EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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

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

Affiliations see next page

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Contents

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

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

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

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Collectors

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

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

Samira M Sadowski, MD
Endocrine Oncology Branch, National Cancer Institute, NIH, Bethesda MD, USA

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

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

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

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

Compilation and Coordination

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

Preliminary

After some long delay with the 2015-3 edition, we are back on schedule with the ESES 2016-1 reference list. With this edition we also introduce a kind of foreword to highlight certain issues in the reference list.

Despite our efforts to keep the list short, this edition is again one of the longer ones with 282 entries (after 192 entries in 2015-3). We will try to keep it shorter – promise.

The impact factors in the journal list (next page) have been updated to the current values of 2014/15.

In this list we have a total of 14 consensus statements/guidelines. Here in particular the **ENETS 2016 Guidelines,** which can be found under the **NET – CG** entries.

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

Yours

Ulrich Beutner

Journals covered

Journal	IF2014	Journal	IF2014
Acta Cytol	1.562†	J Bone Miner Res	6.832
Am J Kidney Dis	5.900	J Clin Endocrinol Metab	6.209
Am J Nephrol	2.669	J Clin Oncol	18.428
Am J Surg	2.291	J Endocrinol	3.718
Am Surgeon	0.818	J Endocrinol Invest	1.448
Ann Surg	8.327	J Nephrol	1.454
Ann Surg Oncol	3.930	J Nucl Med	6.160
ANZ J Surg	1.122	J Surg Oncol	3.244
Br J Surg	5.542	Lancet	45.217
Cancer	4.889	Langenbecks Arch Surg	2.191
Chirurg	0.574	Laryngoscope	2.144
Clin Endocrinol Oxf	3.457	N Engl J Med	55.873
Clin Nucl Med	3.931	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	13.281
Curr Opin Oncol	4.466	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	14.180
Endocr Relat Cancer	4.805	Nephrol Dial Transplant	3.577
Endocr Rev	21.059	Nephron Clin Pract	1.402
Eur Arch Otorhinolaryngol	1.545	Neuroendocrinology	4.373
Eur J Endorcrinol	4.069	Oncologist	4.865
Eur J Surg Oncol	3.009	Otolaryngol Head Neck Surg	2.020
Gland Surg	---	Surg Clin North Am	1.879
Head Neck	2.641	Surg Endosc	3.256
Horm Metab Res	2.121	Surg Laparosc Endosc Percutan Tech	1.140
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	1.794	Surg Oncol	3.270
JAMA Surg (*prev:* Arch Surg)	3.936	Surg Oncol Clin N Am	1.806
Int J Cancer	5.085	Surgery	3.380
J Am Coll Surg	5.122	Thyroid	4.493
J Am Soc Nephrol	9.343	Updates In Surgery	---
J Bone Miner Metab	2.460	World J Surg	2.642

Journal names are links to the journal's homepage!, IF2014: Impact factor 2014, †IF 2013, no IF for 2014

Thyroid

Meta-Analyses

Accuracy of thyroid nodule sonography for the detection of thyroid cancer in children: systematic review and meta-analysis.
Clin Endocrinol (Oxf), 84(3):423-30.
A. Al Nofal, M. R. Gionfriddo, A. Javed, Q. Haydour, J. P. Brito, L. J. Prokop, S. T. Pittock and M. H. Murad. 2016.
INTRODUCTION: Thyroid ultrasound (US) is a widely used tool for evaluating thyroid nodules. Various US features have been suggested as predictors of thyroid cancer in children. OBJECTIVE: To conduct a systematic review and meta-analysis to assess the diagnostic accuracy of different thyroid US features in detecting thyroid cancer in children. METHODS: We searched multiple online databases for cohort studies that enrolled paediatric patients with thyroid nodules (age <21 years) and evaluated the accuracy of 12 relevant ultrasound features. Diagnostic measures were pooled across studies using a random effects model. RESULTS: The search strategy yielded 1199 citations, of which 12 studies met the predefined inclusion criteria (750 nodules). The prevalence of thyroid cancer was 27.2% (40.8% in patients with a history of radiation exposure and 23.2% in patients without a history of exposure to radiation). The most common cancer was papillary thyroid cancer (86.7%). The presence of internal calcifications and enlarged cervical lymph nodes were the US features with the highest likelihood ratio [4.46 (95% CI: 1.87-10.64) and 4.96 (95% CI: 2.01-12.24), respectively] for thyroid cancer. A cystic nodule was the feature with highest likelihood ratio for benign nodules [1.96 (95% CI: 0.87-4.43)]. CONCLUSION: Thyroid US features are not highly accurate predictors of benign or malignant aetiology of thyroid nodules in children. Internal calcification may predict malignancy, and cystic appearance may suggest benign aetiology.
PubMed-ID: 25845503
http://dx.doi.org/10.1111/cen.12786

BRAF(V600E) Is Correlated with Recurrence of Papillary Thyroid Microcarcinoma: A Systematic Review, Multi-Institutional Primary Data Analysis, and Meta-Analysis.
Thyroid, 26(2):248-55.
Y. Chen, P. M. Sadow, H. Suh, K. E. Lee, J. Y. Choi, Y. J. Suh, T. S. Wang and C. C. Lubitz. 2016.
BACKGROUND: Given the increasing incidence of papillary thyroid carcinoma despite stable disease-specific mortality rates, the potential for the disease to reoccur is a key outcome to predict. The BRAF(V600E) mutation has been associated with recurrent disease in larger tumors. However, its correlation in papillary thyroid microcarcinoma (PTMC) is not clear in individual series. METHODS: The MEDLINE, EMBASE, Web of Science, and Cochrane databases were searched for studies including patients with PTMC undergoing initial surgical treatment. Studies with at least two years of follow-up, BRAF genotyping (the comparator), and recurrence as an outcome were included, as were unpublished primary data on 485 patients from two institutions. The metameter analyzed was odds ratio (OR) for recurrence between patients with BRAF(V600E) versus BRAF wild type (BRAFwt). RESULTS: The initial search identified 431 references. After screening of the abstracts for inclusion, 44 manuscripts were reviewed in full by two independent reviewers. Four published studies and primary data from two institutional cohorts were included in the final analysis. A meta-analysis of 2247 PTMC patients revealed that patients with a BRAF(V600E) mutation had a higher likelihood for recurrence (odds ratio 2.09 [confidence interval 1.31-3.33], p = 0.002). CONCLUSIONS: This meta-analysis shows that BRAF mutational status correlates with recurrence of PTMCs, highlighting the potential utility of genotyping in preoperative and postoperative planning. BRAF mutation may be helpful in risk-stratifying patients with PTMC for surgical management versus observation.
PubMed-ID: 26671072
http://dx.doi.org/10.1089/thy.2015.0391

The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis.
World J Surg, 40(1):100-9.
G. Hu, W. Zhu, W. Yang, H. Wang, L. Shen and H. Zhang. 2016.
BACKGROUND: This systematic review and meta-analysis aimed to evaluate the effectiveness of radioactive iodine (RAI) remnant ablation for thyroid cancer-related outcomes of patients with papillary thyroid microcarcinoma (PTMC). METHODS: A systematic literature search of PubMed, EMBASE OvidSP, and EBSCO was conducted. Studies were selected that provided multivariable analysis of the effectiveness of RAI ablation or

provided specific data of a 10 years history of thyroid cancer-related outcomes in patients that presented with PTMC. RESULTS: Nineteen studies met the inclusion criteria. A multivariable analysis of the effectiveness of RAI ablation for any recurrence or thyroid cancer-related mortality in patients with PTMC was performed in several studies, among which only one study reported a positive result. Furthermore, for PTMC patients treated by total or near-total thyroidectomy (TT/NT), with or without RAI ablative therapy, the meta-analysis suggested that RAI ablation did not decrease the 10 years history of any tumor recurrence (relative risk [RR] 0.96; 95% confidence interval [CI] 0.63-1.48; P = 0.87), locoregional recurrence (RR 1.15; 95% CI 0.75-1.76; P = 0.51), distant metastases (RR 0.32; 95% CI 0.08-1.32; P = 0.11) or thyroid cancer-related mortality (RR 0.76; 95% CI 0.22-2.63; P = 0.66). CONCLUSIONS: With regard to multivariable analyses, there was almost no positive treatment effect of RAI ablation noted for patients with PTMC. For PTMC patients already treated by TT/NT, incremental RAI ablation may not be beneficial at decreasing the 10 years recurrence of PTMC or incidence of thyroid cancer-related mortality.
PubMed-ID: 26578322
http://dx.doi.org/10.1007/s00268-015-3346-4

Impact of recombinant PTH on management of hypoparathyroidism: a systematic review.
Eur Arch Otorhinolaryngol, 273(4):827-35.
Y. Ramakrishnan and H. C. Cocks. 2016.
The treatment of post-surgical hypoparathyroidism (following thyroid or parathyroid surgery) is challenging. Presently, this condition is treated with calcium and vitamin D supplements rather than replacing the missing parathyroid hormone. Not only is it challenging to maintain normocalcaemia, but concerns of hypercalciuria and ectopic calcification have also been raised using these supplements. There is an ongoing debate whether recombinant parathyroid hormone (rPTH), which as yet is unlicensed for treating hypoPTH, may offer a more physiological solution. The objective of the study was to assess the effectiveness and safety of rPTH in maintaining normocalcaemia and normocalcuria in hypoparathyroidism. This was a systematic review performed using independently developed search strategies including Medline, Embase, CINAHL, Cochrane, Zetoc, conference proceedings and a manual search until 15 July 2014. Data extraction was undertaken by one reviewer (YR). Studies were synthesised through narrative review with tabulation of results. Of 2,141 studies identified, only eleven studies fitted the inclusion criteria. These studies suggest that rPTH is useful in normalising serum calcium levels. Excretion of urinary calcium levels is reduced with PTH 1-34 but remained unchanged in a number of studies using PTH 1-84. Recombinant PTH is well tolerated. The majority of studies included post-surgical hypoparathyroidism with marked heterogeneity. Further prospective, larger, long-term trials are necessary to evaluate the long-term efficacy and adverse profile of rPTH, including head to head comparisons between PTH 1-34 and PTH 1-84.
PubMed-ID: 25567344
http://dx.doi.org/10.1007/s00405-014-3484-6

Efficacy and Safety of Radiofrequency and Ethanol Ablation for Treating Locally Recurrent Thyroid Cancer: A Systematic Review and Meta-Analysis.
Thyroid, 26(3):420-8.
C. H. Suh, J. H. Baek, Y. J. Choi and J. H. Lee. 2016.
BACKGROUND: The aim of this study was to evaluate the efficacy and safety of radiofrequency ablation (RFA) and ethanol ablation (EA) for treating locally recurrent thyroid cancer. MATERIALS AND METHODS: Ovid-MEDLINE and EMBASE databases were searched for studies on the efficacy and safety of RFA and EA for treating locally recurrent thyroid cancer. The pooled proportions of the volume reduction ratio (VRR) >/=50%, complete disappearance, changes in serum level of thyroglobulin (Tg), recurrence, and complications were assessed using random-effects modeling. Heterogeneity among studies was determined using the chi-square statistic for the pooled estimates and the inconsistency index I(2). To overcome heterogeneity, sensitivity analysis was performed. RESULTS: Ten eligible studies were included, with a total sample size of 270 patients and 415 thyroid nodules. The pooled proportion of VRR >/=50% after RFA (100%, recalculated 100%; I(2) = 100%, recalculated I(2) = 55.3%) was higher than that after EA (89.5%; I(2) = 82.4%; p = 0.2764); the pooled proportion of complete disappearance after RFA (68.8%) was higher than that after EA (53.4%; p = 0.3384); and the pooled proportion of recurrence after RFA (0.0%) was lower than that after EA (2.4%, adjusted 1.6%; p = 0.9766). However, these differences were not statistically significant. In addition, the pooled proportion of reduction in serum level of Tg after RFA was 71.6% and after EA was 93.8% (p < 0.0001). The pooled proportion of complications of both RFA (5.8%, adjusted 1.6%) and EA (1.6%) were low (p = 0.8479). The mean number of RFA sessions was <1.3 in five of six RFA studies, and the number of EA sessions was more than two in three of four EA studies. CONCLUSION: Both RFA and EA are acceptable treatment modalities to manage locally recurrent thyroid cancer in terms of efficacy and safety for poor surgical candidates or those who refuse

surgery.
PubMed-ID: 26782174
http://dx.doi.org/10.1089/thy.2015.0545

BRAF-mutated carcinomas among thyroid nodules with prior indeterminate FNA report: a systematic review and meta-analysis.
Clin Endocrinol (Oxf), 84(3):315-20.
P. Trimboli, G. Treglia, E. Condorelli, F. Romanelli, A. Crescenzi, M. Bongiovanni and L. Giovanella. 2016.
BACKGROUND: Several molecular analyses have been investigated for risk stratification of thyroid nodules, with a particular focus on the V600E mutation of the BRAF gene [BRAF(V600E)]. To date, there is no high-level evidence supporting or refuting a role for BRAF analysis in thyroid nodules with prior indeterminate cytology. To obtain more robust evidence, we reviewed and meta-analysed data from published articles. RESEARCH DESIGN AND METHODS: A comprehensive literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted using the terms 'BRAF', 'thyroid' and 'indeterminate'. The search was updated until March 2015, and references of the retrieved articles were also screened. Only original articles reporting BRAF mutation testing within nodules with indeterminate FNA were eligible for inclusion. RESULTS: The literature search revealed 82 articles, of which 8 were eligible for the study. Five studies were prospective and three retrospective. The majority of authors analysed BRAF mutations in FNA samples which were classified by the British or Bethesda system. Of the initial series of studies, a pooled number of 1361 cases were achieved of which 43 were BRAF mutated. Overall, the BRAF mutation rate was 4.6% (95% CI: 1-10.8%), ranging from 0 to 22.9%. When we included only histological series, 978 thyroid nodules were found. Of these, 245 were cancers. CONCLUSIONS: A very low rate of lesions with indeterminate cytology are BRAF mutated. Thus, the role of this biomarker to detect or exclude cancers in patients with such FNA reports is marginal and should be reconsidered in guidelines.
PubMed-ID: 25920006
http://dx.doi.org/10.1111/cen.12806

Randomized controlled trials

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

Safety and tolerability of sorafenib in patients with radioiodine-refractory thyroid cancer.
Endocr Relat Cancer, 22(6):877-87.
F. Worden, M. Fassnacht, Y. Shi, T. Hadjieva, F. Bonichon, M. Gao, L. Fugazzola, Y. Ando, Y. Hasegawa, J. Park do, Y. K. Shong, J. W. Smit, J. Chung, C. Kappeler, G. Meinhardt, M. Schlumberger and M. S. Brose. 2015.
Effective adverse event (AE) management is critical to maintaining patients on anticancer therapies. The DECISION trial was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial which investigated sorafenib for treatment of progressive, advanced, or metastatic radioactive iodine-refractory, differentiated thyroid carcinoma. Four hundred and seventeen adult patients were randomized (1:1) to receive oral sorafenib (400 mg, twice daily) or placebo, until progression, unacceptable toxicity, noncompliance, or withdrawal.

