radiotherapy were used as treatment modalities in 38.3% and 59.8% of patients, respectively. Overall 5-year disease-specific survival (DSS) for all LNEC was 30.2%, with lower grade, lower AJCC stage, and treatment with surgery having higher 5-year DSS. CONCLUSIONS: LNEC often presents as an aggressive tumor at an

advanced stage and has poor survival outcomes. Poor prognostic factors include high histologic grade, advanced stage disease, and not undergoing surgical resection. LNEC may be best treated depending on its histologic differentiation, with surgery being beneficial for early grade tumors while radiotherapy is inconclusive in its benefit for late-stage disease.
PubMed-ID: 26183520
http://dx.doi.org/10.1177/0194599815594386

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

Intraoperative Use of a Portable Large Field of View Gamma Camera and Handheld Gamma Detection Probe for Radioguided Localization and Prediction of Complete Surgical Resection of Gastrinoma: Proof of Concept.
J Am Coll Surg, 221(2):300-8.
N. C. Hall, S. D. Nichols, S. P. Povoski, I. A. James, C. L. Wright, R. Harris, C. R. Schmidt, P. Muscarella, 2nd, N. Latchana, E. W. Martin, Jr. and E. C. Ellison. 2015.
BACKGROUND: Surgical management of Zollinger-Ellison syndrome (ZES) relies on localization and resection of all tumor foci. We describe the benefit of combined intraoperative use of a portable large field of view gamma camera (LFOVGC) and a handheld gamma detection probe (HGDP) for indium-111 ((111)In)-pentetreotide radioguided localization and confirmation of gastrinoma resection in ZES. STUDY DESIGN: Five patients (6 cases) with (111)In-pentetreotide-avid ZES were evaluated. Patients were injected with (111)In-pentetreotide for diagnostic imaging the day before surgery. Intraoperatively, an HGDP and LFOVGC were used to localize (111)In-pentetreotide-avid lesions, guide resection, assess specimens for (111)In-pentetreotide activity, and to verify lack of abnormal post-resection surgical field activity. RESULTS: Large field of view gamma camera imaging and HGDP-assisted detection were helpful for localization and guided resection of tumor and removal of (111)In-pentetreotide-avid tumor foci in all cases. In 3 of 5 patients (3 of 6 cases), these techniques led to detection and resection of additional tumor foci beyond those detected by standard surgical techniques. The (111)In-pentetreotide-positive or-negative specimens correlated with neuroendocrine tumors or benign pathology, respectively. In one patient with mild residual focal activity on post-resection portable LFOVGC imaging, thought to be artifact, had recurrence of disease in the same area 5 months after surgery. CONCLUSIONS: Real-time LFOVGC imaging and HGDP use for surgical management of gastrinoma improve success of localizing and resecting all neuroendocrine tumor-positive tumor foci, providing instantaneous navigational feedback. This approach holds potential for improving long-term patient outcomes in patients with ZES.
PubMed-ID: 26206636
http://dx.doi.org/10.1016/j.jamcollsurg.2015.03.047

Long-Term Survival is not Impaired After the Complete Resection of Neuroendocrine Tumors of the Appendix.
World J Surg, 39(11):2670-6.
T. Steffen, S. M. Ebinger, R. Warschkow, C. Luthi, B. M. Schmied and T. Clerici. 2015.
BACKGROUND: Appendiceal neuroendocrine tumors (aNET) are a common entity in routine medical care, with a rate per appendectomy as high as 0.3-0.9 %. Considering the relatively young age at diagnosis for these patients, exact information about the long-term prognosis of aNET is required. Survival rates vary substantially between 71 and 100 % and are mostly limited to 5 years. This investigation assessed the long-term mortality rates of patients who underwent aNET resections at fifteen hospitals. METHODS: Between 1990 and 2003, the 10-year survival rates of 79 patients were analyzed using risk-adjusted Cox proportional hazard regression models adjusted for population-based baseline mortality. Additionally, prognostic factors for the oncologic outcomes were assessed. RESULTS: The median follow-up of all patients was 12.1 and 13.7 years for those alive. All patients underwent curative R0 resections. No distant metastases were diagnosed. A total of 31 (39.2 %), 29 (36.7 %), 18 (22.8 %), and 1 (1.3 %) patients had stage I, IIA, IIB, and IIIB aNET, respectively, according to the latest classification by the European Neuroendocrine Tumor Society. The 10-year overall and relative survival rates were 83.6 % (95 % CI 75.5-92.6 %) and 96.7 % (95 % CI 87.5-107 %), respectively. The 10-year relative survival rate after resection of aNET did not differ from the survival of the average national population with the same age and gender (p = 0.947). Second primary malignancies (hazard ratio of death 7.0, 95 % CI 1.6-30.6) were identified as a significant prognosticator for long-term survival. CONCLUSIONS: Long-term survival is not significantly depreciated after the curative resection of aNET.
PubMed-ID: 26223340
http://dx.doi.org/10.1007/s00268-015-3164-8

Development of 68Ga- and 89Zr-Labeled Exendin-4 as Potential Radiotracers for the Imaging of Insulinomas by PET.
J Nucl Med, 56(10):1569-74.
A. Bauman, I. E. Valverde, C. A. Fischer, S. Vomstein and T. L. Mindt. 2015.
Clinical studies have demonstrated the potential of radiometallated exendin-4 derivatives for the imaging of glucagonlike peptide-1 receptor-overexpressing insulinomas. Recently investigated exendin-4 derivatives were radiolabeled with the SPECT isotopes 99mTc or 111In. Despite promising results, the low spatial resolution associated with SPECT and the occasional need to perform imaging several days after injection for the demarcation of insulinomas from the kidneys represent current limitations. The aim of this work was the development of exendin-4 derivatives for the imaging of insulinomas by high-resolution PET at early or late time points after injection of the radiotracer. METHODS: An exendin-4 derivative conjugated to desferrioxamine (DFO) was used for radiolabeling with the PET isotopes 68Ga and 89Zr. Both radiotracers were evaluated in vitro with RIN-m5F cells for their cell internalization properties as well as affinities and specificities toward the glucagonlike peptide-1 receptor. Serum stabilities of the radiopeptides were assessed in blood serum, and their distribution coefficient was determined by the shake-flask method. Biodistribution experiments were performed with nude mice bearing RIN-m5F xenografts. For all experiments, clinically evaluated [Lys40-(AHX-DTPA-111In)NH2]exendin-4 was used as a reference compound. RESULTS: [Lys40-(AHX-DFO)NH2]exendin-4 was labeled with 89Zr and 68Ga in high radiochemical yield and purity. In vitro experiments showed favorable cell uptake and receptor affinity for [Lys40-(AHX-DFO-68Ga)NH2]exendin-4, and [Lys40-(AHX-DFO-89Zr)NH2]exendin-4 and [Lys40-(AHX-DTPA-111In)NH2]exendin-4 performed similarly well. In biodistribution experiments, [Lys40-(AHX-DFO-68Ga)NH2]exendin-4 exhibited a significantly enhanced tumor uptake 1 h after injection in comparison to the other 2 radiotracers. Tumor uptake of [Lys40-(AHX-DFO-89Zr)NH2]exendin-4 was comparable to that of [Lys40-(AHX-DTPA-111In)NH2]exendin-4 at 1-48 h after injection. All compounds showed a fast blood clearance and low accumulation in receptor-negative organs and tissue with the exception of the kidneys, a known characteristic for exendin-4-based radiotracers. CONCLUSION: 68Ga- and 89Zr-radiolabeled [Lys40-(AHX-DFO)NH2]exendin-4 exhibit characteristics comparable or superior to the clinically tested reference compound [Lys40-(AHX-DTPA-111In)NH2]exendin-4 and, thus, represent potential new tracers for the imaging of insulinomas by PET.
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http://dx.doi.org/10.2967/jnumed.115.159186

