EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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Jan- Apr 2015

Data retrival from Pubmed: June 16, 2015

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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

ENDOCRINE TUMOURS: Familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis.
Eur J Endocrinol, 172(6):R253-R62.
X. Wang, W. Cheng, J. Li, A. Su, T. Wei, F. Liu and J. Zhu. 2015.
OBJECTIVE: There is controversy as to whether familial nonmedullary thyroid carcinoma (FNMTC) is more aggressive than sporadic NMTC (SNMTC). The aim of the study was to evaluate the biological characteristics of patients with FNMTC by a meta-analysis. METHODS: Four databases (PubMed, EMBASE, the Cochrane library databases, and the Web of Science) were searched to identify studies published before September, 2014. All original studies that compared clinical characteristics and prognosis of patients with FNMTC and SNMTC were included. The pooled effect sizes of interesting parameters were calculated by odds ratio (OR), standard mean difference (SMD), or hazard ratio (HR). RESULTS: Twelve studies with a total of 12 741 participants were included in this analysis. FNMTC patients had an increased rate of recurrence (OR=1.72, 95% CI: 1.34 to 2.20) and decreased disease-free survival (DFS) (HR=1.83, 95% CI: 1.34 to 2.52) in comparison with SNMTC patients. FNMTC possessed more aggressive biological behaviors, characterized by younger age at diagnosis (SMD=-0.91, 95% CI: -1.59 to -0.22), higher risk of multifocal (OR=1.50, 95% CI: 1.32 to 1.71), bilateral (OR=1.29, 95% CI: 1.00 to 1.66), extrathyroidal invasion (OR=1.20, 95% CI: 1.02 to 1.41), and lymph node metastasis (OR=1.18, 95% CI: 1.01 to 1.38). CONCLUSION: FNMTC is a more aggressive disease and possesses higher recurrence rate and lower DFS. More attention and careful consideration should be paid regarding the decision about treatment for patients with FNMTC.
PubMed-ID: 25637073
http://dx.doi.org/10.1530/EJE-14-0960

Impact of thyroid nodule size on prevalence and post-test probability of malignancy: a systematic review.
Laryngoscope, 125(1):263-72.
J. J. Shin, D. Caragacianu and G. W. Randolph. 2015.
OBJECTIVES/HYPOTHESIS: Large thyroid nodules may be associated with higher risk of malignancy and less-accurate fine-needle aspiration (FNA) results, but there is currently no overarching consensus. We therefore tested two null hypotheses: 1) thyroid nodule size >3 to 4 cm is not associated with a higher baseline prevalence of malignancy (i.e., the associated pretest probability is the same, regardless of size), and 2) thyroid nodule size >3 to 4 cm is not associated with worse diagnostic accuracy (i.e., the associated sensitivity, false-negative rate, and post-test probability of malignancy is not affected by nodule diameter). STUDY DESIGN: Computerized searches of PubMed, Embase, and The Cochrane Library through July 2013 were performed, supplemented with manual searches. METHODS: A priori criteria were defined to determine inclusion and exclusion of studies. Searches and data extraction were performed by independent reviewers and focused on FNA histopathologic findings and their relationship to nodule size, study design, and potential confounders. RESULTS: Criterion-meeting studies (n = 15) included a total of 13,180 participants. The preponderance of prospective comparative studies showed a statistically significantly higher prevalence of malignancy in large nodules. Although data are mixed, evidence from the best-reported studies suggests sensitivity, false-negative rates, and frequency of true negatives among benign FNA results are worse in large nodules. CONCLUSIONS: Large nodules have a higher pretest probability of malignancy. Data from larger studies suggest reduced FNA diagnostic accuracy in nodules >3 to 4 cm in diameter. Surgery represents a reasonable clinical option for nodules >3 cm.
PubMed-ID: 24965892
http://dx.doi.org/10.1002/lary.24784

Biochemical cure after reoperations for medullary thyroid carcinoma: a meta-analysis.
Ann Surg Oncol, 22(1):96-102.
K. J. Rowland, L. X. Jin and J. F. Moley. 2015.
BACKGROUND: Despite meticulous surgical techniques, calcitonin levels remain detectable in 40 % to 66 % of patients after initial surgery for medullary thyroid carcinoma (MTC), and the optimal surgical management for persistent or recurrent disease remains controversial. Previous studies suggest that biochemical cure, defined by normalization of postoperative calcitonin measurements, predicts disease-free survival. Reoperative approaches range from targeted removal of detectable disease to comprehensive compartment-oriented lymph node

clearance. METHODS: A proportional meta-analysis of clinical case series of postoperative calcitonin clearance after reoperation for MTC was performed. Studies were obtained from PubMed, Embase, Scopus, and the Cochrane Library. RESULTS: Twenty-seven articles capturing data of 984 patients met the inclusion criteria for the meta-analysis. Overall, normalization of calcitonin after reoperation for MTC occurred in 16.2 % of patients [95 % confidence interval (CI) 14.0-18.5]. Stratified by operative procedure, targeted selective lymph node removal procedures had a normalization of calcitonin in 10.5 % of patients (95 % CI 6.4-14.7), while compartment-oriented procedures had a higher rate of normalization at 18.6 % (95 % CI 15.9-21.3). CONCLUSIONS: The rate of calcitonin normalization after reoperation for MTC is enhanced through use of a meticulous compartment-oriented lymph node dissection. Compartment-oriented lymph node dissection results in calcitonin normalization in 18.6 % of reoperative MTC patients and is the procedure of choice in patients in whom the goal is biochemical cure.
PubMed-ID: 25234024
http://dx.doi.org/10.1245/s10434-014-4102-y

Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies.
Thyroid, 25(5):538-50.
L. R. Remonti, C. K. Kramer, C. B. Leitao, L. C. Pinto and J. L. Gross. 2015.
BACKGROUND: Thyroid nodules are a common finding in the general population, and their detection is increasing with the widespread use of ultrasound (US). Thyroid cancer is found in 5-15% of cases depending on sex, age, and exposure to other risk factors. Some US parameters have been associated with increased risk of malignancy. However, no characteristic seems sufficiently reliable in isolation to diagnose malignancy. The objective of this meta-analysis was to evaluate the diagnostic performance of US features for thyroid malignancy in patients with unselected thyroid nodules and nodules with indeterminate fine-needle aspiration (FNA) cytology. METHODS: Electronic databases were reviewed for studies published prior to July 2012 that evaluated US features of thyroid nodules and reported postoperative histopathologic diagnosis. A manual search of references of review and key articles, and previous meta-analyses was also performed. A separate meta-analysis was performed including only nodules with indeterminate cytology. Analyzed features were solid structure, hypoechogenicity, irregular margins, absence of halo, microcalcifications, central vascularization, solitary nodule, heterogeneity, taller than wide shape, and absence of elasticity. RESULTS: Fifty-two observational studies (12,786 nodules) were included. Nine studies included nodules with indeterminate cytology as a separate category, comprising 1851 nodules. In unselected nodules, all US features were significantly associated with malignancy with an odds ratio varying from 1.78 to 35.7, and microcalcifications, irregular margins, and a taller than wide shape had high specificities (Sp; 87.8%, 83.1%, 96.6%) and positive likelihood ratios (LHR; 3.26, 2.99, 8.07). Absence of elasticity was the single feature with the best diagnostic performance (sensitivity 87.9%, Sp 86.2%, and positive LHR 6.39). The presence of central vascularization was the most specific US feature in nodules with indeterminate cytology (Sp 96% and positive LHR 2.13). CONCLUSIONS: US features in isolation do not provide reliable information to select nodules that should have a FNA performed. A combination of US characteristics with higher likelihood ratios and consequently with higher post-test probabilities of malignancy-microcalcifications, or a taller than wide shape, or irregular margins, or absence of elasticity-will probably identify nodules with an increased risk for malignancy. Further studies are required to standardize elastography techniques and evaluate outcomes, especially in nodules with an indeterminate cytology.
PubMed-ID: 25747526
http://dx.doi.org/10.1089/thy.2014.0353

Prognostic value of genetic mutations in thyroid cancer: a meta-analysis.
Thyroid, 25(1):63-70.
K. Pak, S. Suh, S. J. Kim and I. J. Kim. 2015.
BACKGROUND: Genetic mutations have been found to be associated with thyroid cancer. Previous studies have been focused on the relation between genetic mutations and thyroid cancer. We sought to evaluate the prognostic value of the three most common genetic mutations (BRAF, RAS, and RET) in patients with thyroid cancer. METHODS: Sources from MEDLINE (inception to December 2013) and EMBASE (inception to December 2013) were searched. Studies of thyroid cancer with results of genetic mutations and studies that reported survival data were included and two authors performed the data extraction independently. Any discrepancies were resolved by a consensus. RESULTS: Fourteen studies assessing BRAF mutations, 6 RAS mutations, 4 RET mutations, and 1 with analysis of both BRAF and RAS mutations were included in this meta-analysis. Patients with papillary thyroid cancer with BRAF mutations showed a 1.59-fold higher risk of events or a 2.66-fold higher risk of death than patients with papillary thyroid cancer without a BRAF mutation. Also,

patients with RAS mutations showed a 2.90-fold higher risk of death by thyroid cancer than patients without a RAS mutation. In addition, patients with medullary thyroid cancer with RET mutations showed a 5.82-fold higher risk of death by the disease than without a RET mutation. CONCLUSIONS: Genetic mutations should be considered as a poor prognostic marker in thyroid cancer and may lead to better management of individual patients. However, the use of genetic mutations as prognostic markers should not be generalized, but individualized in the specific clinic setting.
PubMed-ID: 25244593
http://dx.doi.org/10.1089/thy.2014.0241

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

BRAFV600E mutation in papillary thyroid microcarcinoma: a meta-analysis.
Endocr Relat Cancer, 22(2):159-68.
F. Li, G. Chen, C. Sheng, A. M. Gusdon, Y. Huang, Z. Lv, H. Xu, M. Xing and S. Qu. 2015.
The prognostic value of the BRAFV600E mutation, resulting in poor clinical outcomes of papillary thyroid carcinoma, has been generally confirmed. However, the association of BRAFV600E with aggressive clinical behaviors of papillary thyroid microcarcinoma (PTMC) has not been firmly established in individual studies. We performed this meta-analysis to examine the relationship between BRAFV600E mutation and the clinicopathological features of PTMC. We conducted a systematic search in PubMed, EMBASE, and the Cochrane library for relevant studies. We selected all the studies that reported clinicopathological features of PTMC patients with information available on BRAFV600E mutation status. Nineteen studies involving a total of 3437 patients met these selection criteria and were included in the analyses. The average prevalence of the BRAFV600E mutation was 47.48%, with no significant difference with respect to patient sex (male versus female) and age (younger than 45 years versus 45 years or older). Compared with the WT BRAF gene, the BRAFV600E mutation was associated with tumor multifocality (odds ratio (OR) 1.38; 95% CI, 1.04-1.82), extrathyroidal extension (OR 3.09; 95% CI, 2.24-4.26), lymph node metastases (OR 2.43; 95% CI, 1.28-4.60), and advanced stage (OR 2.39; 95% CI, 1.38-4.15) of PTMC. Thus, our findings from this large meta-analysis definitively demonstrate that BRAFV600E-mutation-positive PTMC are more likely to manifest with aggressive clinicopathological characteristics. In appropriate clinical settings, testing for the BRAFV600E mutation is likely to be useful in assisting the risk stratification and management of PTMC.
PubMed-ID: 25593071
http://dx.doi.org/10.1530/ERC-14-0531

A systematic review and meta-analysis evaluating completeness and outcomes of robotic thyroidectomy.
Laryngoscope, 125(2):509-18.
B. H. Lang, C. K. Wong, J. S. Tsang, K. P. Wong and K. Y. Wan. 2015.
OBJECTIVES/HYPOTHESIS: Despite immense interest, robotic-assisted thyroidectomy (RT) remains

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

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

Therapy of endocrine disease: response and toxicity of small-molecule tyrosine kinase inhibitors in patients with thyroid carcinoma: a systematic review and meta-analysis.
Eur J Endocrinol, 172(5):R215-25.
E. N. Klein Hesselink, D. Steenvoorden, E. Kapiteijn, E. P. Corssmit, A. N. van der Horst-Schrivers, J. D. Lefrandt, T. P. Links and O. M. Dekkers. 2015.
CONTEXT: Many tyrosine kinase inhibitors (TKIs) have been studied in patients with thyroid carcinoma (TC). However, the effect and toxicity of various TKIs in differentiated TC (DTC) and medullary TC (MTC) patients have not been directly compared. The aim of the present systematic review and meta-analysis was to systematically summarize response and toxicity of TKIs in TC patients. METHODS: All major databases were systematically searched for publications on TKIs in TC. Primary endpoint was objective response; secondary endpoints were clinical benefit, percentage TKI dose reduction/discontinuation, hand-foot syndrome, diarrhea, and nausea/vomiting. Meta-analysis was performed using an exact likelihood approach and a logistic regression. Pooled percentages and 95% CIs were reported. RESULTS: In total, 22 publications were included. For DTC patients, gefitinib induced no objective responses. Pooled percentage was highest for pazopanib, 49 (95% CI 33-64)%, and was 17 (95% CI 12-24)% for sorafenib. For MTC, gefitinib and imatinib induced no objective

responses, whereas sunitinib induced objective response in 43 (95% CI 14-77)%. For vandetanib and cabozantinib, these numbers were 40 (95% CI 34-46)% and 27 (95% CI 22-32)% respectively. Clinical benefit was found in 53 (95% CI 48-59)% of DTC patients on sorafenib, and in 84 (95% CI 79-88)% and 55 (95% CI 49-61)% of MTC patients on vandetanib and cabozantinib respectively. All TKIs were associated with considerable toxicity. CONCLUSION: The currently studied TKIs show a modest response, while side effects are not negligible. Therefore, we suggest to solely consider TKIs in TC patients with rapid progressive disease, for whom the benefits of treatment outweigh toxicity.
PubMed-ID: 25572389
http://dx.doi.org/10.1530/EJE-14-0788

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

Effectiveness of preventative and other surgical measures on hypocalcemia following bilateral thyroid surgery: a systematic review and meta-analysis.
Thyroid, 25(1):95-106.
R. Antakia, O. Edafe, L. Uttley and S. P. Balasubramanian. 2015.
BACKGROUND: A variety of measures have been proposed to reduce the incidence of post-thyroidectomy hypocalcemia. The aim of this study was to perform a systematic review and meta-analysis of preventive and other surgical measures on post-thyroidectomy hypocalcemia as reported in the literature. METHODS: Comprehensive searches of the PubMed, EMBASE, and Cochrane databases were performed, and the quality of included papers was assessed using the Cochrane risk of bias tool or a modified Newcastle-Ottawa Scale (NOS). The results of all included studies were summarized, and meta-analyses were performed where appropriate. RESULTS: Thirty-nine randomized controlled trials (RCTs) and 37 observational studies were included. Measures studied included hemostatic techniques, extent of thyroidectomy and central neck dissection, surgical approach, calcium/vitamin D/thiazide diuretic supplements, parathyroid gland autotransplantation (PGAT) and intraoperative parathyroid gland (PG) identification, truncal ligation of inferior thyroid artery (ITA), preoperative magnesium infusion, and use of magnification loupes and Surgicel. Measures associated with significantly lower rates of transient hypocalcemia in meta-analysis were postoperative calcium and vitamin D supplementation compared to either calcium supplements alone (odds ratio (OR) 0.66; p=0.04) or no supplements (OR 0.34; p=0.007), and bilateral subtotal thyroidectomy (BST) compared to Hartley Dunhill (HD) procedure (OR 0.35; p=0.01). Meta-analyses did not demonstrate any measure to be significantly associated with a reduction in permanent hypocalcemia. CONCLUSION: This review identified postoperative calcium and vitamin D supplementation and bilateral subtotal thyroidectomy (over HD) as being effective in prevention of transient hypocalcemia. However, the majority of RCTs were of low quality, primarily due to a lack of blinding. The wide variability in study design, definitions of hypocalcemia, and methods of assessment prevented meaningful summation of results for permanent hypocalcemia.

PubMed-ID: 25203484
http://dx.doi.org/10.1089/thy.2014.0101

Randomized controlled trials

Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules.
J Clin Endocrinol Metab, 100(2):460-6.
R. Cesareo, V. Pasqualini, C. Simeoni, M. Sacchi, E. Saralli, G. Campagna and R. Cianni. 2015.
CONTEXT: Ultrasound-guided radiofrequency ablation (RFA) of solid thyroid nodules (TNs) is a minimally invasive procedure that may induce a volume reduction of symptomatic solid benign TNs. OBJECTIVE: The aim of the study was to evaluate the effectiveness and safety of RFA in debulking benign TNs. DESIGN AND PATIENTS: Eighty-four consecutive patients with symptomatic and cytologically benign solid nodules were randomly assigned to either a single RFA session (group A; n = 42) or follow-up (group B; n = 42) at our center. Entry criteria were a solid thyroid nodule or predominantly solid (with a fluid component </= 30% of the volume), normal thyroid function, no autoimmunity, and no previous thyroid gland treatment. Three subgroups were formed according to the baseline volume of nodules: small (</= 12 mL), medium (from 12 to 30 mL), or large (>30 mL). METHODS: In group A RFA was performed in a single session with the moving-shot technique. Volume and local symptom changes were evaluated 1 and 6 months after RFA. RESULTS: In group A, the volume decreased from 24.5.5 +/- 19.6 to 8.6 +/- 9.5 6 months after RFA (P = .001). The greatest volume reduction was in small nodules. The pressure symptom score improved only in medium and large nodules (P < .001), whereas the cosmetic score improved in all treated patients (P < .001). The rate of thyroid volumetric reduction was not statistically different between solid and predominantly solid nodules. Only one patient experienced permanent right paramedian vocal cord palsy with inspiratory stridor without dysphonia. In group B, nodule volume remained unchanged, whereas the symptom score was worse at the 6-month evaluation (P = .01). CONCLUSIONS: RFA is effective in reducing thyroid nodule volume. The best reduction rate was observed in small TNs. The thyroid volumetric reduction does not change according to the sonographic features. The mean treatment duration was longer in larger TNs.
PubMed-ID: 25387256
http://dx.doi.org/10.1210/jc.2014-2186

A comparison of the outcome using Ligasure small jaw and clamp-and-tie technique in thyroidectomy: a randomized single center study.
Langenbecks Arch Surg, 400(2):247-52.
S. Coiro, F. M. Frattaroli, F. De Lucia, E. Manna, F. Fabi, J. M. Frattaroli and G. Pappalardo. 2015.
PURPOSE: Hypoparathyroidism and paralysis of the recurrent laryngeal nerve (RLN) still remain the most frequent specific complications of thyroid surgery. This study evaluates the effects of employment of a recently introduced device (LigaSure Small Jaw, LSJ), compared to the traditional clamp-and-tie (CT) technique, on the short- and long-term outcome of the patients who underwent thyroidectomy. METHODS: This prospective, randomized study included 190 patients enrolled from October 2011 to July 2013. The numbers of patients in the LSJ group and the CT group were both 95. We studied the following: operative times, intraoperative and postoperative blood losses, intact parathormone (iPTH) and calcium serum levels, and the incidence of RLN paralysis. RESULTS: The two cohorts were homogeneous for age, sex, surgical indication, BMI, ASA score, and estimated thyroid volume. Operation time has been 73.90 +/- 23.35 min in group CT and 60.20 +/- 22.36 min in group LSJ (p = 0.002). Intraoperative blood losses have been 47 +/- 18 ml in group CT and 38 +/- 14 in group LSJ (p = 0.002), while postoperative blood losses have been 45 +/- 21 ml in group CT and 40 +/- 20 in group LSJ (p = 0.105). The mean calcium blood level in group CT has been 8.12, 7.79, and 7.92 mg/dl in the first, second, and third postoperative days, respectively, as well as 8.26, 7.97, and 8.22 mg/dl for group LSJ (p > 0.05). Basal and post-thyroidectomy iPTH levels have been 46.49 and 23.64 pg/ml in group CT (Delta = 49.15 %), as well as 51.06 and 27.73 (Delta = 45.69 %) in group LSJ (p > 0.05). Permanent RLN paralysis was 1.05 % in LSJ group and 0 % in CT group. CONCLUSION: The employment of LSJ reduces in a statistically significant way both operative times and intraoperative blood losses. No significant differences were found as far as postoperative RLN paralysis and hypoparathyroidism.
PubMed-ID: 25582310
http://dx.doi.org/10.1007/s00423-014-1270-y

Thiamazole Pretreatment Lowers the (131)I Activity Needed to Cure Hyperthyroidism in Patients With Nodular Goiter.
J Clin Endocrinol Metab, 100(6):2261-7.
A. Kyrilli, B. N. Tang, V. Huyge, D. Blocklet, S. Goldman, B. Corvilain and R. Moreno-Reyes. 2015.
CONTEXT: Relatively low radioiodine uptake (RAIU) represents a common obstacle for radioiodine ((131)I) therapy in patients with multinodular goiter complicated by hyperthyroidism. OBJECTIVE: To evaluate whether thiamazole (MTZ) pretreatment can increase (131)I therapeutic efficacy. DESIGN AND SETTING: Twenty-two patients with multinodular goiter, subclinical hyperthyroidism, and RAIU < 50% were randomized to receive either a low-iodine diet (LID; n = 10) or MTZ 30 mg/d (n = 12) for 42 days. Thyroid function and 24-hour RAIU were measured before and after treatment. Thyroid volume was evaluated by either magnetic resonance imaging or single photon emission computed tomography. RESULTS: Mean 24-hour RAIU increased significantly from 32 +/- 10% to 63 +/- 18% in the MTZ group (P < .001). Consequently, there was a 31% decrease in the calculated median therapeutic (131)I activity after MTZ (P < .05). No significant changes in 24-hour RAIU were observed after diet. In the MTZ group, median serum TSH levels increased significantly by 9% and mean serum free T4 and free T3 concentrations decreased by 22% and 15%, respectively, whereas no changes in thyroid function were observed in the LID group. Thyroid volume did not significantly change in either of the two groups. At 12 months after radioiodine treatment, median serum TSH was within the normal range in both groups. CONCLUSIONS: MTZ treatment before (131)I therapy resulted in an average 2-fold increase in thyroid RAIU and enhanced the efficiency of radioiodine therapy assessed at 12 months. MTZ pretreatment is therefore a safe, easily accessible alternative to recombinant human TSH stimulation and a more effective option than LID.
PubMed-ID: 25867812
http://dx.doi.org/10.1210/jc.2015-1026

Pain and surgical outcomes with and without neck extension in standard open thyroidectomy: a prospective randomized trial.
Head Neck, 37(3):407-12.
B. H. Lang, S. H. Ng and K. P. Wong. 2015.
BACKGROUND: The purpose of this study was to compare surgical outcomes between those patients who underwent open thyroidectomy with and without neck extension. METHODS: One hundred eighty patients were randomized into 2 groups, with neck extension (group I) and without neck extension (group II). Outcomes included pain score on postoperative day 0, day 1, and the first clinic visit, operating time, blood loss, recurrent laryngeal nerve (RLN) injury, and hypoparathyroidism. RESULTS: Pain scores in group II were significantly lower on postoperative day 1 (2.38 vs 3.08; p = .022) and at the first clinic visit (0.57 vs 0.78; p = .026). There was a significant direct correlation between degree of neck extension and pain score on day 1 (p = .159 and p = .033). Other outcomes seemed comparable. However, the overall RLN injury rate was not significantly different between the 2 groups (5.3% vs 2.0%; p = .212). CONCLUSION: Compared to group I, pain on postoperative day 1 and at the first visit in group II were significantly less, but both groups had similar overall RLN injury rate.
PubMed-ID: 24431099
http://dx.doi.org/10.1002/hed.23611

Lenvatinib versus placebo in radioiodine-refractory thyroid cancer.
N Engl J Med, 372(7):621-30.
M. Schlumberger, M. Tahara, L. J. Wirth, B. Robinson, M. S. Brose, R. Elisei, M. A. Habra, K. Newbold, M. H. Shah, A. O. Hoff, A. G. Gianoukakis, N. Kiyota, M. H. Taylor, S. B. Kim, M. K. Krzyzanowska, C. E. Dutcus, B. de las Heras, J. Zhu and S. I. Sherman. 2015.
BACKGROUND: Lenvatinib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor alpha, RET, and KIT, showed clinical activity in a phase 2 study involving patients with differentiated thyroid cancer that was refractory to radioiodine (iodine-131). METHODS: In our phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131, we randomly assigned 261 patients to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety. RESULTS: The median progression-free survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. The response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses) and 1.5% in the placebo group (P<0.001). The median overall survival was not reached in either

group. Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related. CONCLUSIONS: Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival and the response rate among patients with iodine-131-refractory thyroid cancer. Patients who received lenvatinib had more adverse effects. (Funded by Eisai; SELECT ClinicalTrials.gov number, NCT01321554.).
PubMed-ID: 25671254
http://dx.doi.org/10.1056/NEJMoa1406470

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,
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

Antimicrobial prophylaxis for the prevention of surgical site infection after thyroid and parathyroid surgery: a prospective randomized trial.
World J Surg, 39(5):1282-7.
T. Uruno, C. Masaki, A. Suzuki, K. Ohkuwa, H. Shibuya, W. Kitagawa, M. Nagahama, K. Sugino and K. Ito. 2015.
BACKGROUND AND OBJECTIVE: The effectiveness of antimicrobial prophylaxis (AMP) in the prevention of surgical site infection (SSI) following thyroid and parathyroid surgery remains uncertain. The objective of this prospective randomized controlled trial (Ito-RCT1) was to assess the effectiveness of AMP in clean neck surgery performed to treat thyroid and parathyroid disease. METHODS: Participants comprised patients scheduled for clean neck surgery for thyroid and parathyroid disease at Ito Hospital. Patients whose surgery included sternotomy or resection of the trachea, larynx, pharynx, or esophagus were excluded. AMP consisted of 2 g of piperacillin (PIPC) (group A, n = 541) or 1 g of cefazolin (CEZ) (group B, n = 541) administered intravenously immediately after endotracheal intubation. Patients in the control group (Group C, n = 1,082) did not receive AMP. RESULTS: Statistical analysis was performed to compare the AMP group (Group A + Group B) with the control group (Group C). Drug-induced acute reactions correlated to PIPC or CEZ did not occur in the AMP group. No significant differences in the postoperative incidence of liver or renal dysfunction were seen between the AMP and control groups. Postoperative incidence of urinary tract infection was significantly higher in the control group (p = 0.002). The incidence of SSI events was very low, with only 1 event (0.09 %) in the AMP group and 3 events (0.28 %) in the control group, and this difference between groups was not significant (p = 0.371). CONCLUSIONS: AMP is not necessary to prevent SSI after clean thyroid or parathyroid surgery.
PubMed-ID: 25566977
http://dx.doi.org/10.1007/s00268-014-2932-1

Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study.
J Clin Endocrinol Metab, 100(4):1316-24.
D. Viola, G. Materazzi, L. Valerio, E. Molinaro, L. Agate, P. Faviana, V. Seccia, E. Sensi, C. Romei, P. Piaggi, L. Torregrossa, S. Sellari-Franceschini, F. Basolo, P. Vitti, R. Elisei and P. Miccoli. 2015.
BACKGROUND: The benefits of prophylactic central compartment lymph node dissection (pCCND) in papillary thyroid cancer (PTC) are still under investigation. This treatment seems to reduce PTC recurrence/mortality rates but has a higher risk of surgical complications. The lack of prospective randomized trials does not allow definitive recommendations. The aim of this prospective randomized controlled study was to evaluate the clinical advantages and disadvantages of pCCND. PATIENTS: A total of 181 patients with PTC without evidence of preoperative/intraoperative lymph node metastases (cN0) were randomly assigned to either Group A (n = 88) and treated with total thyroidectomy (TTx) or Group B (n = 93) and treated with TTx + pCCND. RESULTS: After 5 years of followup, no difference was observed in the outcome of the two groups. However, a higher percentage of Group A were treated with a higher number of (131)I courses (P = .002), whereas a higher prevalence of permanent hypoparathyroidism was observed in Group B (P = .02). No preoperative predictors of central compartment lymph node metastases (N1a) were identified. Only three patients were upstaged, and the therapeutic strategy changed in only one case. CONCLUSIONS: cN0 patients with PTC treated either with TTx or TTx + pCCND showed a similar outcome. One advantage of TTx + pCCND was a reduced necessity to repeat (131)I treatments, but the disadvantage was a higher prevalence of permanent hypoparathyroidism. Almost 50% of patients with PTC had micrometastatic lymph nodes in the central compartment, but none of the presurgical features analyzed, including BRAF mutation, was able to predict their presence; moreover, to be aware of their presence does not seem to have any effect on the outcome.
PubMed-ID: 25590215
http://dx.doi.org/10.1210/jc.2014-3825

Consensus Statements/Guidelines

Consensus statements in surgery: intra-operative neural monitoring for thyroid surgery.
ANZ J Surg, 85(1-2):5-7.
L. Delbridge, I. Gough, D. Lisewski, P. Middleton, J. Miller, R. Parkyn, C. Pyke, J. Shaw, P. Stanton, M. Sywak and D. Townend. 2015.
PubMed-ID: 25759889

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

recommendations based on scientific evidence and expert opinion for the management of thyroid nodules and DTC in children and adolescents. In our opinion, these represent the current optimal care for children and adolescents with these conditions.
PubMed-ID: 25900731
http://dx.doi.org/10.1089/thy.2014.0460

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

Other Articles

Robotic modified radical neck dissection by bilateral axillary breast approach for papillary thyroid carcinoma with lateral neck metastasis.
Head Neck, 37(1):37-45.
B. Seup Kim, K. H. Kang and S. J. Park. 2015.
BACKGROUND: The purpose of this study was to evaluate the safety of robotic modified radical neck dissection compared to open modified radical neck dissection. METHODS: We enrolled 78 patients who were diagnosed with papillary thyroid cancer and underwent total thyroidectomy, bilateral central neck dissection, and modified radical neck dissection between March 2011 and February 2013. Of these patients, 65 underwent an open procedure and 13 underwent a robotic procedure using the bilateral axillary breast approach (BABA). These 2 groups were retrospectively compared. RESULTS: The mean age, sex, body mass index (BMI), and tumor size were not significantly different between groups. There were no differences in the number of retrieved lymph nodes, metastatic lymph nodes, or stimulated thyroglobulin level between the 2 groups. The operation time was longer in the robotic group than in the open group. CONCLUSION: Robotic modified radical neck dissection using BABA is safe and shows oncologic and postoperative outcomes comparable to those of the open procedure.
PubMed-ID: 24214362
http://dx.doi.org/10.1002/hed.23545

Thyroid autoimmunity and risk of malignancy in thyroid nodules submitted to fine-needle aspiration cytology.
Head Neck, 37(2):260-4.
G. Grani, A. Calvanese, G. Carbotta, M. D'Alessandri, A. Nesca, M. Bianchini, M. Del Sordo, M. Vitale and A. Fumarola. 2015.
BACKGROUND: Whether the risk of cancer is increased in patients with chronic autoimmune thyroiditis is a controversial issue. METHODS: Between May 2005 and October 2012, 3777 fine-needle aspiration cytologies (FNACs) were performed on 2562 patients. Serum FT4, thyroid-stimulating hormone (TSH), anti-thyroglobulin antibody (TgAb), and anti-thyroperoxidase antibody (TPOAb) were determined. RESULTS: Patients with suspicious cytology were younger and presented smaller maximum lesion diameter. In patients with TgAb positivity, suspicious cytology was detected more frequently (9.4%) than patients without TgAb (5.7%; p = .04). No significant difference was recorded between benign and suspicious cytology in the positive TPOAb rate. Risk

factors for suspicious cytology were younger age (odds ratio [OR], 0.94), smaller maximum diameter (0.95), single lesion (1.85), microcalcifications (3.45), and TgAb (1.74). Mixed solid/fluid content resulted as being a protective factor (0.34). According to multivariate logistic regression analysis, age, mixed content, and microcalcification confirmed significance. CONCLUSION: Thyroid nodule malignancy in patients with Hashimoto thyroiditis is not more frequent than in patients without thyroiditis.
PubMed-ID: 24375752
http://dx.doi.org/10.1002/hed.23587

Retroauricular robotic thyroidectomy with concomitant neck-lift surgery.
Ann Surg Oncol, 22(1):172.
S. E. Mohamed, A. Saeed, T. Moulthrop and E. Kandil. 2015.
BACKGROUND: Robotic-assisted thyroid surgery using a retroauricular approach was reported as a novel remote access technique for hemithyroidectomy. We report our experience with this remote access technique using a single incision in the retroauricular crease and occipital hairline incision. For the first time, we show additional neck-lift surgery performed concomitantly to achieve better cosmetic outcomes. METHODS: Robotic retroauricular left hemithyroidectomy with concomitant neck-lift surgery was performed in a 59-year-old female patient who was referred for management of a 1.7 cm thyroid nodule located in the mid-lower right thyroid lobe, with fine-needle aspiration biopsy suggestive for follicular neoplasm. The patient had redundant submental skin in her neck, and was planning for a future neck-lift surgery. A concomitant neck lift was performed by the plastic surgeon using the same retroauricular approach to perform the operation. The patient agreed to participate in Institutional Review Board approved protocol. RESULTS: Total operative time was 115 min-flap creation time was 50 min, robot docking time was 10 min, operative console time was 25 min, and concomitant neck-lift surgery extended for 30 min. Estimated blood loss was approximately 30 ml. The patient was discharged home on the same day of surgery and had no postoperative complications. Final pathology confirmed benign follicular adenoma. CONCLUSIONS: Our experience with robotic retroauricular thyroidectomy showed that it is a feasible and safe remote access approach. We suggest that concomitant neck lift can be done in a select group of patients with excess skin on the neck. This approach can be offered to patients with benign and indeterminate thyroid lesions, and future prospective studies are warranted to evaluate the oncological efficacy of this approach in patients with thyroid cancer.
PubMed-ID: 24419757
http://dx.doi.org/10.1245/s10434-013-3470-z

Evaluation of serum thyroid-stimulating hormone as indicator for fine-needle aspiration in patients with thyroid nodules.
Head Neck, 37(4):498-504.
J. S. Choi, C. M. Nam, E. K. Kim, H. J. Moon, K. H. Han and J. Y. Kwak. 2015.
BACKGROUND: Recently, it has been reported that the risk of thyroid malignancy increases with increasing concentrations of serum thyroid-stimulating hormone (TSH). The purpose of this study was to determine whether or not serum TSH can be a predictor for thyroid malignancy when considering the relevant ultrasound features and clinical risk factors. METHODS: This retrospective study included 1200 euthyroid patients with 1269 thyroid nodules who underwent ultrasound-guided fine-needle aspiration (FNA) biopsy between January and June 2009. Serum TSH, ultrasound feature, and clinical parameters were compared according to final diagnosis. Subgroup analyses were performed according to nodule size. RESULTS: Serum TSH did not show a positive association with malignancy for all nodules and the micronodule subgroup in multivariate analysis, although they showed significant association with thyroid malignancy for the macronodule subgroup. For all nodules and the 2 subgroups, suspicious ultrasound features and younger age were significantly associated with malignancy in univariate and multivariate analyses. CONCLUSION: Our study suggests that TSH alone is not as useful as ultrasound features in deciding whether or not to perform FNA in patients with micronodules.
PubMed-ID: 24435826
http://dx.doi.org/10.1002/hed.23616

Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia.
Head Neck, 37(3):393-9.
P. Prazenica, L. O'Keeffe and R. Holy. 2015.
BACKGROUND: The purpose of this study was to evaluate preoperative features, surgical details, and postoperative findings related to the identification of parathyroid glands and to establish the relationship between identification of parathyroid glands and postoperative hypocalcemia. METHODS: Seven hundred eighty-eight total thyroidectomies performed between January 2002 and April 2012 by a single surgeon were studied. To

evaluate the impact of parathyroid glands identification on study variables, patients were stratified into 2 study groups: group 1 with 0 to 2 parathyroid glands identified and group 2 with 3 to 4 parathyroid glands identified. RESULTS: Multivariate analysis identified younger age (p = .007), female sex (p = .001), and no usage of the Biclamp hemostatic technique (p < .001) related to the higher number of parathyroid glands identified. Univariate analysis revealed a higher incidence of temporary hypocalcemia (p = .015) and permanent hypoparathyroidism (p = .040) in group 2 than in group 1. CONCLUSION: Identification of a higher number of parathyroid glands is associated with a higher incidence of postoperative temporary hypocalcemia and permanent hypoparathyroidism.
PubMed-ID: 24700518
http://dx.doi.org/10.1002/hed.23613

Shear wave elastography in evaluation of cervical lymph node metastasis of papillary thyroid carcinoma: elasticity index as a prognostic implication.
Ann Surg Oncol, 22(1):111-6.
W. S. Jung, J. A. Kim, E. J. Son, J. H. Youk and C. S. Park. 2015.
PURPOSE: The aim of this study was to evaluate the usefulness of shear wave elastography (SWE) for predicting cervical lymph node (LN) metastasis and the prognostic implication of SWE as histopathologic factors of papillary thyroid carcinoma (PTC). METHODS: Eighty-four LNs of 66 patients with PTC underwent B-mode ultrasonography (BUS) and SWE before ultrasound-guided fine-needle aspiration biopsy or preoperative evaluation. SWE elasticity indices (EI) of mean (Emean), minimum (Emin), maximum (Emax) and the ratio of Emean in LNs and surrounding muscle (Emean-m) were measured at the stiffest portion of LNs (kPa). SWE EI were correlated with the pathologic diagnosis and the histopathologic findings, including number and size of metastatic LNs, the ratio of the number of metastatic LN/dissected LN, and the presence of extranodal extension. Diagnostic performances of SWE EI and BUS for predicting LN metastasis were assessed using receiver operating curve analysis. RESULTS: All SWE EI were significantly higher in metastatic LNs than in benign LNs (p < 0.005). Combined Emean [area under the curve (AUC) 0.811] or Emin (AUC 0.812) with BUS showed significantly higher AUC than BUS (0.738) for predicting metastatic LNs (p = 0.041 and 0.033, respectively). The number of positive LNs/dissected LNs and the largest LN size were significantly correlated with SWE EI (p < 0.05 and p < 0.005, respectively). Metastatic LNs with extranodal extension showed significantly higher SWE EI (p < 0.005) than those without extranodal extension. CONCLUSIONS: Combined use of SWE and BUS was adjunctive to the diagnostic performance of BUS for the prediction of LN metastasis of PTC, and quantitative SWE could predict pathologic prognostic factors of LN metastasis of PTC.
PubMed-ID: 24740830
http://dx.doi.org/10.1245/s10434-014-3627-4

[Surgical strategy during intended total thyroidectomy after loss of EMG signal on the first side of resection].
Chirurg, 86(2):154-63.
R. Schneider, K. Lorenz, C. Sekulla, A. Machens, P. Nguyen-Thanh and H. Dralle. 2015.
BACKGROUND: Unambiguous identification of the recurrent laryngeal nerve with detection of nerve dysfunction giving rise to postoperative vocal cord palsy (VCP) is the principal objective of intraoperative neuromonitoring (IONM) in thyroid surgery. Because intraoperative loss of the electromyographic (EMG) signal (LOS) does not result in VCP in one third of patients, controversy surrounds the issue of whether a change in strategy is needed in planned total thyroidectomy after LOS on the first side of resection. PATIENTS AND METHODS: This was a retrospective institutional study of 1,049 consecutive patients (2,086 nerves at risk) with intended bilateral thyroid surgery who were operated on between April 2010 and July 2012 with the use of IONM. The rates of temporary and permanent VCP were analyzed on the basis of the IONM results of the first side of resection and the extent of contralateral resection for completion: resection without LOS (group 1); resection with LOS and contralateral thyroidectomy (group 2); resection with LOS and contralateral subtotal resection (group 3); resection with LOS without any contralateral resection (group 4). RESULTS: LOS on the first side of resection was noted in 27 patients (2.6 %). All VCPs were unilateral. The rates of temporary and permanent VCP were 2.5 and 0.4 %, respectively, overall; specifically: group 1: 0.5 and 0 %; group 2: 64 and 9.1 %; group 3: 100 and 50 %; group 4: 83 and 8.3 %, respectively. CONCLUSION: Because an abnormal intraoperative electromyogram carries an 80 % risk for early postoperative VCP, the initial plan of bilateral surgery needs to be critically reviewed after LOS has occurred on the first side of resection, taking into account the underlying thyroid disease of the patient and surgeon expertise. Since more than 80 % of affected nerves will fully recover after the operation, staged completion thyroidectomy is recommended.
PubMed-ID: 24823999
http://dx.doi.org/10.1007/s00104-014-2751-9

Robotic thyroidectomy using bilateral axillo-breast approach: Comparison of surgical results with open conventional thyroidectomy.
J Surg Oncol, 111(2):141-5.
H. Y. Kwak, H. Y. Kim, H. Y. Lee, S. P. Jung, S. U. Woo, G. S. Son, J. B. Lee and J. W. Bae. 2015.
BACKGROUND: The aim of the present study was to compare the surgical outcomes of robotic thyroidectomy using the bilateral axillo-breast approach (BABA) with open conventional thyroidectomy. METHODS: Database of patients who underwent thyroidectomy with cervical lymph node dissection after diagnosed as papillary thyroid carcinoma between July 2008 and February 2013 were examined. Clinicopathologic characteristics, surgical outcomes, and postoperative morbidities of robot group and open group were investigated. RESULTS: The dominant tumor size (P=0.974), body mass index (BMI) (P=0.426), and the mean number of metastatic lymph nodes in central compartment neck dissection (P=0.269) were comparable between the two groups. The mean number of retrieved central lymph nodes was higher in the open group than in the robot group (P=0.001). Postoperative complications were comparable: hypoparathyroidism in 2 weeks (P=0.296) and 3 months (P=0.446) after the surgery; vocal cord palsy in 2 weeks (P=0.363) and 3 months (P=0.312); hematoma (P=0.162); and wound infection (P=0.421). CONCLUSIONS: Robotic thyroidectomy using BABA may be a technically feasible and safe procedure comparable to conventional open surgery especially in node-negative patients.
PubMed-ID: 24898201
http://dx.doi.org/10.1002/jso.23674