Progression-free survival, the primary endpoint of DECISION, was reported previously. To elucidate the patterns and management of AEs in sorafenib-treated patients in the DECISION trial, this report describes detailed, by-treatment-cycle analyses of the incidence, prevalence, and severity of hand-foot skin reaction (HFSR), rash/desquamation, hypertension, diarrhea, fatigue, weight loss, increased serum thyroid stimulating hormone, and hypocalcemia, as well as the interventions used to manage these AEs. By-cycle incidence of the above-selected AEs with sorafenib was generally highest in cycle 1 or 2 then decreased. AE prevalence generally increased over cycles 2-6 then stabilized or declined. Among these AEs, only weight loss tended to increase in severity (from grade 1 to 2) over time; severity of HFSR and rash/desquamation declined over time. AEs were mostly grade 1 or 2, and were generally managed with dose interruptions/reductions, and concomitant medications (e.g. antidiarrheals, antihypertensives, dermatologic preparations). Most dose interruptions/reductions occurred in early cycles. In conclusion, AEs with sorafenib in DECISION were typically grade 1 or 2, occurred early during the treatment course, and were manageable over time.
PubMed-ID: 26370187
http://dx.doi.org/10.1530/ERC-15-0252

Consensus Statements/Guidelines

American Thyroid Association Statement on Remote-Access Thyroid Surgery.
Thyroid, 26(3):331-7.
E. Berber, V. Bernet, T. J. Fahey, 3rd, E. Kebebew, A. Shaha, B. C. Stack, Jr., M. Stang, D. L. Steward and D. J. Terris. 2016.
BACKGROUND: Remote-access techniques have been described over the recent years as a method of removing the thyroid gland without an incision in the neck. However, there is confusion related to the number of techniques available and the ideal patient selection criteria for a given technique. The aims of this review were to develop a simple classification of these approaches, describe the optimal patient selection criteria, evaluate the outcomes objectively, and define the barriers to adoption. METHODS: A review of the literature was performed to identify the described techniques. A simple classification was developed. Technical details, outcomes, and the learning curve were described. Expert opinion consensus was formulated regarding recommendations for patient selection and performance of remote-access thyroid surgery. RESULTS: Remote-access thyroid procedures can be categorized into endoscopic or robotic breast, bilateral axillo-breast, axillary, and facelift approaches. The experience in the United States involves the latter two techniques. The limited data in the literature suggest long operative times, a steep learning curve, and higher costs with remote-access thyroid surgery compared with conventional thyroidectomy. Nevertheless, a consensus was reached that, in appropriate hands, it can be a viable option for patients with unilateral small nodules who wish to avoid a neck incision. CONCLUSIONS: Remote-access thyroidectomy has a role in a small group of patients who fit strict selection criteria. These approaches require an additional level of expertise, and therefore should be done by surgeons performing a high volume of thyroid and robotic surgery.
PubMed-ID: 26858014
http://dx.doi.org/10.1089/thy.2015.0407

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.
Thyroid, 26(1):1-133.
B. R. Haugen, E. K. Alexander, K. C. Bible, G. M. Doherty, S. J. Mandel, Y. E. Nikiforov, F. Pacini, G. W. Randolph, A. M. Sawka, M. Schlumberger, K. G. Schuff, S. I. Sherman, J. A. Sosa, D. L. Steward, R. M. Tuttle and L. Wartofsky. 2016.
BACKGROUND: Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. Since the American Thyroid Association's (ATA's) guidelines for the management of these disorders were revised in 2009, significant scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer. METHODS: The specific clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on knowledge synthesis methods, including electronic database searching, review and selection of relevant citations, and critical appraisal of selected studies. Published English language articles on adults were eligible for inclusion. The

American College of Physicians Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations for therapeutic interventions. We developed a similarly formatted system to appraise the quality of such studies and resultant recommendations. The guideline panel had complete editorial independence from the ATA. Competing interests of guideline task force members were regularly updated, managed, and communicated to the ATA and task force members. RESULTS: The revised guidelines for the management of thyroid nodules include recommendations regarding initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, use of molecular markers, and management of benign thyroid nodules. Recommendations regarding the initial management of thyroid cancer include those relating to screening for thyroid cancer, staging and risk assessment, surgical management, radioiodine remnant ablation and therapy, and thyrotropin suppression therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using imaging and serum thyroglobulin, thyroid hormone therapy, management of recurrent and metastatic disease, consideration for clinical trials and targeted therapy, as well as directions for future research. CONCLUSIONS: We have developed evidence-based recommendations to inform clinical decision-making in the management of thyroid nodules and differentiated thyroid cancer. They represent, in our opinion, contemporary optimal care for patients with these disorders.
PubMed-ID: 26462967
http://dx.doi.org/10.1089/thy.2015.0020

Other Articles

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

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

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

Follicular variant of papillary thyroid carcinoma with B-type Raf(V600E) showing higher frequency of suspicious sonographic features and multifocality.
Head Neck, 37(11):1590-5.
D. Y. Shin, K. J. Kim, S. Chang, H. Kim, S. Hwang, W. Kim, J. Bae, S. Park, S. W. Kang, W. Y. Chung and E. J. Lee. 2015.
BACKGROUND: The purpose of this study was to investigate the correlation between B-type Raf (BRAF) kinase mutation and clinicopathological features of follicular variant of papillary thyroid carcinoma (PTC). METHODS: Eighty-four patients with pathologically confirmed follicular variant of PTC, who underwent a preoperative BRAF(V600E) study, were analyzed. Clinicopathological parameters and ultrasonographic features were compared between the BRAF(V600E) -positive and negative groups. RESULTS: A total of 41.7% of the patients showed BRAF(V600E) . The BRAF(V600E) -positive group showed the smaller tumor size (7.3 +/- 3.6 mm vs 10.7 +/- 8.9 mm; p = .018) and the more frequent multifocality (25.7% vs 8.2%; p = .028). Follicular variant of PTC with BRAF(V600E) showed suspicious ultrasonographic features (88.6% vs 57.1%; p = .002) more frequently. BRAF(V600E) positivity is associated with multifocality after adjusting for age, sex, the presence of suspicious ultrasonographic features, pathological tumor size, and thyrotropin level. CONCLUSION: BRAF(V600E) was correlated with smaller tumor size and suspicious ultrasonographic features in follicular variant of PTC. BRAF(V600E) was a significant parameter for predicting multifocality of follicular variant of PTC.
PubMed-ID: 24909403
http://dx.doi.org/10.1002/hed.23793

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

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

Utility of BRAF mutation detection in fine-needle aspiration biopsy samples read as "suspicious for papillary thyroid carcinoma".
Head Neck, 37(12):1788-93.
S. M. Jara, R. Bhatnagar, H. Guan, C. D. Gocke, S. Z. Ali and R. P. Tufano. 2015.
BACKGROUND: The purpose of this study was to evaluate the diagnostic utility of BRAF mutation testing on thyroid nodules "suspicious for papillary thyroid carcinoma" (PTC) cytology. METHODS: A chart review of patients with fine-needle aspiration (FNA) results "suspicious for PTC" with subsequent thyroidectomy was performed. Corresponding archived FNA slides underwent BRAF mutation testing. RESULTS: Sixty-six patients with FNA "suspicious for PTC" underwent thyroidectomy. Forty-two (63.6%) had PTC diagnosed on final histopathology, whereas 21 (31.8%) had benign findings. Thirty-five patients (83%) with histologically proven PTC underwent total thyroidectomy, whereas 7 (17%) underwent hemithyroidectomy. BRAF mutation was detected in 17 of 49 samples (34.6%) available for testing and had 45.5% sensitivity, 87.5% specificity, 88.2% positive predictive value (PPV), and 43.8% negative predictive value (NPV) for diagnosing PTC. Two of 4 patients (50%) who underwent hemithyroidectomy with subsequent completion thyroidectomy had mutated BRAF detected. CONCLUSION: BRAF testing is a useful adjunct to improve PPV for patients with "suspicious for PTC" cytology.
PubMed-ID: 24989827
http://dx.doi.org/10.1002/hed.23829

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

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

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

Lateral neck recurrence from papillary thyroid carcinoma: Predictive factors and prognostic significance.
Laryngoscope, 125(9):2226-31.
D. Giordano, A. Frasoldati, J. L. Kasperbauer, E. Gabrielli, C. Pernice, M. Zini, C. Pedroni, S. Cavuto and V. Barbieri. 2015.
OBJECTIVES/HYPOTHESIS: The aim of this study was to identify any possible predictive factors of lateral neck recurrence in patients with papillary thyroid carcinoma with no ultrasonographic and/or cytological evidence of lymph node metastasis at time of diagnosis. The influence of lateral neck recurrence on survival was also

investigated. STUDY DESIGN: Observational retrospective study. METHODS: Retrospective review of clinical records of 610 patients surgically treated for papillary thyroid carcinoma with clinically negative lymph nodes at the Otolaryngology Unit of the Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, from January 1984 to December 2008. RESULTS: Lateral neck recurrences were ipsilateral to the primary tumor in all cases and were associated with the occurrence of more aggressive histological variants and central neck metastasis. Lateral neck recurrences were more frequently observed in patients with distant metastases and were associated with a reduced disease-specific survival. CONCLUSION: Lateral neck compartment ipsilateral to the tumor was the most common site of recurrence, with about half of cases appearing in the first 28 months of follow-up. In patients with papillary thyroid carcinoma, detection of lateral neck metastases prior to first surgery is crucial to surgical planning. Aggressive histological variants and postsurgical evidence of lymph node metastasis from papillary thyroid carcinoma in central neck compartment are associated with a higher risk of lateral neck recurrence. In these patients, a closer postsurgical ultrasound surveillance of the lateral neck compartments seems worthwhile. LEVEL OF EVIDENCE: 4.
PubMed-ID: 25510637
http://dx.doi.org/10.1002/lary.25094

A 2013 European survey of clinical practice patterns in the management of Graves' disease.
Clin Endocrinol (Oxf), 84(1):115-20.
L. Bartalena, H. B. Burch, K. D. Burman and G. J. Kahaly. 2016.
OBJECTIVE: Management of Graves' disease (GD) in Europe was published in 1987. Aim of this survey was to provide an update on clinical practice in Europe, and to compare it with a 2011 American survey. DESIGN: Members of the European Thyroid Association (ETA) were asked to participate in a survey on management of GD, using the same questionnaire of a recent American survey. RESULTS: A total of 147 ETA members participated. In addition to serum TSH and free T4 assays, most respondents would request TSH-receptor autoantibody (TRAb) measurement (85.6%) and thyroid ultrasound (70.6%) to confirm aetiology, while isotopic studies were selected by 37.7%. Antithyroid drug (ATD) therapy was the preferred first-line treatment (83.8%). Compared to the previous European survey, Europeans currently more frequently use TRAb measurement and thyroid ultrasound for diagnosis and evaluation, but first-line treatment remains ATDs in a similar percentage of respondents. Current clinical practice patterns differ from those in North America, where isotopic studies are more frequently used, and radioiodine (RAI) still is first-line treatment. When RAI treatment is selected in the presence of mild Graves' orbitopathy and/or associated risk factors for its occurrence/exacerbation, steroid prophylaxis is frequently used. The preferred ATD in pregnancy is propylthiouracil in the first trimester and methimazole in the second and third trimesters, similar to North America. CONCLUSIONS: Significant changes in clinical practice patterns in Europe were noted compared to the previous European survey, as well as persisting differences in diagnosis and therapy between Europe and North America.
PubMed-ID: 25581877
http://dx.doi.org/10.1111/cen.12688

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

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

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

Intermediate-risk differentiated thyroid carcinoma patients who were surgically ablated do not need adjuvant radioiodine therapy: long-term outcome study.
Clin Endocrinol (Oxf), 84(3):408-16.
S. Ballal, R. Soundararajan, A. Garg, S. Chopra and C. Bal. 2016.
OBJECTIVE: The mute question is whether patients with DTC of intermediate risk of recurrence, second most common presentation, who were surgically ablated in the first place, ever needed adjuvant RAI therapy? This study exclusively evaluated the long-term outcome in intermediate-risk patients with DTC. DESIGN: Two-arm retrospective cohort study conducted between years 1991 and 2012. SETTING: Institutional practice. PATIENTS: Intermediate-risk DTC patients, with pathologically proven T1/2 N1 M0, T3 with/without N1 M0 disease, with a minimum follow-up of 12 months, were included. Of 254 patients who fulfilled the inclusion/exclusion criteria, 125 patients were surgically ablated (Gr-I) and 129 patients had significant remnant and/nodal disease (Gr-II). No radioiodine in Gr-I and adjuvant RAI therapy was administered in Gr-II patients. MEASUREMENTS: Baseline characteristics were compared and overall survival, event-free survival, disease-free survival/overall remission rates and recurrence rates were calculated for both the groups. RESULTS: All baseline patient characteristics were comparable except 24-h RAIU between two groups. Depending on adjuvant radioiodine therapy outcome, Gr-II patients were subclassified as Gr-IIa (ablated) and Gr-IIb (not

ablated). With a median follow-up duration of 10.3 years (range: 1-21 years), 12/125 (9.6%) patients had disease recurrence and 10 (8%) showed persistent disease in Gr-I. In Gr-IIa, 6/102 (5.9%) patients recurred but only one of them was successfully ablated with (131) I, and 5 (4.9%) had persistent disease. However, in Gr-IIb, 27 patients who failed first-dose adjuvant RAI therapy, 8/27 (29.6%) showed persistent disease (P = 0.000). Overall survival was 100%; however, disease-free survival rates were 92% and 90%, in Gr-I and Gr-II, respectively. CONCLUSION: Intermediate-risk surgically ablated patients do not need adjuvant RAI therapy and patients who failed to achieve ablation with first dose of (131) I may be dynamically risk stratified as high-risk category and managed aggressively.
PubMed-ID: 25823589
http://dx.doi.org/10.1111/cen.12779

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

Correlation between polymorphisms of BRAF gene and papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 84(3):431-7.
R. Jiang, C. Zhao, H. Xu, M. Zhao, X. Sun, X. Wang and W. Song. 2016.
BACKGROUND: Papillary thyroid carcinoma (PTC), which accounts for 80% of all thyroid cancers, has an increasing incidence over these years. Single nucleotide polymorphisms (SNPs) of BRAF were considered to be one of well-established risk factors leading to development of PTC. The aim of this study was to investigate whether the common mutations of BRAF could elevate significantly the risk of PTC in a Chinese population. METHODS: Four SNPs (rs11762469, rs17623204, rs1267636 and rs3748093) of BRAF were selected through our filter by Haploview 4.2 software with HapMap databases. We used the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to genotype the four SNPs in blood samples of 618 subjects (206 patients with PTC and 412 healthy controls). The correlation between BRAF polymorphisms and PTC risk was assessed using student t-test and chi-square test. RESULTS: The results showed that mutation in rs3748093 was significantly associated with an increased risk of PTC in allele model (A allele vs. T allele, OR = 1.68, 95% CI = 1.16-2.43, P = 0.006), dominant model (TA + AA vs TT, OR = 1.64, 95% CI = 1.08-2.48, P = 0.019) and homozygote model (AA vs. TT, OR = 2.94, 95% CI = 1.00-8.61, P = 0.040). However, the other three SNPs (rs11762469, rs17623204 and rs1267636) were shown to have no association with the risk of PTC. CONCLUSIONS: Our results indicated that polymorphism of rs3748093*A was significantly correlated with an increased risk of PTC in a Chinese population. Further investigation on the aetiological mechanism of PTC is needed to validate our results.
PubMed-ID: 25916409
http://dx.doi.org/10.1111/cen.12804

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

Association between single nucleotide polymorphisms of upstream transcription factor 1 (USF1) and susceptibility to papillary thyroid cancer.
Clin Endocrinol (Oxf), 84(4):564-70.
Q. Yuan, Q. Bu, G. Li, J. Zhang, T. Cui, R. Zhu and D. Mu. 2016.
BACKGROUND: Thyroid cancer, predominantly by papillary thyroid cancer (PTC), is a malignant tumour of endocrine system with increasing incidence rate worldwide. Upstream transcription factor 1 (USF1) regulates a variety of biological processes by transactivation of functional genes. In this study, we investigated the association between USF1 polymorphisms and PTC risk. MATERIAL & METHODS: A total of 334 patients with PTC, 186 patients with benign nodules (BN) and 668 healthy controls were enrolled in our study. Tag-SNPs were identified in Chinese Han in Beijing (CHB) from International HapMap Project Databases. Genomic DNAs were extracted by TaqMan Blood DNA kits. SNPs of USF1 were genotyped by TaqMan SNPs genotyping assay. Odds ratios (OR) and corresponding 95% confidence interval (CI) were used to assess the association between USF1 genetic variants and PTC risk. The statistical analyses were carried out with spss 13.0 software. RESULTS: Five tag-SNPs were retrieved to capture all the genetic variants of USF1. Among the five tag-SNPs, genetic variants in rs2516838, rs3737787 and rs2516839 have significant association with PTC risk. The rs2516838 polymorphisms dominant model (CG+GG vs CC: OR = 0.71; 95% CI: 0.52-0.97; P = 0.033) and allelic model (C vs G: OR = 0.031; 95% CI: 0.56-0.97; P = 0.031) indicated it may act as a protective factor against PTC. On the contrary, the results of rs3737787 polymorphisms: dominant model (CT+TT vs CC: OR = 1.55; 95%CI: 1.09-2.02; P = 0.001) and allelic model (C vs T: OR = 1.35; 95%CI: 1.10-1.64; P = 0.003), as well as the results of rs2516839 polymorphisms: dominant model (GA+AA vs GG: OR = 1.77; 95%CI: 1.31-2.38; P < 0.001) and allelic model (G vs A: OR = 1.36; 95%CI: 1.13-1.63; P = 0.014), revealed that they may act as risk factors for PTC. CONCLUSION: In this study, we found the SNPs of rs2516838 (mutant G alleles vs wild C alleles), rs3737787 (mutant T alleles vs wild C alleles) and rs2516839 (mutant A alleles vs wild G alleles) were significantly associated with PTC risk. Further large-scale studies with different ethnicities are still needed to validate our findings and explore the underlying mechanism of USF1 in PTC development.
PubMed-ID: 26052935
http://dx.doi.org/10.1111/cen.12832