Succinate Dehydrogenase (SDH)-Deficient Pancreatic Neuroendocrine Tumor Expands the SDH-Related Tumor Spectrum.
J Clin Endocrinol Metab, 100(10):E1386-93.
N. D. Niemeijer, T. G. Papathomas, E. Korpershoek, R. R. de Krijger, L. Oudijk, H. Morreau, J. P. Bayley, F. J. Hes, J. C. Jansen, W. N. Dinjens and E. P. Corssmit. 2015.

CONTEXT: Mutations in genes encoding the subunits of succinate dehydrogenase (SDH) can lead to pheochromocytoma/paraganglioma formation. However, SDH mutations have also been linked to nonparaganglionic tumors. OBJECTIVE: The objective was to investigate which nonparaganglionic tumors belong to the SDH-associated tumor spectrum. DESIGN: This was a retrospective cohort study. SETTING: The setting was a tertiary referral center. PATIENTS: Patients included all consecutive SDHA/SDHB/SDHC and SDHD mutation carriers followed at the Department of Endocrinology of the Leiden University Medical Center who were affected by non-pheochromocytoma/paraganglioma solid tumors. MAIN OUTCOME MEASURES: Main outcome measures were SDHA/SDHB immunohistochemistry, mutation analysis, and loss of heterozygosity analysis of the involved SDH-encoding genes. RESULTS: Twenty-five of 35 tumors (from 26 patients) showed positive staining on SDHB and SDHA immunohistochemistry. Eight tumors showed negative staining for SDHB and positive staining for SDHA: a pancreatic neuroendocrine tumor, a macroprolactinoma, two gastric gastrointestinal stromal tumors, an abdominal ganglioneuroma, and three renal cell carcinomas. With the exception of the abdominal ganglioneuroma, loss of heterozygosity was detected in all tumors. A prolactinoma in a patient with a germline SDHA mutation was the only tumor immunonegative for both SDHA and SDHB. Sanger sequencing of this tumor revealed a somatic mutation (p.D38V) as a likely second hit leading to biallelic inactivation of SDHA. One tumor (breast cancer) showed heterogeneous SDHB staining, positive SDHA staining, and retention of heterozygosity. CONCLUSIONS: This study strengthens the etiological association of SDH genes with pituitary neoplasia, renal tumorigenesis, and gastric gastrointestinal stromal tumors. Furthermore, our results indicate that pancreatic neuroendocrine tumor also falls within the SDH-related tumor spectrum.
PubMed-ID: 26259135
http://dx.doi.org/10.1210/jc.2015-2689

Developing treatment for adrenocortical carcinoma.
Endocr Relat Cancer, 22(6):R325-38.
T. M. Kerkhofs, M. H. Ettaieb, I. G. Hermsen and H. R. Haak. 2015.
Cancer of the adrenal cortex (ACC) is a rare endocrine malignancy with limited treatment options. Patients typically present with autonomous hormonal overproduction and/or a large abdominal mass. Hormonal assays and medical imaging can be diagnostic, but urinary steroid profiling might be a more sensitive technique to assess malignancy in adrenal tumours. The stage of the disease at diagnosis is the most important prognostic factor. The current staging system needs refinement, especially to separate aggressive from indolent disease in stage IV patients and to select patients who need adjuvant treatment after complete surgical resection. Regarding the latter, assessing the proliferation index Ki-67 seems the best tool currently available. Genomic profiling is expected to become of clinical relevance in the future. Medical therapy is centred on the adrenolytic drug mitotane, which carries considerable toxicity and is not easy to manage. Its tolerability and long plasma level build-up phase may be improved by therapeutic drug monitoring based on pharmacokinetic modelling and intensive counselling of patients. Current chemotherapy regimens can offer disease stabilization in about 50% of patients, but an objective response should be expected in <25%. Research on targeted therapy and immunotherapy is difficult in this rare disease with often heavily pre-treated patients and has not yet been successful. Quality of care should be ensured by treating patients in centres with established experience in multidisciplinary oncologic care, who adhere to prevailing guidelines and state-of-the-art in diagnostic and treatment concepts. International collaboration in fundamental research and clinical trials is the key to further elucidate the pathogenesis and to improve patient care.
PubMed-ID: 26259571
http://dx.doi.org/10.1530/ERC-15-0318

Efficacy of Endoscopic Mucosal Resection for Management of Small Duodenal Neuroendocrine Tumors.
Surg Laparosc Endosc Percutan Tech, 25(5):e134-9.
S. R. Shroff, V. M. Kushnir, S. B. Wani, N. Gupta, S. S. Jonnalagadda, F. Murad, D. S. Early, D. K. Mullady, S. A. Edmundowicz and R. R. Azar. 2015.
BACKGROUND: Endoscopic mucosal resection (EMR) for small (<20 mm) duodenal neuroendocrine tumors (NETs) remains controversial because of their rarity. MATERIALS AND METHODS: This is a retrospective cohort study of patients with surgically or endoscopically resected duodenal NETs from 2001 to 2011. The primary outcome is the rate of disease-free status following resection. A secondary outcome is the sensitivity of endoscopic ultrasound (EUS) in determining NET appropriateness for EMR. RESULTS: Thirty patients underwent resection of duodenal NETs (EMR 20, surgery 10). Tumor was present at the margins in 40% of EMR-resected NETs and 10% of surgically resected NETs. Five patients who underwent EMR had residual disease treated with repeat EMR (3) and surgery (2). EUS demonstrated 96% sensitivity in determining lesions limited to the submucosa. CONCLUSIONS: EMR for small duodenal NETs can be a safe and effective

alternative to surgery in carefully selected patients. EUS is a useful adjunct in determining depth of invasion for duodenal NETs.
PubMed-ID: 26271024
http://dx.doi.org/10.1097/SLE.0000000000000192

Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate.
J Nucl Med, 56(11):1647-53.
E. I. van Vliet, C. H. van Eijck, R. R. de Krijger, E. J. Nieveen van Dijkum, J. J. Teunissen, B. L. Kam, W. W. de Herder, R. A. Feelders, B. A. Bonsing, T. Brabander, E. P. Krenning and D. J. Kwekkeboom. 2015.
Pancreatic neuroendocrine tumors (NETs) are rare neoplasms for which surgery has almost the only potential for cure. When surgery is not possible because of tumor size and vascular involvement, neoadjuvant treatment with [(177)Lu-DOTA(0),Tyr(3)]octreotate ((177)Lu-octreotate) may be an option. METHODS: We studied 29 Dutch patients with a pathology-proven nonfunctioning pancreatic NET treated with (177)Lu-octreotate. All patients had a borderline or unresectable pancreatic tumor (group 1) or oligometastatic disease (defined as </=3 liver metastases) (group 2). Progression-free survival (PFS) was analyzed using the Kaplan-Meier method and Cox proportional hazards modeling. RESULTS: After the treatment with (177)Lu-octreotate, successful surgery was performed in 9 of 29 patients (31%). Six patients had a Whipple procedure, 2 patients had a pylorus-preserving pancreaticoduodenectomy, and 1 patient had a distal pancreatectomy and splenectomy. The median PFS was 69 mo for patients with successful surgery and 49 mo for the other patients. For comparison, the median PFS in 90 other patients with a nonfunctioning pancreatic NET with more than 3 liver metastases or other metastases was 25 mo. CONCLUSION: Neoadjuvant treatment with (177)Lu-octreotate is a valuable option for patients with initially unresectable pancreatic NETs.
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http://dx.doi.org/10.2967/jnumed.115.158899

Primary RET-mutated lung neuroendocrine carcinoma in MEN2B: response to RET-targeted therapy.
Endocr Relat Cancer, 22(5):L19-22.
J. L. Geiger, S. I. Chiosea, S. M. Challinor, M. N. Nikiforova and J. E. Bauman. 2015.
PubMed-ID: 26285607
http://dx.doi.org/10.1530/ERC-15-0307

Novel somatic mutations and distinct molecular signature in aldosterone-producing adenomas.
Endocr Relat Cancer, 22(5):735-44.
T. Akerstrom, H. S. Willenberg, K. Cupisti, J. Ip, S. Backman, A. Moser, R. Maharjan, B. Robinson, K. A. Iwen, H. Dralle, D. V. C, M. Backdahl, J. Botling, P. Stalberg, G. Westin, M. K. Walz, H. Lehnert, S. Sidhu, J. Zedenius, P. Bjorklund and P. Hellman. 2015.
Aldosterone-producing adenomas (APAs) are found in 1.5-3.0% of hypertensive patients in primary care and can be cured by surgery. Elucidation of genetic events may improve our understanding of these tumors and ultimately improve patient care. Approximately 40% of APAs harbor a missense mutation in the KCNJ5 gene. More recently, somatic mutations in CACNA1D, ATP1A1 and ATP2B3, also important for membrane potential/intracellular Ca(2) (+) regulation, were observed in APAs. In this study, we analyzed 165 APAs for mutations in selected regions of these genes. We then correlated mutational findings with clinical and molecular phenotype using transcriptome analysis, immunohistochemistry and semiquantitative PCR. Somatic mutations in CACNA1D in 3.0% (one novel mutation), ATP1A1 in 6.1% (six novel mutations) and ATP2B3 in 3.0% (two novel mutations) were detected. All observed mutations were located in previously described hotspot regions. Patients with tumors harboring mutations in CACNA1D, ATP1A1 and ATP2B3 were operated at an older age, were more often male and had tumors that were smaller than those in patients with KCNJ5 mutated tumors. Microarray transcriptome analysis segregated KCNJ5 mutated tumors from ATP1A1/ATP2B3 mutated tumors and those without mutation. We observed significant transcription upregulation of CYP11B2, as well as the previously described glomerulosa-specific gene NPNT, in ATP1A1/ATP2B3 mutated tumors compared to KCNJ5 mutated tumors. In summary, we describe novel somatic mutations in proteins regulating the membrane potential/intracellular Ca(2) (+) levels, and also a distinct mRNA and clinical signature, dependent on genetic alteration.
PubMed-ID: 26285814
http://dx.doi.org/10.1530/ERC-15-0321

Adrenal gland: Aldosterone-producing mutations in normal adrenal glands.
Nat Rev Endocrinol, 11(10):567.
T. Geach. 2015.
PubMed-ID: 26303598
http://dx.doi.org/10.1038/nrendo.2015.145

Time Evolution of DOTATOC Uptake in Neuroendocrine Tumors in View of a Possible Application of Radioguided Surgery with beta- Decay.
J Nucl Med, 56(10):1501-6.
F. Collamati, F. Bellini, V. Bocci, E. De Lucia, V. Ferri, F. Fioroni, E. Grassi, M. Iori, M. Marafini, S. Morganti, R. Paramatti, V. Patera, L. Recchia, A. Russomando, A. Sarti, A. Sciubba, M. Senzacqua, E. Solfaroli Camillocci, A. Versari, C. Voena and R. Faccini. 2015.
A novel radioguided surgery (RGS) technique exploiting beta- radiation has been proposed. To develop such a technique, a suitable radiotracer able to deliver a beta- emitter to the tumor has to be identified. A first candidate is represented by 90Y-labeled DOTATOC, a compound commonly used today for peptide radioreceptor therapy. The application of this beta- RGS to neuroendocrine tumors (NET) requires study of the uptake of DOTATOC and its time evolution both in tumors and in healthy organs and evaluation of the corresponding performance of the technique. METHODS: Uptake by lesions and healthy organs (kidneys, spleen, liver and healthy muscle) was estimated on 177Lu-DOTATOC SPECT/CT scans of 15 patients affected by NET with different localizations, treated at IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy. For each patient, SPECT/CT images, acquired at 0.5, 4, 20, 40, and 70 h after injection, were studied. For each lesion, the tumor-to-nontumor ratio (TNR) with respect to all healthy organs and its time evolution were studied. A subset of patients showing hepatic lesions was selected, and the TNR with respect to the nearby healthy tissue was calculated. By means of a Monte Carlo simulation of the probe for beta- RGS, the activity that is to be administered for a successful detection was estimated lesion-by-lesion. RESULTS: Uptake of DOTATOC on NETs maximized at about 24 h after injection. The cases of hepatic lesions showed a TNR with respect to the tumor margins compatible with the application of beta- RGS. In particular, 0.1-mL residuals are expected to be detectable within 1 s with 5% false-negative and 1% false-positive by administering the patient as little as 1 MBq/kg. CONCLUSION: The balance between tumor uptake and metabolic washout in healthy tissue causes the TNR to increase with time, reaching its maximum after 24 h, and this characteristic can be exploited when a radiotracer with a long half-life, such as 90Y, is used. In particular, if 90Y-DOTATOC is used with liver NET metastases, the proposed RGS technique is believed to be feasible by injecting an activity that is one third of that commonly used for PET imaging.
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http://dx.doi.org/10.2967/jnumed.115.160481