Modified robotic-assisted thyroidectomy: an initial experience with the retroauricular approach.
Laryngoscope, 125(3):767-71.
E. Kandil, A. Saeed, S. E. Mohamed, N. Alsaleh, R. Aslam and T. Moulthrop. 2015.
OBJECTIVES/HYPOTHESIS: New approaches for robotic-assisted thyroidectomy, including the retroauricular approach, were recently described. We have modified the established surgical approach for retroauricular robotic thyroidectomy. Herein, we report our initial experience to identify challenges and limitations of this new surgical approach. STUDY DESIGN: Prospective case series. METHODS: This study was performed under institutional review board approval for patients who underwent retroauricular robotic hemithyroidectomy at an academic North American institution. The retroauricular approach was modified by using the space between the two heads of the sternocleidomastoid muscle as our working space. Additionally, selected patients underwent concomitant neck lift surgery with robotic thyroid surgery. Clinical characteristics, total operative time, blood loss, surgical outcomes, and length of hospital stay were evaluated. RESULTS: Twelve female patients were included in this study. Mean age was 45 +/- 4.43 years, and mean body mass index was 28.6 +/- 2.15. Mean thyroid nodule size was 1.15 +/- 0.26 cm(3). All cases were completed successfully via single retroauricular incision. There was no conversion to an open approach. Four out of 12 patients (33%) underwent additional concomitant neck lift surgery, with a mean total operative time of 156 +/- 15.88 minutes. The mean operative time for the remaining eight patients who underwent the robotic approach without additional neck lift surgery was 145.4 +/- 10.08 minutes. There were no cases of permanent vocal cord paralysis or permanent hypoparathyroidism. Mean blood loss was 22.4 +/- 4.32 mL. Four patients (33%) were discharged home on the same day of surgery, and the remaining eight patients were discharged after an overnight stay. CONCLUSIONS: Single-incision retroauricular robotic hemithyroidectomy can be a safe and feasible alternative to other remote access techniques. Neck lift surgery can be performed safely in a select group of patients. However, future studies are warranted to further evaluate the benefits and limitations of this novel approach.
PubMed-ID: 24932761
http://dx.doi.org/10.1002/lary.24786

The vagus nerve, recurrent laryngeal nerve, and external branch of the superior laryngeal nerve have unique latencies allowing for intraoperative documentation of intact neural function during thyroid surgery.
Laryngoscope, 125(2):E84-9.
N. Sritharan, M. Chase, D. Kamani, M. Randolph and G. W. Randolph. 2015.
OBJECTIVES/HYPOTHESIS: To define normative amplitude and latency of vagus, recurrent laryngeal nerve (RLN), and external branch of superior laryngeal nerve (EBSLN) and to apply them to postoperative neural function documentation. To our knowledge, this is the first study to report electrophysiologic characteristics of all three nerves in a consecutive patient series. STUDY DESIGN: Prospective. METHODS: Quantitative analysis of evoked waveform data was performed on both sides in consecutive patients undergoing thyroid surgery by a single surgeon. Mean values, standard error of mean, and standard deviation were calculated for latency (in milliseconds) and amplitude (in microvolts) of the vagus nerves, RLN, and EBSLN. Pre- and postoperative vocal

cord function was normal in all patients. RESULTS: Normative latency analysis showed mean right and left vagal latency of 5.47 ms (+/-0.73) and 8.14 ms (+/-0.86), respectively (P < .0001). Pooled RLN latency was 3.96 ms (+/-0.69), and pooled EBSLN latency was 3.56 ms (+/-0.49), both significantly shorter than vagal latencies (P < .0001). There was no association between amplitude and latency parameters and tumor-size (> or <5 cm), body mass index (> or <25), age (> or <50 years), gender, or degree of neural dissection. CONCLUSIONS: The unique right vagus, left vagus, and RLN latencies are characteristic of the individual nerves and allow identification (through the characteristic waveform latency) of an intact left or right vagus/RLN system. Timed recording of vagal waveform after thyroid lobectomy consequently documents intact ipsilateral vagal-RLN neural circuit and may be placed into the medical record as electrophysiologic documentation of existence of postresection complete neural integrity. LEVEL OF EVIDENCE: 4.
PubMed-ID: 24945758
http://dx.doi.org/10.1002/lary.24781

Prophylactic thyroidectomy: who needs it, when, and why.
J Surg Oncol, 111(1):61-5.
T. S. Wang, A. Opoku-Boateng, S. A. Roman and J. A. Sosa. 2015.
The most common hereditary thyroid cancer is medullary thyroid cancer, which can be associated with MEN 2A, MEN 2B, or FMTC. In these patients, prophylactic thyroidectomy is recommended; timing of surgery is dependent on the specific RET mutation. Prophylactic thyroidectomy should include total thyroidectomy and accompanying central compartment neck dissection should be done for patients at high risk for micro-metastatic disease only. Surgery should be performed at tertiary care institutions by high-volume thyroid surgeons.
PubMed-ID: 24965542
http://dx.doi.org/10.1002/jso.23697

Risk factors for recurrence of papillary thyroid carcinoma with clinically node-positive lateral neck.
Ann Surg Oncol, 22(1):117-24.
C. W. Lee, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim. 2015.
BACKGROUND: Papillary thyroid carcinoma (PTC) with clinically node-positive lateral neck is more likely to recur after surgery than node-negative PTC. The present study investigated the risk factors for recurrence in PTC patients with clinically node-positive lateral neck. MATERIALS AND METHODS: This study involved 136 patients with pathologically confirmed PTC and a clinically lymph node (LN)-positive lateral neck but no initial distant metastasis who underwent total thyroidectomy with therapeutic central and lateral neck dissection. Clinicopathologic characteristics, intraoperative findings, postoperative thyroglobulin (Tg) levels, and post-treatment recurrences were examined. Univariate and multivariate analyses were performed to identify factors associated with recurrence-free survival (RFS). RESULTS: During a median follow-up of 62 months (range 33-90 months), 27 (19.9 %) patients had locoregional or distant recurrences. Univariate analyses showed that primary tumor size (p = 0.049), recurrent laryngeal nerve invasion (p = 0.035), the maximal size of metastatic LN foci (>/=1.5 cm; p = 0.012), extranodal extension (p = 0.025), total LN ratio (>/=0.26; p = 0.008), American Thyroid Association (ATA) risk categories (p < 0.001), and stimulated serum Tg level (>/=4.4; p < 0.001) at the time of radioactive iodine ablation therapy just after thyroidectomy were significant predictors of RFS. Multivariate analyses showed that the maximal size of metastatic foci (p = 0.037), ATA risk categories (p < 0.001), and stimulated Tg level (p < 0.001) were independent predictors of RFS. CONCLUSIONS: Maximal size of metastatic foci, ATA risk categories, and stimulated serum Tg levels are predictive of recurrence after surgery. Careful follow-up of patients with these risk factors is therefore recommended.
PubMed-ID: 25034816
http://dx.doi.org/10.1245/s10434-014-3900-6

The nonrecurrent laryngeal nerve: anatomic and electrophysiologic algorithm for reliable identification.
Laryngoscope, 125(2):503-8.
D. Kamani, A. S. Potenza, C. R. Cernea, Y. V. Kamani and G. W. Randolph. 2015.
OBJECTIVES/HYPOTHESIS: The recurrent laryngeal nerve (RLN) intraoperative monitoring (IONM) provides a new functional dynamic that adds to visual identification of the RLN to optimize its intraoperative management. Intraoperative monitoring has been applied to the initial identification of the RLN. We now apply IONM to the identification of the nonrecurrent laryngeal nerve (NRLN) and provide electrophysiologic and anatomic parameters to facilitate this technique of neural identification for the NRLN, which is at increased risk of injury during thyroid surgery. STUDY DESIGN: Retrospective. METHODS: A study of cases of the NRLN from consecutive thyroid surgeries with IONM was conducted. Preoperative and postoperative laryngoscopy was documented in all cases. RESULTS: Ten right-sided nerves (0.6%) were identified as NRLN. One hundred percent of NRLNs had documented normal preoperative and postoperative laryngeal function. Distal and

proximal vagal nerve stimulation points that allowed for the electrophysiologic prediction of a nonrecurrence in all patients were identified. Electrophysiological normative parameters of NRLN were compared to those of the normal right RLN and right vagus nerves. CONCLUSION: Nonrecurrent laryngeal nerve is present in 0.6% of patients undergoing thyroid surgery. Intraoperative monitoring involving vagal stimulation at the defined distal and proximal points provides reliable electrophysiologic intraoperative verification of the presence of the NRLN. Three anatomical subtypes of right NRLN are noted that enable early identification of the NRLN. In conjunction with detailed knowledge of the NRLN anatomic pathways, they also may be helpful in preventing injury to the NRLN, which has been shown to be at higher risk during thyroid surgery. We provide an anatomic and electrophysiologic algorithm for reliable identification of the NRLN. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25042210
http://dx.doi.org/10.1002/lary.24823

A staged thyroidectomy approach for gastric bypass patients.
Laryngoscope, 125(4):1028-30.
Z. Gooi, B. K. Ward, D. J. Mener, O. B. Ozgursoy and S. I. Pai. 2015.
PubMed-ID: 25043176
http://dx.doi.org/10.1002/lary.24835

Management of airway compromise following thyroid cyst hemorrhage after thrombolytic therapy.
Laryngoscope, 125(3):604-7.
S. C. Gallant, M. A. Fritz, B. C. Paul and P. D. Costantino. 2015.
The risk of hemorrhage after therapeutic administration of tissue plasminogen activator (tPA) is well known. Cases of postadministration hemorrhage have been reported within many organ systems. We present a case of a 62-year-old female with undiagnosed thyroid goiter who received tPA for acute ischemic stroke and developed acute airway compromise. The surgical airway response team was called due to inability to ventilate or intubate. An incision into the mass during attempted tracheotomy released colloid and blood, decompressing the airway and facilitating ventilation and intubation. Hemithyroidectomy for mass removal was delayed for 3 days to allow normalization of post-tPA coagulopathy.
PubMed-ID: 25043767
http://dx.doi.org/10.1002/lary.24841

Evaluating for a geospatial relationship between radon levels and thyroid cancer in Pennsylvania.
Laryngoscope, 125(1):E45-9.
N. Goyal, F. Camacho, J. Mangano and D. Goldenberg. 2015.
OBJECTIVES/HYPOTHESIS: To determine whether there is an association between radon levels and the rise in incidence of thyroid cancer in Pennsylvania. STUDY DESIGN: Epidemiological study of the state of Pennsylvania. METHODS: We used information from the Pennsylvania Cancer Registry and the Pennsylvania Department of Energy. From the registry, information regarding thyroid incidence by county and zip code was recorded. Information regarding radon levels per county was recorded from the state. Poisson regression models were fit predicting county-level thyroid incidence and change as a function of radon/lagged radon levels. To account for measurement error in the radon levels, a Bayesian Model extending the Poisson models was fit. Geospatial clustering analysis was also performed. RESULTS: No association was noted between cumulative radon levels and thyroid incidence. In the Poisson modeling, no significant association was noted between county radon level and thyroid cancer incidence (P = .23). Looking for a lag between the radon level and its effect, no significant effect was seen with a lag of 0 to 6 years between exposure and effect (P = .063 to P = .59). The Bayesian models also failed to show a statistically significant association. A cluster of high thyroid cancer incidence was found in western Pennsylvania. CONCLUSIONS: Through a variety of models, no association was elicited between annual radon levels recorded in Pennsylvania and the rising incidence of thyroid cancer. However, a cluster of thyroid cancer incidence was found in western Pennsylvania. Further studies may be helpful in looking for other exposures or associations.
PubMed-ID: 25043810
http://dx.doi.org/10.1002/lary.24815

Prognostic significance of tumor multifocality in papillary thyroid carcinoma and its relationship with primary tumor size: a retrospective study of 2,309 consecutive patients.
Ann Surg Oncol, 22(1):125-31.
K. J. Kim, S. M. Kim, Y. S. Lee, W. Y. Chung, H. S. Chang and C. S. Park. 2015.
BACKGROUND: Tumor multifocality is frequently observed in papillary thyroid carcinoma (PTC), but its prognostic value is controversial. We investigated the prognostic significance of multifocality in PTCs larger than

1 cm and papillary thyroid microcarcinomas (PTMC). METHODS: Medical records and pathologic results of 2,309 patients who received thyroidectomy and lymph node dissection for PTC were retrospectively reviewed. We identified 648 patients who had PTC with a primary tumor exceeding 1 cm, and 1,661 patients with PTMC. In each group, we compared patients with unifocal and multifocal disease. Cox regression analyses of disease persistence and recurrence were performed to identify the prognostic significance of multifocality. RESULTS: The mean follow-up period was 5.6 years. In the analyses of PTCs larger than 1 cm, the multifocal group included more extensive thyroid surgeries ($p = 0.039$), radioactive iodine therapies with higher doses ($p < 0.001$), and significantly higher rates of disease persistence and recurrence ($p = 0.001$) compared with the unifocal group. In analogous analyses of patients with PTMC, disease persistence and recurrence did not differ significantly between the unifocal and multifocal groups. Cox regression analyses indicated that multifocality was an independent risk factor for disease persistence and recurrence in patients who had PTC with a tumor exceeding 1 cm, but not in patients with PTMC. CONCLUSION: Tumor multifocality appears to be an important prognostic factor for PTCs larger than 1 cm, but may have little or no prognostic significance for PTMC.
PubMed-ID: 25092159
http://dx.doi.org/10.1245/s10434-014-3899-8

Lymph node metastases do not impact survival in follicular variant papillary thyroid cancer.
Ann Surg Oncol, 22(1):158-63.
D. F. Schneider, D. Elfenbein, R. V. Lloyd, H. Chen and R. S. Sippel. 2015.
INTRODUCTION: Follicular variant of papillary thyroid cancer (FVPTC) is the most common and fastest growing subtype of papillary thyroid cancer (PTC) with features of both PTC and follicular thyroid cancer (FTC). The purpose of this study was to determine the patient and tumor features associated with lymph node metastases (LNM) in FVPTC. METHODS: This was a retrospective review of adult (>/=18) patients with histologically confirmed diagnoses of FVPTC within the SEER database between 1988 and 2009. LNM were defined by at least two lymph nodes with metastatic disease. To determine factors associated with LNM, we constructed a multivariate logistic regression model from significant variables ($p < 0.05$) identified on univariate analysis. Similarly, we used a Cox proportional hazards model to understand the relative importance of LNM in determining disease-specific mortality (DSM). RESULTS: Of the 20,357 cases of FVPTC with lymph node data available, 1,761 (8.7%) had LNM; 61.1% of these LNM were located in the central neck and 38.9% were in the lateral neck. Extrathyroidal extension (odds ratio [OR] 2.6, 95% confidence interval [CI] 2.2-3.0, $p < 0.01$) and multifocality (OR 3.0, 95% CI 2.5-3.6, $p < 0.01$) were the strongest predictors of LNM. Importantly, LNM did not independently predict DSM ($p = 0.52$). Tumor size >4 cm (hazards ratio [HR] 5.3, 95% CI 2.2-12.8, $p < 0.01$) and extrathyroidal extension (HR 8.2, 95% CI 3.0-22.0, $p < 0.01$) were the strongest predictors of DSM. CONCLUSIONS: LNM occur in less than 10% of patients with FVPTC but do not impact DSM. Instead, DSM in FVPTC is related to size and local invasion.
PubMed-ID: 25092163
http://dx.doi.org/10.1245/s10434-014-3964-3

Molecular markers for thyroid cancer diagnosis, prognosis, and targeted therapy.
J Surg Oncol, 111(1):43-50.
L. Yip. 2015.
Molecular markers including gene expression profiles, somatic gene alterations, and circulating peripheral markers have augmented diagnostic, prognostic, and therapeutic options for thyroid cancer patients.
PubMed-ID: 25155423
http://dx.doi.org/10.1002/jso.23768

American Thyroid Association statement on preoperative imaging for thyroid cancer surgery.
Thyroid, 25(1):3-14.
M. W. Yeh, A. J. Bauer, V. A. Bernet, R. L. Ferris, L. A. Loevner, S. J. Mandel, L. A. Orloff, G. W. Randolph and D. L. Steward. 2015.
BACKGROUND: The success of surgery for thyroid cancer hinges on thorough and accurate preoperative imaging, which enables complete clearance of the primary tumor and affected lymph node compartments. This working group was charged by the Surgical Affairs Committee of the American Thyroid Association to examine the available literature and to review the most appropriate imaging studies for the planning of initial and revision surgery for thyroid cancer. SUMMARY: Ultrasound remains the most important imaging modality in the evaluation of thyroid cancer, and should be used routinely to assess both the primary tumor and all associated cervical lymph node basins preoperatively. Positive lymph nodes may be distinguished from normal nodes based upon size, shape, echogenicity, hypervascularity, loss of hilar architecture, and the presence of calcifications. Ultrasound-guided fine-needle aspiration of suspicious lymph nodes may be useful in guiding the extent of

surgery. Cross-sectional imaging (computed tomography with contrast or magnetic resonance imaging) may be considered in select circumstances to better characterize tumor invasion and bulky, inferiorly located, or posteriorly located lymph nodes, or when ultrasound expertise is not available. The above recommendations are applicable to both initial and revision surgery. Functional imaging with positron emission tomography (PET) or PET-CT may be helpful in cases of recurrent cancer with positive tumor markers and negative anatomic imaging.
PubMed-ID: 25188202
http://dx.doi.org/10.1089/thy.2014.0096

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

Preventing postoperative hypocalcemia in patients with Graves disease: a prospective study.
Ann Surg Oncol, 22(3):952-8.
S. C. Oltmann, A. V. Brekke, D. F. Schneider, S. C. Schaefer, H. Chen and R. S. Sippel. 2015.
BACKGROUND: Hypocalcemia occurs after total thyroidectomy (TT) for Graves disease via parathyroid injury and/or from increased bone turnover. Current management is to supplement calcium after surgery. This study evaluates the impact of preoperative calcium supplementation on hypocalcemia after Graves TT. METHODS: A prospective study of patients with Graves disease undergoing TT was performed. Patients with Graves disease managed over a 9-month period took 1 g of calcium carbonate (CC) three times a day for 2 weeks before TT. Those managed the previous year without supplementation served as historic controls. Age-, gender-, and thyroid weight-matched, non-Graves TT patients were procedure controls. Patient demographics, postoperative laboratory values, complaints, and medications were reviewed. Parathyroid hormone (PTH)-based postoperative protocols dictated postoperative CC and calcitriol use. RESULTS: Forty-five patients with Graves disease were treated with CC before TT, and 38 patients with Graves disease were not. Forty control subjects without Graves disease were identified. Age, gender, and thyroid weight were comparable. Preoperative calcium and PTH levels were equivalent. PTH values immediately after surgery, at postoperative day 1, and at 2-week follow-up were equivalent. Postoperative use of scheduled CC ($p = 0.10$) and calcitriol ($p = 0.60$) was similar. Postoperatively, patients with untreated Graves disease had lower serum calcium levels than pretreated patients with Graves disease or control subjects without Graves disease (8.3 mg/dL vs. 8.6 vs. 8.6, $p = 0.05$). Complaints of numbness and tingling were more common in nontreated Graves disease (26%) than in pretreated Graves disease (9%) or in control subjects without Graves disease (10%, $p < 0.05$). CONCLUSIONS: Calcium supplementation before TT for Graves disease significantly reduced biochemical and symptomatic postoperative hypocalcemia. Preoperative calcium supplementation is a simple treatment that can reduce symptoms of hypocalcemia after Graves TT.
PubMed-ID: 25212835
http://dx.doi.org/10.1245/s10434-014-4077-8

Intraoperative frozen section for the evaluation of extrathyroidal extension in papillary thyroid cancer.
World J Surg, 39(1):187-93.
Y. M. Park, S. G. Wang, J. Y. Goh, D. H. Shin, I. J. Kim and B. J. Lee. 2015.
BACKGROUND: We investigated extrathyroidal extension (ETE) through frozen biopsy for intraoperative decision making in patients with papillary thyroid cancer (PTC). METHODS: During the period of the study an operation was performed in 268 patients with PTC and ETE was evaluated using intraoperative frozen biopsies of thyroid tissue. RESULTS: Extrathyroidal extension was confirmed in 54 patients (20 %) on frozen biopsy. Fifty-three patients among 54 patients showing ETE on frozen biopsy were confirmed on permanent pathologic analysis. Accordingly, frozen biopsy had a sensitivity of 66 %, a specificity of 99 %, a positive predictive value of 98 %, and a negative predictive value of 87 %. Tumor size (OR 4.373; CI 2.257-8.475, $p = <0.001$) was an independent factor for predicting ETE on frozen biopsy. CONCLUSIONS: Intraoperative frozen biopsy can be an useful tool in identifying the presence of ETE. It can also help the operator decide the extent of surgery and

central neck dissection in patients with PTC.
PubMed-ID: 25231704
http://dx.doi.org/10.1007/s00268-014-2795-5

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

Intraoperative diagnosis of central compartment lymph node metastasis predicts recurrence of patients with papillary thyroid carcinoma and clinically node-negative lateral neck and may guide extent of initial surgery.
World J Surg, 39(1):194-202.
C. W. Lee, G. Gong and J. L. Roh. 2015.
BACKGROUND: Although lymph node (LN) metastasis (LNM) of papillary thyroid carcinoma (PTC) is common, routine prophylactic LN dissection (LND) is still controversial. The purpose of this study was to investigate risk factors for recurrence of PTC with clinically node-negative lateral neck to determine the utility of intraoperative LN biopsy. MATERIALS AND METHODS: This study involved 185 patients with pathologically confirmed PTC and clinically node-negative lateral neck. All patients underwent thyroidectomy with or without ipsilateral or bilateral central LND after intraoperative central LN biopsy. Routine lateral neck LND was not performed. Clinicopathologic and intraoperative findings and post-treatment recurrences were recorded. Univariate and multivariate analyses with Cox-proportional hazards model were used to identify factors associated with recurrence. RESULTS: During a follow-up of 50-96 months, six (3.2 %) patients had recurrences in lateral cervical LNs at a median 28 months (range 7-57 months) after surgery. Overall, 2- and 5-year RFS rates were 98.4 and 96.7 %, respectively. Univariate analyses revealed that tumor size ($P = 0.005$), bilaterality ($P = 0.033$), T4 disease ($P < 0.001$), and intraoperative diagnosis of central LNM ($P = 0.001$) were significantly predictive of recurrence. Multivariate analyses showed that T4 disease ($P = 0.049$) and intraoperative diagnosis of central LNM ($P = 0.027$) were independently predictive of recurrence. CONCLUSIONS: Prophylactic lateral neck LND is not advocated for PTC with clinically node-negative lateral neck. Intraoperative LN biopsy may help identify patients at risk for recurrence and those who would benefit from LND.
PubMed-ID: 25234198
http://dx.doi.org/10.1007/s00268-014-2800-z

[Surgical assessment of complications after thyroid gland operations].
Chirurg, 86(1):70-7.
H. Dralle. 2015.
BACKGROUND: The extent, magnitude and technical equipment used for thyroid surgery has changed considerably in Germany during the last decade. The number of thyroidectomies due to benign goiter have decreased while the extent of thyroidectomy, nowadays preferentially total thyroidectomy, has increased. Due to an increased awareness of surgical complications the number of malpractice claims is increasing. OBJECTIVES:

In contrast to surgical databases the frequency of complications in malpractice claims reflects the individual impact of complications on the quality of life. In contrast to surgical databases unilateral and bilateral vocal fold palsy are therefore at the forefront of malpractice claims. As guidelines are often not applicable for the individual surgical expert review, the question arises which are the relevant criteria for the professional expert witness assessing the severity of the individual complication. RESULTS: While in surgical databases major complications after thyroidectomy, such as vocal fold palsy, hypoparathyroidism, hemorrhage and infections are equally frequent (1-3 %), in malpractice claims vocal fold palsy is significantly more frequent (50 %) compared to hypoparathyroidism (15 %), hemorrhage and infections (about 5 % each). To avoid bilateral nerve palsy intraoperative nerve monitoring has become of utmost importance for surgical strategy and malpractice suits alike. For surgical expert review documentation of individual risk-oriented indications, the surgical approach and postoperative management are highly important. CONCLUSION: Guidelines only define the treatment corridors of good clinical practice. Surgical expert reviews in malpractice suits concerning quality of care and causality between surgical management, complications and sequelae of complications are therefore highly dependent on the grounds and documentation of risk-oriented indications for thyroidectomy, intraoperative and postoperative surgical management.
PubMed-ID: 25234502
http://dx.doi.org/10.1007/s00104-014-2819-6

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

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

Chasing calcitonin: reoperations for medullary thyroid carcinoma.
Ann Surg Oncol, 22(1):7-8.

C. J. Balentine and H. Chen. 2015.
PubMed-ID: 25249261
http://dx.doi.org/10.1245/s10434-014-4109-4

Clinical and molecular features of Hurthle cell carcinoma of the thyroid.
J Clin Endocrinol Metab, 100(1):55-62.
A. M. Chindris, J. D. Casler, V. J. Bernet, M. Rivera, C. Thomas, J. M. Kachergus, B. M. Necela, I. D. Hay, S. A. Westphal, C. S. Grant, G. B. Thompson, R. T. Schlinkert, E. A. Thompson and R. C. Smallridge. 2015.
CONTEXT: Hurthle cell cancer (HCC) of the thyroid remains the subject of controversy with respect to natural course, treatment, and follow-up. OBJECTIVE: The objective of the study was to evaluate the clinical and molecular features associated with outcome in HCC. DESIGN: The study was a review of 173 HCC cases treated at Mayo Clinic over 11 years with a median 5.8-year follow-up. RESULTS: None of the patients with minimally invasive histology had persistent disease, clinical recurrence, or disease-related death. Male gender and TNM stage were independently associated with increased risk of clinical recurrence or death in widely invasive patients. The 5-year cumulative probability of clinical recurrence or death was higher in patients with TNM stage III-IV (females, 74%; males, 91%) compared with patients with TNM stage I-II (females, 0%; males, 17%). Pulmonary metastases were best identified by computed tomography, whereas radioactive iodine scans were positive in only two of 27 cases. Thyroglobulin was detectable in patients with clinical disease, with the notable exception of five patients with distant metastases. The common TERT C228T promoter mutation was detected in both widely invasive and minimally invasive tumors. TERT mRNA was below the limit of detection in all samples. CONCLUSION: Widely invasive HCC with TNM stage III-IV is aggressive, with low probability of recurrence-free survival. Males have worse outcomes than females. Minimally invasive HCC appears to be considerably less aggressive. Radioactive iodine scan performs poorly in detecting distant disease. Although the TERT gene is mutated in HCC, the role of this mutation remains to be demonstrated.
PubMed-ID: 25259908
http://dx.doi.org/10.1210/jc.2014-1634

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

BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer.
Thyroid, 25(1):71-7.
G. S. Falchook, M. Millward, D. Hong, A. Naing, S. Piha-Paul, S. G. Waguespack, M. E. Cabanillas, S. I. Sherman, B. Ma, M. Curtis, V. Goodman and R. Kurzrock. 2015.
BACKGROUND: Mutations of v-raf murine sarcoma viral oncogene homolog B (BRAF) are commonly identified in papillary and anaplastic thyroid carcinoma and are associated with worse prognosis compared with the wild type. BRAF inhibition in papillary thyroid carcinoma cell lines and xenografts inhibits proliferation and decreases downstream phosphorylation. Our objectives were to analyze safety and efficacy of the selective BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid carcinoma. METHODS: We present the subset of patients with BRAF-mutant thyroid carcinoma enrolled in a larger phase 1 study, the main results of which are reported elsewhere. RESULTS: Fourteen patients with BRAF(V600E)-mutant thyroid carcinoma were enrolled,

of whom 13 (93%) had received prior radioactive iodine. The median duration on treatment was 8.4 months, and seven (50%) patients received treatment for >/=10 months. The most common treatment-related adverse events were skin papillomas (n=8, 57%), hyperkeratosis (n=5, 36%), and alopecia (n=4, 29%), all of which were grade 1. Treatment-related adverse events grade >/=3 included grade 4 elevated lipase and grade 3 elevated amylase, fatigue, febrile neutropenia, and cutaneous squamous cell carcinoma (n=1 for each). Four (29%) partial responses were observed, and nine (64%) patients achieved at least 10% decrease. Only one responder progressed while on the study drug after a response duration of 9.3 months. The other three responders had not progressed, with response duration of 4.6+, 10.4+, and 21.4+ months. With seven (50%) patients showing no progression at the time of study completion, the median progression-free survival was 11.3 months. CONCLUSIONS: Dabrafenib was well tolerated and resulted in durable responses in BRAF-mutant differentiated thyroid carcinoma patients.
PubMed-ID: 25285888
http://dx.doi.org/10.1089/thy.2014.0123

Respiratory variation predicts optimal endotracheal tube placement for intra-operative nerve monitoring in thyroid and parathyroid surgery.
World J Surg, 39(2):393-9.
K. J. Chambers, A. Pearse, J. Coveney, S. Rogers, D. Kamani, N. Sritharan and G. W. Randolph. 2015.
BACKGROUND: Intra-operative nerve monitoring (IONM) of the recurrent laryngeal nerve (RLN) during thyroid and parathyroid surgery is thought to aid in identification and dissection of the RLN. While utilization of IONM is increasing, one area of variability in its application is the assessment of adequate endotracheal tube electrode placement for IONM during the case. The main objective of this study is to assess the overall success of utilizing respiratory variation to confirm proper endotracheal tube placement for RLN monitoring. METHODS: A prospective study of RLN monitoring during thyroid and parathyroid surgery at an academic referral center. RESULTS: Fifty-five cases were included. Fifty (91 %) achieved optimal respiratory variation during endotracheal tube position. Five (9 %) required repeat laryngoscopy to confirm correct endotracheal tube placement following patient positioning. For the respiratory variation group, average amplitude achieved during initial vagus, maximum vagus, initial RLN, and maximal RLN was 700 (+/- 474) mA, 921 (+/- 616) mA, 887 (+/- 584) mA, and 1330 (+/- 843) mA during evoked stimulation, respectively. For the repeat laryngoscopy group, average amplitude achieved during initial vagus, maximum vagus, initial RLN, and maximal RLN evoked stimulation was 591 (+/- 364) mA, 959 (+/- 306) mA, 771 (+/- 424) mA, and 1462 (+/- 855) mA during evoked stimulation, respectively. There was no statistical difference between the two groups for average initial vagus amplitude ($p = 0.62$), average maximum vagus amplitude ($p = 0.89$), average initial RLN amplitude ($p = 0.67$), or average maximum RLN amplitude ($p = 0.74$). CONCLUSION: The findings of this study support the International Neural Monitoring Study Group recommendation that confirmation of endotracheal tube electrode placement be performed either by confirmation of adequate respiratory variation or by repeat direct laryngoscopy.
PubMed-ID: 25297816
http://dx.doi.org/10.1007/s00268-014-2820-8

Genetic predisposition to papillary thyroid carcinoma: involvement of FOXE1, TSHR, and a novel lincRNA gene, PTCSC2.
J Clin Endocrinol Metab, 100(1):E164-72.
H. He, W. Li, S. Liyanarachchi, J. Jendrzejewski, M. Srinivas, R. V. Davuluri, R. Nagy and A. de la Chapelle. 2015.
CONTEXT: By genome-wide association studies, the risk allele [A] of SNP rs965513 predisposes strongly to papillary thyroid carcinoma (PTC). It is located in a gene-poor region of 9q22, some 60 kb from the FOXE1 gene. The underlying mechanisms remain to be discovered. OBJECTIVE: Our objective was to identify novel transcripts in the 9q22 locus and correlate gene expression levels with the genotypes of rs965513. DESIGN: We performed 3' and 5' rapid amplification of cDNA ends and RT-PCR to detect novel transcripts. One novel transcript was forcibly expressed in a cell line followed by gene expression array analysis. We genotyped rs965513 from PTC patients and measured gene expression levels by real-time RT-PCR in unaffected thyroid tissue and matched tumor. SETTING: This was a laboratory-based study using cells from clinical tissue samples and a cancer cell line. MAIN OUTCOME MEASURES: We detected previously uncharacterized transcripts and evaluated the gene expression levels and the correlation with the risk allele of rs965513, age, gender, chronic lymphocyte thyroiditis (CLT), and TSH levels. RESULTS: We found a novel long intergenic noncoding RNA gene and named it papillary thyroid cancer susceptibility candidate 2 (PTCSC2). Transcripts of PTCSC2 are down-regulated in PTC tumors. The risk allele [A] of rs965513 was significantly associated with low expression of unspliced PTCSC2, FOXE1, and TSHR in unaffected thyroid tissue. We also observed a significant association of age and CLT with PTCSC2 unspliced transcript levels. The correlation between the rs965513 genotype and

the PTCSC2 unspliced transcript levels remained significant after adjusting for age, gender, and CLT. Forced expression of PTCSC2 in the BCPAP cell line affected the expression of a subset of noncoding and coding transcripts with enrichment of genes functionally involved in cell cycle and cancer. CONCLUSIONS: Our data suggest a role for PTCSC2, FOXE1, and TSHR in the predisposition to PTC.
PubMed-ID: 25303483
http://dx.doi.org/10.1210/jc.2014-2147

Patient with tracheal duplication cyst clinically misdiagnosed as a thyroid nodule.
J Clin Endocrinol Metab, 100(1):19-20.
A. Shifrin, M. Zheng, S. Jurewicz and J. Vernick. 2015.
PubMed-ID: 25313910
http://dx.doi.org/10.1210/jc.2014-2106

Diagnosis of small papillary thyroid cancer via sensor-navigated (124)iodine PET/ultrasound ((124)I-PET/US) fusion.
J Clin Endocrinol Metab, 100(1):13-4.
M. Freesmeyer, T. Winkens and A. Darr. 2015.
PubMed-ID: 25313915
http://dx.doi.org/10.1210/jc.2014-3003

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

Prognostic significance of thyroglobulin antibody epitopes in differentiated thyroid cancer.
J Clin Endocrinol Metab, 100(1):100-8.
G. A. Lupoli, O. E. Okosieme, C. Evans, P. M. Clark, A. J. Pickett, L. D. Premawardhana, G. Lupoli and J. H. Lazarus. 2015.
CONTEXT: Thyroglobulin antibodies (TgAbs) are surrogate markers of disease recurrence or persistence in differentiated thyroid cancer (DTC). However, the prognostic significance of TgAb heterogeneity in DTC has not been investigated. OBJECTIVE: To evaluate the relationship between TgAb epitope specificities and clinical outcomes in DTC patients. DESIGN: We studied 61 TgAb-positive patients with DTC, post-thyroidectomy and remnant ablation (7 males, 54 females; age-range 16-80 years, median follow-up duration 8.9 years). TgAb epitope reactivities were mapped using a panel of 10 thyroglobulin (Tg) monoclonal antibodies delineating six antigenic Tg clusters in competitive ELISA studies. Sera from 45 patients with Hashimoto's thyroiditis (HT) and 22 TgAb-positive healthy subjects served as autoimmune and healthy controls. Tg was measured by immunoradiometric assay (IRMA), electrochemiluminescence immunoassay (ECLIA), and RIA, while TgAbs was measured by ELISA and ECLIA methods. RESULTS: Samples from 26 DTC patients showed TgAb epitope restriction similar to HT patients, while 35 patients exhibited nonspecific reactivity comparable to healthy controls. DTC patients with epitope restriction had higher rates of recurrent/persistent disease (81% vs 17%, P < .001), higher median TgAb concentration (887.0 vs 82.0 kIU/L; P < .001), and a higher prevalence of thyroid lymphocytic infiltration (71.4% vs 26.8%; P < .001) compared to patients with nonspecific reactivity. Samples with epitope restriction also had a lower median Tg-IRMA/RIA ratio (3.0% vs 36.0%; P < .001) denoting greater degrees of Tg assay interference. CONCLUSIONS: TgAb epitope restriction is associated with a less favorable prognosis than nonspecific reactivity in DTC patients. TgAb epitope specificities may have prognostic value in DTC.
PubMed-ID: 25322272
http://dx.doi.org/10.1210/jc.2014-2725

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

Association between BRAF V600E mutation and recurrence of papillary thyroid cancer.
J Clin Oncol, 33(1):42-50.
M. Xing, A. S. Alzahrani, K. A. Carson, Y. K. Shong, T. Y. Kim, D. Viola, R. Elisei, B. Bendlova, L. Yip, C. Mian, F. Vianello, R. M. Tuttle, E. Robenshtok, J. A. Fagin, E. Puxeddu, L. Fugazzola, A. Czarniecka, B. Jarzab, C. J. O'Neill, M. S. Sywak, A. K. Lam, G. Riesco-Eizaguirre, P. Santisteban, H. Nakayama, R. Clifton-Bligh, G. Tallini,

E. H. Holt and V. Sykorova. 2015.
PURPOSE: To investigate the prognostic value of BRAF V600E mutation for the recurrence of papillary thyroid cancer (PTC). PATIENTS AND METHODS: This was a retrospective multicenter study of the relationship between BRAF V600E mutation and recurrence of PTC in 2,099 patients (1,615 women and 484 men), with a median age of 45 years (interquartile range [IQR], 34 to 58 years) and a median follow-up time of 36 months (IQR, 14 to 75 months). RESULTS: The overall BRAF V600E mutation prevalence was 48.5% (1,017 of 2,099). PTC recurrence occurred in 20.9% (213 of 1,017) of BRAF V600E mutation-positive and 11.6% (125 of 1,082) of BRAF V600E mutation-negative patients. Recurrence rates were 47.71 (95% CI, 41.72 to 54.57) versus 26.03 (95% CI, 21.85 to 31.02) per 1,000 person-years in BRAF mutation-positive versus -negative patients (P < .001), with a hazard ratio (HR) of 1.82 (95% CI, 1.46 to 2.28), which remained significant in a multivariable model adjusting for patient sex and age at diagnosis, medical center, and various conventional pathologic factors. Significant association between BRAF mutation and PTC recurrence was also found in patients with conventionally low-risk disease stage I or II and micro-PTC and within various subtypes of PTC. For example, in BRAF mutation-positive versus -negative follicular-variant PTC, recurrence occurred in 21.3% (19 of 89) and 7.0% (24 of 342) of patients, respectively, with recurrence rates of 53.84 (95% CI, 34.34 to 84.40) versus 19.47 (95% CI, 13.05 to 29.04) per 1,000 person-years (P < .001) and an HR of 3.20 (95% CI, 1.46 to 7.02) after adjustment for clinicopathologic factors. BRAF mutation was associated with poorer recurrence-free probability in Kaplan-Meier survival analyses in various clinicopathologic categories. CONCLUSION: This large multicenter study demonstrates an independent prognostic value of BRAF V600E mutation for PTC recurrence in various clinicopathologic categories.
PubMed-ID: 25332244
http://dx.doi.org/10.1200/JCO.2014.56.8253

Relevance of BRAF(V600E) mutation testing versus RAS point mutations and RET/PTC rearrangements evaluation in the diagnosis of thyroid cancer.
Thyroid, 25(2):221-8.
M. Rossi, M. Buratto, F. Tagliati, R. Rossi, S. Lupo, G. Trasforini, G. Lanza, P. Franceschetti, S. Bruni, E. Degli Uberti and M. C. Zatelli. 2015.
BACKGROUND: A molecular profile including BRAF and RAS mutations as well as RET/PTC rearrangement evaluation has been proposed to provide an accurate presurgical assessment of thyroid nodules and to reduce the number of unnecessary diagnostic surgeries, sparing patients' health and saving healthcare resources. However, the application of such molecular analyses may provide different results among different centers and populations in real-life settings. Our aims were to evaluate the diagnostic utility of assessing the presence of BRAF and RAS mutations and RET/PTC1 and RET/PTC3 rearrangements in all cytological categories in an Italian group of thyroid nodule patients assessed prospectively, and to understand whether and which mutation testing might be helpful in cytologically indeterminate nodules. METHODS: A total of 911 patients were submitted to ultrasound and fine-needle aspiration biopsy examination. Cytological evaluation was performed in parallel with molecular testing and compared to pathological results in 940 thyroid nodules, including 140 indeterminate lesions. RESULTS: BRAF mutation testing provided the best contribution to cancer diagnosis, allowing the disease to be detected at an early stage, and identifying indeterminate nodules in which diagnostic lobectomy could be spared. On the contrary, RAS and RET/PTC analysis did not further increase diagnostic sensitivity for thyroid cancer. In addition, we found RET/PTC rearrangements in benign lesions, indicating that this molecular marker might not be useful for the detection of thyroid cancer. CONCLUSION: BRAF(V600E) mutation analysis is superior to RAS point mutations and evaluation of RET/PTC rearrangements in the diagnosis of thyroid cancer, even in indeterminate lesions.
PubMed-ID: 25333496
http://dx.doi.org/10.1089/thy.2014.0338

Impact of extent of surgery on survival for papillary thyroid cancer patients younger than 45 years.
J Clin Endocrinol Metab, 100(1):115-21.
M. A. Adam, J. Pura, P. Goffredo, M. A. Dinan, T. Hyslop, S. D. Reed, R. P. Scheri, S. A. Roman and J. A. Sosa. 2015.
CONTEXT: Papillary thyroid cancer (PTC) patients <45 years old are considered to have an excellent prognosis; however, current guidelines recommend total thyroidectomy for PTC tumors >1.0 cm, regardless of age. OBJECTIVE: Our objective was to examine the impact of extent of surgery on overall survival (OS) in patients <45 years old with stage I PTC of 1.1 to 4.0 cm. DESIGN, SETTING, AND PATIENTS: Adult patients <45 years of age undergoing surgery for stage I PTC were identified from the National Cancer Data Base (NCDB, 1998-2006) and the Surveillance, Epidemiology, and End RESULTS dataset (SEER, 1988-2006). MAIN OUTCOME MEASURE: Multivariable modeling was used to compare OS for patients undergoing total thyroidectomy vs

lobectomy. RESULTS: In total, 29 522 patients in NCDB (3151 lobectomy, 26 371 total thyroidectomy) and 13 510 in SEER (1379 lobectomy, 12 131 total thyroidectomy) were included. Compared with patients undergoing lobectomy, patients having total thyroidectomy more often had extrathyroidal and lymph node disease. At 14 years, unadjusted OS was equivalent between total thyroidectomy and lobectomy in both databases. After adjustment, OS was similar for total thyroidectomy compared with lobectomy across all patients with tumors of 1.1 to 4.0 cm (NCDB: hazard ratio = 1.45 [confidence interval = 0.88-2.51], P = 0.19; SEER: 0.95 (0.70-1.29), P = 0.75) and when stratified by tumor size: 1.1 to 2.0 cm (NCDB: 1.12 [0.50-2.51], P = 0.78; SEER: 0.95 [0.56-1.62], P = 0.86) and 2.1 to 4.0 cm (NCDB: 1.93 [0.88-4.23], P = 0.10; SEER: 0.94 [0.60-1.49], P = 0.80). CONCLUSIONS: After adjusting for patient and clinical characteristics, total thyroidectomy compared with thyroid lobectomy was not associated with improved survival for patients <45 years of age with stage I PTC of 1.1 to 4.0 cm. Additional clinical and pathologic factors should be considered when choosing extent of resection.
PubMed-ID: 25337927
http://dx.doi.org/10.1210/jc.2014-3039