Comparison of differentiated thyroid cancer in children and adolescents (</=20 years) with young adults.
Clin Endocrinol (Oxf), 84(4):571-7.
A. S. Alzahrani, D. Alkhafaji, M. Tuli, H. Al-Hindi and B. B. Sadiq. 2016.
CONTEXT: Age is a major prognostic factor in differentiated thyroid cancer (DTC). It is not clear if paediatric DTC has a different histopathological profile and outcome than DTC in adult patients <45 years of age. OBJECTIVE: To assess whether DTC in children and adolescents differs from young age group by comparing paediatric DTC (age </= 20) with DTC in patients >20 to <45 years of age. PATIENTS AND METHODS: We studied all cases of paediatric DTC seen during the period 1998-2011. We compared this group with a large sample of 213 consecutive adult patients in the age group >20 to <45 years seen during the period 1998-1999 in terms of their pathological features, extent of the disease and long-term outcome. Both groups were managed by the same team at a single institution. RESULTS: A total of 310 DTC were studied including 97 paediatric patients [median age 17 years (range, 8-20)] and 213 young adult patients [median age 33 years (range, 20.5-44.9)]. There was no difference in gender distribution, tumour subtypes, size and tumour multifocality, but there was a significantly higher rate of extrathyroidal extension [40/75 (53.3%) vs 81/213 (38.0%), P = 0.03], lymph node [57/73 (78%) vs 102/183 (55.7%), P < 0.0001] and distant metastases [16/97 (16.5%) vs 8/213 (3.8%), P <

0.0001] in the paediatric than the adult groups. Kaplan-Meier analysis showed a higher risk of persistent/recurrent disease in the paediatric group than adults (log-rank test 0.03). However, there was no mortality secondary to DTC in both groups. CONCLUSION: Paediatric DTC is distinct from DTC in the young adults (age >20 to <45 years). It is characterized by a higher rate of extrathyroidal extension, lymph node and distant metastases and a higher risk of persistent/recurrent DTC.
PubMed-ID: 26118454
http://dx.doi.org/10.1111/cen.12845

Low iodine diet in differentiated thyroid cancer: a review.
Clin Endocrinol (Oxf), 84(1):3-12.
J. H. Li, Z. H. He, V. Bansal and J. V. Hennessey. 2016.
Radioactive iodine (RAI) ablation is a beneficial, adjuvant therapy for the management of differentiated thyroid cancer (DTC) after thyroidectomy. The goal of RAI is to destroy remnant thyroid and microscopic cancerous tissue. Radioactive iodine uptake is enhanced by elevating TSH levels and initiating a low iodine diet (LID) prior to ablation. An ideal LID should preferably not exceed 50 mcg/day of dietary iodine for 1-2 weeks, although the duration may be shortened to a week with a structured patient education programme. A pre-ablation spot urinary iodine concentration (UIC) of <100 mcg/l and/or a urinary iodine to creatinine ratio (UICR) of <100 mcg/gCr would support an adequate LID preparation. Hyponatraemia, most likely due to iatrogenic hypothyroidism, is a potential side effect associated with LID and occurs during and a few days after the LID. Although the overall incidence of hyponatraemia is low, patients at high risk (older age, female sex, use of thiazide diuretics) may benefit from serum sodium monitoring. The existing evidence on the impact of LID on RAI ablation has been largely inconsistent due to retrospective study designs and the lack of an objective measurement of urinary iodine levels. Future large prospective randomized control trials are needed to elucidate and confirm the crucial role of LID in achieving successful RAI ablation and greater disease-free survival in DTC.
PubMed-ID: 26118628
http://dx.doi.org/10.1111/cen.12846

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

Postoperative biochemical remission of serum calcitonin is the best predictive factor for recurrence-free survival of medullary thyroid cancer: a large-scale retrospective analysis over 30 years.
Clin Endocrinol (Oxf), 84(4):587-97.
K. Y. Jung, S. M. Kim, W. S. Yoo, B. W. Kim, Y. S. Lee, K. W. Kim, K. E. Lee, J. J. Jeong, K. H. Nam, S. H. Lee, J. H. Hah, W. Y. Chung, K. H. Yi, J. Park do, Y. K. Youn, M. W. Sung, B. Y. Cho, C. S. Park, Y. J. Park and H. S. Chang. 2016.
CONTEXT: The increase in thyroid screening in the general population may lead to earlier detection of medullary thyroid carcinoma (MTC). OBJECTIVE: We aimed to evaluate secular trends in clinicopathological

characteristics and long-term prognosis of MTC and its prognostic factors. DESIGN: This was a retrospective analysis from 1982 to 2012. PATIENTS: Three hundred and thirty-one patients with MTC were included and grouped based on the year of diagnosis (1982-2000, 2001-2005, 2006-2010 and 2011-2012). MEASUREMENTS: These included recurrence and mortality as well as biochemical remission (BCR) of serum calcitonin. RESULTS: Mean tumour size (from 2.5 cm to 1.7 cm, P < 0.001) and percentage of extrathyroidal extension (from 52.0% to 26.0%, P = 0.026) decreased. The percentage of patients achieving BCR within six postoperative months (po-BCR) increased with time (from 39.6% to 76.1%, P < 0.001). The 5-year overall recurrence rate significantly decreased in 2006-2012 compared to 1982-2005 (10% vs 18%, respectively, P = 0.031), although the 5-year survival rate did not improve (92% vs 92%, P = 0.929). Failure to achieve po-BCR was the strongest predictive factor associated with recurrence (hazard ratio [HR] = 58.04, 95% CI 7.14-472.11; P < 0.001). Male gender (HR = 3.18, 95% CI 1.18-8.56; P = 0.022), tumour size >2 cm (HR = 18.33, 95% CI 2.35-143.06; P = 0.006) and distant metastasis (HR = 4.00, 95% CI 1.31-12.21; P = 0.015) were significant prognostic factors for mortality. CONCLUSIONS: Clinicopathological characteristics and recurrence of MTC improved with time. Po-BCR was the best predictive factor for recurrence-free survival.
PubMed-ID: 26175307
http://dx.doi.org/10.1111/cen.12852

Thyroid Hurthle cell tumors: research of potential markers of malignancy.
J Endocrinol Invest, 39(2):153-8.
G. Donatini, A. Beaulieu, M. Castagnet, J. L. Kraimps, P. Levillain and G. Fromont. 2016.
INTRODUCTION: Hurthle cell tumors (HCTs) are rare thyroid neoplasia. To date, capsular and/or vascular invasion are the only findings predicting malignancy. Recently, mutation of 19p13, encoding two proteins involved in cell proliferation and apoptosis (GRIM-19 and p19), has been described. The aim of our study is to evaluate the cellular proliferation index (Ki67), GRIM-19 and p19 expression as diagnostic markers of malignancy in HCT. MATERIALS AND METHODS: Eighty patients with HCT (32 carcinomas, 48 adenomas) whom underwent surgery in our center were included. Samples of both neoplastic lesions and adjacent normal thyroid tissue were analyzed by means of tissue micro-arrays. Correlations between expressions of Ki67, GRIM-19 and p19 and final histology were analyzed. RESULTS: Mean size of the lesion was higher in carcinomas than in adenomas (p = 0.01). GRIM-19 and p19 were significantly underexpressed in Hurthle cells tumors compared to normal tissue (p = 0.0004 and p = 0.0001, respectively). Ki67 and GRIM-19 were, respectively, higher and down-expressed in carcinomas compared to adenomas (p = 0.0004 and p = 0.005, respectively). On multivariate analysis, size correlates with carcinoma diagnosis. Neither GRIM-19 nor Ki67 index was related to size. The expression of p19 was reduced in both adenoma and carcinoma but differences were not statistically significant (p = 0.13). CONCLUSIONS: Our study suggest that Ki67 and GRIM-19 correlate with malignancy in HCT. The expression of p19 is down-regulated in HCT, but it is not diagnostic of carcinoma. Ki67 and GRIM-19 may potentially help as cytological markers of malignancy in HCT.
PubMed-ID: 26188382
http://dx.doi.org/10.1007/s40618-015-0356-x

BRAF (V600E) mutation in isthmic malignant thyroid nodules.
Clin Endocrinol (Oxf), 84(1):152-3.
A. Campenni, L. Giovanella, A. Alibrandi, M. Siracusa, R. M. Ruggeri and S. Baldari. 2016.
PubMed-ID: 26190162
http://dx.doi.org/10.1111/cen.12858

Clinicopathological features and prognosis of familial papillary thyroid carcinoma - a large-scale, matched, case-control study.
Clin Endocrinol (Oxf), 84(4):598-606.
J. Cao, C. Chen, C. Chen, Q. L. Wang and M. H. Ge. 2016.
OBJECTIVE: It remains controversial whether or not the aggressiveness of familial nonmedullary thyroid cancer (FNMTC) differs from sporadic carcinoma. The aim of this study was to determine the clinicopathological features and prognosis of FNMTC. DESIGN: A matched-case comparative study. METHODS: Three hundred and seventy-two patients with familial papillary thyroid carcinoma (FPTC) were enrolled as the study group, and another 372 patients with sporadic PTC were enrolled as controls and matched for gender, age, tumour/node/metastasis (TNM) staging and approximate duration of follow-up. We compared the differences in the clinicopathological features and prognosis between the subgroups. RESULTS: Compared with sporadic PTC, patients with FPTC were more likely to present tumour multicentricity, bilateral growth and a concomitant nodular goitre (P < 0.05). In papillary thyroid microcarcinoma (PTMC), a higher recurrence rate was noted in patients with a family history of PTC, and this remained independently predictive on multivariate analysis. The

patients with FPTC in the second generation showed an earlier age of onset, more frequent Hashimoto's thyroiditis and a higher recurrence rate than the first generation, while the first-generation offspring of patients had a higher incidence of nodular goitre than the second generation. CONCLUSIONS: The presence of familial history in PTC indicates an increase in biological aggressiveness, and patients in the second generation may exhibit the 'genetic anticipation' phenomenon. At present, the available data are not sufficient to support a more aggressive approach for FPTC. However, a family history of PTC is an independent risk factor for recurrence in patients with PTMC.
PubMed-ID: 26191611
http://dx.doi.org/10.1111/cen.12859

A prospective 1-year comparative study of transaxillary total thyroidectomy regarding functional outcomes: Is it really promising?
Surg Endosc, 30(4):1599-606.
D. Y. Lee, S. Lim, S. H. Kang, K. H. Oh, J. G. Cho, S. K. Baek, J. S. Woo, S. Y. Kwon and K. Y. Jung. 2016.
BACKGROUND: The purpose of this study was to evaluate postoperative voice outcomes and functional parameters in total thyroidectomy via a transaxillary (TA) approach. METHODS: Seventy-six patients who underwent total thyroidectomy via a TA approach (TA group) were included. A total of 204 patients who underwent conventional open total thyroidectomy (conventional group) in the same time period were analyzed as a control group. All patients underwent prospective functional evaluations before surgery and at 1 week and 1, 3, 6, and 12 months postoperatively using a comprehensive battery of functional assessments. RESULTS: There was no conversion to conventional open thyroidectomy in the TA group. Operation time and the amount of drainage were significantly higher in the TA group than in the conventional group ($p < 0.001$ and $p = 0.033$, respectively), while vocal cord paralysis, hypoparathyroidism, and hematoma were not different among two groups ($p = 0.215$, 0.290, and 0.385, respectively). Regarding GRBAS, the TA group showed a more aggravated tendency postoperatively, although statistical significance was attained only at postoperative 6 months ($p = 0.043$). The voice handicap index abruptly increased postoperatively in the TA group, showing significant differences with the conventional group at postoperative 1 week and 1 month ($p < 0.001$ and $p = 0.001$, respectively). Fundamental frequency and maximal vocal pitch did not significantly change postoperatively in either group. The conventional group showed a more rapid decline in pain than the TA group, and paresthesias on the neck and chest were more aggravated in the TA group during the early postoperative period. The dysphagia handicap index was higher in the TA group, while cosmesis was better in the TA group at all postoperative periods. CONCLUSIONS: Although cosmetic outcome was better with the TA approach, the longer operation time, aggravated subjective voice outcomes, paresthesia, and swallowing function need to be considered in selecting the operative approach.
PubMed-ID: 26194250
http://dx.doi.org/10.1007/s00464-015-4386-4

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

4-IPP, a selective MIF inhibitor, causes mitotic catastrophe in thyroid carcinomas.
Endocr Relat Cancer, 22(5):759-75.
L. Varinelli, D. Caccia, C. C. Volpi, C. Caccia, M. De Bortoli, E. Taverna, A. V. Gualeni, V. Leoni, A. Gloghini, G. Manenti and I. Bongarzone. 2015.
Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that is over-expressed in several human neoplastic cells. When MIF binds its receptor (CD74) and co-receptor (CD44), it initiates signaling cascades that orchestrate cell proliferation and survival, and it can directly modulate the activity of AMPK. These activities indicate that MIF potentially regulates cell survival and metabolism. We found that MIF was primarily co-expressed with CD74 in 16 out of 23 papillary thyroid carcinoma (PTC) and in all the 27 available anaplastic thyroid carcinoma (ATC) biopsy samples. MIF and CD74 were co-expressed in TPC-1 and HTC-C3 cell lines. The selective MIF inhibitor, 4-iodo-6-phenylpyrimidine (4-IPP), blocked MIF/CD74 internalization, activated JNK, and dose-dependently inhibited proliferation inducing apoptosis and mitotic cell death. In two CD74-negative cell lines, NIM-1 and K1, 4-IPP treatment partially reduced proliferation. Coordinated MIF and CD74 expression appeared to confer in tumor cells the plasticity necessary to escape cell cycle regulation, metabolic changes, and stress conditions. MIF/CD74 signaling removal made cells susceptible to apoptosis and mitotic cell death. This finding suggests a possible avenue for targeting DNA endoreduplication, thus preventing the proliferation of therapy-resistant cell subpopulations. This study highlights MIF/CD74 axis as an important player in the biology of aggressive thyroid neoplasms.
PubMed-ID: 26206776
http://dx.doi.org/10.1530/ERC-15-0299

Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer.
Ann Surg Oncol, 23(2):410-5.
I. J. Nixon, D. Kuk, V. Wreesmann, L. Morris, F. L. Palmer, I. Ganly, S. G. Patel, B. Singh, R. M. Tuttle, A. R. Shaha, M. Gonen and J. P. Shah. 2016.
BACKGROUND: Age 45 years is used as a cutoff in the staging of well-differentiated thyroid cancer (WDTC) as it represents the median age of most datasets. The aim of this study was to determine a statistically optimized age threshold using a large dataset of patients treated at a comprehensive cancer center. METHODS: Overall, 1807 patients with a median follow-up of 109 months were included in the study. Recursive partitioning was used to determine which American Joint Committee on Cancer (AJCC) variables were most predictive of disease-specific death, and whether a different cutoff for age would be found. From the resulting tree, a new age cutoff was picked and patients were restaged using this new cutoff. RESULTS: The 10-year disease-specific survival (DSS) by Union for International Cancer Control (AJCC/UICC) stage was 99.6, 100, 96, and 81 % for stages I-IV, respectively. Using recursive partitioning, the presence of distant metastasis was the most powerful predictor of DSS. For M0 patients, age was the next most powerful predictor, with a cutoff of 56 years. For M1 patients, a cutoff at 54 years was most predictive. Having reviewed the analysis, age 55 years was selected as a more robust age cutoff than 45 years. The 10-year DSS by new stage (using age 55 years as the cutoff) was 99.2, 98, 100, and 74 % for stages I-IV, respectively. CONCLUSION: A change in age cutoff in the AJCC/UICC staging for WDTC to 55 years would improve the accuracy of the system and appropriately prevent low-risk patients being overstaged and overtreated.
PubMed-ID: 26215199
http://dx.doi.org/10.1245/s10434-015-4762-2