18F-FLT PET/CT in the Evaluation of Pheochromocytomas and Paragangliomas: A Pilot Study.
J Nucl Med, 56(12):1849-54.
E. M. Blanchet, D. Taieb, C. Millo, V. Martucci, C. C. Chen, M. Merino, P. Herscovitch and K. Pacak. 2015.
(18)F-FDG PET/CT has been proven to be a highly sensitive method for pheochromocytomas/paragangliomas (PHEOs/PGLs) associated with succinate dehydrogenase (SDH) mutations. This finding has been attributed to altered tumor cell metabolism resulting from these mutations and does not provide additional prognostic information to genotype. Therefore, identification of new biomarkers for aggressiveness is needed. A high Ki-67 index was proposed to be an additional prognostic factor. This pilot study aimed to evaluate 3'-deoxy-3'-(18)F-fluorothymidine ((18)F-FLT) PET/CT, a PET proliferation tracer, as a potential imaging agent in a series of 12 PHEO/PGL patients with different genetic backgrounds, to compare (18)F-FLT uptake with (18)F-FDG PET/CT, and to evaluate classic factors of aggressiveness. METHODS: Twelve patients (7 metastatic and 5 nonmetastatic) were prospectively evaluated with (18)F-FDG and (18)F-FLT and followed for at least 2 y after the initial imaging work-up. Uptake was assessed at a lesion level, visually and quantitatively by maximum standardized uptake values (SUVmax) for both tracers. (18)F-FLT uptake was compared with risk factors known to be linked with a poor prognosis in PGLs (SDHB-mutated status, lesion size, dopaminergic phenotype) and with (18)F-FDG uptake. RESULTS: In 12 patients, 77 lesions were assessed. All lesions had low (18)F-FLT uptake (median SUVmax, 2.25; range, 0.7-4.5). There was no apparent superiority of (18)F-FLT uptake in progressive lesions, and most of the lesions showed a mismatch, with high (18)F-FDG uptake (median SUVmax, 10.8; range, 1.1-79.0) contrasting with low (18)F-FLT uptake. CONCLUSION: This study suggests that PHEOs/PGLs-even those that progress-do not exhibit intense (18)F-FLT uptake. It provides the first in vivo demonstration that proliferation may not be a major determinant of (18)F-FDG uptake in these tumors. These findings provide new insight into the biologic behavior of PGL and suggest that antiproliferative agents may be suboptimal for treatment of these tumors.

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http://dx.doi.org/10.2967/jnumed.115.159061

Adrenal gland: Cancer target of mitotane identified.
Nat Rev Endocrinol, 11(11):631.
D. Holmes. 2015.
PubMed-ID: 26370730
http://dx.doi.org/10.1038/nrendo.2015.156

Unraveling the intrafamilial correlations and heritability of tumor types in MEN1: a Groupe d'etude des Tumeurs Endocrines study.
Eur J Endocrinol, 173(6):819-26.
J. Thevenon, A. Bourredjem, L. Faivre, C. Cardot-Bauters, A. Calender, M. Le Bras, S. Giraud, P. Niccoli, M. F. Odou, F. Borson-Chazot, A. Barlier, C. Lombard-Bohas, E. Clauser, A. Tabarin, E. Pasmant, O. Chabre, E. Castermans, P. Ruszniewski, J. Bertherat, B. Delemer, S. Christin-Maitre, A. Beckers, I. Guilhem, V. Rohmer, B. Goichot, P. Caron, E. Baudin, P. Chanson, L. Groussin, H. Du Boullay, G. Weryha, P. Lecomte, F. Schillo, H. Bihan, F. Archambeaud, V. Kerlan, N. Bourcigaux, J. M. Kuhn, B. Verges, M. Rodier, M. Renard, J. L. Sadoul, C. Binquet and P. Goudet. 2015.
BACKGROUND: MEN1, which is secondary to the mutation of the MEN1 gene, is a rare autosomal-dominant disease that predisposes mutation carriers to endocrine tumors. Most studies demonstrated the absence of direct genotype-phenotype correlations. The existence of a higher risk of death in the Groupe d'etude des Tumeurs Endocrines-cohort associated with a mutation in the JunD interacting domain suggests heterogeneity across families in disease expressivity. This study aims to assess the existence of modifying genetic factors by estimating the intrafamilial correlations and heritability of the six main tumor types in MEN1. METHODS: The study included 797 patients from 265 kindred and studied seven phenotypic criteria: parathyroid and pancreatic neuroendocrine tumors (NETs) and pituitary, adrenal, bronchial, and thymic (thNET) tumors and the presence of metastasis. Intrafamilial correlations and heritability estimates were calculated from family tree data using specific validated statistical analysis software. RESULTS: Intrafamilial correlations were significant and decreased along parental degrees distance for pituitary, adrenal and thNETs. The heritability of these three tumor types was consistently strong and significant with 64% (s.e.m.=0.13; P<0.001) for pituitary tumor, 65% (s.e.m.=0.21; P<0.001) for adrenal tumors, and 97% (s.e.m.=0.41; P=0.006) for thNETs. CONCLUSION: The present study shows the existence of modifying genetic factors for thymus, adrenal, and pituitary MEN1 tumor types. The identification of at-risk subgroups of individuals within cohorts is the first step toward personalization of care. Next generation sequencing on this subset of tumors will help identify the molecular basis of MEN1 variable genetic expressivity.
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Copy number variations alter methylation and parallel IGF2 overexpression in adrenal tumors.
Endocr Relat Cancer, 22(6):953-67.
H. M. Nielsen, A. How-Kit, C. Guerin, F. Castinetti, H. K. Vollan, C. De Micco, A. Daunay, D. Taieb, P. Van Loo, C. Besse, V. N. Kristensen, L. L. Hansen, A. Barlier, F. Sebag and J. Tost. 2015.
Overexpression of insulin growth factor 2 (IGF2) is a hallmark of adrenocortical carcinomas and pheochromocytomas. Previous studies investigating the IGF2/H19 locus have mainly focused on a single molecular level such as genomic alterations or altered DNA methylation levels and the causal changes underlying IGF2 overexpression are still not fully established. In the current study, we analyzed 62 tumors of the adrenal gland from patients with Conn's adenoma (CA, n=12), pheochromocytomas (PCC, n=10), adrenocortical benign tumors (ACBT, n=20), and adrenocortical carcinomas (ACC, n=20). Gene expression, somatic copy number variation of chr11p15.5, and DNA methylation status of three differential methylated regions of the IGF2/H19 locus including the H19 imprinting control region were integratively analyzed. IGF2 overexpression was found in 85% of the ACCs and 100% of the PCCs compared to 23% observed in CAs and ACBTs. Copy number aberrations of chr11p15.5 were abundant in both PCCs and ACCs but while PCCs retained a diploid state, ACCs were frequently tetraploid (7/19). Loss of either a single allele or loss of two alleles of the same parental origin in tetraploid samples resulted in a uniparental disomy-like genotype. These copy number changes correlated with hypermethylation of the H19 ICR suggesting that the lost alleles were the unmethylated maternal alleles. Our data provide conclusive evidence that loss of the maternal allele correlates with IGF2 overexpression in adrenal tumors and that hypermethylation of the H19 ICR is a consequence thereof.
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http://dx.doi.org/10.1530/ERC-15-0086