Personalized therapy in patients with anaplastic thyroid cancer: targeting genetic and epigenetic alterations.
J Clin Endocrinol Metab, 100(1):35-42.
N. Smith and C. Nucera. 2015.
CONTEXT: Anaplastic thyroid cancer (ATC) is the most lethal of all thyroid cancers and one of the most aggressive human carcinomas. In the search for effective treatment options, research toward targeted, personalized therapies is proving to be a path with great potential. As we gain a deeper understanding of the genetic (eg, BRAF(V600E), PIK3CA, TP53, hTERT mutations, etc) and epigenetic (eg, histone methylation, histone de-acetylation, microRNA regulatory circuits, etc) alterations driving ATC, we are able to find targets when developing novel therapies to improve the lives of patients. Beyond development, we can look into the effectiveness of already approved targeted therapies (eg, anti-BRAF(V600E) selective inhibitors, tyrosine kinase inhibitors, histone deacetylase inhibitors, inhibitors of DNA methylation, etc) to potentially test in ATC after learning the molecular mechanisms that aid in tumor progression. DESIGN: We performed a literature analysis in Medline through the PubMed web site for studies published between 2003 and 2014 using the following main keywords: anaplastic thyroid cancer, genetic and epigenetic alterations. OBJECTIVE: Here, we outlined the common pathways that are altered in ATC, including the BRAF(V600E)/ERK1/2-MEK1/2 and PI3K-AKT pathways. We then examined the current research looking into personalized, potential targeted therapies in ATC, mentioning those that have been tentatively advanced into clinical trials and those with the potential to reach that stage. We also reviewed side effects of the current and potential targeted therapies used in patients with advanced thyroid cancer. CONCLUSIONS: DNA and RNA next-generation sequencing analysis will be fundamental to unraveling a precise medicine and therapy in patients with ATC. Indeed, given the deep biological heterogeneity/complexity and high histological grade of this malignancy and its tumor microenvironment, personalized therapeutic approaches possibly based on the use of combinatorial targeted therapy will provide a rational approach when finding the optimal way to improve treatments for patients with ATC.
PubMed-ID: 25347569
http://dx.doi.org/10.1210/jc.2014-2803

Hereditary thyroid cancer syndromes and genetic testing.
J Surg Oncol, 111(1):51-60.
K. J. Rowland and J. F. Moley. 2015.
This review focuses on both hereditary medullary thyroid cancer (MTC) and hereditary nonmedullary thyroid cancer (NMTC) and discusses the genetics, clinical diagnosis and evaluation, and surgical approach to treatment of these malignancies. Areas of innovation as well as areas of debate are highlighted and management recommendations are made.
PubMed-ID: 25351655
http://dx.doi.org/10.1002/jso.23769

Efficacy and tolerability of vemurafenib in patients with BRAF(V600E) -positive papillary thyroid cancer: M.D. Anderson Cancer Center off label experience.
J Clin Endocrinol Metab, 100(1):E77-81.
R. Dadu, K. Shah, N. L. Busaidy, S. G. Waguespack, M. A. Habra, A. K. Ying, M. I. Hu, R. Bassett, C. Jimenez, S. I. Sherman and M. E. Cabanillas. 2015.
CONTEXT: Vemurafenib, a selective BRAF inhibitor, appears to have promising clinical activity in patients with papillary thyroid cancer (PTC) harboring the BRAF(V600E) mutation. OBJECTIVE: To determine the efficacy

and safety of vemurafenib when used outside of a clinical trial. DESIGN: A retrospective review at MD Anderson Cancer Center. METHODS: The best responses were evaluated using RECIST v1.1. A single radiologist reviewed all images. Adverse events (AEs) were evaluated using CTCAE v.4.0. RESULTS: We identified 17 patients with advanced PTC harboring the BRAF(V600E) mutation who were treated with vemurafenib outside of a clinical trial. Median age at diagnosis was 63 years, and 53% were male. At vemurafenib start, 3 (18%) patients had disease confined to the neck, and 14 (72%) had distant metastases. Tyrosine kinase inhibitors had been previously administered to 4 (24%) patients. Two (12%) patients discontinued vemurafenib because of AEs before restaging. Best response: partial response (PR) in 7/15 (47%) and stable disease (SD) in 8/15(53%) patients. The rate of durable response (PR plus SD >/= 6 months) was 67%. Median time to treatment failure was 13 months. There was no association between change in thyroglobulin and tumor size. Drug discontinuation, drug interruptions, and dose reductions were needed in 5 (29%), 13 (76%), and 10 (59%) patients, respectively. Most common AEs were fatigue (71%), weight loss (71%), anorexia (65%), arthralgias (59%), hair loss (59%), rash (59%), hand-foot syndrome (53%), calluses (47%), diarrhea (47%), fever (41%), dry mouth (35%), nausea (35%), and verrucous keratosis (35%). Grade >/= 3 AEs were present in 8 (47%) patients. CONCLUSIONS: Vemurafenib is a potentially effective and well-tolerated treatment strategy in patients with advanced PTC harboring the BRAF(V600E) mutation. Our results are similar to those reported in a phase II clinical trial and support the potential role of vemurafenib in this patient population.
PubMed-ID: 25353071
http://dx.doi.org/10.1210/jc.2014-2246

Comparison of the incidence of postoperative hypocalcemia following total thyroidectomy vs completion thyroidectomy.
Otolaryngol Head Neck Surg, 152(1):53-6.
S. Merchavy, T. Marom, V. I. Forest, M. Hier, A. Mlynarek, T. McHugh and R. Payne. 2015.
OBJECTIVE: To study the rate of postoperative hypocalcemia following completion thyroidectomy (CT), in comparison with the hypocalcemia rate following total thyroidectomy (TT). STUDY DESIGN AND SETTING: A retrospective study, performed at the McGill University Thyroid Cancer Center, Montreal, Quebec, Canada, from 2007 to 2012. SUBJECTS AND METHODS: Medical records of adult patients undergoing CT and TT operated by a single surgeon were reviewed. Data were extracted for demographics, postoperative calcium levels, surgical logs, and final surgical pathology. Hypocalcemia was defined as corrected serum calcium level </= 1.90 mmol/L, with concurrent serum parathyroid hormone <8 ng/L, and/or any signs or symptoms of hypocalcemia. RESULTS: There were 68 CTs and 146 TTs. Transient hypocalcemia occurred in 1 of 68 (1.5%) and 18 of 146 (12.5%) patients in the CT and TT groups, respectively. The rate of hypocalcemia was significantly lower in the CT compared with the TT group (P = .02). In both groups, there were no cases of permanent hypocalcemia. CONCLUSION: The risk of transient of hypocalcemia in patients undergoing CT is significantly lower than the rate of hypocalcemia in patients undergoing TT.
PubMed-ID: 25358344
http://dx.doi.org/10.1177/0194599814556250

Analysis of age and disease status as predictors of thyroid cancer-specific mortality using the Surveillance, Epidemiology, and End Results database.
Thyroid, 25(1):125-32.
R. K. Orosco, T. Hussain, K. T. Brumund, D. K. Oh, D. C. Chang and M. Bouvet. 2015.
BACKGROUND: Age at diagnosis is incorporated into all relevant staging systems for differentiated thyroid carcinoma (DTC). There is growing evidence that a specific age cutoff may not be ideal for accurate risk stratification. We sought to evaluate the interplay between age and oncologic variables in patients with DTC using the largest cohort to date. METHODS: The Surveillance, Epidemiology, and End RESULTS (SEER) database was queried to identify patients with DTC as their only malignancy for the period 1973 to 2009. Multivariate analyses using a range of age cutoffs and age subgroupings were utilized in order to search for an optimal age that would provide the most significant risk stratification between young and old patients. The primary outcome was disease-specific survival (DSS) and covariates included: age, race, sex, tumor/nodal/metastasis (TNM) stage, decade of diagnosis, and radioactive iodine therapy. RESULTS: A total of 85,740 patients were identified. Seventy-six percent of patients were American Joint Committee on Cancer (AJCC) stage I, 8% were stage II, 7% were stage III, and 8% were stage IV. Age over 45 years (hazard ratio [HR] 19.2, p<0.001) and metastatic disease (HR 13.1, p<0.001) were the strongest predictors of DSS. Other factors that significantly predicted DSS included: not receiving radioactive iodine (RAI; HR 1.3, p=0.002), T3 (HR 2.6, p<0.001), and T4 disease (HR 3.3, p<0.001), and nodal spread (HR 2.6 to 3.3, p<0.001). Female sex showed a significant protective effect (HR 0.7, p=0.001). Adjusting the age-group cutoff from 25 to 55 years showed consistently high HRs for advanced age, without a distinct change at any point. Comparing HRs for T, N,

and M stage between young and old patient subgroups showed that advanced disease increased the risk for DSS regardless of age, and was oftentimes a worse prognosticator in young patient groups. CONCLUSIONS: The contribution of age at diagnosis to a patient's DSS is considerable, but there is no age cutoff that affords any unique risk-stratification in patients with DTC.
PubMed-ID: 25369076
http://dx.doi.org/10.1089/thy.2014.0116

Clinical review: Thyroid cancer mimics on surveillance neck sonography.
J Clin Endocrinol Metab, 100(2):371-5.
K. Kobaly, S. J. Mandel and J. E. Langer. 2015.
Sonography of the neck is a critical tool in monitoring patients after near-total thyroidectomy for differentiated thyroid cancer. Sonography has proven to be among the most sensitive imaging techniques for the detection of recurrent or residual cancer in the thyroidectomy bed and metastatic cervical lymph nodes. It is important for the sonologist to be familiar with normal postsurgical findings and other disease processes that may imitate malignant lesions. We describe the typical sonographic appearance of benign lesions that can resemble recurrent thyroid cancer.
PubMed-ID: 25375984
http://dx.doi.org/10.1210/jc.2014-2881

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

Voice assessment and voice-related quality of life in patients with benign thyroid disease.
Otolaryngol Head Neck Surg, 152(1):116-21.
A. Pernambuco Lde, M. N. de Almeida, K. G. Matias and E. B. Costa. 2015.
OBJECTIVE: To identify the relationship between vocal self-assessment, the assessment of voice by a speech-language pathologist (SLP), and the effect of voice on the quality of life of patients with benign thyroid diseases. STUDY DESIGN: Cross-sectional study. SETTING: University hospital. SUBJECTS AND METHOD: A total of 67 women with a mean age of 44.7 +/- 14.8 years and a diagnosis of benign thyroid disease were included in the study. Vocal self-assessment and SLP assessment were performed using a visual analogue scale (VAS). The Voice-related Quality of Life Questionnaire (V-RQOL) was used to identify the effect of voice on quality of life. The Mann-Whitney and Kruskal-Wallis nonparametric tests were used. Correlations between assessments were verified by the Spearman correlation test. The significance level was 5%. RESULTS: Patients with vocal complaints had lower scores in all assessments. Patients with thyroid nodules performed worse on the SLP assessment and on the physical functioning domain of V-RQOL. A moderate correlation was found between the self-assessment and quality of life and between the physical functioning domain of V-RQOL and the SLP assessment. A weak correlation existed between the self-assessment and the SLP assessment. CONCLUSION: Patients with benign thyroid diseases had lower scores in vocal self-assessment, the clinical evaluation of voice,

and the V-RQOL. These dimensions of voice assessment showed correlations ranging from mild to moderate and should complement the clinical routine.
PubMed-ID: 25389320
http://dx.doi.org/10.1177/0194599814557468

Cancer-related worry in Canadian thyroid cancer survivors.
J Clin Endocrinol Metab, 100(3):977-85.
L. Bresner, R. Banach, G. Rodin, L. Thabane, S. Ezzat and A. M. Sawka. 2015.
CONTEXT: Little is known about cancer-related worry in thyroid cancer survivors. OBJECTIVES: We quantified cancer-related worry in Canadian thyroid cancer survivors and explored associated factors. DESIGN, SETTING, AND PARTICIPANTS: We performed a cross-sectional, self-administered, written survey of thyroid cancer survivor members of the Thyroid Cancer Canada support group. Independent factors associated with cancer-related worry were identified using a multivariable linear regression analysis. MAIN OUTCOME MEASURE: We used the Assessment of Survivor Concerns (ASC) questionnaire, which includes questions on worry about diagnostic tests, second primary malignancy, recurrence, dying, health, and children's health. RESULTS: The response rate for eligible members was 60.1% (941 of 1567). Most respondents were women (89.0%; 837 of 940), and the age was < 50 years in 54.0% of participants (508 of 941). Thyroid cancer was diagnosed within </= 5 years in 66.1% of participants (622 of 940). The mean overall ASC score was 15.34 (SD, 4.7) (on a scale from 6 [least worry] to 24 [most worry]). Factors associated with increased ASC score included: younger age (P < .001), current suspected or proven recurrent/persistent disease (ie, current proven active disease or abnormal diagnostic tests) (P < .001), partnered marital status (P = .021), having children (P = .029), and </=5 years since thyroid cancer diagnosis (P = .017). CONCLUSIONS: In a population of Canadian thyroid cancer survivors, cancer-related worry was greatest in younger survivors and those with either confirmed or suspected disease activity. Family status and time since thyroid cancer diagnosis were also associated with increased worry. More research is needed to confirm these findings and to develop effective preventative and supportive strategies for those at risk.
PubMed-ID: 25393643
http://dx.doi.org/10.1210/jc.2014-3169

Transaxillary thyroidectomy-A critical appraisal.
J Surg Oncol, 111(2):131-2.
A. R. Shaha. 2015.
PubMed-ID: 25411137
http://dx.doi.org/10.1002/jso.23831

Comprehensive assessment of the disputed RET Y791F variant shows no association with medullary thyroid carcinoma susceptibility.
Endocr Relat Cancer, 22(1):65-76.
R. A. Toledo, R. Hatakana, D. M. Lourenco, Jr., S. C. Lindsey, C. P. Camacho, M. Almeida, J. V. Lima, Jr., T. Sekiya, E. Garralda, M. S. Naslavsky, G. L. Yamamoto, M. Lazar, O. Meirelles, T. J. Sobreira, M. L. Lebrao, Y. A. Duarte, J. Blangero, M. Zatz, J. M. Cerutti, R. M. Maciel and S. P. Toledo. 2015.
Accurate interpretation of germline mutations of the rearranged during transfection (RET) proto-oncogene is vital for the proper recommendation of preventive thyroidectomy in medullary thyroid carcinoma (MTC)-prone carriers. To gain information regarding the most disputed variant of RET, ATA-A Y791F, we sequenced blood DNA samples from a cohort of 2904 cancer-free elderly individuals (1261 via Sanger sequencing and 1643 via whole-exome/genome sequencing). We also accessed the exome sequences of an additional 8069 individuals from non-cancer-related laboratories and public databanks as well as genetic results from the Catalogue of Somatic Mutations in Cancer (COSMIC) project. The mean allelic frequency observed in the controls was 0.0031, with higher occurrences in Central European populations (0.006/0.008). The prevalence of RET Y791F in the control databases was extremely high compared with the 40 known RET pathogenic mutations (P=0.00003), while no somatic occurrence has been reported in tumours. In this study, we report new, unrelated Brazilian individuals with germline RET Y791F-only: two tumour-free elderly controls; two individuals with sporadic MTC whose Y791F-carrying relatives did not show any evidence of tumours; and a 74-year-old phaeochromocytoma patient without MTC. Furthermore, we showed that the co-occurrence of Y791F with the strong RET C634Y mutation explains the aggressive MTC phenotypes observed in a large affected family that was initially reported as Y791F-only. Our literature review revealed that limited analyses have led to the misclassification of RET Y791F as a probable pathogenic variant and, consequently, to the occurrence of unnecessary thyroidectomies. The current study will have a substantial clinical influence, as it reveals, in a comprehensive manner, that RET Y791F only shows no association with MTC susceptibility.

PubMed-ID: 25425582
http://dx.doi.org/10.1530/ERC-14-0491

Development and characterization of six new human papillary thyroid carcinoma cell lines.
J Clin Endocrinol Metab, 100(2):E243-52.
Y. C. Henderson, S. H. Ahn, J. Ryu, Y. Chen, M. D. Williams, A. K. El-Naggar, M. Gagea, R. E. Schweppe, B. R. Haugen, S. Y. Lai and G. L. Clayman. 2015.
CONTEXT: Cell lines are a widely used tool in cancer research. However, despite the relatively high incidence of papillary thyroid carcinoma (PTC), there are only four PTC cell lines available for international research audience. OBJECTIVE: The objective of this study was to establish and characterize new PTC cell lines that represent primary tumor biology. Surgical specimens were obtained to generate PTC cell lines. Short tandem repeat profiling was used to confirm the uniqueness of the cell lines against databases of known cell lines and mutations were assessed using Sequenom. The expression of thyroid-specific genes was examined using real-time PCR. Tumorigenicity was determined using an orthotopic thyroid xenograft tumor mouse model. RESULTS: Six PTC cell lines (five conventional PTCs and one follicular variant of PTC) were generated and found to be unique when compared by short tandem repeat profiling against databases of all existing cell lines. The five conventional PTC cell lines carry the BRAF V600E mutation and the follicular variant of PTC cell line had an NRAS mutation. Five of the six cell lines had a mutation in the promoter of the human telomerase reverse transcriptase gene. None of the cell lines have RET/PTC rearrangements. Three cell lines were tumorigenic in the orthotopic thyroid xenograft tumor mouse model. CONCLUSIONS: These five characterized conventional PTC cell lines and the unique follicular variant of PTC cell line should be valuable reagents for thyroid cancer research. The three tumorigenic cell lines can be used for in vivo testing of targeted therapeutic and novel agents.
PubMed-ID: 25427145
http://dx.doi.org/10.1210/jc.2014-2624

Identification of a Hashimoto thyroiditis susceptibility locus via a genome-wide comparison with Graves' disease.
J Clin Endocrinol Metab, 100(2):E319-24.
D. Oryoji, S. Ueda, K. Yamamoto, J. Yoshimura Noh, K. Okamura, M. Noda, N. Watanabe, A. Yoshihara, K. Ito and T. Sasazuki. 2015.
BACKGROUND: Hashimoto thyroiditis (HT) and Graves' disease (GD) share some immunological features. Determining the genetic basis that distinguishes HT from GD is key for a better understanding of the differences between these two related diseases. AIM: The aim of this study was to identify a non-HLA susceptibility locus that is specific to either HT or GD. DESIGN: We performed a two-stage genome-wide comparison between HT and GD in Japan. During the discovery stage, we performed a logistic regression analysis adjusting for sex using 727 413 single nucleotide polymorphisms (SNPs) for 265 HT and 261 GD patients. During the replication stage, 35 SNPs were analyzed for 181 HT and 286 GD cases. A combined meta-analysis was performed using the results from these two stages. An SNP showing a genome-wide significant level was further analyzed using 1363 healthy controls to determine the specificity of susceptibility. RESULTS: A genome-wide direct comparison between HT and GD revealed an SNP at the VAV3 locus with genome-wide significant association signals (rs7537605: P(combined) = 3.90 x 10(-8); odds ratio(combined) = 1.77; 95% confidence interval = 1.44-2.17). An association analysis using healthy controls showed that rs7537605 is significantly associated with HT (P = 1.24 x 10(-5); odds ratio = 1.60; 95% confidence interval = 1.30-1.97) but not with GD (P = .50), suggesting that the variant specifically affects susceptibility to HT. CONCLUSION: A genome-wide direct comparison between HT and GD revealed an HT-specific variant within VAV3 in the Japanese. Considering physiological roles of VAV3, such as a guanine nucleotide exchange factor, our finding provides new insight into the molecular mechanism of HT.
PubMed-ID: 25429627
http://dx.doi.org/10.1210/jc.2014-3431

Surgery for recurrent goiter: complication rate and role of the thyroid-stimulating hormone-suppressive therapy after the first operation.
Langenbecks Arch Surg, 400(2):253-8.
P. Miccoli, G. Frustaci, A. Fosso, M. Miccoli and G. Materazzi. 2015.
PURPOSE: This report examines outcomes in our series of patients who underwent surgery for recurrent goiter to assess the efficacy of thyroid-stimulating hormone (TSH)-suppressive therapy after the first less than total thyroidectomy. A further outcome was to understand whether redo surgery was burdened with a higher rate of complications. METHODS: We evaluated 214 patients undergoing a completion thyroidectomy for recurrent

goiter who had received, as their first surgery, a bilateral subtotal thyroidectomy. After the first operation, 84 patients were given TSH-suppressive therapy with levothyroxine, 32 were treated with antithyroid drugs, and 92 did not receive any suppressive treatment but only a substitutive therapy. The 84 patients who received levothyroxine at a suppressive dosage (group A) were compared with 92 patients who did not receive levothyroxine or received it only at substitutive dosage (group B). We further compared the complication rate of a similar group of 175 patients who had undergone a primary thyroidectomy. RESULTS: The average age at intervention for relapse in group A patients was significantly lower than that of group B patients: 54.18 vs 60.8 years ($p < 0.001$). The average interval between the first intervention and the intervention for relapse was significantly shorter in group A than in group B: 24 vs 27 years ($p = 0.03$). After the operation, temporary hypoparathyroidism occurred in 37.7 % of patients and definitive hypoparathyroidism in 7.2 %. CONCLUSIONS: Our results clearly show that the interval between the two surgical interventions was significantly reduced in patients undergoing TSH-suppressive therapy with levothyroxine. The incidence of hypoparathyroidism dramatically increased.
PubMed-ID: 25432523
http://dx.doi.org/10.1007/s00423-014-1258-7

Papillary thyroid microcarcinomas located at the middle part of the middle third of the thyroid gland correlates with the presence of neck metastasis.
Surgery, 157(3):526-33.
D. Xiang, L. Xie, Y. Xu, Z. Li, Y. Hong and P. Wang. 2015.
BACKGROUND: Papillary thyroid microcarcinomas (PTMCs), located at upper poles of the thyroid, are associated with lateral neck metastasis (LNM) according to previous reports. Controversy remains regarding the correlation between the location of PTMCs and central neck metastasis (CNM). METHODS: Medical records of 949 patients with PTMCs diagnosed between 2010 and 2013 were reviewed retrospectively. With a subdivision of the middle third of the thyroid gland, correlations between tumor location and CNM/LNM along with other clinicopathologic factors were analyzed by binary logistic regression. RESULTS: PTMCs located in the middle part of the middle third of the thyroid gland (MPMT) showed the greatest rate of CNM (57.5%) among all locations. PTMCs located at isthmus showed the second greatest rate of CNM (44.3%). In the multivariate analysis, MPMT, tumor size >0.5 cm, young and middle age, male sex, multifocality within the affected lobe, and capsular invasion were correlated with CNM. PTMCs located at upper poles and MPMT showed comparatively high rates of LNM (8.6% and 8.3%). Consistent with previous reports, an upper pole location, MPMT, and a tumor size >0.5 cm greatly correlated with LNM in the multivariate analysis. Eleven patients had skip metastases, which only occurred with upper/lower pole locations and MPMT. CONCLUSION: PTMCs located in the MPMT correlated with both CNM and LNM. Tumor location along with other clinicopathologic factors such as young and middle age, male sex, and tumor size >0.5 cm could facilitate preoperative stratification and guide operative management for patients with PTMC.
PubMed-ID: 25433730
http://dx.doi.org/10.1016/j.surg.2014.10.020

Central lymph node metastasis in papillary thyroid microcarcinoma can be stratified according to the number, the size of metastatic foci, and the presence of desmoplasia.
Surgery, 157(1):111-8.
S. Y. Cho, T. H. Lee, Y. H. Ku, H. I. Kim, G. H. Lee and M. J. Kim. 2015.
BACKGROUND: Lymph node (LN) metastasis is common in papillary thyroid microcarcinoma (PTMC). The aim of this study was to investigate the impact of LN metastasis and its risk stratification on PTMC recurrence. METHODS: We retrospectively reviewed the data of 336 patients with PTMC who underwent surgery from 2005 to 2006 at a single institution. LN metastasis was stratified according to the number of metastatic LNs, the ratio of metastatic to removed LNs, the size of metastatic foci in LNs, and the presence of extranodal extension and desmoplasia. RESULTS: Of the 336 patients, 93 (28%) had LN metastasis. During the follow-up of 5.3 years, 16 (4.8%) experienced locoregional recurrence. Among several clinicopathologic factors, LN metastasis was the most important risk factor for recurrence ($P = .02$). Lateral LN metastasis was correlated with recurrence-free survival ($P < .01$), whereas central LN metastasis was not ($P = .20$). When central LN metastasis was stratified, a high number of metastatic LNs (>/=3), larger metastatic foci (>/=0.2 cm), and the presence of desmoplasia were associated with recurrence-free survival ($P < .05$). CONCLUSION: The prognostic significance of central LN metastasis can differ according to the number of metastatic LNs, the size of metastatic foci, and the presence of desmoplasia. Patients with a high number of metastatic LNs, larger metastatic foci, and presence of desmoplasia in LNs should be treated aggressively and supervised carefully for PTMC recurrence.
PubMed-ID: 25444224
http://dx.doi.org/10.1016/j.surg.2014.05.023

Papillary thyroid carcinoma with exclusive involvement of a functioning recurrent laryngeal nerve may be treated with shaving technique.
World J Surg, 39(4):969-74.
H. S. Lee, S. W. Kim, T. Park, G. Y. Nam, J. C. Hong and K. D. Lee. 2015.
OBJECTIVES: We sought to validate the feasibility of preserving a functioning recurrent laryngeal nerve (RLN) invaded by papillary thyroid carcinoma (PTC) using a shaving technique followed by high-dose radioactive iodine (RAI) therapy. METHODS: A retrospective review of 34 patients with locally invasive PTC who had exclusive tumor involvement of a functioning RLN was performed. All patients underwent total thyroidectomy and high-dose RAI therapy. A shaving technique was conducted with the goal of leaving the smallest amount of residual tumor as possible while attempting to preserve nerve function. Clinicopathologic factors and oncologic outcomes of the patients with resected RLN (group A, n = 14) and preserved RLN (group B, n = 20) were compared. RESULTS: The two groups showed no differences in clinicopathologic factors or follow-up period. Mean dose of radioiodine therapy was 245.0 +/- 140.3 mCi (range 100-540 mCi). Permanent postoperative vocal cord paralysis after RLN shaving occurred in two patients of group B (10%). Only one patient (5%) in group B had local recurrence at the thyroid bed where the residual tumor was located. The overall recurrence rate was 35.7% (5/14) and 20.0% (4/20) in groups A and B, respectively showing no significant difference (p = 0.525). There were no cases of death due to PTC during the median follow-up of 75 months (range 36-159 months). CONCLUSIONS: Patients with locally invasive PTC with exclusive involvement of a functioning RLN may be treated by nerve shaving followed by treatment of the macroscopic residual tumor with high-dose RAI therapy.
PubMed-ID: 25446493
http://dx.doi.org/10.1007/s00268-014-2906-3

Severe vitamin D deficiency: a significant predictor of early hypocalcemia after total thyroidectomy.
Otolaryngol Head Neck Surg, 152(3):424-31.
T. Al-Khatib, A. M. Althubaiti, A. Althubaiti, H. H. Mosli, R. O. Alwasiah and L. M. Badawood. 2015.
OBJECTIVE: To assess the role of preoperative serum 25 hydroxyvitamin D as predictor of hypocalcemia after total thyroidectomy. STUDY DESIGN: Retrospective cohort study. SETTING: University teaching hospital. SUBJECTS AND METHODS: All consecutively performed total and completion thyroidectomies from February 2007 to December 2013 were reviewed through a hospital database and patient charts. The relationship between postthyroidectomy laboratory hypocalcemia (serum calcium</=2 mmol/L), clinical hypocalcemia, and preoperative serum 25 hydroxyvitamin D level was evaluated. RESULTS: Two hundred thirteen patients were analyzed. The incidence of postoperative laboratory and clinical hypocalcemia was 19.7% and 17.8%, respectively. The incidence of laboratory and clinical hypocalcemia among severely deficient (<25 nmol/L), deficient (<50 nmol/L), insufficient (<75 nmol/L), and sufficient (>/=75 nmol/L) serum 25 hydroxyvitamin D levels was 54% versus 33.9%, 10% versus 18%, 2.9% versus 11.6%, and 3.1% versus 0%, respectively. Multiple logistic regression analysis revealed preoperative severe vitamin D deficiency as a significant independent predictor of postoperative hypocalcemia (odds ratio [OR], 7.3; 95% confidence interval [CI], 2.3-22.9; P=.001). Parathyroid hormone level was also found to be an independent predictor of postoperative hypocalcemia (OR, 0.6; 95% CI, 0.5-0.8; P=.002). CONCLUSION: Postoperative clinical and laboratory hypocalcemia is significantly associated with low levels of serum 25 hydroxyvitamin D. Our findings identify severe vitamin D deficiency (<25 nmol/L) as an independent predictor of postoperative laboratory hypocalcemia. Early identification and management of patients at risk may reduce morbidity and costs.
PubMed-ID: 25475499
http://dx.doi.org/10.1177/0194599814561209

Impact of clinical risk scores and BRAF V600E mutation status on outcome in papillary thyroid cancer.
Surgery, 157(1):119-25.
S. M. Niederer-Wust, W. Jochum, D. Forbs, M. Brandle, S. Bilz, T. Clerici, R. Oettli, J. Muller, S. R. Haile, S. Ess, S. J. Stoeckli and M. A. Broglie. 2015.
BACKGROUND: To evaluate the relationship between the BRAF V600E mutation and clinicopathologic parameters and to assess the impact of the BRAF V600E mutation and established risk scores on survival in patients with papillary thyroid carcinoma (PTC). METHODS: Retrospective analysis of a consecutive, single-institutional cohort of patients with PTC larger than 1 cm. Clinical risk scores according to the Metastases, Age, Completeness of Resection, Invasion, Size (MACIS), European Organisation for Research and Treatment of Cancer (EORTC), and tumor, node, metastases (TNM) scoring systems were determined. BRAF exon 15 mutation analysis was performed by polymerase chain reaction and Sanger sequencing. RESULTS: BRAF V600E mutations were found in 75/116 (65%) PTC. The rates for 5- and 10-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were 92% and 87%, 98% and 96%, and 96% and

94%, respectively. Low MACIS scores were associated with longer OS (10 y 95% vs 75%, P = .008), DSS (10 y 100% vs 89%, P = .02) and RFS (100% vs 85%, P = .006). Comparable survival advantages were observed for patients with early EORTC scores and low TNM stage. BRAF V600E mutation status was not associated with clinicopathologic characteristics of aggressive behavior such as extrathyroidal extension, lymph node metastases, higher T-categories, male sex, and greater age. Furthermore, BRAF V600E mutation status was not correlated with clinical risk scores and decreased survival. CONCLUSION: In concordance with other studies, we did not find a negative prognostic impact of a positive BRAF V600E mutation status on survival. In contrast, the risk algorithms MACIS, EORTC score, and TNM stage were associated with impaired prognosis. Therefore, clinical staging systems represent better tools for risk stratification than BRAF V600E mutation status.
PubMed-ID: 25482468
http://dx.doi.org/10.1016/j.surg.2014.07.015

Medullary thyroid cancer with undetectable serum calcitonin.
J Clin Endocrinol Metab, 100(2):337-41.
E. F. Brutsaert, A. J. Gersten, A. B. Tassler and M. I. Surks. 2015.
CONTEXT: Calcitonin is a sensitive biomarker that is used for diagnosis and follow-up in medullary thyroid cancer (MTC). In patients with tumors > 1 cm, it is uncommon for preoperative serum calcitonin to be in the normal laboratory reference range in patients with MTC, and even more unusual for serum calcitonin to be undetectable. THE CASE: A 39-year-old woman was found to have a left thyroid nodule on magnetic resonance imaging done for neck pain. Ultrasound and fine-needle aspiration biopsy were performed, and cytopathology was positive for malignant cells. The cells also had features suggestive of a neuroendocrine tumor, and the specimen was immune-stained with calcitonin. There was positive immunoreactivity for calcitonin in isolated cells of the cytospin, highly favoring a diagnosis of MTC. Serum calcitonin was < 2 pg/mL (<6 pg/mL), and serum carcinoembryonic antigen was 3.1 ng/mL (<5.2 ng/mL). Given the low calcitonin levels, procalcitonin was also tested and was elevated at 0.21 ng/mL (< 0.1 ng/mL). The patient subsequently underwent a total thyroidectomy and central and ipsilateral lateral lymph node dissection. Histopathology confirmed a 2.6 x 2.0 x 1.2-cm MTC, with strong, diffuse immunostaining for calcitonin. Postoperatively, serum calcitonin has remained undetectable, carcinoembryonic antigen has remained within the reference range, and procalcitonin has become undetectable. CONCLUSIONS: We present a rare case of a patient with MTC with undetectable preoperative serum calcitonin, whose tumor demonstrated strong, diffuse immunohistochemical staining for calcitonin. We discuss the possible pathogenesis of calcitonin-negative MTC and the challenges in following patients with this condition.
PubMed-ID: 25490273
http://dx.doi.org/10.1210/jc.2014-3095

[Intraoperative avoidance and recognition of recurrent laryngeal nerve palsy in thyroid surgery].
Chirurg, 86(1):6-12.
D. Simon, M. Boucher and P. Schmidt-Wilcke. 2015.
Recurrent laryngeal nerve palsy is an intrinsic complication of thyroid surgery. Prevention of nerve palsy is considered to be a feature of quality in this very frequently performed operation. Risk factors and prevention strategies are demonstrated and discussed with reference to the current literature. Exact knowledge of the anatomy and possible variants of the track of the recurrent laryngeal nerve as well as its visualization and careful dissection are the cornerstones for nerve preservation. The use of intraoperative neuromonitoring allows preservation of the anatomical structure and functional integrity of the nerve and lesions which are not visible can be detected. Preconditions for correct interpretation are a standardized application and preoperative and postoperative laryngoscopy.
PubMed-ID: 25502321
http://dx.doi.org/10.1007/s00104-014-2816-9

[Avoidance and management of hypoparathyroidism after thyroid gland surgery].
Chirurg, 86(1):13-6.
A. Selberherr and B. Niederle. 2015.
Postoperative hypoparathyroidism after bilateral thyroid gland surgery or after interventions for recurrence is defined as intact parathyroid hormone levels (iPTH) < 15 pg/ml with simultaneous normal, below normal and markedly decreased serum calcium levels. After bilateral thyroid surgery and after reoperations a single iPTH measurement performed 12-24 h postoperatively can be used to predict parathyroid metabolism. Patients with an iPTH level >/= 15 pg/ml may be discharged safely, patients with an iPTH < 10 pg/ml must be substituted with calcium and vitamin D and patients with an iPTH between 10 and 15 pg/ml (grey zone) may be discharged if a second measurement 48 h after surgery documents an iPTH >/= 15 pg/ml. This procedure increases the length of hospital stay. Patients in the (grey zone) must be substituted. The iPTH level and its course determine the

necessity, dose and length of calcium and vitamin D substitution.
PubMed-ID: 25502498
http://dx.doi.org/10.1007/s00104-014-2817-8

Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment.
Surgery, 157(2):349-53.
A. Selberherr, C. Scheuba, P. Riss and B. Niederle. 2015.
BACKGROUND: To describe a standardized, efficient, and cost-effective protocol for the diagnosis of temporary/persisting postoperative hypoparathyroidism after (total) thyroidectomy. METHODS: We included 237 consecutive patients who underwent (total) thyroidectomy without central neck dissection for various indications. Serum calcium (sCa) and intact parathyroid hormone (iPTH) levels were measured prospectively on the morning of postoperative day 1 to predict the long-term parathyroid metabolism. On the morning of postoperative day 2, measurements were repeated. Follow-up was performed at 1 and 6 months postoperatively. RESULTS: On the morning of postoperative day 1, patients with iPTH >/= 15 pg/mL (178/237; 75%) and sCa > 2.0 mmol/L were normocalcemic, and "normal" parathyroid metabolism was predicted. iPTH levels of <10 pg/mL and sCa levels of </=2.0 mmol/L were present in 33 of the 237 patients ("disturbed" parathyroid metabolism; 14%). A "gray zone" included patients with "uncertain" parathyroid metabolism demonstrating iPTH levels between 10 and 15 pg/mL (26/237; 11%). Patients with "disturbed" and "uncertain" parathyroid metabolism were given oral calcium and vitamin D. On the morning of the second postoperative day, iPTH turned to "normal" in 10 of those 26 (38%) patients, and no further calcium or vitamin D was given. During follow-up, supplemental calcium and vitamin D was able to be stopped in all but 2 patients ("permanent" hypoparathyroidism; 2/237; 0.8%). CONCLUSION: Measurement of iPTH on the morning after operation allows accurate prediction of postoperative parathyroid function in >/=99% of cases. This simple recommendation is practicable in all surgical units, and is an efficient and cost-effective way to recognize patients who require calcium and vitamin D supplementation.
PubMed-ID: 25532435
http://dx.doi.org/10.1016/j.surg.2014.09.007

[Management of postoperative hemorrhage following thyroid surgery].
Chirurg, 86(1):17-23.
K. Lorenz, C. Sekulla, J. Kern and H. Dralle. 2015.
The incidence of postoperative hemorrhage following thyroid surgery stands at 1%-2 %. This low incidence contrasts with the significant potential complications of postoperative hemorrhage. Influencing factors and measures mentioned in the literature and own studies are discussed. Although an improvement in the postoperative hemorrhage rate was to be expected indirectly due to the increasing use of coagulation-relevant medication, there has been neither an increase in incidence nor a reduction in resultant complications, including primarily recurrent vocal cord paresis, tracheotomy and mortality. Factors that influence surgical success include a meticulous technique and caution, as well as ensuring intensive and qualified postoperative monitoring for a minimum of 4-6 h, thereby permitting immediate revision surgery at any time.
PubMed-ID: 25532753
http://dx.doi.org/10.1007/s00104-014-2818-7

RET fusion as a novel driver of medullary thyroid carcinoma.
J Clin Endocrinol Metab, 100(3):788-93.
E. G. Grubbs, P. K. Ng, J. Bui, N. L. Busaidy, K. Chen, J. E. Lee, X. Lu, H. Lu, F. Meric-Bernstam, G. B. Mills, G. Palmer, N. D. Perrier, K. L. Scott, K. R. Shaw, S. G. Waguespack, M. D. Williams, R. Yelensky and G. J. Cote. 2015.
INTRODUCTION: Oncogenic RET tyrosine kinase gene fusions and activating mutations have recently been identified in lung cancers, prompting initiation of targeted therapy trials in this disease. Although RET point mutation has been identified as a driver of tumorigenesis in medullary thyroid carcinoma (MTC), no fusions have been described to date. OBJECTIVE: We evaluated the role of RET fusion as an oncogenic driver in MTC. METHODS: We describe a patient who died from aggressive sporadic MTC < 10 months after diagnosis. Her tumor was evaluated by means of next-generation sequencing, including an intronic capture strategy. RESULTS: A reciprocal translocation involving RET intron 12 was identified. The fusion was validated using a targeted break apart fluorescence in situ hybridization probe, and RNA sequencing confirmed the existence of an in-frame fusion transcript joining MYH13 exon 35 with RET exon 12. Ectopic expression of fusion product in a murine Ba/F3 cell reporter model established strong oncogenicity. Three tyrosine kinase inhibitors currently used to treat MTC in clinical practice blocked tumorigenic cell growth. CONCLUSION: This finding represents the report of a novel RET fusion, the first of its kind described in MTC. The finding of this potential novel oncogenic

mechanism has clear implications for sporadic MTC, which in the majority of cases has no driver mutation identified. The presence of a RET fusion also provides a plausible target for RET tyrosine kinase inhibitor therapies.
PubMed-ID: 25546157
http://dx.doi.org/10.1210/jc.2014-4153

Modifiable risk factors and thyroid cancer.
Otolaryngol Head Neck Surg, 152(3):432-7.
K. J. Stansifer, J. F. Guynan, B. M. Wachal and R. B. Smith. 2015.
OBJECTIVE: To evaluate the association between modifiable patient risk factors including tobacco use, alcohol consumption, body mass index (BMI), and thyroid cancer. STUDY DESIGN: Retrospective study with chart review. SETTING: Midwest university hospital. SUBJECTS AND METHODS: Retrospective study comparing Midwest patients with thyroid cancer from our Thyroid Tumor and Cancer Registry with Midwest controls without a personal history of cancer. Descriptive statistics were created from patient questionnaires and chart reviews. Odds ratios (ORs) were reported for significant associations. RESULTS: There were 467 patients with cancer and 255 controls. The thyroid cancer group included 404 papillary, 47 follicular, 13 medullary, and 3 anaplastic cancers. When comparing all patients with cancer with controls, smoking more than 100 lifetime cigarettes was associated with a reduced cancer risk (OR, 0.68; 95% confidence interval [CI], 0.50-0.94). Secondhand smoke exposure did not show a statistically significant relationship to thyroid cancer. Compared with never drinking, current drinking was associated with a reduced cancer risk (OR, 0.46; 95% CI, 0.29-0.73) as was consuming 1 to 2 drinks daily compared to drinking <1 drink daily (OR, 0.58; 95% CI, 0.34-0.89). There was no difference between median BMI at age 20 years, lifetime maximum BMI, or current BMI between patients with cancer and controls. CONCLUSION: Our data showed no positive correlation between tobacco use, alcohol consumption, or obesity and thyroid cancer risk. Our data suggest that tobacco use and mild alcohol consumption may be associated with a slightly reduced risk of thyroid cancer. There was no association between BMI and thyroid cancer in our study population.
PubMed-ID: 25552593
http://dx.doi.org/10.1177/0194599814564537

The utility of frozen section examination for determining the extent of thyroidectomy in patients with a thyroid nodule and "atypia/follicular lesion of undetermined significance".
Am J Surg, 209(3):552-6.
S. E. Posillico, S. M. Wilhelm and C. R. McHenry. 2015.
BACKGROUND: The purpose of this study was to evaluate the role of frozen section examination (FSE) for determining the extent of thyroidectomy in patients with nodular thyroid disease and fine-needle aspiration categorized as atypia/follicular lesion of undetermined significance (AFLUS). METHODS: A retrospective review of all patients operated on for a thyroid nodule and AFLUS was completed to determine the role of clinical examination and FSE in intraoperative decision making. RESULTS: One hundred twenty patients with AFLUS underwent thyroidectomy; 18 (15%) had carcinoma. FSE altered management in 36 (62%) of the 58 patients-32 with benign disease and 4 with cancer who underwent lobectomy and total thyroidectomy, respectively. Total thyroidectomy without FSE was performed in 61 (51%) patients with sonographically confirmed bilateral disease. FSE had a 36.4% sensitivity, 100% specificity, 100% positive predictive value, 87% negative predictive value, and 88% accuracy. CONCLUSION: Ultrasound in combination with FSE is of value for determining the extent of thyroidectomy in patients with AFLUS.
PubMed-ID: 25554703
http://dx.doi.org/10.1016/j.amjsurg.2014.09.026