The impact of CLAUDIN-1 on follicular thyroid carcinoma aggressiveness.
Endocr Relat Cancer, 22(5):819-30.
D. Zwanziger, J. Badziong, S. Ting, L. C. Moeller, K. W. Schmid, U. Siebolts, C. Wickenhauser, H. Dralle and D. Fuehrer. 2015.
CLAUDIN-1 belongs to the family of transmembrane tight junction proteins tightening the paracellular cleft of epithelial cells. In human malignancies, CLAUDIN-1 is often dysregulated and located in subcellular compartments, particularly in the nucleus where it may influence cellular behaviour. Here, we studied CLAUDIN-1 in relation to the biological characteristics of follicular thyroid carcinoma (FTC). CLAUDIN-1 immuno-staining showed loss of membrane expression and increased nuclear CLAUDIN-1 localization in FTC metastases. CLAUDIN-1 function was further investigated in two different follicular thyroid carcinoma cell lines: FTC-133 isolated from a regional lymph node metastasis and FTC-238 derived from a lung metastasis. In both cell lines CLAUDIN-1 expression was demonstrated in the cell nuclei with a significantly higher protein expression in FTC-238 compared to FTC-133 cells. Interestingly, in vitro scratch assay revealed enriched nuclear CLAUDIN-1 expression near the scratch. Furthermore, the increase of the pathogenic character of FTC-133 cells by RASV12 transfection was associated with elevated CLAUDIN-1 expression and enhanced cell migration, invasion and proliferation. Likewise over-expression of nuclear CLAUDIN-1 in FTC-133 cells resulted in increased cell

migration and invasion. Conversely, CLAUDIN-1 downregulation in FTC-238 cells by siRNA resulted in decreased cell migration and invasion and was accompanied by reduced phosphoPKC expression. Moreover, activation and inhibition of PKC resulted in CLAUDIN-1 up- and downregulation in FTC cells respectively. These data suggest an impact of CLAUDIN-1 on follicular thyroid carcinoma aggressiveness, which could potentially be influenced by PKC activity.
PubMed-ID: 26219679
http://dx.doi.org/10.1530/ERC-14-0502

The Significance of BRAF V600e Mutation and Preoperative Ultrasound for Central Compartment Lymph Node Metastasis in Papillary Thyroid Microcarcinoma.
World J Surg, 40(3):759-60.
A. K. Coskun. 2016.
PubMed-ID: 26243562
http://dx.doi.org/10.1007/s00268-015-3178-2

Revisiting Low-Risk Thyroid Papillary Microcarcinomas Resected Without Observation: Was Immediate Surgery Necessary?
World J Surg, 40(3):523-8.
Y. Ito, A. Miyauchi, H. Oda, K. Kobayashi, M. Kihara and A. Miya. 2016.
INTRODUCTION: Low-risk thyroid papillary microcarcinomas (PMCs) without evidence of metastasis grow slowly if at all. However, we recommended surgery for tumors touching the trachea (TR) or located in the course of the recurrent laryngeal nerve (RN). Here we compared the cases of low-risk PMC patients who underwent immediate surgery to cases of TR- and RN-involved PMCs. MATERIALS AND METHODS: We enrolled 1143 low-risk PMC patients who underwent immediate surgery in the years 2006-2014. The PMCs of 437 patients touched the TR on imaging studies: 270, 104, and 63 were graded as low, intermediate, and high risk, respectively, for TR invasion based on the angles between the tumor and the TR surface. The tumor was in the course of the RN in 144 patients, with 35 graded low risk and 109 high risk for RN invasion based on the normal rim of the thyroid in the direction of the RN. RESULTS: Invasion of the TR cartilage was observed only in high-risk patients. Peritracheal connective tissue was resected in 21, 15, and 6 of the high-, intermediate- and low-risk patients, respectively. Significant invasion of the RN requiring complete resection was observed in only nine patients at high risk for RN invasion. The incidence of TR invasion in high- and intermediate patients and the incidence of RN invasion in the high-risk patients were significantly higher than those of the low-risk patients. Tumors <7 mm did not show TR or RN invasion. CONCLUSION: Among PMCs that touched the TR or were located in the course of the RN, observation could be the first choice for tumors < 7 mm and those >/= 7 mm judged as low risk for TR or RN invasion. However, for PMCs with high-risk features, immediate surgery after cytological diagnosis by a needle aspiration biopsy is recommended.
PubMed-ID: 26243564
http://dx.doi.org/10.1007/s00268-015-3184-4

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

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

RAS proto-oncogene in medullary thyroid carcinoma.
Endocr Relat Cancer, 22(5):R235-52.
M. M. Moura, B. M. Cavaco and V. Leite. 2015.
Medullary thyroid carcinoma (MTC) is a rare malignancy originating from the calcitonin-secreting parafollicular thyroid C cells. Approximately 75% of cases are sporadic. Rearranged during transfection (RET) proto-oncogene plays a crucial role in MTC development. Besides RET, other oncogenes commonly involved in the pathogenesis of human cancers have also been investigated in MTC. The family of human RAS genes includes the highly homologous HRAS, KRAS, and NRAS genes that encode three distinct proteins. Activating mutations in specific hotspots of the RAS genes are found in about 30% of all human cancers. In thyroid neoplasias, RAS gene point mutations, mainly in NRAS, are detected in benign and malignant tumors arising from the follicular epithelium. However, recent reports have also described RAS mutations in MTC, namely in HRAS and KRAS. Overall, the prevalence of RAS mutations in sporadic MTC varies between 0-43.3%, occurring usually in tumors with WT RET and rarely in those harboring a RET mutation, suggesting that activation of these proto-oncogenes represents alternative genetic events in sporadic MTC tumorigenesis. Thus, the assessment of RAS mutation status can be useful to define therapeutic strategies in RET WT MTC. MTC patients with RAS mutations have an intermediate risk for aggressive cancer, between those with RET mutations in exons 15 and 16, which are associated with the worst prognosis, and cases with other RET mutations, which have the most indolent course of the disease. Recent results from exome sequencing indicate that, besides mutations in RET, HRAS, and KRAS, no other recurrent driver mutations are present in MTC.
PubMed-ID: 26285815
http://dx.doi.org/10.1530/ERC-15-0070

The 8q24 rs6983267G variant is associated with increased thyroid cancer risk.
Endocr Relat Cancer, 22(5):841-9.
R. Sahasrabudhe, A. Estrada, P. Lott, L. Martin, G. Polanco Echeverry, A. Velez, G. Neta, M. Takahasi, V. Saenko, N. Mitsutake, E. Jaeguer, C. S. Duque, A. Rios, M. Bohorquez, R. Prieto, A. Criollo, M. Echeverry, I. Tomlinson and L. G. Carmona. 2015.
The G allele of the rs6983267 single-nucleotide polymorphism, located on chromosome 8q24, has been associated with increased risk of several cancer types. The association between rs6983267G and thyroid cancer (TC) has been tested in different populations, mostly of European ancestry, and has led to inconclusive results. While significant associations have been reported in the British and Polish populations, no association has been detected in populations from Spain, Italy and the USA. To further investigate the role of rs6983267G in TC susceptibility, we evaluated rs6983267 genotypes in three populations of different continental ancestry (British Isles, Colombia and Japan), providing a total of 3067 cases and 8575 controls. We detected significant associations between rs6983267G and TC in the British Isles (odds ratio (OR)=1.19, 95% CI: 1.11-1.27, P=4.03x10(-7)), Japan (OR=1.20, 95% CI: 1.03-1.41, P=0.022) and a borderline significant association of similar

effect direction and size in Colombia (OR=1.19, 95% CI: 0.99-1.44, P=0.069). A meta-analysis of our multi-ethnic study and previously published non-overlapping datasets, which included a total of 5484 cases and 12 594 controls, confirmed the association between rs6983267G and TC (P=1.23x10(-7), OR=1.13, 95% CI: 1.08-1.18). Our results therefore support the notion that rs6983267G is a bona fide TC risk variant that increases the risk of disease by approximately 13%.
PubMed-ID: 26290501
http://dx.doi.org/10.1530/ERC-15-0081

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

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

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

prerequisite for the utilisation of MSCs as gene delivery vehicles.
PubMed-ID: 26307023
http://dx.doi.org/10.1530/ERC-15-0245

Papillary Thyroid Microcarcinoma: An Over-Treated Malignancy?
World J Surg, 40(3):764-5.
Z. Liu and T. Huang. 2016.
PubMed-ID: 26316118
http://dx.doi.org/10.1007/s00268-015-3244-9

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

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

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

disease at 6-12 months after initial treatment and at the last follow up. These associations were stronger in non-CPTC. Thus, this study on a large cohort of TC patients from Middle East demonstrates that TERT promoter mutations are relatively common, especially in the non-CPTC, and are associated with more aggressive histopathological features, BRAF(V600E) mutation, and disease persistence/recurrence than the WT TERT.
PubMed-ID: 26354077
http://dx.doi.org/10.1530/ERC-15-0396

Glucose-deprivation increases thyroid cancer cells sensitivity to metformin.
Endocr Relat Cancer, 22(6):919-32.
A. Bikas, K. Jensen, A. Patel, J. Costello, Jr., D. McDaniel, J. Klubo-Gwiezdzinska, O. Larin, V. Hoperia, K. D. Burman, L. Boyle, L. Wartofsky and V. Vasko. 2015.
Metformin inhibits thyroid cancer cell growth. We sought to determine if variable glucose concentrations in medium alter the anti-cancer efficacy of metformin. Thyroid cancer cells (FTC133 and BCPAP) were cultured in high-glucose (20 mM) and low-glucose (5 mM) medium before treatment with metformin. Cell viability and apoptosis assays were performed. Expression of glycolytic genes was examined by real-time PCR, western blot, and immunostaining. Metformin inhibited cellular proliferation in high-glucose medium and induced cell death in low-glucose medium. In low-, but not in high-glucose medium, metformin induced endoplasmic reticulum stress, autophagy, and oncosis. At micromolar concentrations, metformin induced phosphorylation of AMP-activated protein kinase and blocked p-pS6 in low-glucose medium. Metformin increased the rate of glucose consumption from the medium and prompted medium acidification. Medium supplementation with glucose reversed metformin-inducible morphological changes. Treatment with an inhibitor of glycolysis (2-deoxy-d-glucose (2-DG)) increased thyroid cancer cell sensitivity to metformin. The combination of 2-DG with metformin led to cell death. Thyroid cancer cell lines were characterized by over-expression of glycolytic genes, and metformin decreased the protein level of pyruvate kinase muscle 2 (PKM2). PKM2 expression was detected in recurrent thyroid cancer tissue samples. In conclusion, we have demonstrated that the glucose concentration in the cellular milieu is a factor modulating metformin's anti-cancer activity. These data suggest that the combination of metformin with inhibitors of glycolysis could represent a new strategy for the treatment of thyroid cancer.
PubMed-ID: 26362676
http://dx.doi.org/10.1530/ERC-15-0402

Impact of Microcalcifications on Risk of Malignancy in Thyroid Nodules with Indeterminate or Benign Cytology.
Otolaryngol Head Neck Surg, 154(1):46-51.
C. Brophy, J. Stewart, N. O'Donovan, J. McCarthy, M. Murphy and P. Sheahan. 2016.
OBJECTIVE: Adverse sonographic features such as microcalcification may predict increased likelihood of malignant cytology by fine-needle aspiration and, accordingly, increased risk of malignant histology. Our objective was to study the predictive value of microcalcifications and other sonographic features for malignancy among thyroid nodules with benign or indeterminate cytology. STUDY DESIGN: Case series with chart review. SETTING: Academic teaching hospital. SUBJECTS: Patients (N = 769) with 858 thyroid nodules undergoing 1142 ultrasound fine-needle aspirations; 411 cases had surgical correlation. METHODS: Sonographic features predictive of malignancy were correlated with malignancy as determined by histology. Incidental malignancies occurring outside the index nodule were discounted. RESULTS: Cytology was inadequate (87 cases), benign (518), indeterminate (210), and malignant (44). In 32 cases, initial benign cytology was upgraded to a higher-risk category after repeat ultrasound fine-needle aspiration. Microcalcification (P = .001) and irregular margins (P = .04) were significantly predictive of malignant cytology. Among surgical cases, microcalcification (P < .001) and irregular margins (P = .04) were significantly predictive of malignant histology; 170 patients with initial benign cytology and 161 with indeterminate cytology underwent surgery. Microcalcification was significantly associated with malignancy among cases with indeterminate cytology (P = .04) but not among cases with benign cytology (P = .23); however, only 13 of 33 cases with benign cytology and microcalcifications underwent surgery. CONCLUSION: Presence of microcalcification increases the risk of malignancy in thyroid nodules with indeterminate cytology and may thus aid in selection of cases for surgery.
PubMed-ID: 26392026
http://dx.doi.org/10.1177/0194599815605326

Postoperative Pain After Robotic Thyroidectomy by a Gasless Unilateral Axillo-Breast or Axillary Approach.
Surg Laparosc Endosc Percutan Tech, 25(6):478-82.
C. M. Song, Y. B. Ji, H. S. Bang, K. R. Kim, H. Kim and K. Tae. 2015.
The aim of this study was to compare postoperative pain after robotic thyroidectomy with that after conventional

open thyroidectomy. We analyzed 123 patients who underwent robotic thyroidectomy and 170 patients who underwent conventional open thyroidectomy. Postoperative pain was evaluated on a visual analogue scale rating of 0 to 10, 1 day to 1 month after surgery. Mean pain visual analogue scale scores for the robotic and open groups were 3.33 and 3.57 (P=0.476) on day 1, 2.29 and 2.58 (P=0.285) on day 3, 2.19 and 1.74 (P=0.057) after 1 week, and 0.98 and 1.01 (P=0.843) after 1 month, respectively. There was no difference between the 2 groups in the doses of parenteral analgesic medication administered (robotic vs. open, mean 174 vs. 194 mg, P=0.189). In conclusion, postoperative pain and the dose of analgesic medication in both groups are similar.
PubMed-ID: 26422088
http://dx.doi.org/10.1097/SLE.0000000000000204

A novel lateral-approach laryngeal ultrasonography for vocal cord evaluation.
Surgery, 159(1):52-6.
J. W. Woo, H. Suh, R. Y. Song, J. H. Lee, H. W. Yu, S. J. Kim, Y. J. Chai, J. Y. Choi and K. E. Lee. 2016.
BACKGROUND: Laryngeal ultrasonography (LUS) is a new method of vocal cord (VC) evaluation in patients with risk of vocal cord palsy (VCP). The previously described anterior-approach LUS reportedly, however, has high failure rate of VC visualization in male patients. We devised a novel lateral-approach LUS to overcome this limitation. METHODS: A total of 382 (82 male, 300 female) consecutive LUS and direct laryngoscopy (DL) examinations were performed on perioperative thyroidectomy and parathyroidectomy patients. The anterior-approach LUS was used for female patients whereas the lateral-approach LUS was used for male patients. Findings were cross-validated independently with DL examinations. RESULTS: Both anterior and lateral LUS methods had 100% visualization rate (no failed visualization) with an overall sensitivity of 100% (23/23) and specificity of 99.2% (356/359) for VCP. Among the 300 female patients, 18 patients had VCP. Sensitivity and specificity of anterior-approach LUS were 100% (18/18) and 99.3% (280/282), respectively. Among the 80 male patients, 5 patients had VCP. Sensitivity and specificity of lateral-approach LU were 100% (5/5) and 98.7% (76/77), respectively. CONCLUSION: The new LUS approach significantly enhances the visualization of vocal cords and, therefore, overall diagnostic efficacy of LUS in male patients.
PubMed-ID: 26422765
http://dx.doi.org/10.1016/j.surg.2015.07.043

Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery.
Thyroid, 26(1):150-5.
H. Oda, A. Miyauchi, Y. Ito, K. Yoshioka, A. Nakayama, H. Sasai, H. Masuoka, T. Yabuta, M. Fukushima, T. Higashiyama, M. Kihara, K. Kobayashi and A. Miya. 2016.
BACKGROUND: The incidence of papillary microcarcinoma (PMC) of the thyroid is rapidly increasing globally, making the management of PMC an important clinical issue. Excellent oncological outcomes of active surveillance for low-risk PMC have been reported previously. Here, unfavorable events following active surveillance and surgical treatment for PMC were studied. METHODS: From February 2005 to August 2013, 2153 patients were diagnosed with low-risk PMC. Of these, 1179 patients chose active surveillance and 974 patients chose immediate surgery. The oncological outcomes and the incidences of unfavorable events of these groups were analyzed. RESULTS: In the active surveillance group, 94 patients underwent surgery for various reasons; tumor enlargement and the appearance of novel lymph node metastases were the reasons in 27 (2.3%) and six patients (0.5%), respectively. One of the patients with conversion to surgery had nodal recurrence, and five patients in the immediate surgery group had a recurrence in a cervical node or unresected thyroid lobe. All of these recurrences were successfully treated. None of the patients had distant metastases, and none died of the disease. The immediate surgery group had significantly higher incidences of transient vocal cord paralysis (VCP), transient hypoparathyroidism, and permanent hypoparathyroidism than the active-surveillance group did (4.1% vs. 0.6%, $p < 0.0001$; 16.7% vs. 2.8%, $p < 0.0001$; and 1.6% vs. 0.08%, $p < 0.0001$, respectively). Permanent VCP occurred only in two patients (0.2%) in the immediate surgery group. The proportion of patients on L-thyroxine for supplemental or thyrotropin (TSH)-suppressive purposes was significantly larger in the immediate surgery group than in the active surveillance group (66.1% vs. 20.7%, $p < 0.0001$). The immediate surgery group had significantly higher incidences of postsurgical hematoma and surgical scar in the neck compared with the active surveillance group (0.5% vs. 0%, $p < 0.05$; and 8.0% vs. 100%, $p < 0.0001$, respectively). CONCLUSIONS: The oncological outcomes of the immediate surgery and active surveillance groups were similarly excellent, but the incidences of unfavorable events were definitely higher in the immediate surgery group. Thus, active surveillance is now recommended as the best choice for patients with low-risk PMC.