Prognostic Value of 68Ga-DOTANOC PET/CT SUVmax in Patients with Neuroendocrine Tumors of the Pancreas.
J Nucl Med, 56(12):1843-8.
V. Ambrosini, D. Campana, G. Polverari, C. Peterle, S. Diodato, C. Ricci, V. Allegri, R. Casadei, P. Tomassetti and S. Fanti. 2015.
This study was performed to investigate the role of (68)Ga-DOTANOC SUVmax as a potential prognostic factor in patients with pancreatic neuroendocrine tumor (pNET). METHODS: Among the patients who underwent (68)Ga-DOTANOC PET/CT, we retrospectively collected the data of those who had G1 or G2 pNET (2010 World Health Organization classification), presented with disease on PET/CT and CT, and had at least 6 mo of follow-up. Patients with multiple endocrine neoplasia were excluded. RESULTS: Overall, 43 patients were included. No significant differences in SUVmax were observed with respect to sex, tumor syndrome, stage, World Health Organization classification, or Ki-67. During follow-up (median, 20 mo), 11 patients (35.6%; median, 33 mo; interquartile range, 20-48 mo) had stable disease and 32 (74.4%; median, 19 mo; interquartile range, 14-26 mo) had progressive disease. SUVmax at 24 mo of follow-up was significantly higher (P = 0.022) in patients with stable disease than in patients with progressive disease. The best SUVmax cutoff ranged from 37.8 to 38.0. The major risk factors for progression included an SUVmax of no more than 37.8 (hazard ratio, 3.09; P = 0.003), a Ki-67 of more than 5% (hazard ratio, 2.89; P = 0.009), and medical therapy alone (hazard ratio, 2.36; P = 0.018). Advanced stage (IV) (P = 0.026), an SUVmax of less than 37.8 (P = 0.043), and medical therapy alone (P = 0.015) were also confirmed at multivariate analysis. Median progression-free survival was 23 mo. Significant differences in progression-free survival were observed in relationship to Ki-67 (median, 45 mo for Ki-67 </= 5% and 20 mo for Ki-67 > 5%; P = 0.005), SUVmax (<37.8 vs. >38.0: 16.0 vs. 27.0 mo; P = 0.002), and type of therapy (medical vs. peptide receptor radionuclide therapy: 16.0 vs. 26.0 mo; P = 0.014). CONCLUSION: (68)Ga-DOTANOC SUVmax is a relevant prognostic factor in patients with G1 and G2 pNET, and its routine use will improve disease characterization and management in these patients, who may present with atypical cases showing heterogeneous clinical behavior.
PubMed-ID: 26405169
http://dx.doi.org/10.2967/jnumed.115.162719

Prospective evaluation and treatment of familial carcinoid small intestine neuroendocrine tumors (SI-NETs).
Surgery, 159(1):350-6.
M. S. Hughes, S. C. Azoury, Y. Assadipour, D. M. Straughan, A. N. Trivedi, R. M. Lim, G. Joy, M. T. Voellinger, D. M. Tang, A. M. Venkatesan, C. C. Chen, A. Louie, M. M. Quezado, J. Forbes and S. A. Wank. 2015.
BACKGROUND: The aim of this study was to prospectively screen patients with a positive family history of carcinoid small intestine neuroendocrine tumors (SI-NETs) to elucidate the benefits of early detection and operative intervention. METHODS: A single-center, prospective trial was conducted from 2008 to 2014 that evaluated patients with 2 or more blood relatives with carcinoid SI-NETs. All eligible patients were screened with urine/serum biochemistries and various imaging modalities. Operative intervention was elected in patients found to have at least 1 positive diagnostic study. RESULTS: Twenty-nine patients from 13 families had occult carcinoid SI-NETs (15 female, 14 male). Twenty-four of the 29 patients (83%) had multifocal disease found in either the distal jejunum or ileum. On average, 75.9 cm (range, 13-195) of bowel was resected in 1 segment. Three patients were found to have stage IV disease at operation. All stage I-IIIB patients who had R0 resections have remained disease-free, with a median follow-up of 35 months. CONCLUSION: Familial carcinoid SI-NETs often are asymptomatic and can be diagnosed with aggressive screening. With early detection, there may be a window of opportunity for operative resection to change the natural history of this disease and even prove to be curative.
PubMed-ID: 26454678
http://dx.doi.org/10.1016/j.surg.2015.05.041

Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy?
Surgery, 159(1):320-33.
J. E. Maxwell, S. K. Sherman, T. M. O'Dorisio, A. M. Bellizzi and J. R. Howe. 2015.
INTRODUCTION: Neuroendocrine tumors (NETs) frequently metastasize to the liver. Operative debulking offers symptomatic relief and improved survival; however, the frequent presence of multifocal, bilobar disease and high recurrence rates introduces doubt regarding their optimal management. Parenchyma-sparing debulking (PSD) procedures (ablation, enucleation, wedge resections) may offer similar survival improvements as resection while minimizing morbidity and preserving functional liver tissue. METHODS: Clinicopathologic variables from 228 patients with small bowel or pancreatic NETs managed operatively at one institution were collected. Liver-

directed surgery was carried out when substantial debulking was deemed feasible. Survival was assessed by use of the Kaplan-Meier method. RESULTS: A total of 108 patients with pancreatic NET or small bowel NET underwent liver-directed surgery with primarily PSD procedures. Nearly two-thirds of patients achieved 70% cytoreduction and 84% had concurrent resection of their primary. The median number of lesions treated was 6 (range, 1-36). There were no 30-day operative mortalities. The 30-day major complication rate was 13.0%. Patients who achieved 70% cytoreduction enjoyed improved progression free (median 3.2 years) and overall survival (median not reached). CONCLUSION: PSD procedures are safe and can achieve significant cytoreduction, which is associated with improved survival. Lowering the debulking target threshold to 70% may benefit NET patients by increasing eligibility for cytoreduction.
PubMed-ID: 26454679
http://dx.doi.org/10.1016/j.surg.2015.05.040

Resection versus expectant management of small incidentally discovered nonfunctional pancreatic neuroendocrine tumors.
Surgery, 159(1):302-9.
A. M. Rosenberg, P. Friedmann, J. Del Rivero, S. K. Libutti and A. M. Laird. 2015.
BACKGROUND: Sporadic, nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) are diagnosed with increasing frequency. We compared the risk of tumor growth, metastasis, and mortality between patients treated versus those treated expectantly. METHOD: A retrospective study of patients seen at our institution with sporadic NF-PNETs, with >/= 12 months of follow-up. Kaplan-Meier analysis was performed. RESULTS: Between 1999 and 2014, 35 patients with an incidentally discovered nonfunctional PNET were identified. Twenty underwent resection and 15 were followed with imaging. In the operative group, 8 had NF-PNETs < 2 cm, while 12 had NF-PNETs >/= 2 cm. In the nonoperative expectant management by serial imaging group, 10 had NF-PNETs < 2 cm while 5 had NF-PNETs >/= 2 cm. Small NF-PNETs (<2 cm) in either the operative or nonoperative groups demonstrated no evidence of progression or metastasis (median follow-up of 27.8 months). Morbidity in the operative group was 35% with pancreatic pseudocyst the most common. CONCLUSION: Incidentally discovered NF-PNETs < 2 cm in size can be observed safely with serial imaging.
PubMed-ID: 26547726
http://dx.doi.org/10.1016/j.surg.2015.10.013