Computed tomography for preoperative evaluation of need for sternotomy in surgery for retrosternal goitre.
Langenbecks Arch Surg, 400(3):293-9.
P. Malvemyr, N. Liljeberg, M. Hellstrom and A. Muth. 2015.
PURPOSE: The purposes of this study are to evaluate the usefulness of available CT classifications of retrosternal goitre (RSG) to identify patients needing sternotomy and to examine the effect of neck extension on goitre position. METHODS: From the Scandinavian Quality Register for Thyroid and Parathyroid Surgery, all patients treated for RSG at Sahlgrenska (January 2005 through August 2012) were identified. Medical records and preoperative CT scans were retrospectively reviewed. Paired CT (normal position/neck extension) was done in three patients. RESULTS: Of 1698 patients undergoing thyroid surgery, 158 (9.3 %) were registered as having RSG, of these 38 were excluded (no preoperative CT n = 27, no RSG at preoperative CT n = 11). Of 120 included patients (71 % females, median age 67 years, rate of malignancy 14 %), 104 were managed with a

cervical approach only, 16 (13.3 %) needed sternotomy, of these 13/16 had growth below the aortic arch concavity. Predictors for sternotomy were goitre extension below the aortic arch concavity (positive/negative predictive value (PPV/NPV) 54/97 %, sensitivity/specificity 81/89 %, odds ratio (OR) 36.6, p < 0.001); main mass of RSG to the right of the midline (PPV/NPV 21/95 %, sensitivity/specificity 81/53 %, OR 4.9, p < 0.008); and main mass of RSG retrotracheal (PPV/NPV 31/92 %, sensitivity/specificity 50/83 %, OR 4.8, p < 0.005). The goitre was displaced cranially a mean 11 mm with neck extension, but the relationship to the aortic arch was unchanged. CONCLUSIONS: RSG extension below the aortic arch concavity was confirmed as a significant risk factor for sternotomy, with a NPV for sternotomy of 97 % for less extensive goitres. CT in neck extension provided no additional clinically relevant information.
PubMed-ID: 25557494
http://dx.doi.org/10.1007/s00423-014-1268-5

TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy.
Nat Rev Endocrinol, 11(3):171-81.
T. J. Smith. 2015.
Thyroid-associated ophthalmopathy (TAO) is a vexing and undertreated ocular component of Graves disease in which orbital tissues undergo extensive remodelling. My colleagues and I have introduced the concept that fibrocytes expressing the haematopoietic cell antigen CD34 (CD34(+) fibrocytes), which are precursor cells of bone-marrow-derived monocyte lineage, express the TSH receptor (TSHR). These cells also produce several other proteins whose expression was traditionally thought to be restricted to the thyroid gland. TSHR-expressing fibrocytes in which the receptor is activated by its ligand generate extremely high levels of several inflammatory cytokines. Acting in concert with TSHR, the insulin-like growth factor 1 receptor (IGF-1R) expressed by orbital fibroblasts and fibrocytes seems to be necessary for TSHR-dependent cytokine production, as anti-IGF-1R blocking antibodies attenuate these proinflammatory actions of TSH. Furthermore, circulating fibrocytes are highly abundant in patients with TAO and seem to infiltrate orbital connective tissues, where they might transition to CD34(+) fibroblasts. My research group has postulated that the infiltration of fibrocytes into the orbit, their unique biosynthetic repertoire and their proinflammatory and profibrotic phenotype account for the characteristic properties exhibited by orbital connective tissues that underlie susceptibility to TAO. These insights, which have emerged in the past few years, might be of use in therapeutically targeting pathogenic orbit-infiltrating fibrocytes selectively by utilizing novel biologic agents that interfere with TSHR and IGF-1R signalling.
PubMed-ID: 25560705
http://dx.doi.org/10.1038/nrendo.2014.226

Clinical Presentation of Patients with a Thyroid Follicular Neoplasm: Are there Preoperative Predictors of Malignancy?
Ann Surg Oncol,
A. Najafian, M. T. Olson, E. B. Schneider and M. A. Zeiger. 2015.
BACKGROUND: Studies examining differences in presentation of patients with benign [follicular adenoma (FA)] and malignant follicular thyroid neoplasms [follicular thyroid carcinoma (FTC) or follicular variant papillary thyroid carcinoma (FVPTC)] include only one or two of these subtypes, and none has considered clinical, cytological, and sonographic features together. We therefore examined presenting clinical features of all benign and malignant follicular neoplasm subtypes in an attempt to identify predictors of malignancy. METHODS: Consecutive patients with a surgically resected follicular thyroid neoplasm at a tertiary hospital from 2005 to 2013 were reviewed. Age, gender, symptoms, history, physical findings, nodule size, sonographic, cytologic, and final pathologic results were recorded. Multivariate logistic regression was used to determine variables that contributed to a diagnosis of malignant follicular neoplasm. RESULTS: A total of 616 patients (163 males, 453 females) presented with 441 FAs, 17 FTCs, and 158 FVPTCs. On multivariate analysis, male sex [odds ratio (OR) 1.87, p = 0.008], family history of thyroid cancer (OR 5.16, p < 0.001), and history of head and neck radiation (OR 2.01, p = 0.04) were associated with an increased odds of malignancy; age >45 (OR 2.03, p = 0.001), dysphagia (OR 3.48, p = 0.001) or pressure sensation (OR 3.00, p = 003), concomitant hyperthyroidism (OR 4.76, p = 0.01), nodules >/=4 cm (OR 3.68, p < 0.001), and multinodularity on physical examination (OR 1.93, p = 0.004) were associated with an increased odds of a benign lesion. CONCLUSIONS: Independent clinical predictors exist that might be helpful in preoperative differentiation of benign and malignant follicular neoplasms. A combination of these predictors with both FNA and molecular results may help us to improve the clinical management of patients with follicular thyroid lesions.
PubMed-ID: 25564170
http://dx.doi.org/10.1245/s10434-014-4324-z

Thyroid incidentalomas in patients with multiple endocrine neoplasia type 1.
Eur J Endocrinol, 172(4):337-42.
L. Lodewijk, P. J. Bongers, J. W. Kist, E. B. Conemans, J. M. de Laat, C. R. Pieterman, A. N. van der Horst-Schrivers, C. Jorna, A. R. Hermus, O. M. Dekkers, W. W. de Herder, M. L. Drent, P. H. Bisschop, B. Havekes, I. H. Rinkes, M. R. Vriens and G. D. Valk. 2015.
OBJECTIVE: Currently, little is known about the prevalence of thyroid tumors in multiple endocrine neoplasia type 1 (MEN1) patients and it is unclear whether tumorigenesis of these thyroid tumors is MEN1-related. The aim of the study was to assess the prevalence of thyroid incidentalomas in MEN1 patients compared with nonMEN1 patients and to verify whether thyroid tumorigenesis is MEN1-related. DESIGN: A cross-sectional study. METHODS: The study included two groups: patients with MEN1 and a matched non-MEN1 control group without known thyroid disease, who underwent an ultrasound of the neck for the localization of parathyroid adenoma. Ninety-five MEN1 patients underwent ultrasound of the neck and were matched on gender and age with non-MEN1 patients. The prevalence of thyroid incidentalomas described in the ultrasound report was scored. Multinodular goiters, solitary nodes, and cysts were scored as incidentalomas. Presence of nuclear menin expression was evaluated by menin immunostaining of the thyroid tumors. RESULTS: In the MEN1 group, 43 (45%) patients had a thyroid incidentaloma compared with 48 (51%) in the non-MEN1 group, of which 14 (15%) and 16 (17%), respectively, were solitary nodes. Menin was expressed in the nuclei of all evaluated thyroid tumors. CONCLUSIONS: MEN1 patients do not have a higher prevalence of thyroid incidentalomas compared with primary hyperparathyroidism patients without the diagnosis of MEN1. Menin was expressed in the thyroid tumors of MEN1 patients.
PubMed-ID: 25572387
http://dx.doi.org/10.1530/EJE-14-0897

Psychosocial distress in patients with thyroid cancer.
Otolaryngol Head Neck Surg, 152(4):644-9.
L. Buchmann, S. Ashby, R. B. Cannon and J. P. Hunt. 2015.
OBJECTIVE: The purpose of this study is to evaluate levels of psychosocial distress in thyroid cancer patients. An analysis of factors contributing to levels of distress is included. STUDY DESIGN: Individual retrospective cohort study. SETTING: Head and neck cancer clinic at the Huntsman Cancer Institute. SUBJECTS AND METHODS: A total of 118 newly diagnosed thyroid cancer patients were included in the study. Univariate and multivariate analyses evaluated levels of and factors contributing to distress. RESULTS: Almost half (43.3%) of patients had significant distress. Those with self-reported psychiatric history, use of antidepressant medication, and history of radiation treatment had higher levels of distress. On multivariate analysis, patient endorsement of emotional issues predicted a higher distress level. CONCLUSIONS: Thyroid cancer patients have high distress levels. Identification of thyroid cancer patients with high distress levels is important to offer additional support during cancer therapy.
PubMed-ID: 25573679
http://dx.doi.org/10.1177/0194599814565761

Prognostic indicators in well-differentiated thyroid carcinoma when controlling for stage and treatment.
Laryngoscope, 125(4):1021-7.
K. A. Krook, S. A. Fedewa and A. Y. Chen. 2015.
OBJECTIVES/HYPOTHESIS: The incidence of thyroid carcinoma is rising. Few studies have examined patient characteristics that influence survival when adjusting for treatment and tumor stage/extent. STUDY DESIGN: Retrospective analysis was performed using the Surveillance Epidemiology and End Results registry data among patients diagnosed with well-differentiated thyroid (WDT) carcinoma during 1988-2009. METHODS: Kaplan-Meir survival curves were used to estimate 5- and 10-year cause-specific and overall survival differences by sociodemographics, clinical characteristics, and treatment. Multivariate Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). RESULTS: A total of 83,985 patients were identified with WDT carcinoma. Blacks had higher hazard of death at 5 years (HR, 1.67; 95% CI, 1.42-1.96) and 10 years (HR, 1.57; 95% CI, 1.37-1.80) when compared to Caucasians, but there were no significant differences in cause-specific deaths. Hispanics had higher overall and cause-specific 5-year and 10-year hazard of death (5-year cause-specific: HR, 1.56; 95% CI, 1.23-1.99). Age was the most significant predictor of cause-specific and overall survival, with risk increasing in a nonlinear fashion. After age 45 years, the HR for 5- and 10-year cause-specific survival rose drastically, reaching an HR of 153 for individuals aged 85 years and older (HR, 153.45; 95% CI, 97.84-240.67). CONCLUSIONS: Age was the strongest factor associated with WDT cancer in our study. African Americans had worse overall survival, although only Hispanics had a significantly worse cause-specific survival. These factors should be taken into account in counseling patients and treatment planning.

PubMed-ID: 25583017
http://dx.doi.org/10.1002/lary.25017

TERT promoter mutations are associated with distant metastases in papillary thyroid carcinoma.
Eur J Endocrinol, 172(4):403-13.
G. Gandolfi, M. Ragazzi, A. Frasoldati, S. Piana, A. Ciarrocchi and V. Sancisi. 2015.
OBJECTIVE: Transcriptional activating mutations in the promoter of the telomerase reverse transcriptase (TERT) gene were reported at high frequency in aggressive poorly differentiated and anaplastic thyroid cancers. By contrast, the relevance of these mutations in the metastatic behavior of well-differentiated thyroid cancer is still to be defined. The aim of this work was to investigate the frequency of TERT promoter mutations in a remarkable cohort of well-differentiated papillary thyroid carcinoma that developed distant metastases (DM-PTCs) and to establish whether these mutations may be predictive of metastatic behavior. DESIGN: We analyzed the frequency of TERT promoter mutations in a group of 43 highly aggressive DM-PTCs. As controls, we analyzed these mutations in a group of 78 PTCs without distant metastases (control-PTCs). The possible correlation between TERT promoter mutations and BRAF V600E mutation was also investigated. METHODS: TERT promoter mutational status was evaluated by direct sequencing of the hotspot harboring the C228T and the C250T mutations. RESULTS: In the overall cohort of 121 PTCs analyzed, 17% of cases (21/121) carried a mutation in the TERT promoter. Noticeably, 33% of DM-PTCs were mutated in the TERT promoter while only 9% of the control-PTCs showed a mutation in this locus. We also observed a positive association between BRAF V600E and TERT C228T mutations in the cohort of DM-PTCs. CONCLUSIONS: These results indicate that TERT promoter mutations are associated with the development of distant metastases in PTCs and may help in predicting aggressive behavior in this type of tumor.
PubMed-ID: 25583906
http://dx.doi.org/10.1530/EJE-14-0837

Estrogen receptor alpha induces prosurvival autophagy in papillary thyroid cancer via stimulating reactive oxygen species and extracellular signal regulated kinases.
J Clin Endocrinol Metab, 100(4):E561-71.
D. Fan, S. Y. Liu, C. A. van Hasselt, A. C. Vlantis, E. K. Ng, H. Zhang, Y. Dong, S. K. Ng, R. Chu, A. B. Chan, J. Du, W. Wei, X. Liu, Z. Liu, M. Xing and G. G. Chen. 2015.
CONTEXT: The incidence of papillary thyroid cancer (PTC) shows a predominance in females, with a male:female ratio of 1:3, and none of the known risk factors are associated with gender difference. Increasing evidence indicates a role of estrogen in thyroid tumorigenesis, but the mechanism involved remains largely unknown. OBJECTIVE: This study aimed to assess the contribution of autophagy to estrogen receptor alpha (ERalpha)-mediated growth of PTC. DESIGN: The expression of ERalpha in thyroid tissue of patients with PTC tissues was analyzed. Cell viability, proliferation, and apoptosis were evaluated after chemical and genetic inhibition of autophagy. Autophagy in PTC cell lines BCPAP and BCPAP-ERalpha was assessed. RESULTS: ERalpha expression was increased in PTC tissues compared with the adjacent nontumor tissues. Estrogen induced autophagy in an ERalpha-dependent manner. Autophagy induced by estrogen/ERalpha is associated with generation of reactive oxygen species, activation of ERK1/2, and the survival/growth of PTC cells. Chemical and genetic inhibition of autophagy dramatically decreased tumor cell survival and promoted apoptosis, confirming the positive role of autophagy in the growth of PTC. CONCLUSIONS: ERalpha contributes to the growth of PTC by enhancing an important prosurvival catabolic process, autophagy, in PTC cells. The inhibition of autophagy promotes apoptosis, implicating a novel strategy for the treatment of ERalpha-positive PTC.
PubMed-ID: 25594859
http://dx.doi.org/10.1210/jc.2014-3257

A registry-based study of thyroid paraganglioma: histological and genetic characteristics.
Endocr Relat Cancer, 22(2):191-204.
E. von Dobschuetz, H. Leijon, C. Schalin-Jantti, F. Schiavi, M. Brauckhoff, M. Peczkowska, G. Spiazzi, S. Dematte, M. E. Cecchini, P. Sartorato, J. Krajewska, K. Hasse-Lazar, K. Roszkowska-Purska, E. Taschin, A. Malinoc, L. A. Akslen, J. Arola, D. Lange, A. Fassina, G. Pennelli, M. Barbareschi, J. Luettges, A. Prejbisz, A. Januszewicz, T. Strate, B. Bausch, F. Castinetti, B. Jarzab, G. Opocher, C. Eng and H. P. Neumann. 2015.
The precise diagnosis of thyroid neoplasias will guide surgical management. Primary thyroid paraganglioma has been rarely reported. Data on prevalence, immunohistochemistry (IHC), and molecular genetics in a systematic series of such patients are pending. We performed a multinational population-based study on thyroid paraganglioma and analyzed prevalence, IHC, and molecular genetics. Patients with thyroid paraganglioma were recruited from the European-American-Head-and-Neck-Paraganglioma-Registry. Demographic and clinical data were registered. Histopathology and IHC were re-investigated. All patients with thyroid paraganglioma

underwent molecular genetic analyses of the SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, TMEM127, and MAX genes. Analyses included Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) for detection of large rearrangements. Of 947 registrants, eight candidates were initially identified. After immunohistochemical analyses of these eight subjects, 5 (0.5%) were confirmed to have thyroid paraganglioma. IHC was positive for chromogranin, synaptophysin, and S-100 and negative for calcitonin in all five thyroid paragangliomas, whereas the three excluded candidate tumors stained positive for pan-cytokeratin, a marker excluding endocrine tumors. Germline variants, probably representing mutations, were found in four of the five confirmed thyroid paraganglioma cases, two each in SDHA and SDHB, whereas the excluded cases had no mutations in the tested genes. Thyroid paraganglioma is a finite entity, which must be differentiated from medullary thyroid carcinoma, because medical, surgical, and genetic management for each is different. Notably, approximately 80% of thyroid paragangliomas are associated with germline variants, with implications for additional tumors and a potential risk for the family. As opposed to sporadic tumors, surgical management and extent of resection are different for heritable tumors, each guided by the precise gene involved.
PubMed-ID: 25595276
http://dx.doi.org/10.1530/ERC-14-0558

Importance of in situ preservation of parathyroid glands during total thyroidectomy.
Br J Surg, 102(4):359-67.
L. Lorente-Poch, J. J. Sancho, S. Ruiz and A. Sitges-Serra. 2015.
BACKGROUND: Parathyroid failure is the most common complication after total thyroidectomy but factors involved are not completely understood. Accidental parathyroidectomy and parathyroid autotransplantation resulting in fewer than four parathyroid glands remaining in situ, and intensity of medical treatment of postoperative hypocalcaemia may have relevant roles. The aim of this study was to determine the relationship between the number of parathyroid glands remaining in situ and parathyroid failure after total thyroidectomy. METHODS: Consecutive patients undergoing first-time total thyroidectomy were studied prospectively, recording the number of Parathyroid Glands Remaining In Situ (PGRIS = 4 - (glands autografted + glands in the specimen)) and the occurrence of postoperative hypocalcaemia, and protracted and permanent hypoparathyroidism. Demographic, disease-related, laboratory and surgical variables were recorded. Patients were classified according to the PGRIS number into group 1-2 (one or two PGRIS), group 3 (three PGRIS) and group 4 (all four glands remaining in situ), and were followed for at least 1 year. RESULTS: A total of 657 patients were included, 43 in PGRIS group 1-2, 186 in group 3 and 428 in group 4. The prevalence of hypocalcaemia, and of protracted and permanent hypoparathyroidism was inversely related to the PGRIS score (group 1-2: 74, 44 and 16 per cent respectively; group 3: 51.1, 24.7 and 6.5 per cent; group 4: 35.3, 13.1 and 2.6 per cent; $P < 0.001$). Intact parathyroid hormone concentrations at 24 h and 1 month were inversely correlated with PGRIS score ($P < 0.001$). Logistic regression identified PGRIS score as the most powerful variable influencing acute and chronic parathyroid failure. In addition, a normal-high serum calcium concentration 1 month after thyroidectomy influenced positively the recovery rate from protracted hypoparathyroidism in all PGRIS categories. CONCLUSION: In situ parathyroid preservation is critical in preventing permanent hypoparathyroidism after total thyroidectomy. Active medical treatment of postoperative hypocalcaemia has a positive synergistic effect.
PubMed-ID: 25605285
http://dx.doi.org/10.1002/bjs.9676

A Prospective 1-Year Comparative Study of Endoscopic Thyroidectomy Via a Retroauricular Approach Versus Conventional Open Thyroidectomy at a Single Institution.
Ann Surg Oncol,
E. J. Chung, M. W. Park, J. G. Cho, S. K. Baek, S. Y. Kwon, J. S. Woo and K. Y. Jung. 2015.
OBJECTIVE: The objective of this study was to evaluate the feasibility and safety of performing an endoscopic thyroidectomy (ETE) via a retroauricular approach. METHODS: Forty-seven patients who underwent ETE via a retroauricular approach were included, and a total of 47 patients who underwent conventional open thyroid lobectomy in the same period were analyzed as a control group. All patients underwent prospective functional evaluations before the operation and 1 week, and 1, 3, 6, and 12 months postoperatively using a comprehensive battery of functional assessments. RESULTS: The mean total operative time was 152 +/- 48 min, with a mean endoscopic procedure time of 58 +/- 18 min. One patient developed temporary vocal fold paralysis. Although most of the parameters for the functional outcome were worse in the ETE group, these differences were transient. Subjective worsening on the voice handicap index and dysphagia handicap index normalized by 3 months postoperatively. The average pain score on a visual analog scale at 1 week after surgery was 2.84, representing a tolerable range of discomfort. The mean paresthesia/hyperesthesia score was worse in the ETE group than the open surgery group by postoperative month 6; however, these differences eventually

disappeared. Thirty-six of the 47 patients in the ETE group were satisfied or extremely satisfied with the retroauricular incision by 6 months after surgery. CONCLUSIONS: ETE via a retroauricular approach is a safe, feasible, and cosmetically desirable treatment option, with outcomes comparable to conventional open thyroidectomy in the longer term.
PubMed-ID: 25605517
http://dx.doi.org/10.1245/s10434-014-4361-7

Thyroglobulin level in fine-needle aspirates for preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma: two different cutoff values according to serum thyroglobulin level.
Thyroid, 25(4):410-6.
M. J. Jeon, W. G. Kim, E. K. Jang, Y. M. Choi, Y. M. Lee, T. Y. Sung, J. H. Yoon, K. W. Chung, S. J. Hong, J. H. Baek, J. H. Lee, T. Y. Kim, Y. K. Shong and W. B. Kim. 2015.
BACKGROUND: Measurement of thyroglobulin (Tg) in the washout fluid of fine-needle aspirates (FNA-Tg) is useful for diagnosis of lymph node (LN) metastasis in papillary thyroid carcinoma (PTC). However, the cutoff value of FNA-Tg in the preoperative state is not defined clearly. This study aimed to evaluate the optimal cutoff value of preoperative FNA-Tg according to serum Tg level. METHODS: FNA-Tg was measured in 135 PTC patients (160 LNs) for preoperative diagnosis of cervical LN metastasis. RESULTS: Of the 160 LNs, 119 (74%) were surgically removed and 110 (69%) were diagnosed as malignant. When we adopted a FNA-Tg of 1.0 mug/L as the cutoff value, the sensitivity and specificity were 99% and 76%, respectively. FNA-Tg levels were correlated with serum Tg levels (Pearson's coefficient 0.42, p=0.002) and the FNA-Tg levels of 12 of the 50 benign LNs were above 1.0 mug/L. We classified the LNs into two groups according to serum Tg level regardless of anti-Tg antibody status: a low Tg group (</=1.0 mug/L, n=22, 14%) and a high Tg group (>1.0 mug/L, n=138, 86%). In the low Tg group, the sensitivity and specificity of the FNA-Tg cutoff value of 1.0 mug/L were 93% and 100%, respectively. In the high Tg group, the sensitivity and specificity of the FNA-Tg cutoff value of 19.0 mug/L were 93% and 100%, respectively. A Tg ratio (FNA-Tg level divided by serum Tg level) of 0.5 gave an improved diagnostic performance (sensitivity, 98%; specificity, 98%) in the high Tg group. CONCLUSIONS: FNA-Tg levels in the preoperative state are affected by serum Tg levels when they exceeded 1.0 mug/L. For the preoperative diagnosis of metastatic cervical LNs, it seems reasonable to employ different cutoff values of FNA-Tg depending on serum Tg levels. We propose the use of an optimal cutoff value of FNA-Tg of 1.0 mug/L in patients with low serum Tg levels and a Tg ratio of 0.5 in those with high serum Tg levels irrespective of thyroglobulin antibody status.
PubMed-ID: 25607926
http://dx.doi.org/10.1089/thy.2014.0544

Differentiated thyroid cancer patients more than 60 years old paradoxically show an increased life expectancy.
J Nucl Med, 56(2):190-5.
T. M. Maier, O. Schober, J. Gerss, D. Gorlich, C. Wenning, M. Schaefers, B. Riemann and A. Vrachimis. 2015.
The aim of this study was to compare the overall survival of a large, single-center cohort of patients who had differentiated thyroid cancer (DTC) with that of a matched general population. METHODS: We analyzed 2,428 consecutive patients who had DTC and underwent treatment from 1965 to 2013 at the Department of Nuclear Medicine, University Hospital of Munster, Munster, Germany, according to international standards. Patients were classified on the basis of the current, seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control classification system. Additionally, a subgroup analysis with regard to age at diagnosis was performed. The overall survival of the patients was compared with the expected survival of the general population on the basis of age and sex, as provided by the Federal Statistical Office of Germany. RESULTS: Compared with the expected survival, the overall survival of patients with stage I disease paradoxically was significantly better (P < 0.001). In the subgroup analysis, a significantly lower mortality rate was observed in elderly patients (>/=60 y old) with stage I disease. On the other hand, patients between 20 and 45 y of age and with distant metastases at diagnosis had a significantly increased standardized mortality rate. In contrast, other patients with stage II disease and more than 45 y old had a normal mortality rate. The mortality rate was significantly increased in all patients with stage IVC disease. CONCLUSION: Older patients with more limited disease paradoxically had better survival than would be expected on the basis of age and sex, whereas young adults as well as patients more than 45 y old and with distant metastases had increased mortality rates. For all other DTC patients, regardless of age or TNM stage, no significant survival difference was seen.
PubMed-ID: 25613533
http://dx.doi.org/10.2967/jnumed.114.150284

Hypocalcaemia after total thyroidectomy: could intact parathyroid hormone be a predictive factor for transient postoperative hypocalcemia?
Surgery, 157(2):344-8.
A. Puzziello, R. Gervasi, G. Orlando, N. Innaro, M. Vitale and R. Sacco. 2015.
BACKGROUND: Hypocalcemia, the most common complication of thyroidectomy, is a transient condition in up to 27% of patients and a permanent condition approximately 1% of patients. The aim of this prospective study was to evaluate reliability of postoperative intact parathyroid hormone (iPTH) assessment for predicting clinically relevant postthyroidectomy hypocalcemia for a safe early discharge of patients with no overtreatment. METHODS: Seventy-five consecutive patients (age 51 +/- 13 years [mean +/- SD]) undergoing total or completion thyroidectomy with no concomitant parathyroid diseases or renal failure were included in the present study. Serum iPTH level was determined before and 2 hours after thyroidectomy. Serum calcium concentration was determined 1 day before and 2 days postoperatively. RESULTS: The occurrence of postoperative hypocalcemia was correlated both with the absolute and relative iPTH decrease, determined as a ratio of the preoperative value ($P < .0001$). There was a greater difference in relative decrease in iPTH between patients remaining normocalcemic and those with hypocalcemia present on the second postoperative day. Hypocalcemic patients on the second postoperative day had a 62% relative decrease in iPTH 2 hours after thyroidectomy. CONCLUSION: The relative decrease in serum iPTH was greater in patients with hypocalcemia arising on the second postoperative day rather than in patients who remained normocalcemic. The relative decrease in iPTH determined 2 hours after total thyroidectomy together with the serum calcium concentration 24 hours after thyroidectomy proved to be useful predictors of sustained hypocalcemia and might change the clinical management of patients after thyroid surgery to support a longer hospitalization in these selected patients.
PubMed-ID: 25616948
http://dx.doi.org/10.1016/j.surg.2014.09.004

What to do with thyroid nodules showing benign cytology and BRAF(V600E) mutation? A study based on clinical and radiologic features using a highly sensitive analytic method.
Surgery, 157(2):354-61.
S. Y. Kim, E. K. Kim, J. Y. Kwak, H. J. Moon and J. H. Yoon. 2015.
BACKGROUND: BRAF(V600E) mutation analysis has been used as a complementary diagnostic tool to ultrasonography-guided, fine-needle aspiration (US-FNA) in the diagnosis of thyroid nodule with high specificity reported up to 100%. When highly sensitive analytic methods are used, however, false-positive results of BRAF(V600E) mutation analysis have been reported. In this study, we investigated the clinical, US features, and outcome of patients with thyroid nodules with benign cytology but positive BRAF(V600E) mutation using highly sensitive analytic methods from US-FNA. METHODS: This study included 22 nodules in 22 patients (3 men, 19 women; mean age, 53 years) with benign cytology but positive BRAF(V600E) mutation from US-FNA. US features were categorized according to the internal components, echogenicity, margin, calcifications, and shape. Suspicious US features included markedly hypoechogenicity, noncircumscribed margins, micro or mixed calcifications, and nonparallel shape. Nodules were considered to have either concordant or discordant US features to benign cytology. Medical records and imaging studies were reviewed for final cytopathology results and outcomes during follow-up. RESULTS: Among the 22 nodules, 17 nodules were reviewed. Fifteen of 17 nodules were malignant, and 2 were benign. The benign nodules were confirmed as adenomatous hyperplasia with underlying lymphocytic thyroiditis and a fibrotic nodule with dense calcification. Thirteen of the 15 malignant nodules had 2 or more suspicious US features, and all 15 nodules were considered to have discordant cytology considering suspicious US features. Five nodules had been followed with US or US-FNA without resection, and did not show change in size or US features on follow-up US examinations. CONCLUSION: BRAF(V600E) mutation analysis is a highly sensitive diagnostic tool in the diagnosis of papillary thyroid carcinomas. In the management of thyroid nodules with benign cytology but positive BRAF(V600E) mutation, thyroidectomy should be considered in nodules which have 2 or more suspicious US features and are considered discordant on image-cytology correlation.
PubMed-ID: 25616949
http://dx.doi.org/10.1016/j.surg.2014.09.003

MEN1 mutations in Hurthle cell (oncocytic) thyroid carcinoma.
J Clin Endocrinol Metab, 100(4):E611-5.
K. Kasaian, A. M. Chindris, S. M. Wiseman, K. L. Mungall, T. Zeng, K. Tse, J. E. Schein, M. Rivera, B. M. Necela, J. M. Kachergus, J. D. Casler, A. J. Mungall, R. A. Moore, M. A. Marra, J. A. Copland, E. A. Thompson, R. C. Smallridge and S. J. Jones. 2015.
CONTEXT AND OBJECTIVE: Oncocytic thyroid carcinoma, also known as Hurthle cell thyroid carcinoma, accounts for only a small percentage of all thyroid cancers. However, this malignancy often presents at an

advanced stage and poses unique challenges to patients and clinicians. Surgical resection of the tumor accompanied in some cases by radioactive iodine treatment, radiation, and chemotherapy are the established modes of therapy. Knowledge of the perturbed oncogenic pathways can provide better understanding of the mechanism of disease and thus opportunities for more effective clinical management. DESIGN AND PATIENTS: Initially, two oncocytic thyroid carcinomas and their matched normal tissues were profiled using whole genome sequencing. Subsequently, 72 oncocytic thyroid carcinomas, one cell line, and five Hurthle cell adenomas were examined by targeted sequencing for the presence of mutations in the multiple endocrine neoplasia I (MEN1) gene. RESULTS: Here we report the identification of MEN1 loss-of-function mutations in 4% of patients diagnosed with oncocytic thyroid carcinoma. Whole genome sequence data also revealed large regions of copy number variation encompassing nearly the entire genomes of these tumors. CONCLUSION: Menin, a ubiquitously expressed nuclear protein, is a well-characterized tumor suppressor whose loss is the cause of MEN1 syndrome. Menin is involved in several major cellular pathways such as regulation of transcription, control of cell cycle, apoptosis, and DNA damage repair pathways. Mutations of this gene in a subset of Hurthle cell tumors point to a potential role for this protein and its associated pathways in thyroid tumorigenesis.
PubMed-ID: 25625803
http://dx.doi.org/10.1210/jc.2014-3622

Vandetanib for the treatment of advanced medullary thyroid cancer outside a clinical trial: results from a French cohort.
Thyroid, 25(4):386-91.
C. N. Chougnet, I. Borget, S. Leboulleux, C. de la Fouchardiere, F. Bonichon, L. Criniere, P. Niccoli, S. Bardet, O. Schneegans, S. Zanetta, C. Schvartz, D. Drui, B. Chauffert, V. Rohmer and M. Schlumberger. 2015.
BACKGROUND: A randomized phase III trial demonstrated that vandetanib treatment is effective in patients with metastatic medullary thyroid cancer (MTC), leading to regulatory approval, but its use may be associated with toxicities that require specific monitoring and management. The objective of the present study performed in France was to describe the toxicity profile and efficacy of vandetanib treatment when given outside any trial. METHODS: Sixty-eight patients were treated with vandetanib in the frame of a temporary use authorization (ATU) in France from August 2010 to February 2012, when the drug was available on request for patients with locally advanced or metastatic MTC. Patients were registered by the French health authorities, and characteristics, treatment parameters, toxicity profile, and efficacy were retrospectively reviewed. Eight patients were excluded from the analysis because vandetanib treatment was not administered (n=3), had been given in a trial before ATU (n=3), or was given for a non-MTC cancer (n=2). RESULTS: Data from the 60 MTC patients were analyzed. Mean age was 58 years (range 11-83 years), 39 patients were male, and six had hereditary MTC. Fifty-six (93%) had metastatic disease in the mediastinum (82%), bones (65%), liver (53%), or lung (53%), and four had only locally advanced disease. At the time of study evaluation, with a median follow-up of 20 months and a median duration of treatment of 9.7 months (range 0.3-36 months), 15 patients were continuing vandetanib treatment (range 18-36 months). Median progression-free survival was 16.1 months. Twenty-five patients discontinued treatment for disease progression (range 0.3-29 months). Best tumor response was a complete response in one patient, a partial response in 12 (20%), stable disease in 33 (55%), and progression in seven patients (12%). All patients had at least one adverse event (AE) during treatment. The main AEs were skin toxicity, diarrhea, and asthenia. Sixteen patients (27%) discontinued treatment for toxicity, and one patient died from vandetanib-induced cardiac toxicity. CONCLUSIONS: Vandetanib is an effective option for patients with advanced MTC. AEs should be monitored carefully and should be minimized by educating both patients and care providers and by applying symptomatic treatment and dose reduction.
PubMed-ID: 25627619
http://dx.doi.org/10.1089/thy.2014.0361

Preoperative localization of neck recurrences from thyroid cancer: charcoal tattooing under ultrasound guidance.
Thyroid, 25(3):341-6.
L. Chami, D. Hartl, S. Leboulleux, E. Baudin, J. Lumbroso, M. Schlumberger and J. P. Travagli. 2015.
BACKGROUND: Reoperation for thyroid cancer recurrence is a surgical challenge in previously dissected necks, and there is a need for a reliable procedure for surgeon guidance. In this study, the usefulness of preoperative charcoal tattooing for surgical guidance was evaluated. METHODS: From July 2007 to May 2010, 53 patients (40 females; Mage=44 years, range 19-76 years) were prospectively included for preoperative localization of neck recurrences from differentiated (n=46) or medullary thyroid cancer (n=7). Preoperative cytological assessment was performed for at least one lesion in each patient. Ultrasound (US) imaging was performed with high-frequency probes (8-14 Mhz). Micronized peat charcoal (0.5-3 mL) was injected under US guidance using a 25 gauge needle, 0-15 days preoperatively. RESULTS: A total of 106 lesions were selected for charcoal

tattooing. Of these, 101 had been tattooed, and 102 were removed (85 metastases, 17 benign on pathology). The tolerance of charcoal injection was good in all but three patients. A mean volume of 1 mL of charcoal was injected with a mean of two targets per patient. Charcoal labeling facilitated intraoperative detection in 56 "difficult" lesions (i.e., small size, dense fibrosis, anatomical pitfalls), and charcoal trace facilitated intraoperative guidance in 17 lesions. Feasibility and usefulness rates were 83% and 70.7% respectively. CONCLUSION: These findings suggest that charcoal tattooing under US guidance is an easy to implement, safe, and useful procedure for surgeon guidance in neck reoperation for thyroid cancer.
PubMed-ID: 25629658
http://dx.doi.org/10.1089/thy.2014.0329

Frequent screening with serial neck ultrasound is more likely to identify false-positive abnormalities than clinically significant disease in the surveillance of intermediate risk papillary thyroid cancer patients without suspicious findings on follow-up ultrasound evaluation.
J Clin Endocrinol Metab, 100(4):1561-7.
S. Peiling Yang, A. M. Bach, R. M. Tuttle and S. A. Fish. 2015.
CONTEXT: American Thyroid Association (ATA) intermediate-risk thyroid cancer patients who achieve an excellent treatment response demonstrate a low risk of structural disease recurrence. Despite this fact, most patients undergo frequent surveillance neck ultrasound (US) during follow-up. OBJECTIVE: The objective of the study was to evaluate the clinical utility of routine screening neck US in ATA intermediate-risk patients documented to have a nonstimulated thyroglobulin less than 1.0 ng/mL and a neck US without suspicious findings after therapy. PATIENTS AND DESIGN: Retrospective review of 90 ATA intermediate-risk papillary thyroid carcinoma patients treated with total thyroidectomy and radioactive iodine ablation in a tertiary referral center. MAIN OUTCOME MEASURES: A comparison between the frequency of finding false-positive US abnormalities and the frequency of identifying structural disease recurrence in the study cohort was measured. RESULTS: Over a median of 10 years, 90 patients had a median of six US (range 2-16). Structural disease recurrence was identified in 10% (9 of 90) at a median of 6.3 years. Recurrence was associated with other clinical indicators of disease in 5 of the 90 patients (5.6%, 5 of 90) and was detected without other signs of recurrence in four patients (4.8%, 4 of 84). False-positive US abnormalities were identified in 57% (51 of 90), leading to additional testing, which failed to identify clinically significant disease. CONCLUSIONS: In ATA intermediate-risk patients who have a nonstimulated thyroglobulin less than 1.0 ng/mL and a neck US without suspicious findings after therapy, frequent US screening during follow-up is more likely to identify false-positive abnormalities than clinically significant structural disease recurrence.
PubMed-ID: 25632970
http://dx.doi.org/10.1210/jc.2014-3651

Bilateral areolar approach endoscopic thyroidectomy for low-risk papillary thyroid carcinoma: a review of 137 cases in a single institute.
Surg Laparosc Endosc Percutan Tech, 25(1):19-22.
W. Gao, L. Liu, G. Ye, W. Lu and L. Teng. 2015.
PURPOSE: The aim of this study was to analyze the clinicopathologic characteristics and postoperative outcomes and to evaluate the feasibility of the bilateral areolar approach (BAA) endoscopic thyroidectomy for low-risk papillary thyroid carcinoma (PTC). MATERIALS AND METHODS: From January 2012 to February 2013, 137 low-risk PTC patients underwent BAA endoscopic thyroidectomy. Their clinicopathologic characteristics and postoperative outcomes (postoperative cosmetic satisfaction, type of thyroidectomy, number of lymph nodes, postoperative complications, and recurrence of disease) were analyzed. RESULTS: The 137 patients comprised 135 female and 2 male individuals. The average age of patients was 32.02+/-8.32 years. The mean tumor size was 0.82+/-0.41 cm. The ratio of minimal extrathyroidal extension patients was 1:19.6. According to the American Joint Committee on Cancer tumor stage, 132 cases were stage I and 5 cases were stage III. The mean follow-up period was 7.80+/-3.86 months (range, 3 to 15 mo, and median, 7 mo). At 3 months, postoperatively, patients were very satisfied with the cosmetic result as evaluated by a 10-point visual analogue scale (9.14+/-1.17). After surgery, the mean number of lymph nodes was 5.70+/-2.92, whereas the mean number of lymph node metastases was 1.06+/-1.96. Regarding the major postoperative complications, the rates of transient recurrent laryngeal nerve palsy and transient hypoparathyroidism were 4.4% and 27.7%, respectively. None of the patients experienced a thyroid cancer-related death or recurrence. CONCLUSIONS: BAA is feasible and safe for the treatment of low-risk PTC patients, with favorable cosmesis. Thus, it is an alternative therapeutic treatment for selected patients with low-risk PTC. However, oncologic safety of BAA thyroidectomy for PTC patients needs to be verified by a large comparative series and long-term follow-up.
PubMed-ID: 25635670
http://dx.doi.org/10.1097/SLE.0b013e3182a50f1f

Robotic thyroid surgery for papillary thyroid carcinoma: lessons learned from 100 consecutive surgeries.
Surg Laparosc Endosc Percutan Tech, 25(1):27-32.
H. Y. Lee, I. S. Yang, S. B. Hwang, J. B. Lee, J. W. Bae and H. Y. Kim. 2015.
PURPOSE: To evaluate the feasibility and safety of robotic thyroidectomy using the da Vinci surgical system. PATIENTS AND METHODS: Between July 2008 and April 2011, the data revealed an initial series of 100 consecutive patients who underwent robotic thyroidectomy with the da Vinci-S surgical system using the bilateral axillo-breast approach for thyroid cancer. Prospectively collected data were analyzed retrospectively. RESULTS: There were 88 cases of total thyroidectomy, 11 cases of lobectomy, and 1 case of total thyroidectomy with modified radical neck dissection. There was no conversion. The mean total operation time was 287.15+/-45.19 minutes for total thyroidectomy and 236.27+/-48.98 minutes for lobectomy. Nineteen patients experienced transient hypocalcemia and 3 patients experienced transient vocal fold palsy. All of the patients recovered within 3 months. CONCLUSIONS: Robotic thyroid surgery for patients with thyroid malignancy is safe and results in fewer postoperative complications than open thyroid surgery.
PubMed-ID: 25635671
http://dx.doi.org/10.1097/SLE.0b013e3182a2b0ae

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

[Postthyroidectomy hypocalcemia : the earlier it appears the longer it persists].
Chirurg, 86(3):286.
K. Lorenz, M. Elwerr and H. Dralle. 2015.
PubMed-ID: 25666084
http://dx.doi.org/10.1007/s00104-015-2989-x

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

Sternotomy for substernal goiter: retrospective study of 52 operations.
Langenbecks Arch Surg, 400(3):301-6.
L. Rolighed, H. Ronning and P. Christiansen. 2015.
PURPOSE: Surgical treatment of substernal goiter occasionally involves sternotomy. Classification and handling of these operations are widely discussed. We aimed to review surgical results after thyroid operations including

median sternotomy. METHODS: A retrospective review of all thyroid operations performed in the department from 01.01.95 to 31.12.12. In 55 of 2065 thyroid operations (2.7 %), median sternotomy was performed. All hospital journals of the patients were collected and carefully reviewed. RESULTS: We included 52 of 55 identified patients. Pathologic examinations discovered malignant disease in 4 patients (8 %) and multinodular goiter in 48 patients (92 %). Mean operation time was 4 h and 5 min (n = 48). Mean estimated blood loss was 464 ml (n = 48). Blood transfusion was given in nine operations (17 %). Median duration of postoperative hospitalization was 7 days (range 4-27 days). Pulmonary complications occurred in 11 patients (21 %): six with pneumonia or atelectasis, three with pneumothorax, and two with pleural effusion. Three patients (6 %) had postoperative hypocalcaemia (permanent in two patients (4 %)). Three patients (6 %) had transient voice changes. Permanent vocal cord paresis was not observed in this series of patients. CONCLUSION: Thyroid operations with sternotomy are complicated procedures accompanied with considerable pulmonary complications. In spite of a large invasive procedure, the risk of hypoparathyroidism or recurrent laryngeal nerve injury was not increased.
PubMed-ID: 25691265
http://dx.doi.org/10.1007/s00423-015-1288-9