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http://dx.doi.org/10.1089/thy.2015.0313

Recurrence of papillary thyroid carcinoma with lateral cervical node metastases: Predictive factors and operative management.
Surgery, 159(3):755-62.
N. Chereau, C. Buffet, C. Tresallet, F. Tissier, L. Leenhardt and F. Menegaux. 2016.
BACKGROUND: Lateral neck lymph node (LN) metastases (N1b) have been identified as independent risk factors of recurrence in patients with papillary thyroid carcinoma (PTC). OBJECTIVE: This study aimed to determine the predictive factors of recurrence in N1b PTC patients and to clarify the postoperative event patterns. METHODS: All patients who underwent operation for N1b PTC between 1978 and 2012 were reviewed. The median follow-up period was 6.5 years. RESULTS: In total, 344 N1b patients were included. Twenty-four patients (7%) were lost to long-term follow-up. Among the remaining 320 patients, the mean (+/- SD) follow-up time was 8.9 +/- 8.8 years (median, 6.5; range, 2-36.4). Eighty-two patients (26%) presented with lymph node recurrence (LR). Multivariate analyses showed that LN metastases with extracapsular extension and the LN ratio (ratio between the number of N1 and number of resected LN) in the lateral compartment were independent predictors of recurrent disease. The median time to reoperation was 19 months (range, 3-173), with 79% of reoperations occurring within 2 years after the initial thyroidectomy. Reoperations for LR (75 patients) were performed in 76% of the patients with a focused minimal access approach or selective LN dissection. After curative reoperative surgery for recurrence, complications occurred in 6 patients (8%), including a 1% permanent complication rate. CONCLUSION: Extranodal extension of LN metastases and the LN ratio in the lateral compartment are prognostic factors for recurrence. In most cases, reoperation for LR can be performed with a focused minimal access approach, with a low morbidity rate.
PubMed-ID: 26435440
http://dx.doi.org/10.1016/j.surg.2015.08.033

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

The Overwhelming Majority but not All Motor Fibers of the Bifid Recurrent Laryngeal Nerve are Located in the Anterior Extralaryngeal Branch.
World J Surg, 40(3):629-35.
M. Barczynski, M. Stopa, A. Konturek and W. Nowak. 2016.
BACKGROUND: Few small studies reported that motor fibers are located exclusively in the anterior branch of the bifid recurrent laryngeal nerve (RLN). The aim of this study was to investigate the location of the motor fibers to the intrinsic muscles of the larynx among the bifid RLNs, and assess the prevalence of RLN injury with respect to nerve branching in a pragmatic trial. METHODS: This was a prospective cohort study of 1250 patients who underwent total thyroidectomy with intraoperative neural monitoring. The primary outcome was the position of the motor fibers in the bifid nerves. Adduction of the vocal folds was detected by the endotracheal tube electromyography and abduction by finger palpation of muscle contraction in the posterior cricoarytenoid. The secondary outcomes were the prevalence of the RLN branching and the prevalence of RLN injury in bifid versus non-bifid nerves. RESULTS: The bifid RLNs were identified in 613/2500 (24.5%) nerves at risk, including 92 (7.4%) patients with bilateral bifurcations. The motor fibers were present exclusively in the anterior branch in 605/613 (98.7%) bifid nerves, and in both the RLN branches in 8/613 (1.3%) bifid nerves. Prevalence of RLN injury was 5.2 versus 1.6% for the bifid versus non-bifid nerves ($p < 0.001$), odds ratio 2.98 (95% confidence interval 1.79-4.95; $p < 0.001$). CONCLUSIONS: The motor fibers of the RLN are located in the anterior extralaryngeal branch in the vast majority of but not in all patients. In rare cases, the motor fibers for adduction or abduction are located in the posterior branch of the RLN. As the bifid nerves are more prone to injury than non-branched nerves, meticulous dissection is recommended to assure preservation of all the branches of the RLN during thyroidectomy.
PubMed-ID: 26438241
http://dx.doi.org/10.1007/s00268-015-3257-4

Increased Expression of FGF19 Contributes to Tumor Progression and Cell Motility of Human Thyroid Cancer.
Otolaryngol Head Neck Surg, 154(1):52-8.
X. Zhang, Z. Wang, L. Tian, J. Xie, G. Zou and F. Jiang. 2016.
OBJECTIVE: Numerous reports indicate a role for aberrant expression of fibroblast growth factor 19 (FGF19) in tumor development and progression, and several drugs have been developed to target it. The aim of this study was to investigate the clinical significance of FGF19 and examine whether it plays any roles in progression of thyroid cancer. STUDY DESIGN: Translation research. SETTING: Navy General Hospital of Chinese PLA, China. SUBJECTS AND METHODS: Expression patterns of FGF19 protein in 100 paired formalin-fixed and paraffin-embedded cancerous and adjacent noncancerous tissues from patients with thyroid cancer were detected by immunohistochemistry. Then, in vitro migration and invasion assays of siRNA-targeted FGF19-transfected cells were performed. RESULTS: Positive immunostaining of FGF19 protein expression was localized in cytoplasm with or without membrane of malignant cells and was observed in 82 (82.0%) of 100 patients with thyroid cancer. Statistically, the expression level of FGF19 protein in thyroid cancer tissues was significantly higher than that in normal tissues. In addition, FGF19 overexpression was significantly associated with the advanced tumor node metastasis staging (P = .008), the presence of extrathyroidal invasion (P = .01), lymph nodes metastasis (P = .01), and distant metastasis (P = .02). Furthermore, knockdown of FGF19 by transfection of siRNA-FGF19 could efficiently suppress the migration and invasion abilities of thyroid cancer cells in vitro. CONCLUSION: Our data revealed that the increased expression of FGF19 might be involved in the malignant behaviors of thyroid cancer, highlighting its potential as a molecular marker for early diagnosis and as a possible target for therapeutic intervention of this disease.
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http://dx.doi.org/10.1177/0194599815609534

Intraoperative high-dose calcium stimulation test in patients with sporadic medullary thyroid carcinoma is highly accurate in predicting lateral neck metastases.
Surgery, 159(1):70-6.
C. De Crea, M. Raffaelli, V. Milano, C. Carrozza, C. Zuppi, R. Bellantone and C. P. Lombardi. 2016.
BACKGROUND: Intraoperative measurement of calcitonin is not highly accurate in predicting the completeness of the operative resection after total thyroidectomy combined with central neck dissection (TT-CND) in patients with medullary thyroid carcinoma (MTC). We evaluated whether an intraoperative, high-dose calcium stimulation test (IO-CST) after TT-CND can predict lateral neck involvement. METHODS: Eleven patients who underwent primary operation for sporadic MTC were included. High-dose (25 mg/kg) calcium gluconate was administered after TT-CND with calcitonin measured at 2, 5, and 10 minutes after the calcium gluconate infusion. RESULTS: There were 2 males and 9 females (mean age, 51 years; range, 18-88). Three patients showed lateral neck metastases. At a mean follow-up of 7.0 months (range, 2-10), 1 patient showed distant metastases and 1 a slightly increased calcitonin level. After IO-CST, serum calcitonin increased in all the 3 patients with lateral neck metastases, and it remained unchanged or decreased in the other patients without lateral neck metastases. Percent variation of serum calcitonin after IO-CST was 92% in patients with lateral neck metastases and -3.1 +/- 4.9% in patients without lateral neck metastases. CONCLUSION: Calcitonin measurement after IO-CST in patients with sporadic MTC can be highly accurate in predicting lateral neck nodes involvement. These results could represent a stimulus toward the development of a quick calcitonin assay.
PubMed-ID: 26456123
http://dx.doi.org/10.1016/j.surg.2015.08.022

Genome-wide analysis of differentially expressed miRNA in PLX4720-resistant and parental human thyroid cancer cell lines.
Surgery, 159(1):152-62.
S. Varmeh, P. Vanden Borre, V. Gunda, E. Brauner, T. Holm, Y. Wang, R. I. Sadreyev and S. Parangi. 2016.
BACKGROUND: Investigating BRAF((V600E)) inhibitors (BRAFi) as a strategy to treat patients with aggressive thyroid tumors harboring the BRAF((V600E)) mutant currently is in progress, and drug resistance is expected to pose a challenge. MicroRNAs (miRNAs) are involved in development of resistance to a variety of drugs in different malignancies. METHODS: miRNA expression profiles in the human anaplastic thyroid cancer cell line (8505c) were compared with its PLX4720-resistant counterpart (8505c-R) by the use of Illumina deep sequencing. We conducted a functional annotation and pathway analysis of the putative and experimentally validated target genes of the significantly altered miRNAs. RESULTS: We identified 61 known and 2 novel miRNAs whose expression was altered greatly in 8505c-R. Quantitative reverse-transcription polymerase chain reaction validated altered expression of 7 selected miRNAs in 8505c-R and BCPAP-R (PLX4720-resistant papillary thyroid cancer cell line). We found 14 and 25 miRNAs whose expression levels changed substantially in

8505c and 8505c-R, respectively, after treatment with BRAFi. The mitogen-activated protein kinase and phosphatidylinositol 3-kinase-AKT pathways were among the prominent targets of many of the deregulated miRNAs. CONCLUSION: We have identified a number of miRNAs that could be used as biomarkers of resistance to BRAFi in patients with thyroid cancer. In addition, these miRNAs can be explored as potential therapeutic targets in combination with BRAFi to overcome resistance.
PubMed-ID: 26456124
http://dx.doi.org/10.1016/j.surg.2015.06.046

Post-thyroidectomy hypocalcemia is related to parathyroid dysfunction even in patients with normal parathyroid hormone concentrations early after surgery.
Surgery, 159(1):78-84.
M. Raffaelli, C. De Crea, G. D'Amato, U. Moscato, C. Bellantone, C. Carrozza and C. P. Lombardi. 2016.
BACKGROUND: Hypocalcemia may develop even in the presence of normal postoperative parathyroid hormone (PTH) concentrations. We aimed to identify risk factors of hypocalcemia in patients with normal PTH concentration early after total thyroidectomy (TT). METHODS: We included 1,504 consecutive patients who underwent TT between January 2012 and December 2013. Significant hypocalcemia was defined as serum calcium concentrations of <8.0 mg/dL. RESULTS: Overall, 333 patients had subnormal PTH 4 hours after surgery (4-hour PTH; <10 pg/mL) and received oral calcium (OC) and calcitriol supplementation. Among the 1,171 patients with normal 4-hour PTH (>/= 10 pg/mL; euparathyroid), 211 experienced hypocalcemia and required OC administration. Among the euparathyroid patients, no difference was found between normocalcemic and hypocalcemic patients in terms of age, hormonal status, preoperative PTH, 25-hydroxy vitamin D (25OH-VD), magnesium, and phosphate concentrations. On univariate analysis, euparathyroid hypocalcemic patients were more frequently females, had significantly lower preoperative serum calcium and 4-hour PTH concentrations, and greater decreases in PTH. Independent risk factors for hypocalcemia with normal 4-hour PTH were preoperative serum calcium concentration and PTH decline of >/= 50%. CONCLUSION: Female sex, toxic goiter, and 25OH-VD deficiency are not risk factors for post-TT hypocalcemia. Relative parathyroid insufficiency seems to be the principal mechanism of post-thyroidectomy hypocalcemia, even in patients with normal postoperative PTH concentrations.
PubMed-ID: 26456131
http://dx.doi.org/10.1016/j.surg.2015.07.038

Risk of Complications with Energy-Based Surgical Devices in Thyroid Surgery: A National Multicenter Register Study.
World J Surg, 40(1):117-23.
J. Carlander, P. Wagner, O. Gimm, E. Nordenstrom, S. Jansson, L. Bergkvist and K. Johansson. 2016.
BACKGROUND: Energy-based surgical devices (EBD) combining cutting and coagulation are increasingly used in thyroid surgery. However, there is a lack of information about potential benefits and risk of complications outside controlled trials. The aims of this national multicenter register study were to describe the use of EDB, their potential effect on complication rates, and on operation time. MATERIALS AND METHODS: The Scandinavian Quality Register for Thyroid and Parathyroid surgery includes 35 surgical units in Sweden and covered 88% of the thyroid procedures performed during 2008-2009. The use of the EBD was specifically registered for 12 months, and 1297 patients were included. Surgically related complications and operation time were evaluated. The clamp-and-tie group (C-A-T) constituted the control group for comparison with procedures where EBD was used. RESULTS: The thyroid procedures performed included C-A-T (16.6%), bipolar electrosurgery (ES: 56.5%), electronic vessel sealing (EVS: 12.2%), and ultrasonic dissection (UD: 14.5%). Mean operative time was longer with EVS ($p < 0.001$) and shorter with UD ($p < 0.05$) than in the other groups. The bipolar ES group and the EVS group had higher incidence of calcium treatment at discharge and after 6 weeks than the UD group. No significant difference in nerve injury was found between the groups. There was a significant more frequent use of topical hemostatic agents in the EBD group compared to C-A-T. CONCLUSION: In this national multicenter study, the use of UD shortened and EVS increased operating time. There was a higher risk of calcium treatment at discharge and after 6 weeks after use of EVS and bipolar ES than after UD use. There was a significant more frequent use of topical hemostatic agents in the EBD groups compared to C-A-T.
PubMed-ID: 26470699
http://dx.doi.org/10.1007/s00268-015-3270-7

Outpatient thyroid surgery: Safety of an optimized protocol in more than 1,000 patients.
Surgery, 159(2):518-23.
J. M. Segel, W. S. Duke, J. R. White, J. L. Waller and D. J. Terris. 2016.
OBJECTIVES: Outpatient thyroid surgery is becoming increasingly common. The aim of this study was to clarify the principles for safe outpatient thyroid surgery and review our outcomes with the use of a protocol for outpatient thyroidectomy in a large patient cohort. STUDY DESIGN: A systematic analysis of a prospectively maintained database of outcomes of thyroidectomy in a tertiary endocrine surgery practice. SETTING: Academic medical center. SUBJECTS AND METHODS: A protocol for outpatient thyroidectomy was conceived and refined over 3 years. A prospective analysis of all thyroidectomies accomplished by a single surgeon who used this protocol from May 2006 to November 2013 was then undertaken. Patient demographics, operative and pathologic data, admission status, complications, and readmission rates were recorded. RESULTS: A total of 1,311 thyroidectomy procedures were performed during the study period, of which 1,026 (78.3 %) were conducted on an outpatient basis. The readmission rate for outpatients was 0.9%, with only 1 readmission in the last 200 procedures. Inpatients (which included patients in the 23-hour "observation" category) were readmitted more often than outpatients (3.5% vs 0.9%, P < .01). Outpatient management increased steadily throughout the study period (from 59.7% to 92.3%, P < .01), despite a larger mean nodule size and a greater rate of malignancy over time. There were no changes in the complication rate across the study timeframe except for the incidence of temporary hypocalcemia, which decreased over time (P < .01). CONCLUSION: Outpatient thyroid surgery is safe in appropriately selected patients using an optimized and systematic protocol.
PubMed-ID: 26471720
http://dx.doi.org/10.1016/j.surg.2015.08.007