Laparoscopic Versus Open Surgery for Gastric Gastrointestinal Stromal Tumors: What Is the Impact on Postoperative Outcome and Oncologic Results?
Ann Surg, 262(5):831-9; discussion 29-40.
G. Piessen, J. H. Lefevre, M. Cabau, A. Duhamel, H. Behal, T. Perniceni, J. Y. Mabrut, J. M. Regimbeau, S. Bonvalot, G. A. Tiberio, M. Mathonnet, N. Regenet, A. Guillaud, O. Glehen, P. Mariani, Q. Denost, L. Maggiori, L. Benhaim, G. Manceau, D. Mutter, J. P. Bail, B. Meunier, J. Porcheron, C. Mariette and C. Brigand. 2015.
OBJECTIVES: The aim of the study was to compare the postoperative and oncologic outcomes of laparoscopic versus open surgery for gastric gastrointestinal stromal tumors (gGISTs). BACKGROUND: The feasibility of the laparoscopic approach for gGIST resection has been demonstrated; however, its impact on outcomes, particularly its oncologic safety for tumors greater than 5 cm, remains unknown. METHODS: Among 1413 patients treated for a GIST in 61 European centers between 2001 and 2013, patients who underwent primary resection for a gGIST smaller than 20 cm (N = 666), by either laparoscopy (group L, n = 282) or open surgery (group O, n = 384), were compared. Multivariable analyses and propensity score matching were used to compensate for differences in baseline characteristics. RESULTS: In-hospital mortality and morbidity rates in groups L and O were 0.4% versus 2.1% (P = 0.086) and 11.3% vs 19.5% (P = 0.004), respectively. Laparoscopic resection was independently protective against in-hospital morbidity (odds ratio 0.54, P = 0.014). The rate of R0 resection was 95.7% in group L and 92.7% in group O (P = 0.103). After 1:1 propensity score matching (n = 224), the groups were comparable according to age, sex, tumor location and size, mitotic index, American Society of Anesthesiology score, and the extent of surgical resection. After adjustment for BMI, overall morbidity (10.3% vs 19.6%; P = 0.005), surgical morbidity (4.9% vs 9.8%; P = 0.048), and medical morbidity (6.2% vs 13.4%; P = 0.01) were significantly lower in group L. Five-year recurrence-free survival was significantly better in group L (91.7% vs 85.2%; P = 0.011). In tumors greater than 5 cm, in-hospital morbidity and 5-year recurrence-free survival were similar between the groups (P = 0.255 and P = 0.423, respectively). CONCLUSIONS: Laparoscopic resection for gGISTs is associated with favorable short-term outcomes without compromising oncologic results.
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Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study.
Ann Surg Oncol, 23(4):1361-70.
E. Sadot, D. L. Reidy-Lagunes, L. H. Tang, R. K. Do, M. Gonen, M. I. D'Angelica, R. P. DeMatteo, T. P. Kingham, B. Groot Koerkamp, B. R. Untch, M. F. Brennan, W. R. Jarnagin and P. J. Allen. 2015.
OBJECTIVE: To analyze the natural history of small asymptomatic pancreatic neuroendocrine tumors (PanNET) and to present a matched comparison between groups who underwent either initial observation or resection. Management approach for small PanNET is uncertain. METHODS: Incidentally discovered, sporadic, small (<3 cm), stage I-II PanNET were analyzed retrospectively between 1993 and 2013. Diagnosis was determined either by pathology or imaging characteristics. Intention-to-treat analysis was applied. RESULTS: A total of 464 patients were reviewed. Observation was recommended for 104 patients (observation group), and these patients were matched to 77 patients in the resection group based on tumor size at initial imaging. The observation group was significantly older (median 63 vs. 59 years, p = 0.04) and tended towards shorter follow-up (44 vs. 57 months, p = 0.06). Within the observation group, 26 of the 104 patients (25 %) underwent subsequent tumor resection after a median observation interval of 30 months (range 7-135). At the time of last follow-up of the observation group, the median tumor size had not changed (1.2 cm, p = 0.7), and no patient had developed evidence of metastases. Within the resection group, low-grade (G1) pathology was recorded in 72 (95 %) tumors and 5 (6 %) developed a recurrence, which occurred after a median of 5.1 (range 2.9-8.1) years. No patient in either group died from disease. Death from other causes occurred in 11 of 181 (6 %) patients. CONCLUSIONS: In this study, no patient who was initially observed developed metastases or died from disease after a median follow-up of 44 months. Observation for stable, small, incidentally discovered PanNET is reasonable in selected patients.
PubMed-ID: 26597365
http://dx.doi.org/10.1245/s10434-015-4986-1

Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: Morphology matters.
Surgery, 159(3):862-71.
S. Crippa, S. Partelli, C. Bassi, R. Berardi, P. Capelli, A. Scarpa, G. Zamboni and M. Falconi. 2015.
BACKGROUND: Limited data are available for pancreatic neuroendocrine carcinomas (NEC) defined by 2010 World Health Organization (WHO) criteria (mitotic count >20 mitoses/10 high-power fields and/or a Ki67 index of >20%), because most studies encompass heterogeneous cohorts of extrapulmonary/gastrointestinal NEC. Our aim was to evaluate the clinicopathologic characteristics, treatment, and prognosis of patients with pancreatic NEC defined by the 2010 WHO criteria. METHODS: We conducted a retrospective analysis of 59 patients with a histologic diagnosis of NEC between 1990 and 2012. All cases were re-reviewed and classified according to the WHO 2010 classification and the WHO 2000 criteria. RESULTS: All patients had stage III pancreatic NEC (n = 34; 58%) or IV pancreatic NEC (n = 25; 43%). Overall, 49 (83%) had poorly differentiated (PD) and 10 (17%) had a well-differentiated (WD) morphology. Fifteen patients (26%) were operated with curative intent (R0/R1), and 8 (14%) were R2 resections. Median disease-specific survival (DSS) for the entire cohort was 14 months. Median DSS did not differ between patient not undergoing resection and those undergoing R2 resection (10 vs 12 months; P > .46), but DSS was greater for patients who underwent R0/R1 resection compared with those with no resection/R2 resection (35 vs 11 months; P < .005). WD morphologic NEC had a greater survival than PD ones (43 vs 12 months; P = .004). Performance status, R2 resection/no resection, PD morphologic NEC, and no medical treatment were independent predictors of poor survival. CONCLUSION: Pancreatic NEC constitute a heterogeneous group of tumors. Although NEC is an aggressive disease, curative resection in localized disease is associated with improved survival. Morphologic WD pancreatic NEC represents a subgroup with what seems to be a markedly improved survival. Within the NEC category, tumor treatment should be individualized considering tumor morphology as well as the other 2010 WHO criteria.
PubMed-ID: 26602841
http://dx.doi.org/10.1016/j.surg.2015.09.012