Intratumor heterogeneity and clonal evolution in an aggressive papillary thyroid cancer and matched metastases.
Endocr Relat Cancer, 22(2):205-16.
S. Le Pennec, T. Konopka, D. Gacquer, D. Fimereli, M. Tarabichi, G. Tomas, F. Savagner, M. Decaussin-Petrucci, C. Tresallet, G. Andry, D. Larsimont, V. Detours and C. Maenhaut. 2015.
The contribution of intratumor heterogeneity to thyroid metastatic cancers is still unknown. The clonal relationships between the primary thyroid tumors and lymph nodes (LN) or distant metastases are also poorly understood. The objective of this study was to determine the phylogenetic relationships between matched primary thyroid tumors and metastases. We searched for non-synonymous single-nucleotide variants (nsSNVs), gene fusions, alternative transcripts, and loss of heterozygosity (LOH) by paired-end massively parallel sequencing of cDNA (RNA-Seq) in a patient diagnosed with an aggressive papillary thyroid cancer (PTC). Seven tumor samples from a stage IVc PTC patient were analyzed by RNA-Seq: two areas from the primary tumor, four areas from two LN metastases, and one area from a pleural metastasis (PLM). A large panel of other thyroid tumors was used for Sanger sequencing screening. We identified seven new nsSNVs. Some of these were early events clonally present in both the primary PTC and the three matched metastases. Other nsSNVs were private to the primary tumor, the LN metastases and/or the PLM. Three new gene fusions were identified. A novel cancer-specific KAZN alternative transcript was detected in this aggressive PTC and in dozens of additional thyroid tumors. The PLM harbored an exclusive whole-chromosome 19 LOH. We have presented the first, to our knowledge, deep sequencing study comparing the mutational spectra in a PTC and both LN and distant metastases. This study has yielded novel findings concerning intra-tumor heterogeneity, clonal evolution and metastases dissemination in thyroid cancer.
PubMed-ID: 25691441
http://dx.doi.org/10.1530/ERC-14-0351

Germline and somatic SDHx alterations in apparently sporadic differentiated thyroid cancer.
Endocr Relat Cancer, 22(2):121-30.
Y. Ni, S. Seballos, S. Ganapathi, D. Gurin, B. Fletcher, J. Ngeow, R. Nagy, R. T. Kloos, M. D. Ringel, T. LaFramboise and C. Eng. 2015.
Along with breast and endometrial cancers, thyroid cancer is a major component cancer in Cowden syndrome (CS). Germline variants in SDHB/C/D (SDHx) genes account for subsets of CS/CS-like cases, conferring a higher risk of breast and thyroid cancers over those with only germline PTEN mutations. To investigate whether SDHx alterations at both germline and somatic levels occur in apparently sporadic breast cancer and differentiated thyroid cancer (DTC), we analyzed SDHx genes in the following four groups: i) 48 individuals with sporadic invasive breast adenocarcinoma for germline mutation; ii) 48 (expanded to 241) DTC for germline mutation; iii) 37 pairs DTC tumor-normal tissues for germline and somatic mutation and mRNA expression levels; and iv) data from 476 patients in the Cancer Genome Atlas thyroid carcinoma dataset for validation. No germline SDHx variant was found in a pilot series of 48 breast cancer cases. As germline SDHx variants were found in our pilot of 48 thyroid cancer cases, we expanded to three series of DTC comprising a total 754 cases, and found 48 (6%) with germline SDHx variants ($P<0.001$ compared with 0/350 controls). In 513 tumors, we found 27 (5%) with large somatic duplications within chromosome 1 encompassing SDHC. Both papillary and follicular thyroid tumors showed consistent loss of SDHC/D gene expression ($P<0.001$), which is associated with earlier disease onset and higher pathological-TNM stage. Therefore, we conclude that both germline and somatic SDHx mutations/variants occur in sporadic DTC but are very rare in sporadic breast cancer, and overall

loss of SDHx gene expression is a signature of DTC.
PubMed-ID: 25694510
http://dx.doi.org/10.1530/ERC-14-0537

Sorafenib for patients with differentiated thyroid cancer.
Lancet, 385(9964):227-8.
P. Boudou-Rouquette, A. Thomas-Schoemann, A. Bellesoeur and F. Goldwasser. 2015.
PubMed-ID: 25706704
http://dx.doi.org/10.1016/S0140-6736(15)60054-X

Sorafenib for patients with differentiated thyroid cancer.
Lancet, 385(9964):227.
O. Huillard, B. Blanchet, J. P. Durand and F. Goldwasser. 2015.
PubMed-ID: 25706705
http://dx.doi.org/10.1016/S0140-6736(15)60053-8

Sorafenib for patients with differentiated thyroid cancer--authors' reply.
Lancet, 385(9964):228-9.
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Sorafenib for patients with differentiated thyroid cancer.
Lancet, 385(9964):228.
H. J. Lee, H. Ryu, Y. S. Choi, I. C. Song, H. J. Yun, D. Y. Jo and S. Kim. 2015.
PubMed-ID: 25706707
http://dx.doi.org/10.1016/S0140-6736(15)60055-1

Is there a case for selective, rather than routine, preoperative laryngoscopy in thyroid surgery?
Gland Surg, 4(1):8-18.
G. Franch-Arcas, C. Gonzalez-Sanchez, Y. Y. Aguilera-Molina, O. Rozo-Coronel, J. S. Estevez-Alonso and A. Munoz-Herrera. 2015.
BACKGROUND: According to some authors, routine preoperative laryngoscopy should be the standard of care in all patients undergoing thyroid surgery. The rationale for this approach is (I) the risk that a patient has a preoperative vocal cord palsy (VCP) without symptoms; (II) the presence of VCP preoperatively is suggestive of invasive malignancy; (III) it is relevant for the use of intraoperative nerve monitoring; and (IV) surgical strategy may be better defined if a paralysed vocal cord is detected preoperatively. METHODS: This is a review of studies of patients who underwent routine preoperative laryngoscopy to anticipate preoperative VCP and that evaluated related risk factors, including previous surgery, voice function complaints, and a diagnosis of malignancy. The estimated risk of sustaining preoperative VCF in the absence of these factors was determined. The relevant current guidelines from different professional bodies are also addressed. RESULTS: The level of evidence that supports routine preoperative laryngoscopy is weak. The risk of harboring preoperative VCP in the absence of previous neck or other risk-related surgery, advanced malignancy or voice symptoms is very low (0.5% of cases). CONCLUSIONS: Selective rather than routine use of preoperative laryngoscopy may be acceptable provided that the risk of undetected paralysis is as low as can be reasonably ascertained from the available literature.
PubMed-ID: 25713775
http://dx.doi.org/10.3978/j.issn.2227-684X.2015.01.04

Defining the syndromes of parathyroid failure after total thyroidectomy.
Gland Surg, 4(1):82-90.
L. Lorente-Poch, J. J. Sancho, J. L. Munoz-Nova, P. Sanchez-Velazquez and A. Sitges-Serra. 2015.
Acute and chronic parathyroid insufficiency syndromes are the most common complication after total thyroidectomy. Permanent hypoparathyroidism imposes an important medical burden on patient lifestyle due to the need for lifetime medication, regular visits and significant long-term costs. Its true prevalence has been underestimated due to lack of clear definitions, inadequate follow-up and conflicts of interest when reporting individual patient series. The aim of this review is to propose precise definitions for the different syndromes associated to parathyroid failure based on the follow-up and management of patients developing hypocalcemia (<8 mg/dL at 24 hours) after first-time total thyroidectomy for cancer or goiter at our unit. Short and long-term

post-thyroidectomy parathyroid failure presents as three different metabolic syndromes: (I) postoperative hypocalcemia is defined as a s-Ca <8 mg/dL (<2 mmol/L) within 24 hours after surgery requiring calcium/vit D replacement therapy at the time of hospital discharge; (II) protracted hypoparathyroidism as a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium/vit D replacement at 4-6 weeks; and (III) permanent hypoparathyroidism as a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium/vit D replacement 1 year after total thyroidectomy. Each of these syndromes has its own pattern of recovery and should be approached with different therapeutic strategies.
PubMed-ID: 25713783
http://dx.doi.org/10.3978/j.issn.2227-684X.2014.12.04

Review of the bethesda system for reporting thyroid cytopathology: a local study in bohol island, Philippines.
Acta Cytol, 59(1):77-82.
A. L. Salillas, F. C. Sun and E. G. Almocera. 2015.
OBJECTIVES: The aim of this study was to evaluate the adaptability and reproducibility of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) in a local setting and to determine the risk of malignancy for each category. MATERIALS AND METHODS: A retrospective cross-sectional study of 80 thyroid fine-needle aspiration cytology cases using the BSRTC with corresponding histopathology was done between September 2009 and December 2012. Agreement scores were calculated using kappa statistics. RESULTS: Consensus among two readers was attained for 73 cases (91.25%). No disagreement was noted for the malignant cases. The strength of agreement was very good, with a kappa statistic of 0.90. The risk of malignancy observed histologically was as follows: benign 3%, atypia of undetermined significance (AUS) 50%, suspicious for follicular/Hurthle cell neoplasm 50%, suspicious for malignancy 78%, and malignant 100%. CONCLUSION: In this study, there is an outstanding reproducibility for the classification scheme. The application of the BSRTC as the standardized reporting is readily adaptable and therefore its application in larger medical centers is highly recommended. Our findings of a higher risk of malignancy seen in AUS (50%) and malignant (100%) categories in those who underwent surgical resection corroborated other published studies. Conveying this risk to clinical colleagues is important and will facilitate optimal patient care. (c) 2015 S. Karger AG, Basel.
PubMed-ID: 25720460
http://dx.doi.org/10.1159/000371752

In silico analysis of RET variants in medullary thyroid cancer: from the computer to the bedside.
Otolaryngol Head Neck Surg, 152(4):650-4.
T. E. Heineman, R. Joshi, M. A. Cohen, W. I. Kuhel and D. I. Kutler. 2015.
OBJECTIVE: The American Thyroid Association (ATA) medullary thyroid cancer (MTC) guidelines group RET variants, in the setting of familial medullary thyroid cancer and multiple endocrine neoplasia type 2, into 4 classes of severity based on epidemiological data. The aim of this study was to determine if genotype correlates with phenotype in RET missense mutations. STUDY DESIGN: In silico mutational tolerance prediction. SETTING: Academic research hospital. SUBJECTS AND METHODS: We analyzed all RET variants currently listed in the ATA guidelines for the management of MTC using 2 computer-based (in silico) mutation tolerance prediction approaches: PolyPhen-2 HumVar and PolyPhen-2 HumDiv. Our analysis also included 27 different RET single-nucleotide polymorphisms resulting in missense variants. RESULTS: There was a statistically significant difference in the overall HumDiv score between ATA groups A and B (P = .025) and a statistically significant different HumVar score between benign polymorphisms and ATA group A (P = .023). Overall, RET variants associated with a less aggressive clinical phenotype generally had a lower Hum Div/Var score. CONCLUSIONS: Polyphen-2 Hum Div/Var may provide additional clinical data to help distinguish benign from MEN2/familial medullary thyroid carcinoma-causing RET variants as well as less aggressive phenotypes (ATA A) from more aggressive ones (ATA B-C). In silico genetic analyses, with proper validation, may predict the phenotypic severity of RET variants, providing clinicians with a tool to aid clinical decision making in cases in which the RET variant is currently unknown or little epidemiological data are available.
PubMed-ID: 25733075
http://dx.doi.org/10.1177/0194599815569709

Preablation 131-I Scans With SPECT/CT Contribute to Thyroid Cancer Risk Stratification and 131-I Therapy Planning.
J Clin Endocrinol Metab, 100(5):1895-902.
A. M. Avram, N. H. Esfandiari and K. K. Wong. 2015.
CONTEXT: The use of preablation diagnostic radioiodine scans for risk stratification and radioiodine therapy planning for differentiated thyroid cancer (DTC) remains controversial. OBJECTIVE: The objective was to assess

the contribution of preablation diagnostic 131-I scans with SPECT/CT (Dx 131-I scan) to (1) the risk stratification and (2) the postoperative management of DTC. DESIGN: The study was designed as a prospective sequential patient series. SETTING: The study was conducted at a University hospital. PATIENTS: Three hundred twenty patients (pts) with DTC (219F; 101M, mean age 47.3 +/- 16.4 y, range 10-90) were studied. INTERVENTION: Using clinical and histopathology information an endocrinologist performed risk stratification and determined postoperative management with respect to radioiodine therapy (RAI) planning. The decision to withhold or to administer RAI, and the recommended low, medium or high therapeutic 131-I activity were recorded. Dx 131-I scans were performed and interpreted by two nuclear medicine physicians as showing thyroid remnant, cervical nodal, or distant metastases. The endocrinologist then reperformed risk stratification and reformulated management after consideration of Dx 131-I scans and stimulated thyroglobulin (Tg) information. MAIN OUTCOME MEASURE: Main outcome measures were changes in risk stratification and management after Dx 131-I scans. RESULTS: Detection of unsuspected nodal and distant metastases and elevated stimulated Tg levels resulted in a change in the estimated risk of recurrence in 15% of patients, and management in 31% of patients, as compared to initial risk stratification and management based on histopathology alone. CONCLUSIONS: Both imaging data and stimulated thyroglobulin levels acquired at the time of Dx 131-I scans are consequential for 131-I therapy planning, providing information that changes risk stratification in 15% of patients as compared to recurrence risk estimation based on histopathology alone. Dx 131-I scans contribute to risk stratification by defining residual nodal and distant metastatic disease, changing clinical management in 29.4% of patients.
PubMed-ID: 25734251
http://dx.doi.org/10.1210/jc.2014-4043

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

Necessity of therapy for post-thyroidectomy hypocalcaemia: a multi-centre experience.
Langenbecks Arch Surg, 400(3):319-24.
L. De Pasquale, P. V. Sartori, L. Vicentini, E. Beretta, M. Boniardi, E. Leopaldi, P. Gini, L. La Manna, L. Cozzaglio, G. B. Steffano, S. Andreani, S. Badiali, G. M. Cantoni, A. Galimberti, G. Ghilardi, M. Gusmeroli, R. Maggiore, E. Morenghi, J. Pauna, L. Poggi and V. Testa. 2015.
PURPOSE: Hypoparathyroidism is one of the most common and most feared complications of total thyroidectomy (TT). The aim of this study is to detect possible markers that may facilitate early tracing of hypocalcaemia-prone patients in order to reduce clinical cost by optimizing patient discharge and to avoid unnecessary treatment. METHODS: Over an 18-month period, 995 patients, 23 % male and 77 % female, aged 52.9 +/- 13.4 years, underwent TT in ten Lombardy hospitals. The following parameters were analyzed: calcaemia before and 12-24 and 48 h after surgery, pre- and post-operative parathyroid hormone (PTH) at 24 h and pre-operative 25OH vitamin D. RESULTS: Mortality was nil and morbidity was 22.4 %. Mean 24-h calcaemia and PTH were 2.17 +/- 0.15 mmol/l and 31.81 +/- 20.35 pg/ml, respectively; mean 24-h PTH decay was 36.7 +/- 34.12 %. Four hundred seventy-three (47.5 %) patients were hypocalcaemic at discharge; 142 of whom had transient hypoparathyroidism that became permanent in 27. Patients developing hypocalcaemia had significantly higher values of PTH and calcium decay. At multiple logistic regression, only 24-h calcium decay, PTH drop and

the presence of symptoms and parathyroid auto-grafting were significantly related to hypoparathyroidism. The association of these factors had a 99.2 % negative predictive value (NPV) for the development of hypoparathyroidism. A 70 % PTH drop had a 93.75 NPV for transient hypoparathyroidism. A 12 % calcaemia decay had a 95.7 NPV for hypoparathyroidism. CONCLUSIONS: Hypocalcaemic asymptomatic patients with less than 70 % PTH and 12 % calcaemia decay may be safely discharged without treatment. Symptomatic patients and those with parathyroid grafting should receive calcium and vitamin D.
PubMed-ID: 25749741
http://dx.doi.org/10.1007/s00423-015-1292-0

Surgical management of laryngeal invasion by papillary thyroid carcinoma: a retrospective analysis.
Thyroid, 25(5):528-33.
S. Moritani. 2015.
BACKGROUND: Papillary thyroid carcinoma (PTC) has an excellent prognosis. Although rare, PTC invasion into the upper aerodigestive tract can adversely affect patient prognosis and quality of life. This study investigated the impact of tumor excision on the prognosis and postoperative status of patients with PTC invasion of the larynx. METHODS: Data on PTC patients who underwent surgery at the author's institution between April 1981 and March 2010 were retrospectively reviewed, and 55 patients with thyroid cartilage invasion were enrolled. Curative resection was performed for all patients, and laryngeal function was preserved or reconstructed when possible. RESULTS: Of the 55 patients, 40 and 15 patients had superficial and intraluminal invasion of the larynx, respectively. The 10-year disease-specific survival rates were 81.0% and 61.4% in patients who underwent surgery for superficial and intraluminal invasion of the larynx, respectively. Only two patients (3.6%) had an isolated locoregional recurrence in the larynx. Four patients (7.3%) underwent total laryngectomy during the initial surgery or surgery for laryngeal recurrence. Permanent stoma remained in 26 patients (47%): 14 with laryngeal invasion, and 12 with invasion of other aerodigestive structures. The number of invaded aerodigestive structures including the larynx was correlated with the presence of permanent stoma. CONCLUSIONS: In many patients, PTC invasion of the larynx remained at the thyroid cartilage or paraglottic space. Most patients did not require total laryngectomy. Good locoregional control was achieved with surgical tumor excision in patients with laryngeal invasion. Distant metastases were the major cause of death in patients with PTC invasion of the larynx.
PubMed-ID: 25757392
http://dx.doi.org/10.1089/thy.2014.0485

Surgical Management of Cricotracheal Invasion by Papillary Thyroid Carcinoma.
Ann Surg Oncol,
S. Moritani. 2015.
BACKGROUND: In general, patients with papillary thyroid carcinoma (PTC) have an excellent postoperative prognosis. Those with cricoid and/or tracheal PTC invasion, however, are at a higher risk of postoperative morbidity and airway insufficiency. METHODS: We investigated postoperative airway outcomes, locoregional recurrence, and survival rates in patients with PTC who underwent cricotracheal resection. The records of PTC patients who underwent surgery at our institution between 1981 and 2009 were reviewed retrospectively, and 110 patients with cricotracheal invasion were enrolled. Curative resection was performed in all patients, and cricotracheal function was preserved or reconstructed when possible. RESULTS: Of the 110 patients, 57 and 53 patients had superficial and intraluminal invasion of the larynx, respectively. After the initial surgery, the 10-year disease-specific survival rates were 90.8 and 44.4 % in patients with superficial and intraluminal invasion of the cricotracheal area, respectively. Only six patients (5.5 %) had an isolated upper aerodigestive tract recurrence. Five patients were managed with an additional window resection as salvage surgery. Consequently, only one patient (0.9 %) underwent total laryngectomy. Altogether, 31 patients (28.0 %) had a permanent stoma, 9 and 15 of which were caused by cricotracheal invasion and invasion of other aerodigestive structures, respectively. CONCLUSIONS: Window resection for intraluminal cricotracheal invasion by PTC produced good surgical outcomes that resulted in a low local recurrence rate and survival rates that resembled those associated with other surgical treatments. Treatment of multiple organ invasion of the aerodigestive tract was necessary to improve postoperative functional outcomes in these patients.
PubMed-ID: 25786744
http://dx.doi.org/10.1245/s10434-015-4492-5

Thyroidectomy in the professional singer-neural monitored surgical outcomes.
Thyroid, 25(6):665-71.
G. W. Randolph, N. Sritharan, P. Song, R. Franco, Jr., D. Kamani and G. Woodson. 2015.
BACKGROUND: Voice changes commonly occur from thyroidectomy and may be due to neural or nonneural

causes. Such changes can be a source of significant morbidity for any patient, but thyroidectomy in the professional singer carries special significance. We test the hypothesis that the career of singers and professional voice users is not impaired after neural monitored thyroid surgery. METHODS: A quantitative analysis of pre- and postoperative neural monitored thyroid surgery voice outcomes utilizing three validated vocal instruments-Voice Handicap Index (VHI), Singing Voice Handicap Index (SVHI), and Evaluation of Ability to Sing Easily (EASE)-in a unique series of professional singers/voice users was performed. Additional quantitative analysis related to final intraoperative electromyography (EMG) amplitude, the time to return to performance, and vocal parameters affected during this interval was performed. RESULTS: Twenty-seven vocal professionals undergoing thyroidectomy were identified, of whom 60% had surgery for thyroid cancer. Pre- and postsurgery flexible fiberoptic laryngeal exams were normal in all patients. Return to performance rate was 100%, and mean time to performance was 2.26 months (+/-1.61). All three vocal instrument mean scores, pre-op vs. post-op, were unchanged: VHI, 4.15 (+/-5.22) vs. 4.04 (+/-3.85), p=0.9301; SVHI, 11.26 (+/-14.41) vs.12.07 (+/-13.09), p=0.8297; and EASE, 6.19 (+/-9.19) vs. 6.00 (+/-7.72), p=0.9348. The vocal parameters most affected from surgery until first performances were vocal fatigue (89%), high range (89%), pitch control and modulation (74%), and strength (81%). Final mean intraoperative EMG amplitude was within normal limits for intraoperative stimulation and had no relationship with time to first professional performance (p=0.7199). CONCLUSIONS: Neural monitored thyroidectomy, including for thyroid malignancy, in professional voice users is safe without any changes in three different voice/singing instruments, with 100% return to performance. Intraoperative EMG data at the conclusion of surgery and postoperative laryngeal exam were normal in all patients. Specific vocal parameters are transiently affected during the postoperative recovery phase, which is important to outline in the consent process of this unique patient population and may provide insight into the physiologic state of the larynx subsequent to thyroid surgery.
PubMed-ID: 25790153
http://dx.doi.org/10.1089/thy.2014.0467

Using diffusion-weighted MRI to predict aggressive histological features in papillary thyroid carcinoma: a novel tool for pre-operative risk stratification in thyroid cancer.
Thyroid, 25(6):672-80.
Y. Lu, A. L. Moreira, V. Hatzoglou, H. E. Stambuk, M. Gonen, Y. Mazaheri, J. O. Deasy, A. R. Shaha, R. M. Tuttle and A. Shukla-Dave. 2015.
BACKGROUND: Initial management recommendations of papillary thyroid carcinoma (PTC) are very dependent on preoperative studies designed to evaluate the presence of PTC with aggressive features. The purpose of this study was to evaluate whether diffusion-weighted magnetic resonance imaging (DW-MRI) before surgery can be used as a tool to stratify tumor aggressiveness in patients with PTC. METHODS: In this prospective study, 28 patients with PTC underwent DW-MRI studies on a three Tesla MR scanner prior to thyroidectomy. Due to image quality, 21 patients were finally suitable for further analysis. Apparent diffusion coefficients (ADCs) of normal thyroid tissues and PTCs for 21 patients were calculated. Tumor aggressiveness was defined by surgical histopathology. The Mann-Whitney U test was used to compare the difference in ADCs among groups of normal thyroid tissues and PTCs with and without features of tumor aggressiveness. Receiver operating characteristic (ROC) analysis was performed to assess the discriminative specificity, sensitivity, and accuracy of and determine the cutoff value for the ADC in stratifying PTCs with tumor aggressiveness. RESULTS: There was no significant difference in ADC values between normal thyroid tissues and PTCs. However, ADC values of PTCs with extrathyroidal extension (ETE; 1.53+/-0.25x10(-3) mm(2)/s) were significantly lower than corresponding values from PTCs without ETE (2.37+/-0.67x10(-3) mm(2)/s; p<0.005). ADC values identified 3 papillary carcinoma patients with extrathyroidal extension that would have otherwise been candidates for observation based on ultrasound evaluations. The cutoff value of ADC to discriminate PTCs with and without ETE was determined at 1.85x10(-3) mm(2)/s with a sensitivity of 85%, specificity of 85%, and ROC curve area of 0.85. CONCLUSION: ADC value derived from DW-MRI before surgery has the potential to stratify ETE in patients with PTCs.
PubMed-ID: 25809949
http://dx.doi.org/10.1089/thy.2014.0419

The Effect of Thyroiditis on the Yield of Central Compartment Lymph Nodes in Patients with Papillary Thyroid Cancer.
Ann Surg Oncol,
V. Lai, T. W. Yen, B. T. Rose, G. G. Fareau, S. M. Misustin, D. B. Evans and T. S. Wang. 2015.
BACKGROUND: In patients who have undergone thyroidectomy and central compartment neck dissection (CCND) for papillary thyroid cancer (PTC), visualization of enlarged lymph nodes may lead to more extensive CCND. This study sought to determine the effect of patient age and the presence of thyroiditis on the number of

malignant and total lymph nodes resected in patients who underwent CCND for PTC. METHODS: This retrospective review examined a prospective database of patients who underwent total thyroidectomy and CCND for PTC between April 2009 and June 2013 and had thyroiditis on the final pathology. The patients were categorized into age groups by decade (18-29, 30-39, 40-49, 50-59, and >/=60 years) and compared with a control group of patients matched by age, gender, and tumor size. RESULTS: Of 74 patients with thyroiditis, 64 (87 %) were women. The median age of the patients was 47.5 years (range 18.2-72.0 years). The patients with thyroiditis had more lymph nodes resected than those without thyroiditis (median 11 vs 7; p < 0.01). However, these patients had fewer malignant lymph nodes (median 0 vs 1.5; p = 0.06), resulting in a lower lymph node ratio (0 vs 0.18; p = 0.02) for the entire cohort, but particularly for the youngest (18-29 years) and oldest (>/=60 years) age groups. CONCLUSIONS: Patients with thyroiditis and PTC who underwent CCND had more lymph nodes resected but a had lower proportion of metastatic lymph nodes than those without thyroiditis. Given the relatively low yield of malignant cervical lymphadenopathy, a more judicious approach to CCND might be considered, particularly for the youngest and oldest patients with PTC and thyroiditis.
PubMed-ID: 25851341
http://dx.doi.org/10.1245/s10434-015-4551-y

Pediatric Thyroid Microcarcinoma.
Ann Surg Oncol,
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

Evidence that TSH Receptor A-Subunit Multimers, Not Monomers, Drive Antibody Affinity Maturation in Graves' Disease.
J Clin Endocrinol Metab, 100(6):E871-5.
B. Rapoport, H. A. Aliesky, C. R. Chen and S. M. McLachlan. 2015.
CONTEXT: The TSH receptor (TSHR) A-subunit shed from the cell surface contributes to the induction and/or affinity maturation of pathogenic TSHR autoantibodies in Graves' disease. OBJECTIVE: This study aimed to determine whether the quaternary structure (multimerization) of shed A-subunits influences pathogenic TSHR autoantibody generation. DESIGN: The isolated TSHR A-subunit generated by transfected mammalian cells exists in two forms; one (active) is recognized only by Graves' TSHR autoantibodies, the second (inactive) is recognized only by mouse monoclonal antibody (mAb) 3BD10. Recent evidence suggests that both Graves' TSHR autoantibodies and mAb 3BD10 recognize the A-subunit monomer. Therefore, if the A-subunit monomer is an immunogen, Graves' sera should have antibodies to both active and inactive A-subunits. Conversely, restriction of TSHR autoantibodies to active A-subunits would be evidence of a role for shed A-subunit multimers, not monomers, in the pathogenesis of Graves' disease. Therefore, we tested a panel of Graves' sera for their relative recognition of active and inactive A-subunits. RESULTS: Of 34 sera from unselected Graves' patients, 28 were unequivocally positive in a clinical TSH binding inhibition assay. None of the latter sera, as well as 8/9 sera from control individuals, recognized inactive A-subunits on ELISA. In contrast to Graves' sera, antibodies induced in mice, not by shedding from the TSHR holoreceptor, but by immunization with adenovirus expressing the free human A-subunit, were directed to both the active and inactive A-subunit forms. CONCLUSIONS: The present study supports the concept that pathogenic TSHR autoantibody affinity maturation

in Graves' disease is driven by A-subunit multimers, not monomers.
PubMed-ID: 25856215
http://dx.doi.org/10.1210/jc.2015-1528

A Patient with a Thyrotropin-secreting Microadenoma and Resistance to Thyroid Hormone (P453T).
J Clin Endocrinol Metab:jc20143994.
X. Teng, T. Jin, G. A. Brent, A. Wu, W. Teng and Z. Shan. 2015.
CONTEXT: Resistance to thyroid hormone (RTH) beta is due to the mutations in the beta -isoform of the thyroid hormone receptor (TRbeta). Thyrotropin-secreting adenomas (TSHomas) are presumed to represent clonal expansion and have been reported to contain TRbeta gene mutations. Mice with a knock-in mutation in TRbeta gene spontaneously develop TSHomas, although no patient as yet has been reported to have both a TSHoma and RTHbeta. OBJECTIVE: We investigated a 12-year-old girl with elevated serum T4 concentration, inappropriately high TSH levels and a pituitary adenoma. DESIGN AND INTERVENTION: Clinical, biochemical, and radiological assessments were performed at baseline and after a transsphenoidal pituitary adenomectomy. RESULTS: The girl's laboratory results included: TSH 21.12mIU/L (0.35-4.94 mIU/L); FT3 14.25pmol/L (2.63-5.7 pmol/L); FT4 28.79pmol/L (9.01-19.05 pmol/L); serum alpha-GSU 0.32ng/ml (0.22-0.39 ng/ml) and alpha/TSH molar ratio 0.15. Thyroid radioiodine uptake was increased, 94.4% at 24 hours. A T3 suppression test showed incomplete suppression of the serum TSH concentration and blunted response of the peripheral thyroid hormone markers. The sequence of TRbeta exons confirmed a P453T mutation in the TRbeta gene. Pituitary magnetic resonance image revealed an microadenoma in the left side of the pituitary. The patient underwent transsphenoidal pituitary adenomectomy. Histologically, the tumor stained positively for TSH-beta ,alpha-GSU, GH, PRL and ACTH. After removal of the tumor, her thyroid function improved significantly, as well as experiencing the onset of menarch and an increase in linear growth. CONCLUSIONS: This patient with RTHbeta had a TSHoma consistent with previous findings linking somatic TRbeta mutations to TSHomas.
PubMed-ID: 25867808
http://dx.doi.org/10.1210/jc.2014-3994

High Diagnostic Accuracy Based on CLDN10, HMGA2, and LAMB3 Transcripts in Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 100(6):E890-9.
M. C. Barros-Filho, F. A. Marchi, C. A. Pinto, S. R. Rogatto and L. P. Kowalski. 2015.
CONTEXT: Thyroid nodules are common in adult population and papillary thyroid carcinoma (PTC) is the most frequent malignant finding. The natural history of PTC remains poorly understood and current diagnostic methods limitations are responsible for a significant number of potentially avoidable surgeries. OBJECTIVE: This study aimed to identify molecular markers to improve the diagnosis of thyroid lesions. DESIGN: Gene expression profiling was performed using microarray in 61 PTC and 13 surrounding normal tissues (NT). A reliable gene list was established using cross-study validation (138 matched PTC/NT from external databases). Results were collectively interpreted by in silico analysis. A panel of 28 transcripts was evaluated by RT-qPCR, including benign thyroid lesions (BTL) and other follicular cell-derived thyroid carcinomas (OFDTC). A diagnostic algorithm was developed (training set: 23 NT, 8 BTL, and 86 PTC), validated (independent set: 10 NT, 140 BTL, 120 PTC, and 12 OFDTC) and associated with clinical features. RESULTS: GABRB2 was ranked as the most frequently up-regulated gene in PTC (cross-study validation). Altered genes in PTC suggested a loss of T4 responsiveness and dysregulation of retinoic acid metabolism, highlighting the putative activation of EZH2 and histone deacetylases (predicted in silico). An algorithm combining CLDN10, HMGA2, and LAMB3 transcripts was able to discriminate tumors from BTL samples (94% sensitivity and 96% specificity in validation set). High algorithm scores were associated with regional lymph node metastases. CONCLUSIONS: A promising tool with high performance for PTC diagnosis based on three transcripts was designed with the potential to predict lymph node metastasis risk.
PubMed-ID: 25867809
http://dx.doi.org/10.1210/jc.2014-4053

Is an Increase in Thyroid Nodule Volume a Risk Factor for Malignancy?
Thyroid,
H. Nakamura, M. Hirokawa, H. Ota, M. Kihara, A. Miya and A. Miyauchi. 2015.
BACKGROUND: Most benign thyroid nodules found on fine-needle aspiration cytology (FNAC) can be followed with periodic ultrasonography. During follow-up, when nodules grow, re-aspiration or surgical resection for a histologic diagnosis is recommended. However, there is little evidence regarding the malignancy risk associated with nodule growth. METHOD: We retrospectively reviewed the records of 542 patients with FNAC-diagnosed adenomatous nodules (ANs) who underwent surgery in 2011-2012 at Kuma Hospital. Among them, 196 patients

had surgical resection because of nodule volume growth (median, 1.94 times; range, 1.21-27.60) during the observation period (mean, 45.9 months). Excluding nodule growth, the remaining 346 patients underwent surgery for various reasons including the large size of nodules or the appearance of undefined ultrasound features suspicious for malignancy during follow-up. For comparison, we reviewed 409 patients with FNAC-diagnosed follicular neoplasms (FNs) operated on in 2011-2013. Most (n=327) underwent surgery shortly after the FNAC diagnosis, while 82 patients were observed for a period of time and had a late operation due to nodule volume growth (median, 2.70 times; range, 1.27-15.82). RESULTS: The histologic diagnoses of the 196 growing FNAC-diagnosed ANs were 158 ANs, 32 follicular adenomas (FAs), 4 follicular tumors of uncertain malignant potential (FT-UMP; 2%), and 2 malignancies (1%). The 346 patients who underwent surgery for reasons other than nodular growth had 16 FT-UMP (4.6%) and 16 malignancies (4.6%). This suggests that nodule growth itself is not a risk factor for malignancy. On the other hand, there were 23 FT-UMP (28%) and 15 malignancies (18.3%) in the 82 growing FNAC-diagnosed FNs, while 44 FT-UMP (13.5%) and 54 malignancies (16.5%) in the 327 FNAC-diagnosed FN patients who underwent immediate surgery. The malignant potential was significantly higher in the growing-FN group than the immediate-surgery FN group ($p<0.05$). No significant difference was found in the volume change between the benign and the FT-UMP plus malignant group in the growing FNs, suggesting that a growth rate does not correlate with malignant potential. CONCLUSION: This is the first demonstration that the malignancy risk is low in FNAC-diagnosed ANs, even if the nodules grow significantly, whereas FNs have a higher risk when they grow.
PubMed-ID: 25872408
http://dx.doi.org/10.1089/thy.2014.0567

Total thyroidectomy as a method of choice in the treatment of Graves' disease - analysis of 1432 patients.
BMC Surg, 15:39.
T. Bojic, I. Paunovic, A. Diklic, V. Zivaljevic, G. Zoric, N. Kalezic, V. Sabljak, N. Slijepcevic, K. Tausanovic, N. Djordjevic, D. Budjevac, L. Djordjevic and A. Karanikolic. 2015.
BACKGROUND: Graves' disease represents an autoimmune disease of the thyroid gland where surgery has an important role in its treatment. The aim of our paper was to analyze the results of surgical treatment, the frequency of microcarcinoma and carcinoma, as well as to compare surgical complications in relation to the various types of operations performed for Graves' disease. METHODS: We analysed 1432 patients (221 male and 1211 female) who underwent surgery for Graves' disease at the Centre for Endocrine Surgery in Belgrade during 15 years (1996-2010). Average age was 34.8 years. Frequency of surgical complications within the groups was analyzed with nonparametric Fisher's test. RESULTS: Total thyroidectomy (TT) was performed in 974 (68%) patients, and Dunhill operation (D) in 221 (15.4). Carcinoma of thyroid gland was found in 146 patients (10.2%), of which 129 (9%) were a microcarcinoma. Complication rates were higher in the TT group, where there were 31 (3.2%) patients with permanent hypoparathyroidism, 9 (0.9%) patients with unilateral recurrent nerve paralysis and 10 (1.0%) patients with postoperative bleeding. Combined complications, such as permanent hypoparathyroidism with bleeding were more common in the D group where there were 2 patients (0,9%), while unilateral recurrent nerve paralysis with bleeding was more common in the TT group where there were 3 cases (0,3%). CONCLUSIONS: Frequency of complications were not significantly statistically different in relation to the type of surgical procedure. Total thyroidectomy represents a safe and efficient method for treating patients with Graves' disease, and it is not followed by a greater frequency of complications in relation to less extensive procedures.
PubMed-ID: 25888210
http://dx.doi.org/10.1186/s12893-015-0023-3

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

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

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

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

PubMed-ID: 25637076
http://dx.doi.org/10.1530/EJE-14-0877

Effects of parathyroidectomy versus observation on the development of vertebral fractures in mild primary hyperparathyroidism.
J Clin Endocrinol Metab, 100(4):1359-67.
K. Lundstam, A. Heck, C. Mollerup, K. Godang, M. Baranowski, Y. Pernow, J. E. Varhaug, O. Hessman, T. Rosen, J. Nordenstrom, S. Jansson, M. Hellstrom and J. Bollerslev. 2015.
CONTEXT: Mild primary hyperparathyroidism (PHPT) is a common disease especially in middle-aged and elderly women. The diagnosis is frequently made incidentally and treatment strategies are widely discussed. OBJECTIVE: To study the effect of parathyroidectomy (PTX) compared with observation (OBS) on biochemistry, safety, bone mineral density (BMD), and new fractures. DESIGN: Prospective, randomized controlled study (SIPH study), with a 5-year follow-up. SETTING: The study was conducted at multicenter, tertiary referral centers. PATIENTS: Of 191 randomized patients with mild PHPT, biochemical data were available for 145 patients after 5 years, with a mean age at inclusion of 62.8 years (OBS group, 9 males) and 62.1 years (PTX group, 10 males). INTERVENTION: Parathyroidectomy vs observation. MAIN OUTCOME MEASURES: Biochemistry, BMD, and new radiographic vertebral fractures. RESULTS: Serum-calcium and PTH-levels normalized after surgery and did not deteriorate by observation. BMD Z-scores were normal at inclusion in the lumbar spine (LS) and femoral neck (FN). For LS, BMD Z-scores were stable for 5 years with observation, but decreased in FN ($P < .02$). After surgery, BMD Z-scores increased significantly in both compartments ($P < .02$ for both), with a highly significant treatment effect of surgery compared to observation ($P < .001$). During follow-up, five new clinically unrecognized vertebral fractures were found in 5 females, all in the OBS group ($P = .058$). CONCLUSION: Even though new vertebral fractures occurred only in the observation group, the frequency was not significantly different from the surgery group. Longer follow-up is needed before firm conclusions can be drawn about the long-term safety of observation, as opposed to surgery.
PubMed-ID: 25636048
http://dx.doi.org/10.1210/jc.2014-3441

Consensus Statements/Guidelines

- None -

Other Articles

Molecular profiling in primary hyperparathyroidism.
Head Neck, 37(2):299-307.
O. A. Segiet, M. Deska, M. Michalski, J. Gawrychowski and R. Wojnicz. 2015.
BACKGROUND: Primary hyperparathyroidism (HPT) is one of the most common endocrine disorders, defined by hypersecretion of parathormone. Primary HPT can be caused by adenoma, hyperplasia, and carcinoma. A great amount of mechanisms contribute to the pathogenesis of this disease, such as genetic predispositions because of the germline-inactivating mutations in the multiple endocrine neoplasia type 1 (MEN1) and HRPT2 tumor suppressor genes. Somatic mutations in these genes were found also in sporadic parathyroid neoplasias. Cell cycle regulators, growth factors, apoptosis-inducing ligands, death receptors, and other transmitter substances have also been implicated in the etiology of primary HPT. Parathyroid carcinoma is often misdiagnosed as parathyroid adenoma and long-term survival is conditioned by the extent of the primary surgical resection, therefore, of great interest is the discovery of definitive diagnostic markers for carcinoma. This article presents current state of knowledge of the molecular pathogenesis of primary HPT.
PubMed-ID: 24595969
http://dx.doi.org/10.1002/hed.23656

CaPTHUS scoring model in primary hyperparathyroidism: can it eliminate the need for ioPTH testing?
Ann Surg Oncol, 22(4):1191-5.
D. M. Elfenbein, S. Weber, D. F. Schneider, R. S. Sippel and H. Chen. 2015.
BACKGROUND: The CaPTHUS model was reported to have a positive predictive value of 100 % to correctly predict single-gland disease in patients with primary hyperparathyroidism, thus obviating the need for

intraoperative parathyroid hormone (ioPTH) testing. We sought to apply the CaPTHUS scoring model in our patient population and assess its utility in predicting long-term biochemical cure. METHODS: We retrospective reviewed all parathyroidectomies for primary hyperparathyroidism performed at our university hospital from 2003 to 2012. We routinely perform ioPTH testing. Biochemical cure was defined as a normal calcium level at 6 months. RESULTS: A total of 1,421 patients met the inclusion criteria: 78 % of patients had a single adenoma at the time of surgery, 98 % had a normal serum calcium at 1 week postoperatively, and 96 % had a normal serum calcium level 6 months postoperatively. Using the CaPTHUS scoring model, 307 patients (22.5 %) had a score of >/= 3, with a positive predictive value of 91 % for single adenoma. A CaPTHUS score of >/= 3 had a positive predictive value of 98 % for biochemical cure at 1 week as well as at 6 months. CONCLUSIONS: In our population, where ioPTH testing is used routinely to guide use of bilateral exploration, patients with a preoperative CaPTHUS score of >/= 3 had good long-term biochemical cure rates. However, the model only predicted adenoma in 91 % of cases. If minimally invasive parathyroidectomy without ioPTH testing had been done for these patients, the cure rate would have dropped from 98 % to an unacceptable 89 %. Even in these patients with high CaPTHUS scores, multigland disease is present in almost 10 %, and ioPTH testing is necessary.
PubMed-ID: 25212837
http://dx.doi.org/10.1245/s10434-014-4080-0

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

Pedicled parathyroid gland autotransposition in secondary and tertiary hyperparathyroidism.
Laryngoscope, 125(4):894-7.
T. Shokri, S. Q. Lew and N. Sadeghi. 2015.
PubMed-ID: 25289604
http://dx.doi.org/10.1002/lary.24962

From hypocalcemia to hypercalcemia-an unusual clinical presentation of a patient with permanent postsurgical hypoparathyroidism.
J Clin Endocrinol Metab, 100(1):21-4.
V. Sundaresh and S. N. Levine. 2015.
CONTEXT: Hypercalcemia associated with lymphomas can be secondary to increased calcitriol [1,25(OH)2 vitamin D3], PTHrP, or osteolytic metastases. OBJECTIVE: A case of calcitriol-mediated hypercalcemia secondary to non-Hodgkin lymphoma in a patient with postsurgical hypoparathyroidism is presented. DESIGN AND SETTING: Single patient managed at a tertiary health care facility in the United States. PATIENT: A 55-year-old white woman had a total thyroidectomy and radioiodine ablation for a 3.5-cm follicular carcinoma. Surgery was complicated by permanent hypoparathyroidism treated with calcium, calcitriol, and cholecalciferol. For over 16 years she had no evidence of either residual thyroid tissue in the neck or metastasis. Her corrected

serum calcium levels were appropriately maintained in the low-normal range. During a routine clinic visit, she had mild hypercalcemia; calcium and cholecalciferol were reduced by 50%, while calcitriol was continued. Two weeks later, she presented with nausea, abdominal pain, and multiple rapidly enlarging cervical and axillary lymph nodes with elevated calcium and calcitriol. A fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan and lymph node biopsy were diagnostic for non-Hodgkin lymphoma. INTERVENTION: Calcium and calcitriol were stopped; hypercalcemia was corrected with iv fluids. Chemotherapy resulted in an excellent response within 7 weeks; calcitriol normalized, and the patient developed recurrent hypocalcemia. Positron emission tomography/computed tomography scans at 7 weeks and 3 months after treatment documented near-complete resolution of the lesions. Outcome and Result: Sixteen months after the treatment of lymphoma, the patient remains free of disease and is on calcium, calcitriol, and cholecalciferol. CONCLUSION: Clinicians should have a high index of suspicion for malignancy when patients presents with rapid and high elevations of serum calcium.
PubMed-ID: 25303492
http://dx.doi.org/10.1210/jc.2014-3063

Safety and efficacy of percutaneous parathyroid ethanol ablation in patients with recurrent primary hyperparathyroidism and multiple endocrine neoplasia type 1.
J Clin Endocrinol Metab, 100(1):E87-90.
N. Singh Ospina, G. B. Thompson, R. A. Lee, C. C. Reading and W. F. Young, Jr. 2015.
CONTEXT: The most common feature of multiple endocrine neoplasia type 1 (MEN1) is primary hyperparathyroidism (PHP), which occurs in approximately 95% of MEN1 patients. Approximately 40-60% of patients with MEN1 develop recurrent hypercalcemia within 10-12 years after their initial parathyroid surgery and the successful management of recurrent PHP is challenging. OBJECTIVE: This study sought to evaluate the safety and efficacy of percutaneous ethanol ablation (PEA) for the treatment of recurrent PHP in patients with MEN1. DESIGN, SETTING, PATIENTS, INTERVENTION, OUTCOME MEASURED: We performed an electronic search to identify patients with a billing code for MEN1 who were seen at Mayo Clinic between 1977 and 2013. Patients with recurrent PHP who underwent PEA were identified and their clinical information was collected. We performed t test analyses to compare mean values. RESULTS: Thirty-seven patients underwent 80 PEA treatments that included 123 sessions of ethanol administration. Twenty-one patients were women (56.8%) and the mean age at diagnosis of PHP was 33.8 years. The mean preprocedure calcium level was 10.7 mg/dl +/- 0.57 (SD) and the mean postprocedure calcium level was 9.6 mg/dl +/- 0.76 ($P < .01$). In 14 treatments (18.9%) the postprocedure calcium was greater than 10.1 mg/dl. Postprocedure hypocalcemia occurred in six treatments (8.1%). Normocalcemia was achieved in 54 of the treatment episodes (73%) and the mean duration of normocalcemia was 24.8 months. PEA was safe with transient hoarseness occurring in four of the treatments (5%). CONCLUSION: The treatment of recurrent PHP in patients with MEN1 represents a challenge that is associated with increased morbidity. PEA is an effective treatment option for achieving normocalcemia in the majority of the patients with MEN1. PEA is associated with low rates of hypocalcemia and no permanent complications.
PubMed-ID: 25337928
http://dx.doi.org/10.1210/jc.2014-3255

Lethal generalized calcinosis and hypercalcemic crisis in primary hyperparathyroidism.
J Clin Endocrinol Metab, 100(1):17-8.
A. Pallauf, J. Schopohl, M. Makeschin, T. Kirchner and M. Reincke. 2015.
PubMed-ID: 25343236
http://dx.doi.org/10.1210/jc.2014-2813

Surgical cure of primary hyperparathyroidism ameliorates gastroesophageal reflux symptoms.
World J Surg, 39(3):706-12.
J. Norman, D. Politz, J. Lopez, D. Boone and A. Stojadinovic. 2015.
OBJECTIVE: Gastroesophageal reflux disease (GERD) symptoms are commonly reported in primary hyperparathyroidism (pHPT). Although a calcium-mediated cause-and-effect relationship has been suggested, it remains unknown if parathyroidectomy improves GERD symptoms. METHODS: Over a 22-month period, 1,175 (39%) of 3,000 consecutive adult patients with pHPT and symptomatic GERD (on prescription reflux medications daily for >/=2 years) undergoing parathyroidectomy were entered into a prospective study. Standardized Frequency Scale for Symptoms of GERD (FSSG) questionnaire was used to assess symptoms before, 1 and 2 years after parathyroidectomy. RESULTS: Daily prescription medication was used by 81%, while 19% used daily non-prescription drugs, both for a mean of 2.9 +/- 0.7 years. GERD symptoms improved (26%) or resolved completely (36%) in 62% of patients ($p < 0.0001$ vs. preoperative baseline) 1 year after parathyroidectomy.