Papillary Thyroid Microcarcinoma: An Over-Treated Malignancy?: Reply.
World J Surg, 40(3):766-7.
T. S. Wang, P. Goffredo, J. A. Sosa and S. A. Roman. 2016.
PubMed-ID: 26475786
http://dx.doi.org/10.1007/s00268-015-3290-3

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

The Prediction of Sonographic features and BRAF Mutation for Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: Reply.
World J Surg, 40(3):761-3.
N. Qu, R. L. Shi, B. Ma, Y. Gao, Y. Wang and Q. H. Ji. 2016.
PubMed-ID: 26493695
http://dx.doi.org/10.1007/s00268-015-3285-0

Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection.
Br J Surg, 103(3):218-25.
I. J. Nixon, L. Y. Wang, I. Ganly, S. G. Patel, L. G. Morris, J. C. Migliacci, R. M. Tuttle, J. P. Shah and A. R. Shaha. 2016.
BACKGROUND: The role of prophylactic central neck dissection (CND) in the management of papillary thyroid

cancer (PTC) is controversial. This report describes outcomes of an observational approach in patients without clinical evidence of nodal disease in PTC. METHODS: All patients who had surgery between 1986 and 2010 without CND for PTC were identified. All patients had careful clinical assessment of the central neck during preoperative and perioperative evaluation, with any suspicious nodal tissue excised for analysis. The cohort included patients in whom lymph nodes had been removed, but no patient had undergone a formal neck dissection. Recurrence-free survival (RFS), central neck RFS and disease-specific survival (DSS) were calculated using the Kaplan-Meier method. RESULTS: Of 1798 patients, 397 (22.1 per cent) were men, 1088 (60.5 per cent) were aged 45 years or more, and 539 (30.0 per cent) had pT3 or pT4 disease. Some 742 patients (41.3 per cent) received adjuvant treatment with radioactive iodine. At a median follow-up of 46 months the 5-year DSS rate was 100 per cent. Five-year RFS and central neck RFS rates were 96.6 and 99.1 per cent respectively. CONCLUSION: Observation of the central neck is safe and should be recommended for all patients with PTC considered before and during surgery to be free of central neck metastasis.
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http://dx.doi.org/10.1002/bjs.10036

Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence.
Surgery, 159(1):11-9.
I. D. Hay, T. R. Johnson, G. B. Thompson, T. J. Sebo and M. S. Reinalda. 2016.
BACKGROUND: This study assessed the influence of extrathyroid extension (EE) on cause-specific mortality (CSM) and tumor recurrence (TR) in patients treated for papillary thyroid carcinoma (PTC). METHODS: We studied outcome in 3,524 patients with PTC without distant metastases at diagnosis. CSM and TR were investigated in 422 patients with gross EE (GEE) or microscopic EE (MEE). RESULTS: The 30-year CSM rate for GEE of 25% was 12-fold greater (P < .001) than 2% seen with surgically intra-thyroid tumors (SIT); no patient who underwent MEE died of PTC. No difference (P = .36) existed in CSM rates between 127 MEE and 3,102 microscopically intra-thyroid tumors (MITs). The 20-year TR rate for GEE was 43% versus 12% with SIT (P < .001). Analyzing only 2,067 pN0 tumors, we found that GEE patients had greater TR rates (all sites), compared with SIT or MEE (P < .001). When 44 MEE were compared with 1,941 MIT cases, TR (all sites) rates were not different (P = .74). In patients aged >45 with tumors <41 mm, 20-year TR rates for MIT (stages I/II) and MEE (stage III) were not different at 4.7% and 3.8% (P = .71). CONCLUSION: MEE without concomitant GEE did not increase rates of either CSM or TR in PTC. Accordingly, these results raise concerns regarding current AJCC staging recommendations.
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http://dx.doi.org/10.1016/j.surg.2015.05.046

Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category III (AUS/FLUS).
Eur J Surg Oncol, 42(1):87-93.
B. Kuru, A. Atmaca, I. A. Tarim, M. Kefeli, K. Topgul, S. Yoruker, M. Elmali and M. Danaci. 2016.
BACKGROUND: Selection of nodules for surgery diagnosed as Bethesda category III [atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) category] is very important. We aimed at to define the predictive factors for malignancy and factors associated with triage to surgery. METHODS: The records of all patients with nodules who underwent fine needle aspiration biopsy (FNAB) and classified by Bethesda reporting system as AUS/FLUS between 2011 and 2015 at our institution were reviewed. Univariate and multivariate analysis were performed to select independent factors associated with thyroid cancer and with triage to surgery. Using independent risk factors for malignancy predictive index categories were created. RESULTS: Of the 485 patients who were classified as AUS/FLUS on initial FNAB, 153 underwent surgery with the associated malignancy rate of 22.8%. The malignancy rates for AUS/FLUS patients with and without repeat FNAB were 37.5% and 16.2%, respectively. Multivariate logistic regression analysis revealed that solid structure, microcalcification, hypoechogenicity, increased vascularization, and irregular margin were found to be significant and independent risk factors associated for malignancy, and solid structure, microcalcifications, increased nodule size (>/=2 cm) and younger patient age (<65 years) were associated with triage to surgery. CONCLUSIONS: Our findings showed that using predictive factors for malignancy in AUS/FLUS category as risk indices, an important proportion of patients (35%) who had nodules without any risk factors could be spared unnecessary surgery. We suggest that predictive indices should be considered for selection of the patients to triage to surgery.
PubMed-ID: 26527545
http://dx.doi.org/10.1016/j.ejso.2015.09.026

Differential Clinicopathological Risk and Prognosis of Major Papillary Thyroid Cancer Variants.
J Clin Endocrinol Metab, 101(1):264-74.
X. Shi, R. Liu, F. Basolo, R. Giannini, X. Shen, D. Teng, H. Guan, Z. Shan, W. Teng, T. J. Musholt, K. Al-Kuraya, L. Fugazzola, C. Colombo, E. Kebebew, B. Jarzab, A. Czarniecka, B. Bendlova, V. Sykorova, M. Sobrinho-Simoes, P. Soares, Y. K. Shong, T. Y. Kim, S. Cheng, S. L. Asa, D. Viola, R. Elisei, L. Yip, C. Mian, F. Vianello, Y. Wang, S. Zhao, G. Oler, J. M. Cerutti, E. Puxeddu, S. Qu, Q. Wei, H. Xu, C. J. O'Neill, M. S. Sywak, R. Clifton-Bligh, A. K. Lam, G. Riesco-Eizaguirre, P. Santisteban, H. Yu, G. Tallini, E. H. Holt, V. Vasko and M. Xing. 2016.
CONTEXT: Individualized management, incorporating papillary thyroid cancer (PTC) variant-specific risk, is conceivably a useful treatment strategy for PTC, which awaits comprehensive data demonstrating differential risks of PTC variants to support. OBJECTIVE: This study sought to establish the differential clinicopathological risk of major PTC variants: conventional PTC (CPTC), follicular-variant PTC (FVPTC), and tall-cell PTC (TCPTC). METHODS: This was a retrospective study of clinicopathological outcomes of 6282 PTC patients (4799 females and 1483 males) from 26 centers and The Cancer Genome Atlas in 14 countries with a median age of 44 years (interquartile range, 33-56 y) and median follow-up time of 37 months (interquartile range, 15-82 mo). RESULTS: The cohort consisted of 4702 (74.8%) patients with CPTC, 1126 (17.9%) with FVPTC, and 239 (3.8%) with TCPTC. The prevalence of high-risk parameters was significantly different among the three variants, including extrathyroidal invasion, lymph node metastasis, stages III/IV, disease recurrence, mortality, and the use (need) of radioiodine treatment (all P < .001), being highest in TCPTC, lowest in FVPTC, and intermediate in CPTC, following an order of TCPTC > CPTC >> FVPTC. Recurrence and mortality in TCPTC, CPTC, and FVPTC were 27.3 and 6.7%, 16.1 and 2.5%, and 9.1 and 0.6%, corresponding to events per 1000 person-years (95% confidence interval [CI]) of 92.47 (64.66-132.26) and 24.61 (12.31-49.21), 34.46 (30.71-38.66), and 5.87 (4.37-7.88), and 24.73 (18.34-33.35) and 1.68 (0.54-5.21), respectively. Mortality hazard ratios of CPTC and TCPTC over FVPTC were 3.44 (95% CI, 1.07-11.11) and 14.96 (95% CI, 3.93-56.89), respectively. Kaplan-Meier survival analyses showed the best prognosis in FVPTC, worst in TCPTC, and intermediate in CPTC in disease recurrence-free probability and disease-specific patient survival. This was particularly the case in patients at least 45 years old. CONCLUSION: This large multicenter study demonstrates differential prognostic risks of the three major PTC variants and establishes a unique risk order of TCPTC > CPTC >> FVPTC, providing important clinical implications for specific variant-based management of PTC.
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http://dx.doi.org/10.1210/jc.2015-2917

Safety of Continuous Intraoperative Neuromonitoring (C-IONM) in Thyroid Surgery.
World J Surg, 40(3):768-9.
A. Bacuzzi, H. Dralle, G. W. Randolph, F. Y. Chiang, H. Y. Kim, M. Barczynski and G. Dionigi. 2016.
PubMed-ID: 26530692
http://dx.doi.org/10.1007/s00268-015-3288-x

Partial Thyroidectomy for Papillary Thyroid Microcarcinoma: Is Completion Total Thyroidectomy Indicated?
World J Surg, 40(3):510-5.
G. Donatini, M. Castagnet, T. Desurmont, N. Rudolph, D. Othman and J. L. Kraimps. 2016.
BACKGROUND: Total thyroidectomy is a well-established surgical approach for the management of papillary thyroid cancer (PTC). However, the best surgical approach for papillary microcarcinoma is nowadays still debated. Both total thyroidectomy and simple lobectomy are used. We report the experience of a single University center in the treatment of thyroid microcarcinoma. METHODS: A retrospective analysis on all patients who underwent thyroid surgery at our institution over a 24-year period (1991-2015) was performed. Patients were grouped according to whether they received total thyroidectomy (Group 1) or lobectomy (Group 2). Follow-up was made by routine clinical and ultrasound examination. Specific outcomes such as recurrence and need for reoperation as well as complications (transient vocal cord paralysis and hypocalcemia) were analyzed. RESULTS: During the study period 880 patients underwent surgery for PTC. Group 1 and 2 consisted, respectively, of 756 and 124 patients. A micro PTC (<10 mm) was present in 251 and 69 specimen of Group 1 and 2. No evidence of disease recurrence in the follow-up was reported in patients with microPTC in Group 1 and in 57 patients of Group 2. In the remaining 12 patients completion thyroidectomy was carried out due to ultrasound findings of contralateral nodules (10), lymphadenopathy (1), and capsular invasion (1). Five of these patients had a contralateral papillary carcinoma on final histopathologic examination. Thus recurrence rate for patients of Group 2 was 7.3%. Morbidity rates were, respectively, for Group 1 and 2: transient nerve palsy 81 and 5 (11 vs. 7.3%, p = ns), transient hypoparathyroidism (Calcium <2.00 mmol/L) 137 (18.6%) and 0 (p < 0.0001). Three of the 12 patients of Group 2 undergoing further surgery had a transient hypoparathyroidism.

CONCLUSIONS: Thyroid lobectomy is an effective surgical strategy to manage papillary microcarcinomas with low complications. Routine completion thyroidectomy is not mandatory. Appropriate selection excluding high-risk patients is of paramount importance in order to achieve the best results.
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http://dx.doi.org/10.1007/s00268-015-3327-7

Quality of Life in Thyroid Cancer is Similar to That of Other Cancers with Worse Survival.
World J Surg, 40(3):551-61.
M. K. Applewhite, B. C. James, S. P. Kaplan, P. Angelos, E. L. Kaplan, R. H. Grogan and B. Aschebrook-Kilfoy. 2016.
BACKGROUND: The incidence of thyroid cancer is increasing. As such, the number of survivors is rising, and it has been shown that their quality of life (QOL) is worse than expected. Using results from the North American Thyroid Cancer Survivorship Study (NATCSS), a large-scale survivorship study, we aim to compare the QOL of thyroid cancer survivors to the QOL of survivors of other types of cancer. METHODS: The NATCSS assessed QOL overall and in four subcategories: physical, psychological, social, and spiritual well-being using the QOL-Cancer Survivor (QOL-CS) instrument. Studies that used the QOL-CS to evaluate survivors of other types of cancers were compared to the NATCSS findings using two-tailed t tests. RESULTS: We compared results from NATCSS to QOL survivorship studies in colon, glioma, breast, and gynecologic cancer. The mean overall QOL in NATCSS was 5.56 (on a scale of 0-10, where 10 is the best). Overall QOL of patients with thyroid cancer was similar to that of patients with colon cancer (mean 5.20, $p = 0.13$), glioma (mean 5.96, $p = 0.23$), and gynecologic cancer (mean 5.59, $p = 0.43$). It was worse than patients surveyed with breast cancer (mean 6.51, $p < 0.01$). CONCLUSIONS: We found the self-reported QOL of thyroid cancer survivors in our study population is overall similar to or worse than that of survivors of other types of cancer surveyed with the same instrument. This should heighten awareness of the significance of a thyroid cancer diagnosis and highlights the need for further research in how to improve care for this enlarging group of patients.
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http://dx.doi.org/10.1007/s00268-015-3300-5

Effectiveness and Mechanism of Preoperative Lugol Solution for Reducing Thyroid Blood Flow in Patients with Euthyroid Graves' Disease.
World J Surg, 40(3):505-9.
S. M. Huang, W. T. Liao, C. F. Lin, H. S. Sun and N. H. Chow. 2016.
BACKGROUND: To reduce intraoperative and postoperative complications, using Lugol solution to preoperatively prepare patients with Graves' disease has (1) rapidly reduced the severity of thyrotoxicosis and (2) reduced the vascularity of the thyroid gland. The vascularity reduction normally accompanies reducing the severity of thyrotoxicosis. However, the effects and mechanism of Lugol solution for reducing blood flow have not been well investigated in the patients with euthyroid (normally functioning thyroid) Graves' disease. METHODS: Twenty-five patients with euthyroid Graves' disease being preoperatively treated with Lugol solution for 10 days were measured, at baseline and on the operative day, for (1) superior thyroid artery blood flow; (2) systemic angiogenic factor (VEGF); and (3) systemic inflammatory factor [interleukin (IL)-16]. RESULTS: All three parameters were significantly ($p < 0.0001$) lower after 10 days of Lugol solution treatment. The average reductions were blood flow: 60% (0.294 vs. 0.117 L/min), serum VEGF: 55% (169.8 vs. 76.7 pg/mL), and serum IL-16: 50% (427.2 vs. 214.2; pg/mL). CONCLUSION: Lugol solution significantly reduced thyroid arterial blood flow, VEGF, and IL-16, even in patients with euthyroid Graves' disease. We recommend routine preoperative Lugol solution treatment for all patients with Graves' disease.
PubMed-ID: 26546192
http://dx.doi.org/10.1007/s00268-015-3298-8