Clinical presentation and outcome of nonfunctional pancreatic neuroendocrine tumors in a modern cohort.
Am J Surg, 210(6):1192-5; discussion 5-6.
D. C. Watley, Q. P. Ly, G. Talmon, C. Are and A. R. Sasson. 2015.
BACKGROUND: The natural history of nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) is largely unstudied due to its rarity. The primary goal of this study was to characterize clinical features and outcomes of incidental NF-PNETs. METHODS: An institutional review board-approved retrospective study of patients with NF-PNET evaluated by the Surgical Oncology of University of Nebraska Medical Center was performed. Patients

were evaluated with dedicated pancreatic and liver imaging using multiphasic computed tomographic scan and dedicated magnetic resonance imaging protocols. RESULTS: Forty-six patients (male, 47.8%) were evaluated, and 35 ultimately resected. Of these, 16 tumors were discovered incidentally. The median age was 62 and 59 years in incidental and symptomatically discovered, respectively. Incidental median size was 2.4 cm vs 6 cm in the symptomatic group, with a P value of .037. The presence of lymphatic and liver metastases was 10% and 25% incidental and 45% and 67% for those with symptoms (lymphatic involvement, P = .05; liver metastases P = .07). Median overall survival was 45 and 76 months (P = .03). CONCLUSIONS: Incidentally discovered NF-PNETs represent a malignancy with more questions than answers. Our series indicates that these cancers are more indolent than previously believed.
PubMed-ID: 26674063
http://dx.doi.org/10.1016/j.amjsurg.2015.08.012

C-Reactive Protein as a New Prognostic Factor for Survival in Patients With Pancreatic Neuroendocrine Neoplasia.
J Clin Endocrinol Metab, 101(3):937-44.
D. Wiese, K. Kampe, J. Waldmann, A. E. Heverhagen, D. K. Bartsch and V. Fendrich. 2015.
CONTEXT: Patients with pancreatic neuroendocrine neoplasia (pNEN) show great variability in prognosis and treatment response. Additional prognostic markers might help in individual therapeutic decision making. OBJECTIVE: The objective of the study was to investigate the association between preoperative plasma levels of C-reactive protein (CRP) and overall survival (OS) in pNEN. DESIGN: This was a single-center, retrospective analysis of long-term prospective patient-database. SETTING: The study was conducted at a tertiary referral center. PATIENTS: All 149 patients with sporadic pNENs were eligible for retrospective analysis. MAIN OUTCOME MEASURE: Cumulative overall survival, compared between patients with elevated and normal CRP levels, was measured. RESULTS: Median OS for patients with elevated CRP levels was 1093 days (SE 1261, 95% confidence interval [CI] 0-3565), compared with 6859 days (SE 1252, 95% CI 4405-9313) for patients with normal CRP levels. Log rank test showed a significant correlation between CRP and OS (P < .001). In univariate Cox regression, patients with elevated CRP levels had a significantly higher hazard ratio for death (3.27; 95%-CI 1.74-6.16; P < .001). This finding persisted after multivariable adjustment. Furthermore, OS was associated with the presence of liver metastases (hazard ratio 3.17; 95% CI 1.88-5.35; P < .001), incomplete resection (R1/R2 status; hazard ratio 3.99; 95% CI 2.16-7.35; P < .001) and Ki-67 percentage (hazard ratio 5.05; 95% CI 2.17-11.76; P < .001). CONCLUSION: CRP is an independent prognostic marker in patients with pNEN. Pretreatment CRP measurements should be considered for incorporation into prospective studies of outcome in patients with pNENs and clinical trials of systemic therapies for these tumors.
PubMed-ID: 26678655
http://dx.doi.org/10.1210/jc.2015-3114

General

Meta-Analyses

Perforation in appendiceal well-differentiated carcinoid and goblet cell tumors: impact on prognosis? A systematic review.
Ann Surg Oncol, 22(3):959-65.
A. Madani, J. D. van der Bilt, E. C. Consten, M. R. Vriens and I. H. Borel Rinkes. 2015.
BACKGROUND: Carcinoid tumors are the most common malignant lesions arising from Appendix and are mostly found incidentally during surgery for appendicitis. Perforation of Appendix occurs in 10-20% of cases with appendicitis. Currently, no guidelines exist for the treatment of perforated carcinoids of Appendix. METHODS: A systematic literature search was performed to identify relevant articles on classical carcinoid or goblet cell carcinoid of Appendix in an attempt to evaluate the impact of perforation on management and prognosis. All articles on carcinoids reporting perforation of Appendix were included. RESULTS: In total, 23 articles on carcinoid of Appendix with an associated perforation were found. Perforation was never investigated or mentioned as a possible negative factor on recurrence or prognosis. Among a total of 103 patients with classical carcinoids and associated perforation, no peritoneal recurrence or death was described, although follow-up data were often unspecified or scarce. Among a total of 18 goblet cell carcinoids with perforation, metastatic spread to the peritoneum was described in one case and two tumor-related deaths occurred among these cases. No specific relation to perforation could be distilled. CONCLUSIONS: The best available evidence suggests that perforation has no influence on prognosis of classical appendiceal carcinoids. In contrast, peritoneal carcinomatosis is much more common in goblet cell carcinoids but the true impact of perforation remains unclear. Careful follow-up should therefore be considered in these cases.
PubMed-ID: 25190118
http://dx.doi.org/10.1245/s10434-014-4023-9

Paraganglioma in Pregnancy: A Case Series and Review of the Literature.
J Clin Endocrinol Metab, 100(8):3202-9.
L. A. Wing, J. V. Conaglen, G. Y. Meyer-Rochow and M. S. Elston. 2015.
CONTEXT: Pregnancies complicated by a pheochromocytoma or paraganglioma are very rare, being estimated to occur in 0.007% of all pregnancies. Both the well-being of the mother and fetus need to be considered, and management can be challenging. The optimal management of women with a pheochromocytoma or paraganglioma in pregnancy is not well established. OBJECTIVE: The objective of the study was to assess whether there is a difference in fetal or maternal mortality between pheochromocytomas and paragangliomas in pregnancy. DESIGN: We present an experience of eight pregnancies in four SDHB germline mutation-positive women with sympathetic paragangliomas, followed by a systematic review of the literature to compare the outcome of paragangliomas with that of pheochromocytomas occurring in pregnancy. RESULTS: In our case series, favorable fetal and maternal outcomes were seen in all eight pregnancies. From the systematic review, maternal and fetal mortality were lower in women with paragangliomas, at 3.6% and 12% respectively, compared with 9.8% and 16% in women with pheochromocytomas. CONCLUSION: Pregnant women with paragangliomas may be at a lower risk of adverse outcome than those with pheochromocytomas, but both maternal and fetal mortality rates are still higher than that of the general obstetric population.
PubMed-ID: 26083822
http://dx.doi.org/10.1210/jc.2015-2122

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Necessity for lifelong follow-up of patients with familial paraganglioma syndrome: A case report.
Head Neck, 37(12):E174-8.
M. J. Persky, M. Adelman, E. Zias and D. Myssiorek. 2015.
BACKGROUND: Patients with established familial paraganglioma (PGL) syndrome may have multiple metachronous lesions. This article illustrates, via imaging and findings, the need for lifetime follow-up of patients with familial PGL syndromes. METHODS: Patients' medical charts and radiological images were reviewed in a retrospective analysis. RESULTS: Over the course of 18 years, this patient developed 2 simultaneous carotid PGLs, a cardiac PGL, and a biochemically active interaortocaval PGL. CONCLUSION: PGLs do not necessarily occur simultaneously in patients with familial PGL syndrome. Lifelong observation is needed to detect these lesions before they become large and symptomatic. Lack of biochemical activity is not a predictor of future lesions being inactive. Cardiac PGLs are rare and require resection.
PubMed-ID: 25783443
http://dx.doi.org/10.1002/hed.24047