Prescription medications for GERD decreased from 81% of enrolled patients to 26% (p < 0.0001) 12 months postoperatively, with 39% having complete symptom relief and taking no medications (p < 0.0001). Daily use of prescription GERD medications decreased to occasional over-the-counter drug use in 35% after parathyroidectomy (p < 0.0001). Mean FSSG scores decreased significantly postoperatively (pre-op: 18.0 +/- 8.0 vs. post-op: 10.0 +/- 5.0; p < 0.0001), with significant improvements in all 12 FSSG categories, including motility (pre-op: 7.3 +/- 3.0 vs. post-op: 4.4 +/- 3.0; p < 0.0001) and acid reflux symptoms (pre-op: 10.8 +/- 5.0 vs. post-op: 5.9 +/- 4.0; p < 0.0001). Symptomatic improvements were durable 2 years after parathyroidectomy. CONCLUSION: Symptomatic GERD is common in pHPT. Parathyroidectomy provides significant, durable relief of both motility and acid reflux symptoms allowing discontinuation of prescription drug use for GERD in most (74%) patients providing yet another indication for parathyroidectomy in pHPT.
PubMed-ID: 25409840
http://dx.doi.org/10.1007/s00268-014-2876-5

What's in a name?: Providing clarity in the definition of minimally invasive parathyroidectomy.
World J Surg, 39(4):975-80.
B. C. James, E. L. Kaplan, R. H. Grogan and P. Angelos. 2015.
BACKGROUND: In recent years minimally invasive parathyroidectomy has become the procedure of choice for many surgeons, but the meaning of the term is unclear. This is confusing for both the medical community and patients. We hypothesize that because the definition of minimally invasive parathyriodectomy in the literature is so variable this term has little meaning. METHODS: We performed a Pubmed search using the terms: parathyroidectomy, minimally invasive, localized, focused, unilateral, radio-guided, video-assisted, and endoscopic. Data were collected for: author, journal title, year published, and all described aspects of parathyroidectomy. RESULTS: We analyzed 443 (44%) articles after applying the exclusion criteria. Eighteen words were used in 75 different combinations to describe minimally invasive parathyroidectomy. We established four categories that encompassed all 75 definitions: 1. operative approach (incision size, describing as open; endoscopic; robotic; or video-assisted), 2. number of glands explored, 3. operative adjuncts, and 4. anesthesia type. Operative approach was the most commonly described attribute and was mentioned in 47% (n = 207) of the articles (mean incision size was found to be 2.2 cm), followed by number of glands explored, operative adjuncts, and anesthesia type. CONCLUSIONS: The finding that there are 75 different definitions for minimally invasive parathyroidectomy confirms that this term is too generic to be useful. We propose a new taxonomic format to describe minimally invasive parathyroidectomy based on the four descriptive categories identified: (operative approach), (# of glands explored), parathyroidectomy using (operative adjuncts) under (anesthesia type). For example, "2 cm, single gland parathyroidectomy using intraoperative parathyroid hormone measurement, under general anesthesia".
PubMed-ID: 25446489
http://dx.doi.org/10.1007/s00268-014-2902-7

Pseudopseudohypoparathyroidism.
Lancet, 385(9973):1123.
C. Simpson, E. Grove and B. A. Houston. 2015.
PubMed-ID: 25484027
http://dx.doi.org/10.1016/S0140-6736(14)61640-8

Primary and metastatic parathyroid malignancies: a rare or underdiagnosed condition?
J Clin Endocrinol Metab, 100(3):E478-81.
A. Shifrin, V. LiVolsi, S. Shifrin-Douglas, M. Zheng, B. Erler, T. Matulewicz and J. Davis. 2015.
OBJECTIVE: Parathyroid gland malignancies are considered rare. The most common of these tumor types is primary parathyroid carcinoma. Metastatic spread from other cancers may also occur with up to 10% of cancers from other sites showing parathyroid involvement at autopsy. Tumor-to-tumor metastases (metastatic spread to parathyroid neoplasm) from remote cancers to the parathyroid gland have been described. METHODS: We did a PubMed literature review and analysis of our own experience of 392 consecutive parathyroidectomies. RESULTS: Primary and secondary parathyroid malignancies can be grouped into three categories: primary parathyroid carcinoma (PPCa), spread of carcinoma into parathyroid glands by contiguous extension from the thyroid gland or other head and neck cancer, and metastatic disease to the parathyroid gland from distant cancers. Studies of tumor-to-tumor spread indicate a predilection of spread to endocrine tumors possibly because of the rich blood supply that is present in endocrine tumors. Two of our 392 parathyroidectomies (0.5%) had cancer: one metastatic (thymic neuroendocrine tumor) and another PPCa. CONCLUSION: Metastatic disease to the parathyroid gland is poorly documented. When performing surgery for primary thyroid cancer, the search for parathyroid gland metastases is often overlooked because of the desire to preserve parathyroid

function. Metastatic disease from other cancers to a benign parathyroid gland or to a parathyroid adenoma probably suggests a grave prognosis because it likely indicates widespread metastatic disease; however, isolated metastases to the parathyroid may occur. Although these lesions may be uncommon they may not be as rare as once thought.
PubMed-ID: 25490272
http://dx.doi.org/10.1210/jc.2014-2760

Tumour-associated fibroblasts contribute to neoangiogenesis in human parathyroid neoplasia.
Endocr Relat Cancer, 22(1):87-98.
C. Verdelli, L. Avagliano, P. Creo, V. Guarnieri, A. Scillitani, L. Vicentini, G. B. Steffano, E. Beretta, L. Soldati, E. Costa, A. Spada, G. P. Bulfamante and S. Corbetta. 2015.
Components of the tumour microenvironment initiate and promote cancer development. In this study, we investigated the stromal component of parathyroid neoplasia. Immunohistochemistry for alpha-smooth muscle actin (alpha-SMA) showed an abundant periacinar distribution of alpha-SMA(+) cells in normal parathyroid glands (n=3). This pattern was progressively lost in parathyroid adenomas (PAds; n=6) where alpha-SMA(+)cells were found to surround new microvessels, as observed in foetal parathyroid glands (n=2). Moreover, in atypical adenomas (n=5) and carcinomas (n=4), alpha-SMA(+) cells disappeared from the parenchyma and accumulated in the capsula and fibrous bands. At variance with normal glands, parathyroid tumours (n=37) expressed high levels of fibroblast-activation protein (FAP) transcripts, a marker of tumour-associated fibroblasts. We analysed the ability of PAd-derived cells to activate fibroblasts using human bone-marrow mesenchymal stem cells (hBM-MSCs). PAd-derived cells induced a significant increase in FAP and vascular endothelial growth factor A (VEGFA) mRNA levels in co-cultured hBM-MSCs. Furthermore, the role of the calcium-sensing receptor (CASR) and of the CXCL12/CXCR4 pathway in the PAd-induced activation of hBM-MSCs was investigated. Treatment of co-cultures of hBM-MSCs and PAd-derived cells with the CXCR4 inhibitor AMD3100 reduced the stimulated VEGFA levels, while CASR activation by the R568 agonist was ineffective. PAd-derived cells co-expressing parathyroid hormone (PTH)/CXCR4 and PTH/CXCL12 were identified by FACS, suggesting a paracrine/autocrine signalling. Finally, CXCR4 blockade by AMD3100 reduced PTH gene expression levels in PAd-derived cells. In conclusion, i) PAd-derived cells activated cells of mesenchymal origin; ii) PAd-associated fibroblasts were involved in tumuor neoangiogenesis and iii) CXCL12/CXCR4 pathway was expressed and active in PAd cells, likely contributing to parathyroid tumour neoangiogenesis and PTH synthesis modulation.
PubMed-ID: 25515730
http://dx.doi.org/10.1530/ERC-14-0161

Comparison of 4D CT, ultrasonography, and 99mTc sestamibi SPECT/CT in localizing single-gland primary hyperparathyroidism.
Otolaryngol Head Neck Surg, 152(3):438-43.
Y. J. Suh, J. Y. Choi, S. J. Kim, I. K. Chun, T. J. Yun, K. E. Lee, J. H. Kim, G. J. Cheon and Y. K. Youn. 2015.
OBJECTIVE: The present study was designed to evaluate 4D computerized tomography (CT) as a means of localizing abnormal parathyroid glands in primary hyperparathyroidism (HPT). STUDY DESIGN: Case series with expertized image review. SETTING: Tertiary care hospital. SUBJECTS AND METHODS: A total of 38 patients were recruited for study, all of whom had undergone focused parathyroidectomy for single-lesion primary HPT between June 2011 and September 2013. In each patient, 3 imaging procedures were performed: cervical ultrasonography (US), 99mTc-sestamibi SPECT/CT (SeS), and 4D CT. Collective imaging data were blindly reviewed and compared. RESULTS: 4D CT outperformed US and SeS in terms of sensitivity (P=.27), specificity (P=.01), positive predictive value (PPV) (P<.01), negative predictive value (NPV) (P=.19), and accuracy (P<.01). In 7.9% (3/38) of patients, 4D CT provided specific anatomic information that was unaffordable by US and SeS. Localization by 4D CT correlated with tissue parathyroid hormone level (P=.02), maximum diameter (P=.01), and volume (P<.01) of abnormal parathyroid glands. CONCLUSION: 4D CT proved helpful in localizing target parathyroid glands of primary HPT that were missed by traditional imaging.
PubMed-ID: 25518904
http://dx.doi.org/10.1177/0194599814562195

Is intraoperative parathyroid hormone testing in patients with renal insufficiency undergoing parathyroidectomy for primary hyperparathyroidism accurate?
Am J Surg, 209(3):483-7.
J. A. Sohn, S. C. Oltmann, D. F. Schneider, R. S. Sippel, H. Chen and D. M. Elfenbein. 2015.
BACKGROUND: Our aim was to determine whether chronic renal insufficiency (CRI) impacted intraoperative parathyroid hormone (ioPTH) monitoring during parathyroidectomy. We hypothesized that ioPTH monitoring in patients with CRI would show slower decline, but would still accurately predict cure. METHODS: A retrospective

review was conducted of patients with primary hyperparathyroidism who underwent curative single adenoma parathyroidectomy. The percentage of patients reaching 50% decline of ioPTH was compared between groups stratified by renal function. RESULTS: Between 2000 and 2013, 950 patients met inclusion criteria. At 5 minutes, 66% of patients with CRI met curative criteria versus 77% of normal renal function patients (P = .001). At 10 minutes, 89% vs 92% met criteria (P = .073), and by 15 minutes, the gap narrowed to 95% vs 97% (P = .142), respectively. CONCLUSIONS: Despite CRI patients with primary hyperparathyroidism having slower ioPTH decline after curative parathyroidectomy, 95% met ioPTH criteria by 15 minutes. Standard ioPTH criteria can be used with CRI patients.
PubMed-ID: 25556028
http://dx.doi.org/10.1016/j.amjsurg.2014.09.022

[Intraoperative management of undetectable parathyroid adenoma].
Chirurg, 86(1):24-8.
C. Dotzenrath. 2015.
Despite new technologies and progress in parathyroid gland imaging, missed parathyroid adenomas are still a problem. In reoperations most adenomas were found in eutopic positions. Adenoma in atypical positions were mostly situated in the thymus or in the esophageal-tracheal groove. Positive parathyroid imaging can be helpful but does not necessarily result in a better success rate than conventional bilateral exploration by an experienced surgeon, which is > 95 %. The knowledge of anatomy and embryological development of parathyroid glands is most important. Intraoperative determination of parathyroid hormone levels can help localize the site of the adenoma. Thyroid resection should only be performed if preoperative or intraoperative ultrasound indicates a tumor in the thyroid gland. The most important factor for a successful parathyroid operation is an experienced surgeon.
PubMed-ID: 25591414
http://dx.doi.org/10.1007/s00104-014-2820-0

Preoperative imaging for focused parathyroidectomy: making a good strategy even better.
Eur J Endocrinol, 172(5):519-26.
C. Guerin, A. Lowery, S. Gabriel, F. Castinetti, M. Philippon, J. Vaillant-Lombard, A. Loundou, J. F. Henry, F. Sebag and D. Taieb. 2015.
OBJECTIVE: Surgical treatment for primary hyperparathyroidism (pHPT) has undergone a major paradigm shift during the last decades from bilateral cervicotomy with four-gland neck exploration to image-guided focused approaches. The primary objective of the present study was to compare the performances of parathyroid scintigraphy (PS), parathyroid ultrasonography (US), and the combination of both procedures for guiding a focused approach on the basis of modified interpretation criteria. METHODS: Data from 199 patients operated for apparent sporadic pHPT and evaluated with US and PS using dual-isotope (123)I/(99m)Tc-sestamibi planar pinhole and single-photon emission computed tomography (SPECT) acqusitions were evaluated. RESULTS: A total of 127 patients underwent a focused approach and the remainder had bilateral cervicotomy. In 42 cases, a focused approach was not performed due to the absence of concordant results between US and PS for a single-gland abnormality. Four patients had persistent disease and three had recurrent disease. A localizing preoperative PS had a sensitivity of 93.3%, positive predictive value of 85.8%, negative predictive value of 73.0%, and accuracy of 83.4% for predicting uniglandular disease. Additional SPECT images accurately localize posterior adenomas that are often missed by US. Compared with PS, US had a lower sensitivity (P<0.01). Our imaging protocol also enabled diagnosis of multiglandular disease in 60.6%. CONCLUSIONS: PS using a highly sensitive dual-tracer subtraction method is the most accurate technique for directing a focused approach. PS could be sufficient for directing a focused approach in the presence of a negative US in two major circumstances: posterior locations due to acquired ectopia that could be missed by US, and previous history of thyroidectomy due to interpretation difficulties.
PubMed-ID: 25637075
http://dx.doi.org/10.1530/EJE-14-0964

The utility of 4-dimensional computed tomography for preoperative localization of primary hyperparathyroidism in patients not localized by sestamibi or ultrasonography.
Surgery, 157(3):534-9.
K. M. Day, M. Elsayed, M. D. Beland and J. M. Monchik. 2015.
BACKGROUND: To determine the sensitivity and clinical application of 4-dimensional computed tomography (4D CT) for the localization of patients with primary hyperparathyroidism when ultrasonography (US) and sestamibi scans (STS) are negative. METHODS: We compiled a database of 872 patients with primary hyperparathyroidism who underwent parathyroid operation by a single surgeon from January 2003 to September

2013. Seventy-three patients who failed to have positive localization by US or STS were identified. Thirty-six underwent operation without a preoperative 4D CT, and 37 underwent operation after 4D CT. RESULTS: In patients not localized by US or STS, 4D CT was 89% sensitive in localizing an abnormal parathyroid gland when reviewed blindly by a radiologist specializing in endocrine localization studies, yielding a positive likelihood ratio of 0.89 and positive predictive value of 74%. Sensitivity, positive likelihood ratio, and positive predictive value for correct gland lateralization were 93%, 0.93, and 80%. The average size of parathyroid glands removed after preoperative localization by 4D CT was 404 mg and 0.57 cm3 (SD = 280, 0.64), compared with 259 mg and 0.39 cm3 (SD = 166, 0.21) in patients not localized by 4D CT. A focused, unilateral exploration was performed in 38% of patients with preoperative localization by 4D CT compared with 19% of patients without 4D CT (chi2 = 3.0, P = .041). CONCLUSION: 4D CT provided a positive localization in a clinically substantial number of patients not able to be localized by US or STS, which enabled an increased rate of successful, focused, unilateral operations compared with patients who did not undergo a 4D CT.
PubMed-ID: 25660183
http://dx.doi.org/10.1016/j.surg.2014.11.010

Is Normocalcemic Primary Hyperparathyroidism Harmful or Harmless?
J Clin Endocrinol Metab, 100(6):2420-4.
G. Chen, Y. Xue, Q. Zhang, T. Xue, J. Yao, H. Huang, J. Liang, L. Li, W. Lin, L. Lin, L. Shi, L. Cai and J. Wen. 2015.
CONTEXT: Primary hyperparathyroidism (PHPT) is reported to be associated with an increased frequency of hypertension, however, information in this regard is sparse in relation to normocalcemic primary hyperparathyroidism (NPHPT). OBJECTIVE: The aim of this study was to determine the association between NPHPT and blood pressure. DESIGN, SETTING, AND PATIENTS: We retrospectively enrolled 940 patients who visited the Fujian Provincial Hospital between September 2010 and December 2013 with a measured serum parathyroid hormone (PTH) and calcium level. Among them, 11 patients were diagnosed with NPHPT, while 296 cases with normal PTH and albumin-adjusted serum calcium. MAIN OUTCOMES MEASURES: Systolic blood pressure (SBP), diastolic blood pressure (DBP), intact serum PTH, and serum calcium were recorded. RESULTS: There were no significant differences between subjects identified with NPHPT and those with normal PTH in terms of age, sex, body mass index, serum calcium, 25-Hydroxyvitamin D, serum creatinine, fasting plasma glucose, triglycerides, total cholesterol, high density lipoprotein, and low density lipoprotein. The subjects with a diagnosis of NPHPT had higher levels of SBP (141.9 +/- 20.2 vs 131.2 +/- 16.5, P = .041) and DBP (85.2 +/- 12.4 vs 76.8 +/- 10.3, P = .026) than the subjects in the cohort with normal PTH. After adjustment for all potential confounders, risks (odds ratios and 95% confidence interval) of SBP and DBP in NPHPT patients were 1.035 (1.000, 1.071) and 1.063 (1.004, 1.125), respectively (P < .05). CONCLUSIONS: The NPHPT had higher risk of high blood pressure than subjects with normal PTH. It is worth considering the necessity of more aggressive therapeutic intervention aimed to normalize PTH even if patients with NPHPT continue to be normocalcemic.
PubMed-ID: 25668199
http://dx.doi.org/10.1210/jc.2014-4432

Management of thyroid nodules incidentally discovered on MIBI scanning for primary hyperparathyroidism.
Langenbecks Arch Surg, 400(3):313-8.
T. Greilsamer, C. Blanchard, N. Christou, D. Drui, C. Ansquer, M. Le Bras, B. Cariou, C. Caillard, E. Mourrain-Langlois, A. S. Delemazure, M. Mathonnet, F. Kraeber-Bodere and E. Mirallie. 2015.
INTRODUCTION: Parathyroid sestamibi scan is routinely performed before parathyroid surgery. A large number of thyroid cancers take up 99mTc-sestamibi (MIBI). Since 2001, thyroid nodules discovered on sestamibi, nodules >2 cm, and/or with suspicious criteria were resected. The aim of this study was to evaluate the results of this policy. METHODS: All patients operated on for hyperparathyroidism, with a MIBI and cervical ultrasonography (US) with a thyroid resection for nodule, were retrospectively included. RESULTS: From 2001 to 2013, 685 patients were operated on for hyperparathyroidism. Some 137 (85 % females) had both preoperative MIBI and cervical US and a thyroid resection. The mean age was 63.2 +/- 12.8 years. Sixty-three patients had a total thyroidectomy and 74 a lobectomy. Thirty-six patients had a thyroid cancer. The median size of cancers was 6.5 mm (0.3-22 mm), and 23 (16.7 %) patients had microcarcinoma. Among the 137 patients, 44 (32 %) had a MIBI+ nodule including 22 cancers. Sixty-one percent of malignant nodules were MIBI+ (22/36). The median size of MIBI+ cancers was 15 mm (9-22 mm) versus 2 mm (0.3-17 mm) for MIBI- cancers (p = 0.03). Twenty-two percent of benign nodules were MIBI+ (22/101). Finally, the sensitivity, specificity, positive predictive value, and negative predictive value of MIBI were 61, 78, 50, and 85 %, respectively. CONCLUSION: Thyroid nodules incidentally discovered on MIBI in hyperparathyroidism patients should be resected.

PubMed-ID: 25694271
http://dx.doi.org/10.1007/s00423-015-1286-y

Diagnostic value and clinical impact of complementary CT scan prior to surgery for non-localized primary hyperparathyroidism.
Langenbecks Arch Surg, 400(3):307-12.
B. Seeliger, P. F. Alesina, J. A. Koch, J. Hinrichs, B. Meier and M. K. Walz. 2015.
INTRODUCTION: Successful localization is mandatory for focused parathyroidectomy. If ultrasound and sestamibi scan are negative, bilateral neck exploration is necessary. We examined the contribution of complementary computed tomography (CT) scan to identify the affected parathyroid gland. METHODS: Between November 1999 and April 2014, 25 patients (20 females and 5 males; mean age 67 +/- 11 years) with negative or dubious standard imaging (ultrasound and sestamibi scan) underwent CT scan prior to parathyroidectomy and were included in this study. Fifteen patients had had previous neck surgery for parathyroidectomy (n = 11) or thyroidectomy (n = 4). Thin-slice CT (n = 9) or four-dimensional (4D) CT imaging (n = 16) was used. Cure was defined as >50 % post-excision fall of intraoperatively measured parathyroid hormone or fall into the normal range, confirmed by normocalcaemia at least 6 months after surgery. RESULTS: Preoperative CT scan provided correct localization in 13 out of 25 patients (52 %) and was false positive once. Parathyroidectomy was performed by a focused approach in 11 of these 13 patients as well as in 1 patient guided by intraoperatively measured parathyroid hormone (ioPTH). Thirteen patients required bilateral neck exploration. The cure rate was 96 % (24/25 patients). One patient has persistent primary hyperparathyroidism (pHPT) and one a recurrent disease. Six patients presented a multiglandular disease. CONCLUSION: A CT scan identifies about half of abnormal parathyroid glands missed by conventional imaging and allows focused surgery in selected cases.
PubMed-ID: 25702138
http://dx.doi.org/10.1007/s00423-015-1282-2

The current status of intraoperative iPTH assay in surgery for primary hyperparathyroidism.
Gland Surg, 4(1):36-43.
M. Barczynski, F. Golkowski and I. Nawrot. 2015.
Intraoperative intact parathyroid hormone (iPTH) monitoring has been accepted by many centers specializing in parathyroid surgery as a useful adjunct during surgery for primary hyperparathyroidism. This method can be utilized in three discreet modes of application: (I) to guide surgical decisions during parathyroidectomy in one of the following clinical contexts: (i) to confirm complete removal of all hyperfunctioning parathyroid tissue, which allows for termination of surgery with confidence that the hyperparathyroid state has been successfully corrected; (ii) to identify patients with additional hyperfunctioning parathyroid tissue following the incomplete removal of diseased parathyroid/s, which necessitates extended neck exploration in order to minimize the risk of operative failure; (II) to differentiate parathyroid from non-parathyroid tissue by iPTH measurement in the fine-needle aspiration washout; (III) to lateralize the side of the neck harboring hyperfunctioning parathyroid tissue by determination of jugular venous gradient in patients with negative or discordant preoperative imaging studies, in order to increase the number of patients eligible for unilateral neck exploration. There are many advantages of minimally invasive parathyroidectomy guided by intraoperative iPTH monitoring, including focused dissection in order to remove the image-indexed parathyroid adenoma with a similar or even higher operative success rate, lower prevalence of complications and shorter operative time when compared to conventional bilateral neck exploration. However, to achieve such excellent results, the surgeon needs to be aware of hormone dynamics during parathyroidectomy and carefully choose the protocol and interpretation criteria that best fit the individual practice. Understanding the nuances of intraoperative iPTH monitoring allows the surgeon for achieving intraoperative confidence in predicting operative success and preventing failure in cases of unsuspected multiglandular disease, while safely limiting neck exploration in the majority of patients with sporadic primary hyperparathyroidism. Thus, parathyroidectomy guided by intraoperative iPTH monitoring for the management of sporadic primary hyperparathyroidism is an ideal option for the treatment of this disease entity. However, the cost-benefit aspects of the standard application of this method still remain a matter of controversy.
PubMed-ID: 25713778
http://dx.doi.org/10.3978/j.issn.2227-684X.2015.01.01

Brief Report: Does PTH Increase With Age, Independent of 25-Hydroxyvitamin D, Phosphate, Renal Function, and Ionized Calcium?
J Clin Endocrinol Metab, 100(5):2131-4.
S. J. Carrivick, J. P. Walsh, S. J. Brown, R. Wardrop and N. C. Hadlow. 2015.
CONTEXT: Circulating PTH concentrations increase with age. It is uncertain whether an age-related PTH increase occurs independent of changes in circulating 25-hydroxyvitamin D, phosphate, renal function, and

ionized calcium. OBJECTIVE: The purpose of this article was to analyze the relationship between PTH and age, controlling for 25-hydroxyvitamin D, phosphate, renal function, and ionized calcium. METHODS: This was a retrospective, cross-sectional study analyzing the relationship between PTH and age in 2 independent datasets (laboratory 1, n = 17 275 and laboratory 2, n = 4878). We further analyzed subgroups after excluding participants with estimated glomerular filtration rate of <60 mL/min/1.73 m(2) or 25-hydroxyvitamin D of <50 nmol/L (for subgroups, n = 12 051 for laboratory 1 and 3473 for laboratory 2). RESULTS: After adjustment for sex, ionized calcium, 25-hydroxyvitamin D, phosphate, and estimated glomerular filtration rate, each 10-year increase in age was associated with a 5.0% increase in PTH (95% confidence interval [CI], 4.4%-5.6%; P < .001) in laboratory 1 and a 4.2% increase in laboratory 2 (95% CI, 3.0%-5.4%; P < .001). In the subgroups, each 10-year increase in age was associated with a 6.1% increase in PTH (95% CI, 5.5%-6.8%; P < .001) in laboratory 1 and a 4.9% increase (95% CI 3.5%-6.2%; P < .001) in laboratory 2. CONCLUSION: PTH concentrations increase with age, independent of 25-hydroxyvitamin D, ionized calcium, phosphate, and renal function. Further research is required to explore the underlying mechanisms and clinical relevance and to determine whether the use of age-related PTH reference ranges improves diagnostic accuracy, particularly in elderly individuals.
PubMed-ID: 25751107
http://dx.doi.org/10.1210/jc.2014-4370

Pregnancy outcomes in women with primary hyperparathyroidism.
J Clin Endocrinol Metab, 100(5):2115-22.
D. Hirsch, V. Kopel, V. Nadler, S. Levy, Y. Toledano and G. Tsvetov. 2015.
OBJECTIVE: Primary hyperparathyroidism (PHPT) during pregnancy may pose considerable risks to mother and fetus. This study examined pregnancy outcomes in women with gestational PHPT in relation to clinical and laboratory parameters. DESIGN: This study was designed as a retrospective case series. METHODS: The study group included 74 women aged 20-40 years who were diagnosed with PHPT after a finding of serum calcium >/= 10.5 mg/dL on routine screening at a health maintenance organization (2005-2013) and who became pregnant during the time of hypercalcemia (124 pregnancies). Clinical and laboratory data were collected from the files. Pregnancy outcomes were compared with 175 normocalcemic pregnant women (431 pregnancies) tested during the same period. RESULTS: The cohort represented 0.03% of all women of reproductive age tested for serum calcium during the study period. Abortion occurred in 12 of 124 pregnancies (9.7%), and other complications occurred in 19 (15.3%) with no statistically significant differences from controls. Hypercalcemia was first detected during pregnancy in 14 of 74 women (18.9%) and before pregnancy (mean, 33.4 +/- 29 mo) in 60. Serum calcium was measured antenatally in 57 of 124 pregnancies (46%); the mean level was 10.7 +/- 0.6 mg/dL (median, 10.6 mg/dL). Measurement of the serum PTH level (with consequent diagnosis of PHPT) was performed during the first studied pregnancy in 17 of 74 women (23%), before pregnancy (mean, 37.8 +/- 25.5 mo; median, 34 mo) in 23 (31.1%), and after delivery (mean, 54.7 +/- 45.7 mo; median, 35 mo) in 34 (45.9%). Forty-three women (58.1%) underwent parathyroidectomy, six during pregnancy, without maternal or fetal complications. No difference was found in abortion or any pregnancy-related complication between patients who subsequently underwent parathyroidectomy and those who did not. No significant correlation was found between calcium level during pregnancy and pregnancy outcomes. CONCLUSIONS: Serum calcium levels are usually only mildly elevated during pregnancy in women with PHPT. A significant proportion of cases go undiagnosed. Mild hypercalcemia in gestational PHPT is generally not associated with an increased risk of obstetrical complications.
PubMed-ID: 25751112
http://dx.doi.org/10.1210/jc.2015-1110

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

Adrenals

Meta-Analyses

Systematic review of surgery and outcomes in patients with primary aldosteronism.
Br J Surg, 102(4):307-17.
A. Muth, O. Ragnarsson, G. Johannsson and B. Wangberg. 2015.
BACKGROUND: Primary aldosteronism (PA) is the most common cause of secondary hypertension. The main aims of this paper were to review outcome after surgical versus medical treatment of PA and partial versus total adrenalectomy in patients with PA. METHODS: Relevant medical literature from PubMed, the Cochrane Library and Embase OvidSP from 1985 to June 2014 was reviewed. RESULTS: Of 2036 records, 43 articles were included in the final analysis. Twenty-one addressed surgical versus medical treatment of PA, four considered partial versus total adrenalectomy for unilateral PA, and 18 series reported on surgical outcomes. Owing to the heterogeneity of protocols and reported outcomes, only a qualitative analysis was performed. In six studies, surgical and medical treatment had comparable outcomes concerning blood pressure, whereas six showed better outcome after surgery. No differences were seen in cardiovascular complications, but surgery was associated with the use of fewer antihypertensive medications after surgery, improved quality of life, and (possibly) lower all-cause mortality compared with medical treatment. Randomized studies indicate a role for partial adrenalectomy in PA, but the high rate of multiple adenomas or adenoma combined with hyperplasia in localized disease is disconcerting. Surgery for unilateral dominant PA normalized BP in a mean of 42 (range 20-72) per cent and the biochemical profile in 96-100 per cent of patients. The mean complication rate in 1056 patients was 4.7 per cent. CONCLUSION: Recommendations for treatment of PA are hampered by the lack of randomized trials, but support surgical resection of unilateral disease. Partial adrenalectomy may be an option in selected patients.
PubMed-ID: 25605481
http://dx.doi.org/10.1002/bjs.9744

Randomized controlled trials

- None –

Consensus Statements/Guidelines

- None -

Other Articles

Mutations in KCNJ5 determines presentation and likelihood of cure in primary hyperaldosteronism.
ANZ J Surg, 85(4):279-83.
J. C. Ip, T. C. Pang, C. K. Pon, J. T. Zhao, M. S. Sywak, A. J. Gill, P. S. Soon and S. B. Sidhu. 2015.
INTRODUCTION: Primary hyperaldosteronism (PA) is a common cause of secondary hypertension. Two recurrent mutations (G151R and L168R) in the potassium channel gene KCNJ5 have been identified that affect the Kir3.4 potassium channel found in the cells of the zona glomerulosa of the adrenal gland. The aim of this study was to determine the prevalence of KCNJ5 mutations in an Australian cohort of patients and to correlate these findings with clinical outcome data, in order to describe the clinical impact on patients who harbour this mutation. METHODS: Direct Sanger sequencing for KCNJ5 on DNA from adrenal tumour tissue of 83 patients with PA in a cohort study was undertaken and mutation status correlated with clinical outcome data. RESULTS: Seventy-one of 83 patients (86%) had adrenocortical adenomas and 12 patients (14%) had bilateral adrenal hyperplasia. A total of 34 (41%) patients were found to have heterozygous somatic mutations in KCNJ5, G151R and L168R. No germ line mutations were identified. Patients with mutations were predominately female (68% versus 49%) and significantly younger at presentation (48 versus 55 years). When correlated with clinical data,

our results demonstrated that patients with KCNJ5 mutations were more likely to be cured following surgery without the requirement for ongoing medications. CONCLUSIONS: Our findings in a large Australian cohort show that patients with mutations in KCNJ5 present earlier with the signs and symptoms of PA benefit from surgical intervention. Moreover, our results highlight the importance of a thorough workup and management plan for younger patients who present with hypertension.
PubMed-ID: 24274318
http://dx.doi.org/10.1111/ans.12470

Factors associated with higher risk of complications after adrenal surgery.
Ann Surg Oncol, 22(1):103-10.
A. Hauch, Z. Al-Qurayshi and E. Kandil. 2015.
BACKGROUND: Surgeon experience has been demonstrated to result in better outcomes after a variety of advanced operations. Less information is available regarding adrenal surgery. We compared the outcomes after adrenalectomy for a variety of indications and determined the effect of surgeon's case volume. METHODS: Cross-sectional analysis was performed using ICD-9 procedure codes included in the Nationwide Inpatient Sample from 2003 to 2009 to identify all adult patients who underwent unilateral or bilateral adrenalectomy for benign or malignant conditions. Logistic regression was used to test for interaction between surgeon case volume (low = 1, intermediate = 2-5, and high = >5 adrenalectomies per year), diagnosis, type of operation performed, and risk of complications. RESULTS: A total of 7,829 adrenalectomies were included. Risk of complications after bilateral adrenalectomy was 23.4 % compared to 15.0 % for unilateral adrenalectomy (odds ratio 2.165, 95 % confidence interval 1.335, 3.512). Malignancy was associated with higher risk of complication (23.1 %) than benign disease (13.2 %) (odds ratio 1.685, 95 % confidence interval 1.371, 2.072). Complication rates for low- and intermediate-volume surgeons were 18.8 and 14.6 %, respectively, and both were significantly higher than complications by high-volume surgeons (11.6 %, $p < 0.05$). Length of stay and charges were both significantly less for high-volume surgeons compared to lower-volume groups ($p < 0.05$). CONCLUSIONS: Low surgeon case volumes and adrenal surgery for malignant or bilateral disease are associated with increased risk of postoperative complications. Length of stay and charges were significantly less when high-volume surgeons perform adrenal surgery.
PubMed-ID: 24793341
http://dx.doi.org/10.1245/s10434-014-3750-2

Clinicopathologic characteristics of incidentally identified pheochromocytoma.
Ann Surg Oncol, 22(1):132-8.
H. Wachtel, I. Cerullo, E. K. Bartlett, R. E. Roses, D. L. Cohen, R. R. Kelz, G. C. Karakousis and D. L. Fraker. 2015.
BACKGROUND: Pheochromocytomas are rare neuroendocrine tumors. With the widespread use of cross-sectional imaging, increasing numbers are identified incidentally, but their clinicopathologic traits have been incompletely characterized. METHODS: We performed a retrospective cohort study of patients who underwent initial adrenalectomy for pheochromocytoma (1997-2014). Patients were classified as identified by guided investigation (GIP) if imaging was performed for symptoms or surveillance and as incidentally identified pheochromocytomas (IIP) if imaging was performed for other indications. Student's t test, Chi square test, or rank-sum tests were used as appropriate. RESULTS: Of 126 patients, 47 % were IIP (n = 59). IIP patients had more nonspecific symptoms, including abdominal or back pain (39.0 vs. 6.0 %, $p < 0.001$), but lower rates of classic symptoms, such as hypertension (54.2 vs. 77.6 %, $p = 0.005$), palpitations or arrhythmias (18.9 vs. 50.0 %, $p = 0.001$), flushing or diaphoresis (25.4 vs. 46.3 %, $p = 0.015$), and headache (20.3 vs. 44.8 %, $p = 0.004$). IIP was associated with lower median 24-hour urine metanephrine (2102 vs. 7299 mug, $p = 0.020$), normetanephrine (2253 vs. 4383 mug, $p = 0.005$), and epinephrine (23 vs. 116 mug, $p = 0.004$) levels. Histopathology demonstrated no difference between IIP and GIP in malignant traits, including extraadrenal extension (8.6 vs. 12.3 %, $p = 0.568$), capsular invasion (26.9 vs. 20.3 %, $p = 0.133$), lymphovascular invasion (25.0 vs. 24.6 %, $p = 0.264$), and necrosis (32.4 vs. 20.0 %, $p = 0.224$). Rates of malignancy were equivalent (5.1 vs. 6.0 %, $p = 0.862$) between IIP and GIP cohorts. CONCLUSIONS: Half of patients presenting for surgical resection of pheochromocytoma were identified incidentally. These patients had equivalent rates of malignancy and pathologic traits associated with malignant potential and require definitive evaluation and early surgical referral.
PubMed-ID: 25047479
http://dx.doi.org/10.1245/s10434-014-3933-x

False-positive rate of positron emission tomography/computed tomography for presumed solitary metastatic adrenal disease in patients with known malignancy.