Transoral Endoscopic Thyroidectomy Vestibular Approach: A Series of the First 60 Human Cases.
World J Surg, 40(3):491-7.
A. Anuwong. 2016.
BACKGROUND: Natural orifice transluminal endoscopic surgery has been adopted for thyroid surgery because of its potential for scar-free operation. However, the previous technique still has some limitations. Thus, we present our initial experience in transoral endoscopic thyroidectomy vestibular approach (TOETVA). METHODS: From April 2014 to January 2015, we used a three-port technique through the oral vestibule, one 10-mm port for laparoscope and two additional 5-mm ports for instruments. The CO2 insufflation pressure was set at 6 mm Hg. An anterior cervical subplatysmal space was created from the oral vestibule down to the sternal notch. The thyroidectomy was done endoscopically using conventional laparoscopic instruments and an ultrasonic device. RESULTS: A series of 60 procedures were accomplished successfully. 42 patients had single-thyroid nodules,

and a lobectomy was performed. 22 patients had multinodular goiters and two patients had Graves' disease, with total thyroidectomy or Hartley-Dunhill procedures performed. Two had papillary thyroid carcinoma, and total thyroidectomy with central node dissection was performed. The median operative time was 115.5 min (range 75-300 min). The median blood loss was 30 mL (range 8-130 mL). Two patients experienced a transient hoarseness, which was resolved within 2 months. One patient experienced a late postoperative hematoma, which was treated conservatively. No mental nerve injury or infections were found. The patients were discharged in an average of 3.6 days (range 2-7 days) postoperatively. CONCLUSION: TOETVA is safe and feasible, resulting in no visible scarring. This technique may provide a method for ideal cosmetic results.
PubMed-ID: 26546193
http://dx.doi.org/10.1007/s00268-015-3320-1

Indeterminate Single Thyroid Nodule: Synergistic Impact of Mutational Markers and Sonographic Features in Triaging Patients to Appropriate Surgery.
Thyroid, 26(3):390-4.
L. De Napoli, S. Bakkar, C. E. Ambrosini, G. Materazzi, A. Proietti, E. Macerola, F. Basolo and P. Miccoli. 2016.
BACKGROUND: Patients labeled as having indeterminate thyroid nodular disease following fine-needle aspiration cytology are at risk of non-optimal initial surgery: an overly radical total thyroidectomy, or an unnecessary two-stage operation. The objective of this study was to assess the impact of combining mutational markers and ultrasonographic (US) features preoperatively on predicting the risk of malignancy in patients with indeterminate nodules, thereby offering them a tailored initial surgical intervention. METHODS: The records of 258 patients who underwent conventional total thyroidectomy for single nodules reported as suspicious for a follicular neoplasm (Bethesda category IV) in a four-year period were reviewed. Main issues addressed included: certain US findings (individually and in combination), mutational markers (BRAF and NRAS), and combinations of both. Correlation of these with malignancy was assessed, as was their ability to predict malignancy. The usefulness of combining the absence of suspicious sonographic features and the absence of mutational markers was also evaluated. RESULTS: Among the 258 patients with an indeterminate diagnosis, only 90 lesions were found to be malignant. The sonographic features that correlated significantly with malignancy were irregular margins, microcalcifications, and a "taller than wide" shape. The presence of irregular margins was the feature with the highest positive predictive value. Combinations of two or more features were always associated with predictivity in excess of 90%, and at times at 100%. NRAS mutation was the most common gene alteration. Both BRAF and NRAS mutations were mutually exclusive and correlated significantly with malignancy. Their predictivity of malignancy was high, particularly when combined with suspicious sonographic features (100%). The major limitation of both suspicious sonographic features and/or mutational markers was their low occurrence in malignancy. The absence of both mutational markers and suspicious sonographic features proved extremely useful in tailoring surgical strategy, as it could have ultimately spared 143/258 patients (55%) an overly radical thyroidectomy. CONCLUSION: The preoperative utility of mutational markers and sonographic features in combination has a synergistic impact. It can predict the risk of malignancy with high accuracy, properly triaging patients to appropriate surgery.
PubMed-ID: 26548748
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Using Transcutaneous Laryngeal Ultrasonography (TLUSG) to Assess Post-thyroidectomy Patients' Vocal Cords: Which Maneuver Best Optimizes Visualization and Assessment Accuracy?
World J Surg, 40(3):652-8.
K. P. Wong, J. W. Woo, J. Y. Li, K. E. Lee, Y. K. Youn and B. H. Lang. 2016.
To assess vocal cord (VC) movement with transcutaneous laryngeal ultrasound (TLUSG), three maneuvers, namely passive (quiet respiration), active (phonation), and Valsalva maneuvers have been described. It remains unclear which maneuver or using more maneuvers provides better visualization and assessment accuracy. We prospectively evaluated 342 post-thyroidectomy patients from two centers. They underwent TLUSG with direct laryngoscopic (DL) validation afterwards. During TLUSG, patients were instructed to perform all three maneuvers (passive, active, and Valsalva). VC visualization rate and accuracy between three maneuvers were compared. Visualization rate tended to be higher in Valsalva maneuver than that in other two maneuvers (92.1% vs. passive: 91.5%; active: 89.8%). While 19 patients had post-operative VC palsy, passive maneuver had lower test specificity than active (94.3 vs. 97.6%, p = 0.01) and Valsalva maneuvers (94.3 vs. 97.4%, p = 0.02). In assessable VCs, passive maneuver has a higher ability to differentiate between mobile VCs and VC palsy (Area under ROC curve--passive: 0.942, active: 0.863, Valsalva: 0.893). TLUSG with more maneuvers did not improve sensitivity or specificity. On applying TLUSG as a screening tool (i.e., only selected patient with "unassessable" VCs or VCP on TLUSG for DL), Valsalva maneuver (85.96%) saved more patients from DL than passive (81.87%) or active (84.81%) maneuver. Passive maneuver has a higher ability to differentiate VC palsy from

normal. Using TLUSG as a screening tool, Valsalva was the preferred maneuver as it was more specific, had high visualization rate, and saved more patients from DL.
PubMed-ID: 26552909
http://dx.doi.org/10.1007/s00268-015-3304-1

Parapharyngeal Metastasis of Papillary Thyroid Carcinoma.
World J Surg, 40(2):350-5.
S. Moritani. 2016.
BACKGROUND: Nodal involvement of papillary thyroid carcinoma (PTC) commonly occurs in the paratracheal region and the internal jugular chain. Lymph node metastasis in the parapharyngeal space (PPS) is rare. In this report, we describe our experience and surgical outcomes of patients with PPS metastasis of PTC. METHODS: Clinical data of patients with PTC who underwent surgery at our institution between January 2006 and December 2013 were retrospectively reviewed, and 22 patients with PPS metastasis were enrolled. RESULTS: There were 2 primary and 20 secondary cases of PPS metastasis. Involvement of the jugular nodes was noted before or at the time of PPS metastasis detection in all cases. A transcervical surgical approach with partial resection of the mandibular angle was performed in 21 patients, while 1 patient underwent extirpation of the PPS metastasis via a transoral approach. Although curative resection was performed in 21 patients, the PPS metastasis was not removable in 1 patient owing to an invaded internal carotid artery at the skull base. Twelve and 6 patients had locoregional and distant recurrence, respectively. Of the 12 patients with locoregional recurrence, isolated locoregional recurrence in the PPS occurred in 1. Eight patients died of distant or locoregional recurrence, with a median survival time of 91.7 months. CONCLUSIONS: For patients who experience recurrence after thyroid surgery, the possibility of PPS metastasis should be considered. In this series, all patients with PPS metastasis also had previous unilateral or bilateral cervical metastasis. Despite curative attempt, most patients experienced local or distant recurrence.
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http://dx.doi.org/10.1007/s00268-015-3321-0

Recurrent Laryngeal Nerve Liberations and Reconstructions: A Single Institution Experience.
World J Surg, 40(3):644-51.
R. Dzodic, I. Markovic, N. Santrac, M. Buta, I. Djurisic and S. Lukic. 2016.
BACKGROUND: Recurrent laryngeal nerve (RLN) palsy rates vary from 0.5 to 10%, even 20% in thyroid cancer surgery. The aim of this paper was to present our experience with RLN liberations and reconstructions after various mechanisms of injury. METHODS: Patients were treated in our institution from year 2000 to 2015. First group (27 patients) had large benign goiters, locally advanced thyroid/parathyroid carcinomas, or incomplete previous surgery of malignant thyroid disease. Second group (5 patients) had reoperations due to RLN paralysis on laryngoscopy. Liberations and reconstructions of injured RLNs were performed. RESULTS: Surgical exploration of central compartment enabled identification of the RLN injury mechanism. Liberations were performed in 11 patients, 2 months to 16 years after RLN injury, by removing misplaced ligations. Immediate or delayed (18 months to 23 years) RLN reconstructions were performed in 21 patients, by direct suture or ansa cervicalis-to-RLN anastomosis (ARA). RLN liberation provided complete voice recovery within 3 weeks in all patients. Patients with direct sutures had better phonation 1 month after reconstruction. Improved phonation was observed 2-6 months after ARA in 43% of patients. CONCLUSIONS: Vocal cords do not regain normal movement once being paralyzed after RLN transection, but they restore tension during phonation by reconstruction. Nerve liberation is a useful method which enables patients with RLN paresis/paralysis a significant improvement in phonation, even complete voice recovery. Reinnervation of vocal cords, using one of the mentioned techniques, should be a standard in thyroid and parathyroid surgery, with aim to improve quality of patient's life.
PubMed-ID: 26552911
http://dx.doi.org/10.1007/s00268-015-3305-0

DICER1 Mutations and Differentiated Thyroid Carcinoma: Evidence of a Direct Association.
J Clin Endocrinol Metab, 101(1):1-5.
M. M. Rutter, P. Jha, K. A. Schultz, A. Sheil, A. K. Harris, A. J. Bauer, A. L. Field, J. Geller and D. A. Hill. 2016.
CONTEXT: DICER1 germline mutation carriers have an increased predisposition to cancer, such as pleuropulmonary blastoma (PPB) and Sertoli-Leydig cell tumor (SLCT), and a high prevalence of multinodular goiter (MNG). Although differentiated thyroid carcinoma (DTC) has been reported in some DICER1 mutation carriers with PPB treated with chemotherapy, the association of DTC with DICER1 mutations is not well established. CASE DESCRIPTION: We report a family with DICER1 mutation and familial DTC without a history of chemotherapy. A 12-year-old female (patient A) and her 14-year-old sister (patient B) presented with MNG.

Family history was notable for a maternal history of DTC and bilateral ovarian SLCT. Both sisters underwent total thyroidectomy. Pathological examination showed nodular hyperplasia and focal papillary thyroid carcinoma within hyperplastic nodules. Subsequently, patient A developed virilization secondary to a unilateral ovarian SLCT. During her evaluation, an incidental cystic nephroma was also found. Three other siblings had MNG on surveillance ultrasound examination; two had thyroidectomies, and one had two microscopic foci of papillary carcinoma. Patient A, her mother, and four affected siblings had a germline heterozygous pathogenic DICER1 mutation c.5441C>T in exon 25, resulting in an amino acid change from p.Ser1814Leu of DICER1. Somatic DICER1 RNase IIIb missense mutations were identified in thyroid nodules from three of the four siblings. CONCLUSIONS: This family provides novel insight into an emerging phenotype for DICER1 syndrome, with evidence that germline DICER1 mutations are associated with an increased risk of developing familial DTC, even in the absence of prior treatment with chemotherapy.
PubMed-ID: 26555935
http://dx.doi.org/10.1210/jc.2015-2169

Changes of Laryngeal Mobility and Symptoms Following Thyroid Surgery: 6-Month Follow-Up.
World J Surg, 40(3):636-43.
A. E. Gohrbandt, A. Aschoff, B. Gohrbandt, A. Keilmann, H. Lang and T. J. Musholt. 2016.
OBJECTIVE: Swallowing disorders are frequent complaints after thyroidectomy even in the absence of recurrent laryngeal nerve palsy. The aim of this study was to assess different symptoms in relation to laryngeal mobility following thyroidectomy. MATERIALS AND METHODS: 53 patients (mean age 52.4 +/- 12.5 years; 36 female) with initially benign diagnosis and intact recurrent nerve functioning were prospectively evaluated. Laryngeal movement was analyzed by ultrasound preoperatively and 1, 3, and 6 months postoperatively. In addition, a dysphagia and voice-specific quality-of-life questionnaire was used. RESULTS: Mean laryngeal movement differed between genders preoperatively and postoperatively resulting in a recovery predominantly in women (reduction of mobility at 1, 3, and 6 months postoperatively in females was 6.0, 3.7, and 1.5 mm, and in males 13.8, 11.7, and 10.3 mm, respectively). Mainly, women reported hoarseness (9 females) and cervical discomfort (7 females, 3 males) 1 month postoperatively. After 6 months, these complaints resolved (cervical discomfort 1 female). CONCLUSION: Laryngeal mobility was significantly impaired postoperatively and only females revealed a recovery close to baseline after 6 months. Although showing only a small grade of recovery of laryngeal movement, subjective clinical symptoms were found to be rare in male patients.
PubMed-ID: 26560148
http://dx.doi.org/10.1007/s00268-015-3323-y

Trends in Prevalence of Thyroid Cancer Over Three Decades: A Retrospective Cohort Study of 17,526 Surgical Patients.
World J Surg, 40(3):538-44.
A. Konturek, M. Barczynski, M. Stopa and W. Nowak. 2016.
INTRODUCTION: Thyroid cancer (TC) incidence has been increasing in recent years. The aim of this study was to investigate our institution-based estimates of operative volumes for TC over the last three decades. MATERIALS AND METHODS: This was a retrospective cohort study of patients undergoing thyroid surgery at our institution. Patient characteristics were reviewed in three subgroups: Group I (treated in 1981-1986), Group II (treated in 1987-2002), and Group III (treated in 2003-2012). RESULTS: TC was diagnosed in 1578/17,526 (9.0%) thyroid operations. Incidence of TC increased from 3.7% in Group I to 10.4% in Group III ($p < 0.001$). Incidence of papillary TC increased form 40.6% in Group I to 81.3% in Group III ($p < 0.001$). In the latter group, 23.5% of all papillary TCs were diagnosed in patients with Hashimoto's disease. Meanwhile, incidence of anaplastic TC decreased from 16.2% in Group I to 2.1% in Group III patients ($p < 0.001$). pT1 tumors were diagnosed in 8.1% Group I and 54.8% Group III ($p < 0.001$), whereas pT4 tumors were identified in 40.5% Group I, 2.4% Group II, and 0.84% Group III subjects ($p < 0.001$). pT3 tumors were found in 51.6% Group I, whereas multifocal papillary TCs were found in 15.7% Group III patients, the latter with a higher prevalence of pN1 stage ($p < 0.001$). CONCLUSIONS: The following trends in surgical volume for TC were identified throughout the study period: a fivefold increase of thyroid operations for TC, a threefold increase in incidence of papillary TC, and an eightfold decrease in incidence of anaplastic TC. It is of interest that a significant increase in incidence of multifocal papillary TC in young female patients with Hashimoto's disease was found over time.
PubMed-ID: 26560150
http://dx.doi.org/10.1007/s00268-015-3322-z

Efficacy of Intraoperative Neuro-Monitoring to Localize the External Branch of the Superior Laryngeal Nerve.
Thyroid, 26(1):174-8.
L. M. Hurtado-Lopez, P. I. Diaz-Hernandez, E. Basurto-Kuba, F. R. Zaldivar-Ramirez and A. Pulido-Cejudo. 2016.
BACKGROUND: This study investigated whether visual localization of the external branch of the superior laryngeal nerve (EBSLN) coincides with its localization via intraoperative neuro-monitoring (IONM) during thyroidectomy and whether its use influences the frequency of injuries. METHODS: A prospective, comparative, cross-sectional, observational study was performed in 240 superior thyroid poles. The metrics were visual identification of the EBSLN and its corroboration with IONM. The frequency of EBSLN injuries was also determined. Statistical analysis was achieved via kappa and chi-square tests, as well as odds ratios (OR). RESULTS: Of the 240 superior thyroid poles, IONM identified 234 (97.5%) EBSLN, whereas 190 (79.1%) were identified visually: OR = 10.35 [CI 4.37-24.65] p < 0.0001. Of the 190 EBSLN identified visually, 150 were confirmed through IONM. Indeed, their structure corresponded to an EBSLN to yield a kappa with a linear weighting value of 0.362. The standard error was 0.0467 [CI 0.2686-0.4554], indicating a fair agreement between the visual and IONM classification. CONCLUSION: IONM identified 97.5% of EBSLN cases. It was higher than the visual identification. There were no injuries to EBSLN identified through IONM.
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http://dx.doi.org/10.1089/thy.2015.0190