Ectopic intravagal parathyroid adenoma.
Head Neck, 37(12):E200-4.
J. Daruwalla, N. Sachithanandan, D. Andrews and J. A. Miller. 2015.
BACKGROUND: Intraneural parathyroid adenomas are rare, with only 9 cases of intravagal adenomas reported. All but one of the reported cases was found after multiple neck explorations. To the best of our knowledge, we report the first case of nonsupernumerary ectopic intravagal parathyroid identified at primary exploration. METHODS AND RESULTS: A 17-year-old girl with primary hyperparathyroidism and nephrolithiasis was referred with a sestamibi scan reporting a left lower parathyroid adenoma. No eutopic parathyroid tissue was identified during full exploration of the left side of the neck. Exploration of the carotid sheath revealed a fusiform swelling of the vagus nerve at the level of the carotid bifurcation. Longitudinal incision of the vagal perineurium revealed a 7-mm parathyroid adenoma, which was enucleated. The patient recovered uneventfully, with normalization of serum calcium, parathyroid hormone (PTH), and normal vocal cord function. CONCLUSION: We believe that this is the first reported case of nonsupernumerary intravagal parathyroid adenoma resected at initial exploration. The vagus nerve is a rare location for a parathyroid adenoma, but one that should be considered, even during primary exploration.
PubMed-ID: 25867456
http://dx.doi.org/10.1002/hed.24068

Multidisciplinary management of locally advanced and widely metastatic paraganglioma in a patient with life-threatening compressive symptoms.
Head Neck, 37(12):E205-8.
V. Neychev, D. Straughan, K. Pacak and E. Kebebew. 2015.
BACKGROUND: Patients presenting with locally advanced, metastatic paraganglioma with life-threatening compressive symptoms of critical anatomic structure pose a significant management challenge. METHODS: We present a case of a 15-year-old patient with enlarging right neck mass causing dysphagia and respiratory compromise from near complete obstruction of the oropharynx. RESULTS: Evaluation of the patient's family history led to the identification of a mutation in the succinate dehydrogenase subunit B (SDSD) gene (G725A). Laboratory and imaging workup revealed an 8.8 x 6.6 x 4.1 cm metabolically and biochemically active right neck mass, a tumor in the left para-aortic region, and multiple bony lesions consistent with widely metastatic disease. Multidisciplinary management included preoperative clinical optimization, coil embolization, and palliative resection of the neck mass. CONCLUSION: Although the currently available treatment options for patients with advanced metastatic paraganglioma render no survival benefit, a multidisciplinary management approach aimed at relief of tumor-related symptoms and catecholamine excess should be undertaken.
PubMed-ID: 25899001
http://dx.doi.org/10.1002/hed.24069

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

Selective Arterial Calcium Stimulation With Hepatic Venous Sampling Differentiates Insulinoma From Nesidioblastosis.
J Clin Endocrinol Metab, 100(11):4189-97.
S. M. Thompson, A. Vella, G. B. Thompson, K. M. Rumilla, F. J. Service, C. S. Grant and J. C. Andrews. 2015.
CONTEXT: In adult patients with endogenous hyperinsulinemic hypoglycemia and negative or inconclusive noninvasive imaging, insulinoma and non-insulinoma pancreatogenous hypoglycemic syndrome (NIPHS) resulting from diffuse nesidioblastosis must be considered in the differential diagnosis. It is not known whether the biochemical results of selective arterial calcium stimulation (SACST) with hepatic venous sampling can differentiate insulinoma from diffuse nesidioblastosis. OBJECTIVE: To determine the specificity of SACST with hepatic venous sampling in differentiating insulinoma from diffuse nesidioblastosis. DESIGN: Retrospective review (January 1996 to March 2014). SETTING: Tertiary referral center. PATIENTS OR OTHER PARTICIPANTS: A total of 116 patients with biochemical evidence of endogenous hyperinsulinemic hypoglycemia and negative or inconclusive noninvasive imaging who were subsequently shown at surgery to have insulinoma (n = 42) or nesidioblastosis (n = 74) after undergoing SACST with hepatic venous sampling. INTERVENTION(S): SACST with hepatic venous sampling before pancreatic exploration. MAIN OUTCOME MEASURE(S): Receiver operating characteristic curves were generated from the biochemical results of SACST to determine the specificity of the maximum hepatic venous insulin concentration (mHVI) and the relative-fold increase in hepatic venous insulin concentration (rHVI) over baseline after calcium injection from the dominant artery in differentiating insulinoma from nesidioblastosis. RESULTS: The mHVI (21.5-fold; P < .001) and rHVI (3.9-fold; P < .001) were significantly higher in the insulinoma group compared to the nesidioblastosis group. The areas under the receiver operating characteristic curve for mHVI and rHVI were excellent (0.94; P < .0001) and good (0.83; P < .0001), respectively, for differentiating insulinoma from nesidioblastosis. mHVI cutoffs of > 91.5 and > 263.5 muIU/mL were 95 and 100% specific for insulinoma, respectively. A 19-fold increase in rHVI over baseline was 99% specific for insulinoma. CONCLUSIONS: These data suggest that the mHVI and rHVI at SACST may be useful in differentiating insulinoma from nesidioblastosis with high specificity in patients with hyperinsulinemic hypoglycemia and negative or inconclusive noninvasive imaging.
PubMed-ID: 26312578
http://dx.doi.org/10.1210/jc.2015-2404

Long-Term Survival After Surgical Treatment of Thymic Carcinoma: A Retrospective Analysis from the Chinese Alliance for Research of Thymoma Database.
Ann Surg Oncol, 23(2):619-25.
H. Fu, Z. T. Gu, W. T. Fang, J. H. Fu, Y. Shen, Y. T. Han, Z. T. Yu, Y. Li, L. J. Tan, L. W. Pang and K. N. Chen. 2015.
BACKGROUND: Thymic carcinoma is a type of rare and highly malignant tumor that originates from the thymic epithelium. Treatment and prognosis of thymic carcinoma remain controversial. We retrospectively analyzed survival data from a large-sample multicenter database in China. METHODS: The Chinese Alliance for Research of Thymoma constructed a retrospective database of patients with thymic epithelial tumors, which enrolled 1930 patients from January 1996 to August 2013, including 329 with thymic carcinomas. In this study, we analyzed clinical, pathologic, and treatment information, measured long-term survival rates, and identified relevant prognostic factors. RESULTS: Of 329 patients, R0 resection was performed in 211 (57.7 %), R1 in 34 (9.2 %), and R2 in 84 (22.5 %).The 3-, 5-, and 10-year survival rates were 78.3, 67.1, and 47.9 %, respectively. In univariate analysis, early Masaoka-Koga stage, R0 resection, and postoperative radiotherapy were associated with better overall survival.Early Masaoka-Koga stage and postoperative radiotherapy were also associated with disease-free survival. In multivariate analyses, R0 resection, Masaoka-Koga stage, and postoperative radiotherapy were significant prognostic factors of survival. CONCLUSIONS: Complete resection is the preferred primary treatment for thymic carcinoma. R0 resection, early Masaoka-Koga stage, and postoperative radiotherapy are significant predictors of improved survival.
PubMed-ID: 26474558
http://dx.doi.org/10.1245/s10434-015-4825-4