Ann Surg Oncol, 22(2):437-40.
B. Kuritzkes, M. Parikh, J. Melamed, N. Hindman and H. L. Pachter. 2015.
PURPOSE: The aim of this study was to determine the diagnostic accuracy of positron emission tomography (PET) in cancer patients undergoing adrenalectomy for presumed metastatic disease, utilizing the gold standard of histopathology. METHODS: We retrospectively reviewed all adrenalectomies for metastatic disease performed at our institution over the last 12 years. Preoperative PET scans were compared with final pathology reports. Statistical analyses were performed with Fisher's exact test for categorical variables and Student's t test for continuous variables. RESULTS: Forty-nine adrenalectomies were performed for metastatic disease. Thirty had preoperative PET imaging and were included in this analysis. Mean age was 65.5 +/- 13.6 years (29-91) and 54 % were male. Mean size was 3.8 cm (0.4-7.1). Primary tumor distribution was 61 % (n = 17) pulmonary; 11 % (n = 3) breast; 7 % (n = 2) gastric; 7 % (n = 2) renal; and 4 % (n = 1) each of brain, lymphoma, melanoma, and uterine. Mean standardized uptake value (SUV) was 11 +/- 7.3 (3.2-30.0). Final pathology revealed that 80 % (25/30) were positive for metastatic disease and 20 % (5/30) were negative. The positive predictive value of PET in correctly identifying adrenal metastatic disease was 83 % (24 true-positive cases and 5 false-positive cases); there was one false-negative PET. False-positive PET results were not correlated with sex (p = 0.35), age (p = 0.24), or maximum SUV units (p = 0.26). CONCLUSIONS: The 20 % false-positive rate for PET-positive adrenalectomies performed for metastatic disease should warrant its inclusion in preoperative counseling to the patient and interaction with the treating oncologist.
PubMed-ID: 25160737
http://dx.doi.org/10.1245/s10434-014-4031-9

Extensive expertise in endocrinology. Adrenal crisis.
Eur J Endocrinol, 172(3):R115-24.
B. Allolio. 2015.
Adrenal crisis is a life-threatening emergency contributing to the excess mortality of patients with adrenal insufficiency. Studies in patients on chronic replacement therapy for adrenal insufficiency have revealed an incidence of 5-10 adrenal crises/100 patient years and suggested a mortality rate from adrenal crisis of 0.5/100 patient years. Patients with adrenal crisis typically present with profoundly impaired well-being, hypotension, nausea and vomiting, and fever responding well to parenteral hydrocortisone administration. Infections are the major precipitating causes of adrenal crisis. Lack of increased cortisol concentrations during infection enhances pro-inflammatory cytokine release and sensitivity to the toxic effects of these cytokines (e.g. tumour necrosis factor alpha). Furthermore, pro-inflammatory cytokines may impair glucocorticoid receptor function aggravating glucocorticoid deficiency. Treatment of adrenal crisis is simple and highly effective consisting of i.v. hydrocortisone (initial bolus of 100 mg followed by 200 mg over 24 h as continuous infusion) and 0.9% saline (1000 ml within the first hour). Prevention of adrenal crisis requires appropriate hydrocortisone dose adjustments to stressful medical procedures (e.g. major surgery) and other stressful events (e.g. infection). Patient education is a key for such dose adjustments but current education concepts are not sufficiently effective. Thus, improved education strategies are needed. Every patient should carry an emergency card and should be provided with an emergency kit for parenteral hydrocortisone self-administration. A hydrocortisone pen would hold a great potential to lower the current barriers to hydrocortisone self-injection. Improved patient education and measures to facilitate parenteral hydrocortisone self-administration in impending crisis are expected to significantly reduce morbidity and mortality from adrenal crisis.
PubMed-ID: 25288693
http://dx.doi.org/10.1530/EJE-14-0824

Update in primary aldosteronism.
J Clin Endocrinol Metab, 100(1):1-10.
M. Stowasser. 2015.
Primary aldosteronism (PA) is a condition well worth detecting because it is a common cause of hypertension and is associated with excessive morbidity for the degree of hypertension and reduced quality of life, all of which can be abrogated with specific surgical or medical treatment. Recent years have seen an explosion in knowledge concerning the genetic bases of this disorder, and particularly of somatic mutations associated with aldosterone-producing adenomas and germline mutations causing rare familial forms, both involving genes encoding ion channels. Inroads have also been made into understanding molecular pathways that may be involved in the development of PA. With evidence continuing to mount for non-blood pressure-dependent adverse effects of aldosterone excess and for superior effects of specific over non-specific treatment, the need for accurate yet readily applicable and available diagnostic approaches and methodologies has become a matter of urgency. Advances in approaches to confirmatory testing, subtype differentiation, and assay methodology are helping to improve feasibility and reliability of the diagnostic workup for PA, and new treatment approaches are

emerging.
PubMed-ID: 25365316
http://dx.doi.org/10.1210/jc.2014-3663

Lack of utility of SDHB mutation testing in adrenergic metastatic phaeochromocytoma.
Eur J Endocrinol, 172(2):89-95.
M. Sue, V. Martucci, F. Frey, J. M. Lenders, H. J. Timmers, M. Peczkowska, A. Prejbisz, B. Swantje, S. R. Bornstein, W. Arlt, M. Fassnacht, F. Beuschlein, M. Robledo, K. Pacak and G. Eisenhofer. 2015.
OBJECTIVE: Testing for succinate dehydrogenase subunit B (SDHB) mutations is recommended in all patients with metastatic phaeochromocytomas and paragangliomas (PPGLs), but may not be required when metastatic disease is accompanied by adrenaline production. This retrospective cohort study aimed to establish the prevalence of SDHB mutations among patients with metastatic PPGLs, characterised by production of adrenaline compared with those without production of adrenaline, and to establish genotype-phenotype features of metastatic PPGLs according to underlying gene mutations. DESIGN AND METHODS: Presence of SDHB mutations or deletions was tested in 205 patients (114 males) aged 42+/-16 years (range 9-86 years) at diagnosis of metastatic PPGLs with and without adrenaline production. RESULTS: Twenty-three of the 205 patients (11%) with metastatic PPGLs had disease characterised by production of adrenaline, as defined by increased plasma concentrations of metanephrine larger than 5% of the combined increase in both normetanephrine and metanephrine. None of these 23 patients had SDHB mutations. Of the other 182 patients with no tumoural adrenaline production, 51% had SDHB mutations. Metastases in bone were 36-41% more prevalent among patients with SDHB mutations or extra-adrenal primary tumours than those without mutations or with adrenal primary tumours. Liver metastases were 81% more prevalent among patients with adrenal than extra-adrenal primary tumours. CONCLUSION: SDHB mutation testing has no utility among patients with adrenaline-producing metastatic PPGLs, but is indicated in other patients with metastatic disease. Our study also reveals novel associations of metastatic spread with primary tumour location and presence of SDHB mutations.
PubMed-ID: 25371406
http://dx.doi.org/10.1530/EJE-14-0756

Paraganglioma and phaeochromocytoma: from genetics to personalized medicine.
Nat Rev Endocrinol, 11(2):101-11.
J. Favier, L. Amar and A. P. Gimenez-Roqueplo. 2015.
Paragangliomas and phaeochromocytomas are neuroendocrine tumours whose pathogenesis and progression are very strongly influenced by genetics. A germline mutation in one of the susceptibility genes identified so far explains approximately 40% of all cases; the remaining 60% are thought to be sporadic cases. At least one-third of these sporadic tumours contain a somatic mutation in a predisposing gene. Genetic testing, which is indicated in every patient, is guided by the clinical presentation as well as by the secretory phenotype and the immunohistochemical characterization of the tumours. The diagnosis of an inherited form drives clinical management and tumour surveillance. Different 'omics' profiling methods have provided a neat classification of these tumours in accordance with their genetic background. Transcriptomic studies have identified two main molecular pathways that underlie development of these tumours, one in which the hypoxic pathway is activated (cluster 1) and another in which the MAPK and mTOR (mammalian target of rapamycin) signalling pathways are activated (cluster 2). DNA methylation profiling has uncovered a hypermethylator phenotype in tumours related to SDHx genes (a group of genes comprising SDHA, SDHB, SDHC, SDHD and SDHAF2) and revealed that succinate acts as an oncometabolite, inhibiting 2-oxoglutarate-dependent dioxygenases, such as hypoxia-inducible factor prolyl-hydroxylases and histone and DNA demethylases. 'Omics' data have suggested new therapeutic targets for patients with a malignant tumour. In the near future, new 'omics'-based tests are likely to be transferred into clinical practice with the goal of establishing personalized medical management for affected patients.
PubMed-ID: 25385035
http://dx.doi.org/10.1038/nrendo.2014.188

SDHD immunohistochemistry: a new tool to validate SDHx mutations in pheochromocytoma/paraganglioma.
J Clin Endocrinol Metab, 100(2):E287-91.
M. Menara, L. Oudijk, C. Badoual, J. Bertherat, C. Lepoutre-Lussey, L. Amar, X. Iturrioz, M. Sibony, F. Zinzindohoue, R. de Krijger, A. P. Gimenez-Roqueplo and J. Favier. 2015.
CONTEXT: Pheochromocytomas (PCC) and paragangliomas (PGL) may be caused by a germline mutation in 12 different predisposing genes. We previously reported that immunohistochemistry is a useful approach to

detect patients harboring SDHx mutations. SDHA immunostaining is negative in SDHA-mutated tumors only, while SDHB immunostaining is negative in samples mutated on all SDHx genes. In some cases of SDHD or SDHC-mutated tumors, a weak diffuse SDHB labeling has however been described. OBJECTIVE: Here, we addressed whether the same procedure could be applicable to detect patients with germline SDHD mutations, by testing two new commercially available anti-SDHD antibodies. DESIGN AND METHODS: We performed a retrospective study on 170 PGL/PCC in which we investigated SDHD and SDHB expression by immunohistochemistry. RESULTS: SDHx-mutated PGL/PCC showed a completely negative SDHB staining (23/27) or a weak cytoplasmic background (4/27). Unexpectedly, we observed that SDHD immunohistochemistry was positive in SDHx-deficient tumors and negative in the other samples. Twenty-six of 27 SDHx tumors (including the four weakly stained for SDHB) were positive for SDHD. Among non-SDHx tumors, 138/143 were positive for SDHB and negative for SDHD. Five cases showed a negative immunostaining for SDHB, but were negative for SDHD. CONCLUSION: Our results demonstrate that a positive SDHD immunostaining predicts the presence of an SDHx gene mutation. Because SDHB negative immunostaining is sometimes difficult to interpret in the case of background, the addition of SDHD positive immunohistochemistry will be a very useful tool to predict or validate SDHx gene variants in PGL/PCC.
PubMed-ID: 25405498
http://dx.doi.org/10.1210/jc.2014-1870

Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas.
J Clin Endocrinol Metab, 100(2):417-21.
M. Lafont, C. Fagour, M. Haissaguerre, G. Darancette, T. Wagner, J. B. Corcuff and A. Tabarin. 2015.
CONTEXT: The per-operative hemodynamic behavior of normotensive incidentally discovered pheochromocytomas is poorly documented. OBJECTIVE: To compare the per-operative hemodynamic instability and early postoperative outcome of normotensive pheochromocytomas, hypertensive pheochromocytomas, and benign non-pheochromocytoma adrenal incidentalomas (AIs). DESIGN: Retrospective cohort treated in a single center. PATIENTS AND METHODS: Fifty patients (10 normotensive pheochromocytomas, 24 hypertensive pheochromocytomas, and 16 AIs) were anesthetized and operated on by the same team, using laparoscopy in 78% of cases. Before surgery, 60% of normotensive and 95.8% of hypertensive pheochromocytomas received pretreatment with alpha-receptor or calcium channel blockers. All of the patients received the same intraoperative hemodynamic monitoring, including continuous direct intra-arterial pressure recording. RESULTS: All the features of hemodynamic instability, with the exception of the diastolic pressure nadir and fluid volume requirements, differed between hypertensive pheochromocytomas and AIs. Conversely, all features of hemodynamic instability were similar in hypertensive and normotensive pheochromocytomas. More specifically, by comparison with AIs, normotensive pheochromocytomas displayed higher maximal systolic pressure; more hypertensive, severe hypertensive, and hypotensive episodes; and a higher minimal heart rate, and also required more interventions to treat undesirable blood pressure elevations. Postoperative complications, all of which were mild, were more frequent in hypertensive pheochromocytomas than in normotensive pheochromocytomas ($P < .03$). CONCLUSIONS: Normotensive pheochromocytomas have roughly comparable per-operative hemodynamic instability to hypertensive pheochromocytomas and differ markedly from non-pheochromocytoma AIs. It is therefore crucial to identify normotensive pheochromocytomas among AIs when surgery is scheduled and to apply the standard of care for pheochromocytoma anesthesia.
PubMed-ID: 25405501
http://dx.doi.org/10.1210/jc.2014-2998

Brain metastasis in patients with adrenocortical carcinoma: a clinical series.
J Clin Endocrinol Metab, 100(2):331-6.
M. Burotto, N. Tageja, A. Rosenberg, S. Mahalingam, M. Quezado, M. Velarde, M. Edgerly and T. Fojo. 2015.
INTRODUCTION: Adrenocortical carcinoma (ACC) is a heterogeneous and rare disease. At presentation or at the time of a recurrence, the disease commonly spreads to the liver, lungs, lymph nodes, and bones. The brain has only rarely been reported as a site of metastases. OBJECTIVE: The aims of this report were to describe the clinical characteristics of patients with ACC who developed brain metastasis and were evaluated at the National Cancer Institute. METHODS: We describe the history and clinical presentation of six patients with ACC and metastatic disease in the brain. Images of the six patients and pathology slides were reviewed when available. RESULTS: The median age at the time of the diagnosis of ACC was 42 years. The median time from the initial diagnosis until the presentation of brain metastasis was 43 months. As a group the patients had previously received multiples lines of chemotherapy (median of three), and they presented with one to three metastatic brain lesions. Four patients underwent metastasectomy, one had radiosurgery, and one had both modalities. Two patients are still alive, three died, between 2 and 14 months after the diagnosis of brain metastases, and

one was lost to follow-up. CONCLUSION: Patients with advanced ACC can rarely present with metastasis to the brain, most often long after the initial diagnosis. Timely diagnosis of brain metastasis with appropriate intervention after discussion in a multidisciplinary meeting can improve the prognosis in this particular scenario.
PubMed-ID: 25412413
http://dx.doi.org/10.1210/jc.2014-2650

Heterogeneous genetic background of the association of pheochromocytoma/paraganglioma and pituitary adenoma: results from a large patient cohort.
J Clin Endocrinol Metab, 100(3):E531-41.
J. Denes, F. Swords, E. Rattenberry, K. Stals, M. Owens, T. Cranston, P. Xekouki, L. Moran, A. Kumar, C. Wassif, N. Fersht, S. E. Baldeweg, D. Morris, S. Lightman, A. Agha, A. Rees, J. Grieve, M. Powell, C. L. Boguszewski, P. Dutta, R. V. Thakker, U. Srirangalingam, C. J. Thompson, M. Druce, C. Higham, J. Davis, R. Eeles, M. Stevenson, B. O'Sullivan, P. Taniere, K. Skordilis, P. Gabrovska, A. Barlier, S. M. Webb, A. Aulinas, W. M. Drake, J. S. Bevan, C. Preda, N. Dalantaeva, A. Ribeiro-Oliveira, Jr., I. T. Garcia, G. Yordanova, V. Iotova, J. Evanson, A. B. Grossman, J. Trouillas, S. Ellard, C. A. Stratakis, E. R. Maher, F. Roncaroli and M. Korbonits. 2015.
CONTEXT: Pituitary adenomas and pheochromocytomas/paragangliomas (pheo/PGL) can occur in the same patient or in the same family. Coexistence of the two diseases could be due to either a common pathogenic mechanism or a coincidence. OBJECTIVE: The objective of the investigation was to study the possible coexistence of pituitary adenoma and pheo/PGL. DESIGN: Thirty-nine cases of sporadic or familial pheo/PGL and pituitary adenomas were investigated. Known pheo/PGL genes (SDHA-D, SDHAF2, RET, VHL, TMEM127, MAX, FH) and pituitary adenoma genes (MEN1, AIP, CDKN1B) were sequenced using next generation or Sanger sequencing. Loss of heterozygosity study and pathological studies were performed on the available tumor samples. SETTING: The study was conducted at university hospitals. PATIENTS: Thirty-nine patients with sporadic of familial pituitary adenoma and pheo/PGL participated in the study. OUTCOME: Outcomes included genetic screening and clinical characteristics. RESULTS: Eleven germline mutations (five SDHB, one SDHC, one SDHD, two VHL, and two MEN1) and four variants of unknown significance (two SDHA, one SDHB, and one SDHAF2) were identified in the studied genes in our patient cohort. Tumor tissue analysis identified LOH at the SDHB locus in three pituitary adenomas and loss of heterozygosity at the MEN1 locus in two pheochromocytomas. All the pituitary adenomas of patients affected by SDHX alterations have a unique histological feature not previously described in this context. CONCLUSIONS: Mutations in the genes known to cause pheo/PGL can rarely be associated with pituitary adenomas, whereas mutation in a gene predisposing to pituitary adenomas (MEN1) can be associated with pheo/PGL. Our findings suggest that genetic testing should be considered in all patients or families with the constellation of pheo/PGL and a pituitary adenoma.
PubMed-ID: 25494863
http://dx.doi.org/10.1210/jc.2014-3399

[Complications of minimally invasive adrenalectomy].
Chirurg, 86(1):29-32.
P. F. Alesina. 2015.
Over the last decade minimally invasive adrenalectomy has become the gold standard in adrenal surgery. Laparoscopic adrenalectomy with the patient in the lateral decubitus position and posterior retroperitoneoscopic adrenalectomy have gained worldwide acceptance. In this overview the complications of minimally invasive adrenalectomy are analyzed based on the published data. Die incidence of intraoperative and postoperative complications ranges from 0 % to 15 % for unilateral adrenalectomy and rises up to 23 % for bilateral surgery. No significant differences were found between laparoscopic and retroperitoneoscopic operations. Nevertheless, splenic injuries and intra-abdominal abscesses are reported only after laparoscopic procedures, while relaxation and/or hypoesthesia of the abdominal wall are typical for posterior retroperitoneoscopic surgery. Conversion to open surgery significantly influences the rate of perioperative and postoperative complications (odds ratio 6.2); therefore, high surgeon and center case volume could improve the results of adrenal surgery.
PubMed-ID: 25502499
http://dx.doi.org/10.1007/s00104-014-2821-z

Genetics of adrenal diseases in 2014: Genetics improves understanding of adrenocortical tumours.
Nat Rev Endocrinol, 11(2):77-8.
X. Bertagna. 2015.
PubMed-ID: 25511311
http://dx.doi.org/10.1038/nrendo.2014.215

Risk of adrenocortical carcinoma in adrenal tumours greater than 8 cm.
World J Surg, 39(5):1268-73.
T. E. Abdel-Aziz, P. Rajeev, G. Sadler, A. Weaver and R. Mihai. 2015.
BACKGROUND: Adrenocortical cancer (ACC) is a rare malignancy. In the absence of metastatic disease, the suspicion of ACC is based on size and radiological appearance. The aim of this study was to analyse the long-term outcome of patients with large adrenal cortical tumours (>8 cm). METHODS: A prospective database recorded clinical, biochemical, operative and histological data on patients operated for cortical adrenal tumours between January 2000 and February 2013. Out of 130 patients operated for cortical adrenal tumours, analysis was restricted to 37 cortical tumours >8 cm. RESULTS: There were 31 (84 %) ACCs and 6 (16 %) benign adenomas ($p < 0.01$). The most common presentation was that of an abdominal mass [17 (55 %) vs. 3 (50 %), ACC vs. benign, respectively]. There was no difference in size between stage II and stage III-IV tumours; however, there was a trend for tumours to be heavier in advanced stages (920 +/- 756 vs. 1,435 +/- 1,022 g, $p = 0.08$, stage II vs. stage III-IV, respectively). No mortality was observed in patients with benign tumours during a median follow-up of 70 months (range 36-99 months). Mortality in the ACC group occurred in 17/31 (55 %) patients. Mitotane was administered in 12 (71 %) patients with stage III-IV ACCs with a 5-year survival rate 25 % compared to 20 % in patients who did not receive Mitotane. In stage II ACC, eight (57 %) patients received Mitotane with a 50 % mortality at 5 years. CONCLUSIONS: The high incidence of ACC in cortical tumours >8 cm underlines the need for adequate surgical resection via open surgery aiming to avoid local recurrence. Beyond surgery, the impact of other therapies is not fully characterised and the efficacy of adjuvant Mitotane treatment is yet to be proven.
PubMed-ID: 25526921
http://dx.doi.org/10.1007/s00268-014-2912-5

Time to recovery of adrenal function after curative surgery for Cushing's syndrome depends on etiology.
J Clin Endocrinol Metab, 100(4):1300-8.
C. M. Berr, G. Di Dalmazi, A. Osswald, K. Ritzel, M. Bidlingmaier, L. L. Geyer, M. Treitl, K. Hallfeldt, W. Rachinger, N. Reisch, R. Blaser, J. Schopohl, F. Beuschlein and M. Reincke. 2015.
CONTEXT: Successful tumor resection in endogenous Cushing's syndrome (CS) results in tertiary adrenal insufficiency requiring hydrocortisone replacement therapy. OBJECTIVE: The aim was to analyze the postsurgical duration of adrenal insufficiency of patients with Cushing's disease (CD), adrenal CS, and ectopic CS. DESIGN: We performed a retrospective analysis based on the case records of 230 patients with CS in our tertiary referral center treated from 1983-2014. The mean follow-up time was 8 years. PATIENTS: We included 91 patients of the three subtypes of CS undergoing curative intended surgery and documented followup after excluding cases with persistent disease, pituitary radiation, concurrent adrenostatic or somatostatin analog treatment, and malignant adrenal disease. RESULTS: The probability of recovering adrenal function within a 5 years followup differed significantly between subtypes ($P = .001$). It was 82% in ectopic CS, 58% in CD and 38% in adrenal CS. In the total cohort with restored adrenal function ($n = 52$) the median time to recovery differed between subtypes: 0.6 years (interquartile range [IQR], 0.03-1.1 y) in ectopic CS, 1.4 years (IQR, 0.9-3.4 y) in CD, and 2.5 years (IQR, 1.6-5.4 y) in adrenal CS ($P = .002$). In CD the Cox proportional-hazards model showed that the probability of recovery was associated with younger age (hazard ratio, 0.896; 95% confidence interval, 0.822-0.976; $P = .012$), independently of sex, body mass index, duration of symptoms, and basal ACTH and cortisol levels. There was no correlation with length and extend of hypercortisolism or postoperative glucocorticoid replacement doses. CONCLUSIONS: Time to recovery of adrenal function is dependent on the underlying etiology of CS.
PubMed-ID: 25546155
http://dx.doi.org/10.1210/jc.2014-3632

Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection.
J Clin Endocrinol Metab, 100(3):841-9.
F. Beuschlein, J. Weigel, W. Saeger, M. Kroiss, V. Wild, F. Daffara, R. Libe, A. Ardito, A. Al Ghuzlan, M. Quinkler, A. Osswald, C. L. Ronchi, R. de Krijger, R. A. Feelders, J. Waldmann, H. S. Willenberg, T. Deutschbein, A. Stell, M. Reincke, M. Papotti, E. Baudin, F. Tissier, H. R. Haak, P. Loli, M. Terzolo, B. Allolio, H. H. Muller and M. Fassnacht. 2015.
BACKGROUND: Recurrence of adrenocortical carcinoma (ACC) even after complete (R0) resection occurs frequently. OBJECTIVE: The aim of this study was to identify markers with prognostic value for patients in this clinical setting. DESIGN, SETTING, AND PARTICIPANTS: From the German ACC registry, 319 patients with the European Network for the Study of Adrenal Tumors stage I-III were identified. As an independent validation cohort, 250 patients from three European countries were included. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Clinical, histological, and immunohistochemical markers were correlated with

recurrence-free (RFS) and overall survival (OS). RESULTS: Although univariable analysis within the German cohort suggested several factors with potential prognostic power, upon multivariable adjustment only a few including age, tumor size, venous tumor thrombus (VTT), and the proliferation marker Ki67 retained significance. Among these, Ki67 provided the single best prognostic value for RFS (hazard ratio [HR] for recurrence, 1.042 per 1% increase; P < .0001) and OS (HR for death, 1.051; P < .0001) which was confirmed in the validation cohort. Accordingly, clinical outcome differed significantly between patients with Ki67 <10%, 10-19%, and >/=20% (for the German cohort: median RFS, 53.2 vs 31.6 vs 9.4 mo; median OS, 180.5 vs 113.5 vs 42.0 mo). Using the combined cohort prognostic scores including tumor size, VTT, and Ki67 were established. Although these scores discriminated slightly better between subgroups, there was no clinically meaningful advantage in comparison with Ki67 alone. CONCLUSION: This largest study on prognostic markers in localized ACC identified Ki67 as the single most important factor predicting recurrence in patients following R0 resection. Thus, evaluation of Ki67 indices should be introduced as standard grading in all pathology reports of patients with ACC.
PubMed-ID: 25559399
http://dx.doi.org/10.1210/jc.2014-3182

Outcome of surgical treatment of primary aldosteronism.
Langenbecks Arch Surg, 400(3):325-31.
M. Citton, G. Viel, G. P. Rossi, F. Mantero, D. Nitti and M. Iacobone. 2015.
PURPOSE: The aim of this retrospective study was to analyze the early and long-term outcomes of the surgical treatment of primary aldosteronism (PA), the most common surgically correctable cause of endocrine hypertension. METHODS: Serum Potassium levels, blood pressure values, and aldosterone/renin ratio (ARR) were assessed in 128 patients undergoing unilateral adrenalectomy for PA, before and after surgery. The role of lateralizing techniques and the relationship between outcome and histopathology findings were also evaluated. RESULTS: Biochemical cure of PA (ARR and kalemia normalization) was achieved in 95 % of patients, at early follow-up. Single aldosterone-producing adenoma, multinodular hyperplasia, and diffuse hyperplasia were found in 46, 45, and 9 % of the patients, respectively. No relationship between histopathology and persistence or recurrence of PA was found. The use of further lateralizing techniques in addition to computed tomography or magnetic resonance was the main predictor of PA cure ($p = 0.02$); adrenal venous sampling (AVS) was more accurate than scintigraphy in PA lateralization ($p < 0.05$). After surgery, hypertension was cured in 55 % and improved in 36 % of patients. Female gender, a lower number of antihypertensive drugs, and a shorter duration of hypertension were the main predictors of hypertension cure. At long-term, recurrent PA occurred in 3.7 % of cases. CONCLUSIONS: Early diagnosis and correct lateralization of hyperaldosteronism by means of AVS are keys to achieve surgical cure of PA and PA-related hypertension. PA may be also caused by unilateral hyperplasia, which may be cured by unilateral adrenalectomy. Recurrences of PA are rare, although a prolonged follow-up is required.
PubMed-ID: 25567077
http://dx.doi.org/10.1007/s00423-014-1269-4

Mast cell hyperplasia is associated with aldosterone hypersecretion in a subset of aldosterone-producing adenomas.
J Clin Endocrinol Metab, 100(4):E550-60.
C. Duparc, L. Moreau, J. F. Dzib, H. G. Boyer, M. Tetsi Nomigni, I. Boutelet, S. Boulkroun, K. Mukai, A. G. Benecke, L. Amar, F. Gobet, T. Meatchi, P. F. Plouin, M. C. Zennaro, E. Louiset and H. Lefebvre. 2015.
CONTEXT: Adrenal mast cells can stimulate aldosterone secretion through the local release of serotonin (5-HT) and activation of the 5-HT4 receptor (5-HT4). In aldosterone-producing adenomas (APAs), 5-HT4 receptor is overexpressed and the administration of 5-HT4 receptor agonists to patients with APA increases plasma aldosterone levels. These data and the well-documented role of mast cells in tumorigenesis suggest that mast cells may be involved in the pathophysiology of APA. OBJECTIVE: The study aimed at investigating the occurrence of mast cells in a series of APA tissues and to examine the influence of mast cells on aldosterone secretion. DESIGN: The occurrence of mast cells in APAs was investigated by immunohistochemistry. Mast cell densities were compared with clinical data. The influence of mast cells on aldosterone production was studied by using cultures of human mast cell and adrenocortical cell lines. RESULTS: In APA tissues, the density of mast cells was found to be increased in comparison with normal adrenals. Mast cells were primarily observed in adrenal cortex adjacent to adenomas or in the adenomas themselves, distinguishing two groups of APAs. A subset of adenomas was found to contain a high density of intratumoral mast cells, which was correlated with aldosterone synthase expression and in vivo aldosterone secretory parameters. Administration of conditioned medium from cultures of human mast cell lines to human adrenocortical cells induced a significant increase in aldosterone synthase (CYP11B2) mRNA expression and aldosterone production. CONCLUSION: APA tissues

commonly contain numerous mast cells that may influence aldosterone secretion through the local release of regulatory factors.
PubMed-ID: 25599386
http://dx.doi.org/10.1210/jc.2014-3660

Computed tomography criteria for discrimination of adrenal adenomas and adrenocortical carcinomas: analysis of the German ACC registry.
Eur J Endocrinol, 172(4):415-22.
S. Petersenn, P. A. Richter, T. Broemel, C. O. Ritter, T. Deutschbein, F. U. Beil, B. Allolio and M. Fassnacht. 2015.
OBJECTIVE: Thresholds of 2-20 hounsfield units (HU) in unenhanced computed tomography (CT) are suggested to discriminate benign adrenal tumors (BATs) from malignant adrenal tumors. However, these studies included only low numbers of adrenocortical carcinomas (ACCs). This study defines a HU threshold by inclusion of a large cohort of ACCs. DESIGN: Retrospective, blinded, comparative analysis of CT scans from 51 patients with ACCs (30 females, median age 49 years) and 25 patients with BATs (12 females, median age 64 years) diagnosed during the period of 2005-2010 was performed. METHODS: Tumor density was evaluated in unenhanced CT by two blinded investigators. RESULTS: Median tumor size was 9 cm (range 2.0-20) for ACCs vs 4 cm (2.0-7.5) for BATs (P<0.0001). In ACCs, the median unenhanced HU value was 34 (range 14-74) in comparison with 5 (-13 to 40) in BATs (P<0.0001). ROC analysis revealed a HU of 21 as threshold with the best diagnostic accuracy (sensitivity 96%, specificity 80%, and AUC 0.89). However, two ACCs that were 5 and 6 cm in size would have been missed. Setting the threshold to 13.9 allowed for 100% sensitivity, but a lower specificity of 68%. CONCLUSIONS: This first large study on ACCs confirmed that the vast majority of ACCs have unenhanced HU >21. However, to avoid misdiagnosing an ACC as benign, a threshold of 13 should be used.
PubMed-ID: 25599706
http://dx.doi.org/10.1530/EJE-14-0916

Does contralateral suppression at adrenal venous sampling predict outcome following unilateral adrenalectomy for primary aldosteronism? A retrospective study.
J Clin Endocrinol Metab, 100(4):1477-84.
M. J. Wolley, R. D. Gordon, A. H. Ahmed and M. Stowasser. 2015.
CONTEXT: In primary aldosteronism (PA), adrenal vein sampling (AVS) distinguishes unilateral and bilateral disease by comparison of aldosterone/cortisol (A/F) ratios. There is controversy about the criteria for interpretation, however, and in particular it is not clear whether contralateral suppression (CS) (defined as A/F(adrenal) </= A/F(peripheral) on the unaffected side) is important. We therefore performed a retrospective study to determine whether CS in surgically treated unilateral PA was associated with blood pressure (BP) and biochemical outcomes. SETTING AND DESIGN: Patients who underwent unilateral adrenalectomy for PA after successful AVS were included if the lateralization index (A/F(dominant):A/F(nondominant)) was >/= 2. Cases were reviewed at 6 to 24 months follow-up for outcomes with respect to the presence and degree of CS. RESULTS: Sixty-six of 80 patients had CS. Baseline characteristics were similar. At postoperative follow-up, those with CS had lower systolic BP (SBP) (128 mm Hg vs 144 mm Hg, P = .001), a greater proportion with cure or improvement of hypertension (96% vs 64%, P = .0034), a greater proportion with biochemical cure of PA on fludrocortisone suppression testing (43 of 49 [88%] vs 4 of 9 [44%], P = .002) and were taking a lower median number of antihypertensive medications (0 vs 1.5, P = .0032). In a multivariate model, the degree of CS and preoperative SBP were both significantly correlated with postoperative SBP, but the lateralization index, sex, and age were not. CONCLUSION: In this study, the presence of CS correlated with good BP and biochemical outcomes from surgery. This finding suggests that CS should be a factor in deciding whether to offer surgery for treatment of PA.
PubMed-ID: 25636049
http://dx.doi.org/10.1210/jc.2014-3676

Diagnosis, treatment and outcome of adrenocortical cancer.
Br J Surg, 102(4):291-306.
R. Mihai. 2015.
BACKGROUND: Adrenocortical cancer (ACC) is a rare disease with a dismal prognosis. The majority of patients are diagnosed with advanced disease and raise difficult management challenges. METHODS: All references identified in PubMed, published between 2004 and 2014, using the keywords 'adrenocortical cancer' or 'adrenal surgery' or both, were uploaded into a database. The database was interrogated using keywords specific for each field studied. RESULTS: In all, 2049 publications were identified. There is ongoing debate about the feasibility and oncological outcomes of laparoscopic adrenalectomy for small ACCs, and data derived from

institutional case series have failed to provide an evidence level above expert opinion. The use of mitotane (1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane) in combination with chemotherapy in the treatment of metastatic disease has been assessed in an international randomized trial (FIRM-ACT trial) involving patients with ACC. Based on this trial, mitotane plus etoposide, doxorubicin and cisplatin is now the established first-line cytotoxic therapy owing to a higher response rate and longer median progression-free survival than achieved with streptozocin-mitotane. For patients with tumours smaller than 5 cm and with no signs of lymph node or distant metastases, survival is favourable with a median exceeding 10 years. However, the overall 5-year survival rate for all patients with ACC is only 30 per cent. CONCLUSION: Open and potentially laparoscopic adrenalectomy for selected patients is the main treatment for non-metastatic ACC, but the overall 5-year survival rate remains low.
PubMed-ID: 25689291
http://dx.doi.org/10.1002/bjs.9743

Pituitary Adenoma With Paraganglioma/Pheochromocytoma (3PAs) and Succinate Dehydrogenase Defects in Humans and Mice.
J Clin Endocrinol Metab, 100(5):E710-9.
P. Xekouki, E. Szarek, P. Bullova, A. Giubellino, M. Quezado, S. A. Mastroyannis, P. Mastorakos, C. A. Wassif, M. Raygada, N. Rentia, L. Dye, A. Cougnoux, D. Koziol, L. Sierra Mde, C. Lyssikatos, E. Belyavskaya, C. Malchoff, J. Moline, C. Eng, L. J. Maher, 3rd, K. Pacak, M. Lodish and C. A. Stratakis. 2015.
CONTEXT: Germline mutations in genes coding succinate dehydrogenase (SDH) subunits A, B, C, and D have been identified in familial paragangliomas (PGLs)/pheochromocytomas (PHEOs) and other tumors. We described a GH-secreting pituitary adenoma (PA) caused by SDHD mutation in a patient with familial PGLs. Additional patients with PAs and SDHx defects have since been reported. DESIGN: We studied 168 patients with unselected sporadic PA and with the association of PAs, PGLs, and/or pheochromocytomas, a condition we named the 3P association (3PAs) for SDHx germline mutations. We also studied the pituitary gland and hormonal profile of Sdhb(+/-) mice and their wild-type littermates at different ages. RESULTS: No SDHx mutations were detected among sporadic PA, whereas three of four familial cases were positive for a mutation (75%). Most of the SDHx-deficient PAs were either prolactinomas or somatotropinomas. Pituitaries of Sdhb(+/-) mice older than 12 months had an increased number mainly of prolactin-secreting cells and several ultrastructural abnormalities such as intranuclear inclusions, altered chromatin nuclear pattern, and abnormal mitochondria. Igf-1 levels of mutant mice tended to be higher across age groups, whereas Prl and Gh levels varied according to age and sex. CONCLUSION: The present study confirms the existence of a new association that we termed 3PAs. It is due mostly to germline SDHx defects, although sporadic cases of 3PAs without SDHx defects also exist. Using Sdhb(+/-) mice, we provide evidence that pituitary hyperplasia in SDHx-deficient cells may be the initial abnormality in the cascade of events leading to PA formation.
PubMed-ID: 25695889
http://dx.doi.org/10.1210/jc.2014-4297

Laparoscopic adrenalectomy--10-year experience at a teaching hospital.
Langenbecks Arch Surg, 400(3):341-7.
S. Sommerey, Y. Foroghi, C. Chiapponi, S. F. Baumbach, K. K. Hallfeldt, R. Ladurner and J. K. Gallwas. 2015.
BACKGROUND: Minimally invasive adrenalectomy has been adopted as the treatment of choice for benign adrenal tumors. This study aimed to investigate the outcome of laparoscopic adrenalectomies performed over a 10-year period at a teaching hospital. METHODS: All laparoscopic adrenalectomies carried out between 1 April 2000 and 31 March 2010 were evaluated with respect to perioperative management, complications, conversion rate, learning curve, tumor size, and surgically relevant characteristics of different adrenal pathologies. RESULTS: Over a period of 10 years, 215 laparoscopic lateral transabdominal adrenalectomies were carried out for Conn's syndrome (n = 90), Cushing's syndrome (n = 72), pheochromocytoma (n = 30), metastatic disease (n = 8), incidentalomas (n = 10), and other rare adrenal pathologies (n = 5). Morbidity, mortality, and conversion rate were 7.0, 0.9, and 4.2 %, respectively. Patients with Cushing's disease and bilateral adrenalectomy showed a higher complication rate. In retrospect, the indication for a laparoscopic approach was at least questionable in five cases. During these 10 years, four surgeons unfamiliar with the technique received intensive training to a defined plan. CONCLUSIONS: Laparoscopic adrenalectomy represents a safe operating technique associated with few complications and a low conversion rate. Patients with severe Cushing's disease are prone to complications and require intensive monitoring postoperatively. Laparoscopic adrenalectomy is associated with a learning curve, and particular emphasis should be given to surgical training.
PubMed-ID: 25721680
http://dx.doi.org/10.1007/s00423-015-1287-x

Surgical resection of metastases to the adrenal gland: a single center experience.
Langenbecks Arch Surg, 400(3):333-9.
I. Hornstein, C. Schwarz, S. Ebbing, M. Hoppe-Lotichius, G. Otto, H. Lang and T. J. Musholt. 2015.
BACKGROUND: Only limited data exist on the treatment and outcome of adrenal metastases that derive from different primary tumor entities. Due to the lack of evidence, it is difficult to determine the indication for surgical resection. METHODS: We assessed the outcome of 45 patients (28 men, 17 women) with adrenal metastases who underwent surgery (1990-2014). The median age at the time of adrenal surgery was 62 years (range 44-77 years). We were able to evaluate follow-up data of 41 patients. RESULTS: Primary tumor types were liver n = 12 (hepatocellular carcinoma n = 9, cholangiocellular carcinoma n = 2, sarcoma n = 1), upper GI tract n = 5 (esophagus n = 2, stomach n = 3), lung n = 9, kidney n = 6, neuroendocrine tumors n = 3, colon n = 2, ovarial n = 2, melanoma n = 2, others n = 4. The overall median survival time was 14 months (95 % CI 8.375-19.625). The survival rates at 1, 2, 5, and 10 years were 60, 31, 21, and 11 %, respectively. There were statistically significant differences in the survival time according to the resection status (R0 vs. R1/R2) ($p < 0.001$) and the type of the primary tumor ($p = 0.009$), while the metachronous or synchronous occurrence of adrenal metastases did not affect the prognosis. CONCLUSIONS: Resection of adrenal metastases can improve the survival if patients are carefully selected, the tumor is completely resected, and the intervention is integrated into a multidisciplinary oncologic treatment strategy.
PubMed-ID: 25726026
http://dx.doi.org/10.1007/s00423-015-1293-z

PRKACA mutations in cortisol-producing adenomas and adrenal hyperplasia: a single-center study of 60 cases.
Eur J Endocrinol, 172(6):677-85.
A. Thiel, A. C. Reis, M. Haase, G. Goh, M. Schott, H. S. Willenberg and U. I. Scholl. 2015.
OBJECTIVE: Cortisol excess due to adrenal adenomas or hyperplasia causes Cushing's syndrome. Recent genetic studies have identified a somatic PRKACA(L206R) mutation as a cause of cortisol-producing adenomas. We aimed to compare the clinical features of PRKACA-mutant lesions with those of CTNNB1 mutations, and to search for similar mutations in unilateral hyperplasia or tumors co-secreting aldosterone. DESIGN, PATIENTS, AND METHODS: In this study, 60 patients with cortisol excess who had adrenalectomies at our institution between 1992 and 2013 were assessed, and somatic mutations were determined by Sanger sequencing. A total of 36 patients had overt Cushing's syndrome, the remainder were subclinical: 59 cases were adenomas (three bilateral) and one was classified as hyperplasia. Four tumors had proven co-secretion of aldosterone. RESULTS: Among cortisol-secreting unilateral lesions without evidence of co-secretion (n=52), we identified somatic mutations in PRKACA (L206R) in 23.1%, CTNNB1 (S45P, S45F) in 23.1%, GNAS (R201C) in 5.8%, and CTNNB1+GNAS (S45P, R201H) in 1.9%. PRKACA and GNAS mutations were mutually exclusive. Of the co-secreting tumors, two (50%) had mutations in KCNJ5 (G151R and L168R). The hyperplastic gland showed a PRKACA(L206R) mutation, while patients with bilateral adenomas did not have known somatic mutations. PRKACA-mutant lesions were associated with younger age, overt Cushing's syndrome, and higher cortisol levels vs non-PRKACA-mutant or CTNNB1-mutant lesions. CTNNB1 mutations were more significantly associated with right than left lesions. CONCLUSIONS: PRKACA(L206R) is present not only in adenomas, but also in unilateral hyperplasia and is associated with more severe autonomous cortisol secretion. Bilateral adenomas may be caused by yet-unknown germline mutations.
PubMed-ID: 25750087
http://dx.doi.org/10.1530/EJE-14-1113

Clinical risk factors of postoperative hyperkalemia after adrenalectomy in patients with aldosterone-producing adenoma.
Eur J Endocrinol, 172(6):725-31.
K. S. Park, J. H. Kim, E. J. Ku, A. R. Hong, M. K. Moon, S. H. Choi, C. S. Shin, S. W. Kim and S. Y. Kim. 2015.
OBJECTIVE: Unilateral adrenalectomy is the first-line treatment for aldosterone-producing adenomas (APA). Hyperkalemia after adrenalectomy because of contralateral zona glomerulosa insufficiency has been reported. We investigated clinical risk factors to predict postoperative hyperkalemia in patients with APA undergoing adrenalectomy. DESIGN AND METHODS: This study was conducted by retrospectively reviewing medical records from 2000 to 2012 at Seoul National University Hospital and two other tertiary centers. Data from 124 patients who underwent adrenalectomy were included. Hyperkalemia was defined as serum potassium >5.5 mmol/l. Clinical preoperative risk factors included age, blood pressure, plasma renin activity (PRA), plasma aldosterone concentration (PAC), serum potassium, serum creatinine, glomerular filtration rate (GFR), the mass size on pathology, and mineralocorticoid receptor (MR) antagonist use. RESULTS: Out of 124 patients, 13 (10.5%) developed postoperative hyperkalemia. The incidences of transient and persistent hyperkalemia were

3.2 and 7.3% respectively. Preoperative PRA and PAC were not significantly different in postoperative hyperkalemic patients compared with normokalemic patients. Patients with persistent hyperkalemia were older, had a longer duration of hypertension, larger mass size on pathology, and lower GFR (all P<0.05). The incidence of postoperative hyperkalemia was not different between MR antagonist users and non-users. CONCLUSION: Older age (>/=53 years), longer duration of hypertension (>/=9.5 years), larger mass size on pathology (>/=1.95 cm), and impaired preoperative renal function (GFR <58.2 ml/min) were associated with prolonged postoperative hyperkalemia in patients with APA. MR antagonist use did not prevent postoperative hyperkalemia.
PubMed-ID: 25766046
http://dx.doi.org/10.1530/EJE-15-0074

Hemodynamic Stability During Pheochromocytoma Resection: Lessons Learned Over the Last Two Decades.
Ann Surg Oncol,
M. Livingstone, K. Duttchen, J. Thompson, Z. Sunderani, G. Hawboldt, M. Sarah Rose and J. Pasieka. 2015.
BACKGROUND: Ideal perioperative management of pheochromocytomas/paragangliomas (pheo) is a subject of debate and can be highly variable. The purpose of this study was to identify potential predictive factors of hemodynamic instability during pheo resection. METHODS: A retrospective review of pheo resections from 1992 to 2013 was undertaken. Intraoperative hemodynamics, patient demographics, tumor characteristics, and perioperative management were examined. Postoperative intensive-care admission, myocardial infarction, stroke, and 30-day mortality were reviewed. Linear regression was used to analyze factors influencing intraoperative hemodynamics. RESULTS: During the 20-year study period, 100 patients underwent pheo resection. Postoperative morbidity and mortality was significantly reduced (p = 0.003) in the last 10 years of practice, and there was a trend towards greater morbidity and mortality with intraoperative hemodynamic instability (p = 0.06). The preoperative dose of phenoxybenzamine and the number of laparoscopic procedures has increased in the last decade [59 mg (95 % CI 32-108) to 106 mg (95 % CI 91-124), p = 0.008, and 27 vs. 54 %, p = 0.05, respectively]. Increased preoperative phenoxybenzamine dose was a significant predictor of improved intraoperative hemodynamic stability (p = 0.01). Lack of intraoperative magnesium use resulted in greater hemodynamic instability as preoperative systolic blood pressure increased (p = 0.002). CONCLUSIONS: Postoperative outcomes following pheo resection have improved over the last two decades. Preoperative alpha-blockade plays a significant role in improving intraoperative hemodynamics and post-op outcomes. Increased doses of phenoxybenzamine and utilization of laparoscopic approaches have likely contributed to improved outcomes in the last decade. Intraoperative magnesium use may provide protection against hemodynamic instability and warrants further study.
PubMed-ID: 25822781
http://dx.doi.org/10.1245/s10434-015-4519-y

Letter to the editor: Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas.
J Clin Endocrinol Metab, 100(4):L31-2.
S. Gaujoux, C. Lentschener and B. Dousset. 2015.
PubMed-ID: 25844770
http://dx.doi.org/10.1210/jc.2014-4401

ARMC5 Mutations in a Large Cohort of Primary Macronodular Adrenal Hyperplasia: Clinical and Functional Consequences.
J Clin Endocrinol Metab, 100(6):E926-35.
S. Espiard, L. Drougat, R. Libe, G. Assie, K. Perlemoine, L. Guignat, G. Barrande, F. Brucker-Davis, F. Doullay, S. Lopez, E. Sonnet, F. Torremocha, D. Pinsard, N. Chabbert-Buffet, M. L. Raffin-Sanson, L. Groussin, F. Borson-Chazot, J. Coste, X. Bertagna, C. A. Stratakis, F. Beuschlein, B. Ragazzon and J. Bertherat. 2015.
CONTEXT: Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause of primary adrenal Cushing's syndrome (CS). ARMC5 germline mutations have been identified recently in PBMAH. OBJECTIVE: To determine the prevalence of ARMC5 mutations and analyze genotype-phenotype correlation in a large cohort of unrelated PBMAH patients with subclinical or clinical CS. PATIENTS AND METHODS: ARMC5 was sequenced in 98 unrelated PBMAH index cases. PBMAH was identified by bilateral adrenal nodular enlargement on computed tomography scan. The effect on apoptosis of ARMC5 missense mutants was tested in H295R and HeLa cells. Clinical and hormonal data were collected including midnight and urinary free cortisol levels, ACTH, androgens, renin/aldosterone ratio, cortisol after overnight dexamethasone suppression test, cortisol and 17-hydroxyprogesterone after ACTH 1-24 stimulation and illegitimate receptor responses. Computed tomography

and histological reports were analyzed. RESULTS: ARMC5-damaging mutations were identified in 24 patients (26%). The missense mutants and the p.F700del deletion were unable to induce apoptosis in both H295R and HeLa cell lines, unlike the wild-type gene. ARMC5-mutated patients showed an overt CS more frequently, compared to wild-type patients: lower ACTH, higher midnight plasma cortisol, urinary free cortisol, and cortisol after dexamethasone suppression test (P = .003, .019, .006, and <.001, respectively). Adrenals of patients with mutations were bigger and had a higher number of nodules (P = .001 and <.001, respectively). CONCLUSIONS: ARMC5 germline mutations are common in PBMAH. Index cases of mutation carriers show a more severe hypercortisolism and larger adrenals. ARMC5 genotyping may help to identify clinical forms of PBMAH better and may also allow earlier diagnosis of this disease.
PubMed-ID: 25853793
http://dx.doi.org/10.1210/jc.2014-4204

Limited value of long-term biochemical follow-up in patients with adrenal incidentalomas-a retrospective cohort study.
BMC Endocr Disord, 15:6.
H. Yeomans, J. Calissendorff, C. Volpe, H. Falhammar and B. Mannheimer. 2015.
BACKGROUND: The prevailing view that advocates long-term hormonal follow-up of adrenal incidentalomas is currently under debate. The purpose of the present study was to examine all adrenal incidentalomas presented during five years to a single centre. We hypothesized that 24-month biochemical follow-up in patients with an initial normal screening would fail to increase the sensitivity in finding hormone producing tumours. METHODS: The present study is a retrospective register based cohort study of 194 patients referred to the Department of Endocrinology at Sodersjukhuset between the years 2006-2010. Computerized medical records were used to find and extract information on patients with newly discovered adrenal incidentalomas. The sensitivity, specificity, positive predictive value and negative predictive value were calculated to evaluate the validity of an initial normal screening when used to identify individuals with hormone producing tumours. RESULTS: Of the incidentalomas 94% consisted of benign, non-functioning tumours. Three patients were diagnosed with cortisol hypersecretion and one with pheochromocytoma. The sensitivity, specificity, positive predictive value and negative predictive value of an initial complete negative screening to predict a hormone producing tumour were 100%, 63%, 12% and 100%, respectively. CONCLUSION: Patients with an initially normal hormonal screening may not need further biochemical follow-up.
PubMed-ID: 25887139
http://dx.doi.org/10.1186/s12902-015-0001-x

Immunohistochemical expression of stem cell markers in pheochromocytomas/paragangliomas is associated with SDHx mutations.
Eur J Endocrinol, 173(1):43-52.
L. Oudijk, C. M. Neuhofer, U. D. Lichtenauer, T. G. Papathomas, E. Korpershoek, H. Stoop, J. W. Oosterhuis, M. Smid, D. F. Restuccia, M. Robledo, A. A. de Cubas, M. Mannelli, A. P. Gimenez-Roqueplo, W. N. Dinjens, F. Beuschlein and R. R. de Krijger. 2015.
OBJECTIVE: Pheochromocytomas (PCCs) are neuroendocrine tumors that occur in the adrenal medulla, whereas paragangliomas (PGLs) arise from paraganglia in the head, neck, thorax, or abdomen. In a variety of tumors, cancer cells with stem cell-like properties seem to form the basis of tumor initiation because of their ability to self-renew and proliferate. Specifically targeting this small cell population may lay the foundation for more effective therapeutic approaches. In the present study, we intended to identify stem cells in PCCs/PGLs. DESIGN: We examined the immunohistochemical expression of 11 stem cell markers (SOX2, LIN28, NGFR, THY1, PREF1, SOX17, NESTIN, CD117, OCT3/4, NANOG, and CD133) on tissue microarrays containing 208 PCCs/PGLs with different genetic backgrounds from five European centers. RESULTS: SOX2, LIN28, NGFR, and THY1 were expressed in more than 10% of tumors, and PREF1, SOX17, NESTIN, and CD117 were expressed in <10% of the samples. OCT3/4, NANOG, and CD133 were not detectable at all. Double staining for chromogranin A/SOX2 and S100/SOX2 demonstrated SOX2 immunopositivity in both tumor and adjacent sustentacular cells. The expression of SOX2, SOX17, NGFR, LIN28, PREF1, and THY1 was significantly associated with mutations in one of the succinate dehydrogenase (SDH) genes. In addition, NGFR expression was significantly correlated with metastatic disease. CONCLUSION: Immunohistochemical expression of stem cell markers was found in a subset of PCCs/PGLs. Further studies are required to validate whether some stem cell-associated markers, such as SOX2, could serve as targets for therapeutic approaches and whether NGFR expression could be utilized as a predictor of malignancy.
PubMed-ID: 25916394
http://dx.doi.org/10.1530/EJE-14-1164

NET

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

GEPNETs update: Radionuclide therapy in neuroendocrine tumors.
Eur J Endocrinol, 172(1):R1-8.
W. A. van der Zwan, L. Bodei, J. Mueller-Brand, W. W. de Herder, L. K. Kvols and D. J. Kwekkeboom. 2015.
Peptide receptor radionuclide therapy (PRRT) is a promising new treatment modality for inoperable or metastasized gastroenteropancreatic neuroendocrine tumors (GEPNETs) patients. Most studies report objective response rates in 15-35% of patients. Also, outcome in terms of progression free survival (PFS) and overall survival compares very favorably with that for somatostatin analogs, chemotherapy, or new, 'targeted' therapies. They also compare favorably to PFS data for liver-directed therapies. Two decades after the introduction of PRRT, there is a growing need for randomized controlled trials comparing PRRT to 'standard' treatment, that is treatment with agents that have proven benefit when tested in randomized trials. Combining PRRT with liver-directed therapies or with targeted therapies could improve treatment results. The question to be answered, however, is whether a combination of therapies performed within a limited time-span from one another results in a better PFS than a strategy in which other therapies are reserved until after (renewed) tumor progression. Randomized clinical trials comparing PRRT with other treatment modalities should be undertaken to determine the best treatment options and treatment sequelae for patients with GEPNETs.
PubMed-ID: 25117465
http://dx.doi.org/10.1530/EJE-14-0488

Merkel cell carcinoma: what makes a difference?
Am J Surg, 209(2):342-6.
J. Tseng, B. Dhungel, J. K. Mills, B. S. Diggs, R. Weerasinghe, J. Fortino and J. T. Vetto. 2015.
BACKGROUND: Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine tumor that may spread via lymphatics and can therefore be staged with sentinel lymph node biopsy (SLNB). MCC is radiosensitive and chemosensitive, although the role of adjuvant therapy is still unclear. We examined the impact of different treatments on the outcome of MCC. METHODS: We performed a retrospective review of state cancer registry data from California, Oregon, and Washington of patients diagnosed with primary skin MCC between 1988 and 2012 (n = 4,038). Data were analyzed using Cox regression and Kaplan-Meier methods to examine disease-specific survival. RESULTS: Patients with positive nodes or no documented nodal evaluation had worse survival compared with node-negative patients. No nodal evaluation had decreased survival compared with lymph node evaluation by SLNB. Completion lymph node dissection conferred improved survival in patients with a positive SLNB. In clinically node-negative patients who had a positive SLNB, radiation and chemotherapy did not affect survival. CONCLUSIONS: Lymph node evaluation is an important component to MCC treatment. The role of adjuvant radiation and chemotherapy needs further evaluation.
PubMed-ID: 25152250
http://dx.doi.org/10.1016/j.amjsurg.2014.06.013

Impact of (68)Ga-DOTATATE PET/CT on the surgical management of primary neuroendocrine tumors of the pancreas or ileum.
Ann Surg Oncol, 22(1):164-71.
H. Ilhan, W. P. Fendler, C. C. Cyran, C. Spitzweg, C. J. Auernhammer, F. J. Gildehaus, P. Bartenstein, M. K. Angele and A. R. Haug. 2015.
BACKGROUND: Resection is the only curative treatment in patients suffering from neuroendocrine tumors (NETs) of the ileum or the pancreas. Accurate preoperative imaging is critical for surgical planning, as even findings of small and distant metastases may profoundly influence surgical management. METHODS: (68)Ga-DOTATATE PET/CT was performed preoperatively in 44 patients suffering from NET of the ileum (n = 26) or the pancreas (n = 18) before surgery at our University Hospital. Data were analyzed retrospectively by an interdisciplinary team of nuclear medicine and visceral surgery specialists. Intended surgical management was documented before and after availability of PET/CT findings. The team judged whether the imaging findings provided additional information relevant to surgical planning. RESULTS: Imaging results altered surgical management in 9 of 44 (20 %) patients, more specifically in 3 of 26 (12 %) patients with NET of the ileum and in 6 of 18 (33 %) patients with NET of the pancreas. PET/CT findings led to a more invasive surgical approach in 6 cases (3 each of ileum and pancreas) and to a less invasive strategy in 3 patients with NET of the pancreas. Although PET/CT results did not alter management in 35 of 44 patients, somatostatin receptor imaging still provided additional information for surgery planning in more than 95 % of the cases. CONCLUSIONS: Additional information provided by (68)Ga-DOTATATE PET/CT in the preoperative workup significantly influences surgical management in one-fifth of our NET patients and, notably, one-third of those suffering from NET of the pancreas.
PubMed-ID: 25190113
http://dx.doi.org/10.1245/s10434-014-3981-2

The status of neuroendocrine tumor imaging: from darkness to light?
Neuroendocrinology, 101(1):1-17.
L. Bodei, A. Sundin, M. Kidd, V. Prasad and I. M. Modlin. 2015.
Diagnostic imaging plays a pivotal role in the diagnosis, staging, treatment selection and follow-up for neuroendocrine tumors. The available diagnostic strategies are morphologic imaging, including computed tomography, magnetic resonance imaging (MRI) and ultrasound techniques, and molecular imaging, including scintigraphy with (111)In-pentetreotide and positron emission tomography with (68)Ga-DOTA-peptides, (18)F-DOPA and (11)C-5-HTP. A combination of anatomic and functional techniques is routinely performed to optimize sensitivity and specificity. The introduction of diffusion-weighted MRI and dynamic contrast-enhanced techniques represents a promising advance in radiologic imaging, whereas new receptor-binding peptides, including somatostatin agonists and antagonists, represent the recent most favorable innovation in molecular imaging. Future development includes the short-term validation of these techniques, but in extension also a more comprehensive multilevel integration of biologic information pertaining to a specific tumor and patient, possibly encompassing genomic considerations, currently evolving as a new entity denoted 'precision medicine'. The ideal is a diagnostic sequence that captures the global status of an individual's tumor and encompasses a multidimensional characterization of tumor location, metabolic performance and target identification. To date, advances in imagery have focused on increasing resolution, discrimination and functional characterization. In the future, the fusion of imagery with the parallel analysis of biological and genomic information has the potential to considerably amplify diagnosis.
PubMed-ID: 25228173
http://dx.doi.org/10.1159/000367850

Efficacy and cost-effectiveness of immediate surgery versus a wait-and-see strategy for sporadic nonfunctioning T1 pancreatic endocrine neoplasms.
Neuroendocrinology, 101(1):25-34.
A. Cucchetti, C. Ricci, G. Ercolani, D. Campana, M. Cescon, M. D'Ambra, A. D. Pinna, F. Minni and R. Casadei. 2015.
BACKGROUND: Whether patients with small (<2 cm), sporadic nonfunctioning pancreatic endocrine tumors (NF-PETs) should directly undergo pancreatic surgery or should be followed longitudinally to detect growth and malignancy still has to be defined. STUDY DESIGN: Based on the pertinent literature of the past decade, a Markov model was developed to investigate this issue. In the wait-and-see strategy arm, surgery was performed if the tumor attained a size >/=2 cm or surpassed 20% of the initial size. In a Monte Carlo probabilistic analysis, 100 hypothetical patients undergoing a wait-and-see strategy were compared to 100 patients directly undergoing surgery, with the aim of investigating the efficacy and cost-effectiveness of the two strategies. RESULTS: During the postdiagnostic lifetime, 63 NF-PETs in the wait-and-see group showed significant growth and underwent

surgery: 38 were stage I, 10 were stage II, 15 were stage III and none were stage IV. In the base-case scenario, the mean life expectancy and quality-adjusted life expectancy were found to be superior after immediate surgery [26.1 years and 11.8 quality-adjusted life years (QALYs)] than with the wait-and-see strategy (22.1 years and 8.3 QALYs) as the consequence of ageing during the wait-and-see follow-up which increased mortality due to surgery, when surgery was needed. The model was sensitive to starting age and length of follow-up; in particular, for patients >65 years of age, the two strategies provided similar results but the wait-and-see strategy was more cost-effective. CONCLUSIONS: The wait-and-see strategy for NF-PETs <2 cm represents a reasonable approach in patients over 65 years of age; otherwise, immediate surgery is preferable.
PubMed-ID: 25228538
http://dx.doi.org/10.1159/000368049

GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETs.
Eur J Endocrinol, 172(4):R151-66.
T. de Baere, F. Deschamps, L. Tselikas, M. Ducreux, D. Planchard, E. Pearson, A. Berdelou, S. Leboulleux, D. Elias and E. Baudin. 2015.
Neuroendocrine tumors from gastro-pancreatic origin (GEP-NET) can be responsible for liver metastases. Such metastases can be the dominant part of the disease as well due to the tumor burden itself or the symptoms related to such liver metastases. Intra-arterial therapies are commonly used in liver only or liver-dominant disease and encompass trans-arterial chemoembolization (TACE), trans-arterial embolization (TAE), and radioembolization (RE). TACE performed with drug emulsified in Lipiodol has been used for the past 20 years with reported overall survival in the range of 3-4 years, with objective response up to 75%. Response to TACE is higher when treatment is used as a first-line therapy and degree of liver involvement is lower. Benefit of TACE over TAE is unproven in randomized study, but reported in retrospective studies namely in pancreatic NETs. RE provides early interesting results that need to be further evaluated in terms of benefit and toxicity. Radiofrequency ablation allows control of small size and numbered liver metastases, with low invasiveness. Ideal metastases to target are one metastasis <5 cm, or three metastases <3 cm, or a sum of diameter of all metastases below 8 cm. Ablation therapies can be applied in the lung or in the bones when needed, and more invasive surgery should be probably saved for large-size metastases. Even if the indication of image-guided therapy in the treatment of GEP-NET liver metastases needs to be refined, such therapies allow for manageable invasive set of treatments able to address oligometastatic patients in liver, lung, and bones. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stage of the disease.
PubMed-ID: 25385817
http://dx.doi.org/10.1530/EJE-14-0630

[Complications of minimally invasive pancreas resection for pancreatic neuroendocrine tumors].
Chirurg, 86(1):33-7.
U. A. Wittel and U. T. Hopt. 2015.
BACKGROUND: Laparoscopic pancreas resections are performed with increasing frequency for pancreatic neuroendocrine tumors and other benign and malignant diseases. OBJECTIVES: This article describes the complications arising from laparoscopic resection of pancreatic neuroendocrine tumors and compares them to complications arising from similar open procedures. METHODS: Case series, reports, trials and meta-analyses were analyzed and the results are described and discussed. RESULTS: The types and the frequencies of complications are comparable for laparoscopic and open resection of pancreatic neuroendocrine tumors. The lack of the ability to perform an intraoperative examination of the pancreas to detect the tumors can be alleviated by laparoscopic ultrasound examination or in the case of tumors expressing somatostatin receptors by preoperative DOTATATE positron emission tomography (PET) computed tomography (CT) scanning. CONCLUSION: The complications arising from the resection of pancreatic neuroendocrine tumors do not justify a recommendation for a laparoscopic or open approach.
PubMed-ID: 25492242
http://dx.doi.org/10.1007/s00104-014-2822-y

Impact of 68Ga-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective.
J Nucl Med, 56(1):70-5.
K. Herrmann, J. Czernin, E. M. Wolin, P. Gupta, M. Barrio, A. Gutierrez, C. Schiepers, S. Mosessian, M. E. Phelps and M. S. Allen-Auerbach. 2015.
Somatostatin receptor imaging with (68)Ga-DOTATATE PET/CT (DOTATATE) is increasingly used for managing patients with neuroendocrine tumors. The objective of this study was to determine referring physicians' perspectives on the impact of DOTATATE on the management of neuroendocrine tumors.

METHODS: A set of 2 questionnaires (pre-PET and post-PET) was sent to the referring physicians of 100 consecutive patients with known or suspected neuroendocrine tumors, who were evaluated with DOTATATE. Questionnaires on 88 patients were returned (response rate, 88%). Referring physicians categorized the DOTATATE findings on the basis of the written PET reports as negative, positive, or equivocal for disease. The likelihood for metastatic disease was scored as low, moderate, or high. The intended management before and changes as a consequence of the PET study were indicated. RESULTS: The indications for PET/CT were initial and subsequent treatment strategy assessments in 14% and 86% of patients, respectively. Referring physicians reported that DOTATATE led to a change in suspicion for metastatic disease in 21 patients (24%; increased and decreased suspicion in 9 [10%] and 12 [14%] patients, respectively). Intended management changes were reported in 53 of 88 (60%) patients. Twenty patients (23%) scheduled to undergo chemotherapy were switched to treatments without chemotherapy, and 6 (7%) were switched from watch-and-wait to other treatment strategies. Conversely, 5 patients (6%) were switched from their initial treatment strategy to watch-and-wait. CONCLUSION: This survey of referring physicians demonstrates a substantial impact of DOTATATE on the intended management of patients with neuroendocrine tumors.
PubMed-ID: 25500825
http://dx.doi.org/10.2967/jnumed.114.148247

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

Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE.
J Nucl Med, 56(2):177-82.
E. Ilan, M. Sandstrom, C. Wassberg, A. Sundin, U. Garske-Roman, B. Eriksson, D. Granberg and M. Lubberink. 2015.
Peptide receptor radionuclide therapy (PRRT) is a promising treatment for patients with neuroendocrine tumors, giving rise to improved survival. Dosimetric calculations in relation to PRRT have been concentrated to normal organ dosimetry in order to limit side effects. However, the relation between the absorbed dose to the tumor and treatment response has so far not been established. Better knowledge in this respect may improve the understanding of treatment effects, allow for improved selection of those patients who are expected to benefit from PRRT, and avoid unnecessary treatments. The aim of the present work was to evaluate the dose-response relationship for pancreatic neuroendocrine tumors treated with PRRT using (177)Lu-DOTATATE. METHODS: Tumor-absorbed dose calculations were performed for 24 lesions in 24 patients with metastasized pancreatic neuroendocrine tumors treated with repeated cycles of (177)Lu-DOTATATE at 8-wk intervals. The absorbed dose calculations relied on sequential SPECT/CT imaging at 24, 96, and 168 h after infusion of (177)Lu-DOTATATE. The unit density sphere model from OLINDA was used for absorbed dose calculations. The

absorbed doses were corrected for partial-volume effect based on phantom measurements. On the basis of these results, only tumors larger than 2.2 cm in diameter at any time during the treatment were included for analysis. To further decrease the effect of partial-volume effect, a subgroup of tumors (>4.0 cm) was analyzed separately. Tumor response was evaluated by CT using Response Evaluation Criteria In Solid Tumors. RESULTS: Tumor-absorbed doses until best response ranged approximately from 10 to 340 Gy. A 2-parameter sigmoid fit was fitted to the data, and a significant correlation between the absorbed dose and tumor reduction was found, with a Pearson correlation coefficient (R(2)) of 0.64 for tumors larger than 2.2 cm and 0.91 for the subgroup of tumors larger than 4.0 cm. The largest tumor reduction was 57% after a total absorbed dose of 170 Gy. CONCLUSION: The results imply a significant correlation between absorbed dose and tumor reduction. However, further studies are necessary to address the large variations in response for similar absorbed doses.
PubMed-ID: 25593115
http://dx.doi.org/10.2967/jnumed.114.148437

MEN1 disease occurring before 21 years old: a 160-patient cohort study from the Groupe d'etude des Tumeurs Endocrines.
J Clin Endocrinol Metab, 100(4):1568-77.
P. Goudet, A. Dalac, M. Le Bras, C. Cardot-Bauters, P. Niccoli, N. Levy-Bohbot, H. du Boullay, X. Bertagna, P. Ruszniewski, F. Borson-Chazot, B. Verges, J. L. Sadoul, F. Menegaux, A. Tabarin, J. M. Kuhn, P. d'Anella, O. Chabre, S. Christin-Maitre, G. Cadiot, C. Binquet and B. Delemer. 2015.
CONTEXT: Multiple endocrine neoplasia Type-1 (MEN1) in young patients is only described by case reports. OBJECTIVE: To improve the knowledge of MEN1 natural history before 21 years old. METHODS: Obtain a description of the first symptoms occurring before 21 years old (clinical symptoms, biological or imaging abnormalities), surgical outcomes related to MEN1 Neuro Endocrine Tumors (NETs) occurring in a group of 160 patients extracted from the "Groupe d'etude des Tumeurs Endocrines" MEN1 cohort. RESULTS: The first symptoms were related to hyperparathyroidism in 122 cases (75%), pituitary adenoma in 55 cases (34%), nonsecreting pancreatic tumor (NSPT) in 14 cases (9%), insulinoma in 20 cases (12%), gastrinoma in three cases (2%), malignant adrenal tumors in 2 cases (1%), and malignant thymic-NET in one case (1%). Hyperparathyrodism was the first lesion in 90 cases (56%). The first symptoms occurred before 10 years old in 22 cases (14%) and before 5 years old in five cases (3%). Surgery was performed before age 21 in 66 patients (41%) with a total of 74 operations: pituitary adenoma (n = 9, 16%), hyperparathyroidism (n = 38, 31%), gastrinoma (n = 1, 33%), NSPT (n = 5, 36%), and all cases of insulinoma, adrenal tumors, and thymic-NET. One patient died before age 21 due to a thymic-NET. Overall, lesions were malignant in four cases. CONCLUSIONS: Various MEN1 lesions occurred frequently before 21 years old, but mainly after 10 years of age. Rare, aggressive tumors may develop at any age. Hyperparathyroidism was the most frequently encountered lesion but was not always the first biological or clinical abnormality to appear during the course of MEN1.
PubMed-ID: 25594862
http://dx.doi.org/10.1210/jc.2014-3659

Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis.
Langenbecks Arch Surg, 400(3):349-58.
F. M. Watzka, C. Fottner, M. Miederer, A. Schad, M. M. Weber, G. Otto, H. Lang and T. J. Musholt. 2015.
BACKGROUND: Patients with neuroendocrine neoplasms (NEN) develop hepatic metastases in 50-95 %. The aims of this study were to evaluate the outcome/prognosis of patients following hepatic surgery and to identify predictive factors for the selection of patient that benefit from hepatic tumor resection. PATIENTS AND METHODS: In a retrospective single-center study (1990 to 2014), 204 patients with hepatic metastasis of NEN were included. Ninety-four were subjected to various forms of liver resection. According to the overall survival, the influence of several prognostic factors like the Ki-67 index, stage of disease, and resection status was evaluated. RESULTS: The primary tumor was located in the small intestine (n = 73), pancreas (n = 58), colon (n = 26), esophagus or stomach (n = 9) and in 38 patients the primary site was unknown. The Ki-67 index was associated with significant different overall survival. Patients with an R0 resection (n = 38) of their hepatic metastasis had a very good 10-year survival of 90.4 %. Patients in whom an R1 (n = 23) or R2 (n = 33) resection of their hepatic metastasis could be achieved had a 10-year survival of 53.4 and 51.4 %, respectively. The majority of the patients (53.9 %) could not be resected and had a poor 10-year survival rate of 19.4 %. Partial or complete control of endocrine-related symptoms was achieved in all patients with functioning tumors following surgery. The overall 5- and 10-year survival rates were 77.9 and 65.2 %, respectively. CONCLUSION: Surgical resection of hepatic NEN metastases can reduce symptoms and improve the survival in selected patients with a Ki-67 index less than 20 %. The expected outcome has to be compared to the outcome of alternative treatment strategies. An R0 situation should be the aim of hepatic surgery, but also patients with R1 or R2 resection show a good survival benefit.

PubMed-ID: 25682055
http://dx.doi.org/10.1007/s00423-015-1277-z

Goblet cell appendiceal tumors--management dilemmas and long-term outcomes.
Surg Oncol, 24(1):47-53.
R. E. Rossi, T. V. Luong, M. E. Caplin, C. Thirlwell, T. Meyer, J. Garcia-Hernandez, A. Baneke, D. Conte and C. Toumpanakis. 2015.
BACKGROUND: Appendiceal Goblet cell tumors (GCTs) are clinically more aggressive, and have a worse outcome than midgut neuroendocrine tumors (mNETs). Guidelines for management of GCTs are limited. METHODS: A retrospective case-study analysis was performed in patients with a diagnosis of GCT, confirmed on histological review. Patients were evaluated clinically, biochemically, and radiologically. RESULTS: 48 patients were identified (TNM stage I-II: 27, stage III: 15, stage IV: 6). Median follow-up was 44 months and was complete in all patients. 68.8% presented with acute appendicitis. 44/48 patients had initial appendectomy, followed by prophylactic right hemicolectomy in 41. 10/48 patients had recurrent disease [median time to recurrence 28 months (range 4-159)]. Of those, 9 received systemic chemotherapy (FOLFOX/FOLFIRI), which was also given in 5/48 patients with disseminated disease at diagnosis. Partial response, stable disease and disease progression was noted in 22%, 22% and 56%, respectively. Adjuvant chemotherapy was also administered in 9/48 patients with stage III disease after right hemicolectomy, however in 3/9 the disease recurred. Median progression/disease-free-survival was 44 months (range 3-159) and overall 5-year survival rate was 41.6%. CONCLUSIONS: The clinical behaviour of GCTs is more similar to colorectal adenocarcinomas than to NETs. A prophylactic right hemicolectomy is recommended to reduce the risk of recurrence. Systemic chemotherapy, using colorectal adenocarcinoma regimens, is indicated for advanced or recurrent disease and has encouraging results. Prospective studies are needed to define the role of adjuvant chemotherapy and the optimal chemotherapy regimen.
PubMed-ID: 25686643
http://dx.doi.org/10.1016/j.suronc.2015.01.001

Management of pancreatic neuroendocrine tumors in patients with MEN 1.
Gland Surg, 4(1):63-8.
S. M. Sadowski and F. Triponez. 2015.
Pancreatic neuroendocrine tumors (PNETs) are frequent and can be non-functional (NF) in patients with multiple endocrine neoplasia type 1 (MEN1). Their identification is of clinical importance because malignant PNETs are reported to be the most common cause of death in patients with MEN1. Once the diagnosis of MEN1 is established in an individual based on clinical manifestations and/or genetic testing results, an active surveillance program is instituted for early detection and treatment of MEN1-associated disease. Ultrasonography, endoscopic ultrasonography (EUS), CT, MRI, selective arterial angiography and somatostatin receptor scintigraphy are all used for localization of tumors. Managing PNETs can be challenging and includes diagnosis, surveillance, adequate staging, and interdisciplinary, multimodal treatments to optimize patient outcome. Treatment includes surgical resection for loco-regional disease, as well as liver directed and targeted chemotherapies for advanced progressive disease. To date, the recommendation for surgical resection in NF-PNETs is based on tumor size, as a higher rate of metastases was found in patients with larger tumors. This review summarizes key concepts in managing PNETs in patients with MEN1.
PubMed-ID: 25713781
http://dx.doi.org/10.3978/j.issn.2227-684X.2014.12.01

Analysis of 177Lu-DOTA-octreotate therapy-induced DNA damage in peripheral blood lymphocytes of patients with neuroendocrine tumors.
J Nucl Med, 56(4):505-11.
D. Denoyer, P. Lobachevsky, P. Jackson, M. Thompson, O. A. Martin and R. J. Hicks. 2015.
Ionizing radiation-induced DNA double-strand breaks (DSBs) can lead to cell death, genome instability, and carcinogenesis. Immunofluorescence detection of phosphorylated histone variant H2AX (gamma-H2AX) is a reliable and sensitive technique to monitor external-beam ionizing radiation-induced DSBs in peripheral blood lymphocytes (PBLs). Here, we investigated whether gamma-H2AX could be used as an in vivo marker to assess normal-tissue toxicity after extended internal irradiation with (177)Lu-DOTA-octreotate (LuTate) peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors. METHODS: We analyzed the kinetics of gamma-H2AX foci in PBLs of 11 patients undergoing PRRT. The number of gamma-H2AX foci was determined before and up to 72 h after treatment. These values were compared with the estimated absorbed dose to blood, spleen, bone marrow, and tumor and with subsequent PBL reduction. RESULTS: The decrease in (177)Lu activity in blood with time followed a biexponential kinetic pattern, with approximately 90% of circulating activity in blood cleared

within 2 h. Absorbed dose to blood, but not to spleen or bone marrow, correlated with the administered (177)Lu activity. PRRT increased gamma-H2AX foci in lymphocytes in all patients, relative to pretherapy values. The response varied significantly between patients, but the average number of foci indicated a general trend toward an increase at 0.5-4 h with a subsequent decrease by 24-72 h after treatment. The peak number of foci correlated with the absorbed dose to tumor and bone marrow and the extent of PBL reduction. CONCLUSION: gamma-H2AX can be exploited in the LuTate PRRT as a biomarker of PBL cytotoxicity. Long-term follow-up studies investigating whether elevated residual gamma-H2AX values are associated with acute myelotoxicity and secondary blood malignancy may be worthwhile.
PubMed-ID: 25722453
http://dx.doi.org/10.2967/jnumed.114.145581

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

[Primary tumor resection of neuroendocrine pancreatic tumors with liver metastases].
Chirurg, 86(4):376.
H. Dralle. 2015.
PubMed-ID: 25828804
http://dx.doi.org/10.1007/s00104-015-3019-8

Management of 1- to 2-cm Carcinoid Tumors of the Appendix: Using the National Cancer Data Base to Address Controversies in General Surgery.
J Am Coll Surg, 220(5):894-903.
D. P. Nussbaum, P. J. Speicher, B. C. Gulack, J. E. Keenan, A. M. Ganapathi, B. R. Englum, D. S. Tyler and D. G. Blazer, 3rd. 2015.
BACKGROUND: The management of 1- to 2-cm appendiceal carcinoid tumors remains controversial. Here we use the National Cancer Data Base (NCDB) to compare long-term outcomes for patients treated via resection of the primary tumor alone vs right hemicolectomy (RHC). STUDY DESIGN: The 1998 to 2011 NCDB User File was queried to identify patients with 1- to 2-cm appendiceal carcinoids. Patients were stratified by surgical technique: resection of the primary tumor alone vs RHC with regional lymphadenectomy. Multivariable logistic regression was used to compare short-term outcomes. Survival was estimated using the Kaplan-Meier method with comparisons based on the log-rank test. RESULTS: A total of 916 patients were identified, including 42% managed with primary resection and 58% with RHC. Patients who underwent RHC had slightly larger tumors and higher-stage tumors; otherwise, there were no baseline differences between groups. The rates of positive margins were similar (5.5% vs 4.5%; p = 0.60). Among all patients, 1- and 5-year survival were 98.1% and 88.7% vs 96.7% and 87.4% (p = 0.52) for those managed via primary resection vs RHC, respectively. Among patients with moderate/high-grade/anaplastic carcinoids, 1- and 5-year survival were 93.3% and 72.0% vs 92.3% and 71.9%, respectively (p = 0.78). After adjustment with Cox proportional hazards modeling, we confirmed that there was no survival benefit for patients undergoing RHC (hazard ratio = 1.14; p = 0.72). CONCLUSIONS: For 1- to 2-cm appendiceal carcinoids, formal resection of the right colon does not appear to improve survival, even for higher-grade tumors. Our findings suggest that resection of the primary tumor alone is adequate for all carcinoids <2 cm.
PubMed-ID: 25840530
http://dx.doi.org/10.1016/j.jamcollsurg.2015.01.005

Erratum to: surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis.
Langenbecks Arch Surg, 400(3):359.
F. M. Watzka, C. Fottner, M. Miederer, A. Schad, M. M. Weber, G. Otto, H. Lang and T. J. Musholt. 2015.
PubMed-ID: 25846243
http://dx.doi.org/10.1007/s00423-015-1294-y

Neuroendocrine tumors of the pancreas: a retrospective single-center analysis using the ENETS TNM-classification and immunohistochemical markers for risk stratification.
BMC Surg, 15:49.
S. M. Brunner, F. Weber, J. M. Werner, A. Agha, S. A. Farkas, H. J. Schlitt and M. Hornung. 2015.

BACKGROUND: This study was performed to assess the 2006 introduced ENETS TNM-classification with respect to patient survival and surgical approach for patients who underwent surgery for a neuroendocrine tumor of the pancreas (PNET). METHODS: Between 2001 and 2010 38 patients after resection of a PNET were investigated regarding tumor localization and size. Further, patient survival with regards to the new TNM-classification, the operation methods and immunohistochemical markers was analyzed. RESULTS: The estimated mean survival time of the 38 patients was 91 +/- 10 months (female 116 +/- 9, male 56 +/- 14 months; p = 0.008). The 5-year survival rate was 63.9%. Patient survival differed significantly depending on tumor size (pT1 107 +/- 13, pT2 94 +/- 16, pT3 44 +/- 7 and pT4 18 +/- 14 months; P = 0.006). Patients without lymph node metastasis survived significantly longer compared to patients with positive lymph node status (108 +/- 9 vs. 19 +/- 5 months; P < 0.001). However, survival in patients with and without distant metastasis did not differ significantly (92 +/- 11 vs. 80 +/- 23 months; P = 0.876). Further, the tumor grading significantly influenced patient survival (G1 111 +/- 12, G2 68 +/- 12 and G3 21 +/- 14 months; P = 0.037). CONCLUSIONS: As part of the TNM-classification especially lymph node status and also tumor size and grading were identified as important factors determining patient survival. Further, gender was demonstrated to significantly influence survival time. If an R0 resection was achieved in patients with distant metastases patient survival was comparable to patients without metastasis.
PubMed-ID: 25928025
http://dx.doi.org/10.1186/s12893-015-0033-1

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity.
Endocr Relat Cancer, 22(1):35-45.
N. Sahnane, D. Furlan, M. Monti, C. Romualdi, A. Vanoli, E. Vicari, E. Solcia, C. Capella, F. Sessa and S. La Rosa. 2015.
Gastroenteropancreatic (GEP) neuroendocrine carcinomas (NECs) and mixed adenoneuroendocrine carcinomas (MANECs) are heterogeneous neoplasms characterized by poor outcome. Microsatellite instability (MSI) has recently been found in colorectal NECs showing a better prognosis than expected. However, the frequency of MSI in a large series of GEP-NEC/MANECs is still unknown. In this work, we investigated the incidence of MSI in GEP-NEC/MANECs and characterized their clinicopathologic and molecular features. MSI analysis and immunohistochemistry for mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) were performed in 89 GEP-NEC/MANECs (six esophageal, 77 gastrointestinal, three pancreatic, and three of the gallbladder). Methylation of 34 genes was studied by methylation-specific multiplex ligation probe amplification. Mutation analysis of BRAF and KRAS was assessed by PCR-pyrosequencing analysis. MSI was observed in 11 NEC/MANECs (12.4%): seven intestinal and four gastric. All but two MSI-cases showed MLH1 methylation and loss of MLH1 protein. The remaining two MSI-cancers showed lack of MSH2 or PMS2 immunohistochemical expression. MSI-NEC/MANECs showed higher methylation levels than microsatellite stable NEC/MANECs (40.6% vs 20.2% methylated genes respectively, P<0.001). BRAF mutation was detected in six out of 88 cases (7%) and KRAS mutation was identified in 15 cases (17%). BRAF mutation was associated with MSI (P<0.0008), while KRAS status did not correlate with any clinicopathologic or molecular feature. Vascular invasion (P=0.0003) and MSI (P=0.0084) were identified as the only independent prognostic factors in multivariate analysis. We conclude that MSI identifies a subset of gastric and intestinal NEC/MANECs with distinct biology and better prognosis. MSI-NEC/MANECs resemble MSI-gastrointestinal adenocarcinomas for frequency, molecular profile and pathogenetic mechanisms.
PubMed-ID: 25465415
http://dx.doi.org/10.1530/ERC-14-0410

[Complications in endocrine surgery].
Chirurg, 86(1):4-5.
H. Dralle. 2015.
PubMed-ID: 25511443
http://dx.doi.org/10.1007/s00104-014-2815-x

Assimilating endocrine anatomy through simulation: a pre-emptive strike!
Am J Surg, 209(3):542-6.
P. G. Rowse, R. K. Ruparel, R. D. Brahmbhatt, B. M. Dy, Y. N. AlJamal, J. Abdelsattar and D. R. Farley. 2015.
BACKGROUND: We sought to determine if endocrine anatomy could be learned with the aid of a hands-on, low-

cost, low-fidelity surgical simulation curriculum and pre-emptive 60-second YouTube video clip. METHODS: A 3-hour endocrine surgery simulation session was held on back-to-back Fridays. A video clip was made available to the 2nd group of learners. A comprehensive 40-point test was administered before (pre-test) and after (post-test) the sessions. RESULTS: General surgery interns (n = 26) participated. The video was viewed 19 times by 80% (12 of 15) of interns with access. Viewers outperformed nonviewers on subsequent post-testing (mean [SD], 29.7 [1.3] vs 24.4 [1.6]; P = .015). Mean scores on the anatomy section of the post-test were higher among viewers than nonviewers (mean [SD] 14.2 [.9] vs 10.3 [1.0]; P = .012). CONCLUSIONS: Low-cost simulation models can be used to teach endocrine anatomy. Pre-emptive viewing of a 60-second video may have been a key factor resulting in higher post-test scores compared with controls, suggesting that the video intervention improved the educational effectiveness of the session.
PubMed-ID: 25578743
http://dx.doi.org/10.1016/j.amjsurg.2014.12.004