Seasonal Difference in Postthyroidectomy Hypocalcemia: A Montreal-Based Study.
Otolaryngol Head Neck Surg, 154(2):263-7.
M. A. Mascarella, V. I. Forest, C. Nhan, R. Leboeuf, M. Tamilia, A. M. Mlynarek and R. J. Payne. 2016.
OBJECTIVE: Hypocalcemia following thyroidectomy often prolongs hospital stay and is potentially life-threatening. The objective of this study is to determine whether the season when thyroidectomy is performed is associated with postoperative hypocalcemia. STUDY DESIGN: Retrospective case series of patients undergoing thyroid surgery from 2009 to 2015. SETTING: Tertiary care academic institution in Montreal, Canada. SUBJECTS AND METHODS: A consecutive sample of 823 patients undergoing thyroidectomy by a single high-volume otolaryngologist for a suspected or confirmed thyroid malignancy. Patient demographics, procedure type, calcium and vitamin D supplementation, and seasonal rate of hypocalcemia postthyroidectomy were calculated and compared. RESULTS: Average seasonal rates of postthyroidectomy hypocalcemia in the winter, spring, summer, and autumn were, respectively, 8.3% (8 of 216), 7.3% (12 of 165), 1.5% (3 of 201), and 3.5% (8 of 228; P < .005). Patients operated in the winter were 5.6 times more likely to develop hypocalcemia as compared with those in the summer (P < .01; 95% confidence interval: 1.7-18.7). In a multiple regression analysis factoring in season when surgery was performed, procedure type, and preoperative vitamin D/calcium supplementation, surgery occurring in the winter predicted a hypocalcemia event (correlation coefficient [SE]: 0.72 [0.024], P = .026; 0.006 [0.025], P = .81; 0.004 [0.019], P = .82, respectively). CONCLUSION: In this study, patients undergoing thyroidectomy in the winter months were more likely to develop postoperative hypocalcemia when compared with those operated in the summer. Further studies are needed to understand the role of vitamin D in the observed seasonal difference in hypocalcemia rates.
PubMed-ID: 26567048
http://dx.doi.org/10.1177/0194599815617126

The Role of Magnesium in Post-thyroidectomy Hypocalcemia.
World J Surg, 40(4):881-8.
A. J. Cherian, M. Gowri, P. Ramakant, T. V. Paul, D. T. Abraham and M. J. Paul. 2016.
BACKGROUND: The purpose of this study was to determine the prevalence of hypomagnesemia in patients undergoing thyroidectomy and evaluate the relationship of hypomagnesemia with transient and severe hypocalcemia. MATERIALS AND METHODS: This was a prospective observational study of 50 patients undergoing thyroidectomy. Blood samples were collected pre- and postoperatively for calcium, albumin, magnesium, phosphorous and parathormone (PTH). Signs, symptoms of hypocalcemia and volume of intravenous fluids used perioperatively were documented. The statistical analysis was performed using STATA I/C 10.1. RESULTS: Preoperatively, twelve patients (24 %) had hypomagnesemia and one (2 %) hypocalcemia. On the first postoperative day, hypomagnesemia was seen in 70 % and hypocalcemia in 30 %. A similar trend was observed in the fall and rise of postoperative calcium and magnesium values (p = 0.41). Severe hypocalcemia was present in three patients (6 %). All three patients had a very low postoperative PTH (<2 pg/ml). Among them, two patients (66 %) had hypomagnesemia and their hypocalcemia responded to intravenous magnesium correction. Significant risk factors for postoperative hypocalcemia include a higher volume of fluid used perioperatively and low postoperative PTH (<8 pg/ml) (p = 0.01 and 0.03, respectively).

CONCLUSION: Preoperative hypomagnesemia (24 %) was prevalent in this cohort of patients. Postoperative hypomagnesemia is a common event (70 %) following total thyroidectomy, and magnesium levels tend to mimic the calcium levels postoperatively. The cause of hypocalcemia post-thyroidectomy in this study is mainly a factor of parathyroid function and fluid status. Severe hypocalcemia is a rare event, and hypomagnesemia is associated in the majority of these patients. The role of magnesium correction to alleviate severe hypocalcemia needs to be further studied.
PubMed-ID: 26578317
http://dx.doi.org/10.1007/s00268-015-3347-3

Natural History of Asymptomatic Papillary Thyroid Microcarcinoma: Time-Dependent Changes in Calcification and Vascularity During Active Surveillance.
World J Surg, 40(3):529-37.
O. Fukuoka, I. Sugitani, A. Ebina, K. Toda, K. Kawabata and K. Yamada. 2016.
BACKGROUND: Prospective trials of non-surgical observation have shown progression rates of only 5-10% in patients with asymptomatic papillary microcarcinoma (PMC). This study investigated time-dependent changes in calcification patterns and tumor vascularity on ultrasonography (US) to clarify the natural course of PMC. METHODS: We examined calcification patterns and tumor vascularity for 480 lesions in 384 patients. Calcification patterns were classified as: (A) none; (B) micro; (C) macro; or (D) rim. Tumor vascularity was classified as rich or poor via color Doppler US. RESULTS: After a mean of 6.8 years of observation, 29 lesions (6.0%) had increased in size. Mean age for initial calcification pattern was 52.1 years for A (n = 135), 54.2 years for B (n = 235), 56.3 years for C (n = 96), and 60.1 years for D (n = 14), and the incidence rates of tumor enlargement were 9.6, 5.5, 3.2, and 0%, respectively. The cumulative rate of upgrade in calcification pattern was 51.8% at 10 years. Lesions with initially rich vascularity (n = 70) had significantly higher rate of tumor enlargement than those with poor vascularity (n = 410); however, the majority of tumor (61.4%) with initially rich vascularity had decreased their blood supply during the follow-up. Multivariate analysis showed that strong calcification (C or D) and poor vascularity at last examination correlated significantly with non-progressive disease. CONCLUSIONS: PMCs in older patients showed significantly stronger calcification patterns and poorer vascularity. Both consolidation of calcification and loss of vascularity occurred in a time-dependent manner during observation and were significant indicators for non-progressive disease.
PubMed-ID: 26581368
http://dx.doi.org/10.1007/s00268-015-3349-1

Prospective Intervention of a Novel Levothyroxine Dosing Protocol Based on Body Mass Index after Thyroidectomy.
J Am Coll Surg, 222(1):83-8.
D. M. Elfenbein, S. Schaefer, C. Shumway, H. Chen, R. S. Sippel and D. F. Schneider. 2016.
BACKGROUND: Weight-based postoperative levothyroxine (LT4) dosing often fails to appropriately dose overweight and underweight patients. Previously, we created an LT4-dosing algorithm based on BMI. We hypothesize that more patients will achieve euthyroidism at their postoperative visit with the use of the protocol. STUDY DESIGN: A prospective evaluation was performed of our previously published BMI-based LT4 dosing. All adults who underwent thyroidectomy for benign disease between January 1, 2011 and December 31, 2013 were included; the new protocol was implemented in October 2012. Serum TSH was measured for all patients 6 to 8 weeks postoperatively, and adjustments were based on TSH. RESULTS: Three hundred and thirty patients were included, with 54% undergoing thyroidectomy after institution of the protocol. The groups were well matched. Before protocol implementation, LT4 was dosed solely by weight and 25% of patients were euthyroid at initial follow-up. After the protocol, 39% of patients were euthyroid (p = 0.01). The percentage of patients who were given too high a dose of LT4 remained the same (46% vs 42%), and there was a significant reduction in the number of patients who were given too little (29% vs 19%; p = 0.05). The effect was most profound in patients with low and normal BMI, and there were slight differences between sexes. CONCLUSIONS: Although correct initial dosing of LT4 remains challenging, this dosing protocol that we developed and implemented has improved patient care by increasing the number of patients who achieve euthyroidism at the first postoperative visit. We have made a change to our original protocol to incorporate sex differences into the calculation.
PubMed-ID: 26584573
http://dx.doi.org/10.1016/j.jamcollsurg.2015.10.005

Determining the Learning Curve of Transcutaneous Laryngeal Ultrasound in Vocal Cord Assessment by CUSUM Analysis of Eight Surgical Residents: When to Abandon Laryngoscopy.
World J Surg, 40(3):659-64.
K. P. Wong, B. H. Lang, S. Lam, K. P. Au, D. T. Chan and N. C. Kotewall. 2016.
Transcutaneous laryngeal ultrasonography (TLUSG) is a promising alternative to laryngoscopy in vocal cords (VCs) assessment which might be challenging in the beginning. However, it remains unclear when an assessor can provide proficient TLUSG enough to abandon direct laryngoscopy . Eight surgical residents (SRs) without prior USG experience were recruited to determine the learning curve. After a standardized training program, SRs would perform 80 consecutive peri-operative VCs assessment using TLUSG. Performances of SRs were quantitatively evaluated by a composite performance score (lower score representing better performance) which comprised total examination time (in seconds), VCs visualization, and assessment accuracy. Cumulative sum (CUSUM) chart was then used to evaluate learning curve. Diagnostic accuracy and demographic data between every twentieth TLUSG were compared. 640 TLUSG examinations had been performed by 8 residents. 95.1% of VCs could be assessed by SRs. The CUSUM curve showed a rising pattern (learning phase) until 7th TLUSG and then flattened. The curve declined continuously after 42nd TLUSG (after reaching a plateau). Rates of assessable VCs were comparable in every twentieth cases performed. It took a longer time to complete TLUSG in 1st-20th than 21st-40th examinations. (45 vs. 32s, p = 0.001). Although statistically not significant, proportion of false-negative results was higher in 21st-40th (2.5%) than 1(st)-20th (0.6%), 41(st)-60th (0.7%), and 61(st)-80th (0.7%) TLUSG performed. After a short formal training, surgeons could master skill in TLUSG after seven examination and assess vocal cord function consistently and accurately after 40 TLUSG.
PubMed-ID: 26585950
http://dx.doi.org/10.1007/s00268-015-3348-2

A Prospective Study on Cardiovascular Dysfunction in Patients with Hyperthyroidism and Its Reversal After Surgical Cure.
World J Surg, 40(3):622-8.
S. Muthukumar, D. Sadacharan, K. Ravikumar, G. Mohanapriya, Z. Hussain and R. V. Suresh. 2016.
BACKGROUND: Cardiovascular dysfunction (CVD) is a major cause of mortality and morbidity in hyperthyroidism. CVD and its reversibility after total thyroidectomy (TT) are not adequately addressed. This prospective case-control study evaluates the effect of hyperthyroidism on myocardium and its reversibility after TT. MATERIALS AND METHODS: Surgical candidates of new onset hyperthyroidism, Group A (n = 41, age < 60 years) was evaluated with 2D Echocardiography, serum n-terminal probrain natriuretic peptide (NT-proBNP) at the time of diagnosis (Point A), after achieving euthyroidism (Point B) with antithyroid drugs, and 3 months after TT (Point C). 20 patients with nontoxic benign thyroid nodules undergoing TT served as controls (Group B). RESULTS: Both groups were age and sex matched. Group A (n = 41) comprises Graves disease (n = 22) and Toxic Multinodular goiter (n = 19). At point A, CVD was evident in 26/41(63.4%), pulmonary hypertension (PHT) in 24/41(58.5%)--mild in 17/41(41.4%) and moderate in 7/41(17%)--dilated cardiomyopathy (DCM) in 8/41(19.5%), heart failure in 4/41(9.7%), and NT-proBNP elevated in 28/41(68.3%). At point B, recovery was observed in PHT 19/26(73.1%), DCM 4/8(50%), heart failure 4/4(100%), NT-proBNP in 3/28(10.7%). At Point C, further improvement occurred in PHT 23/24(95.8%), DCM 7/8(87.5%), heart failure 4/4(100%), and NT-proBNP in 24/28(85.7%). CONCLUSION: Pulmonary hypertension is completely reversible at 3 months after TT and is the most common cardiac event in Hyperthyroidism. Various parameters of CVD improved consistently after surgical cure. NT-proBNP levels correlated well with the severity and duration of CVD and hence can be an objective tool in monitoring of hyperthyroid cardiac dysfunction.
PubMed-ID: 26596841
http://dx.doi.org/10.1007/s00268-015-3352-6

The Usefulness of Preoperative Thyroid-Stimulating Hormone for Predicting Differentiated Thyroid Microcarcinoma.
Otolaryngol Head Neck Surg, 154(2):256-62.
R. L. Shi, T. Liao, N. Qu, F. Liang, J. Y. Chen and Q. H. Ji. 2016.
OBJECTIVE: Thyroid-stimulating hormone (TSH) is a known thyroid growth factor, but the pathogenic role of TSH in thyroid tumorigenesis is controversial. The aim of this study is to examine the relationship between preoperative TSH and differentiated thyroid microcarcinoma (DTMC). DATA SOURCES: We searched PubMed, EMBASE, Ovid, Web of Science, and the Cochrane Library from their inception to March 2015 and performed a systematic literature review of original studies. REVIEW METHODS: Published studies that explored the relationship between preoperative TSH and DTMC were included for the review. We calculated odds ratio referring to different TSH concentrations between DTMC and control groups and used random effects model for the meta-analysis. RESULTS: Nine eligible studies that included 6523 patients were identified. Meta-analysis

revealed that DTMC was associated with high TSH concentration (odds ratio = 1.23, 95% confidence interval = 1.03-1.46, P = .001). Metaregression analysis indicated that the disparity of control groups was the possible factor resulting in heterogeneity among the studies. CONCLUSIONS: The risk of DTMC increases significantly in parallel with TSH concentration. These results support the hypothesis that TSH is involved in tumorgenesis of differentiated thyroid cancer.
PubMed-ID: 26598500
http://dx.doi.org/10.1177/0194599815618388

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

Impact of vocal cord ultrasonography on endocrine surgery practices.
Surgery, 159(1):58-63.
D. Carneiro-Pla, C. C. Solorzano and S. M. Wilhelm. 2016.
BACKGROUND: It is common practice to perform flexible laryngoscopy (FL) to ensure true vocal cord (TVC) mobility in patients with previous neck operations or patients with suspected VC dysfunction. Vocal cord ultrasonography (VCUS) is accurate in identifying TVC paralysis. The goal of this study is to evaluate the impact of VCUS as the initial study to confirm TVC mobility in patients requiring preoperative FL. METHODS: A total of 194 consecutive patients with indications for preoperative FL underwent VCUS. In group 1, 52 patients had FL regardless of the results of VCUS, whereas in group 2, 142 patients had VCUS followed by FL only when VCUS was unsatisfactory. RESULTS: VCUS visualized TVC/arytenoids in 164 of 194 (85%) patients. TVC visualization was more common in women (95%) and in patients without thyroid cartilage calcification (92%) (P < .0005). VCUS predicted all paralyzed TVC. In group 2, 76% of patients had adequate VCUS and avoided preoperative FL. Among 24% of patients in whom VCUS was inadequate, 16 had preoperative FL attributable to a lack of TVC visualization, 6 had abnormal TVC mobility, 11 needed additional confirmations, and 2 had previous FL for another reason. CONCLUSION: VCUS changed surgeon practices by avoiding the need for preoperative FL in the majority of patients. This noninvasive and sensitive method demonstrates TVC mobility and safely precludes preoperative FL in most patients.
PubMed-ID: 26603853
http://dx.doi.org/10.1016/j.surg.2015.06.067

Risk factors and indication for dissection of right paraesophageal lymph node metastasis in papillary thyroid carcinoma.
Eur J Surg Oncol, 42(1):81-6.
L. Zhang, H. Liu, Y. Xie, Y. Xia, B. Zhang, G. Shan and X. Li. 2016.
BACKGROUND: Right paraesophageal lymph nodes (RPELNs) are located behind right recurrent laryngeal nerve which often ignored in central compartment lymph nodes (LNs) dissection of papillary thyroid carcinoma (PTC) patients. The aim of this study was to identify the risk factors for RPELN metastasis and indications for RPELN dissection. METHODS: Medical record of 246 consecutive PTC patients (194 female, 52 male), who underwent total thyroidectomy (244 patients) or right lobectomy (2 patients) with central compartment LN dissection (13 ipsilateral and 233 bilateral), were reviewed. The RPELNs were kept separately during the operation. The clinical pathology data was collected and analyzed. RESULTS: RPELN metastasis was confirmed in 33 patients (13.4%) and were discovered in 18.5% (31/168) of right lesion, 34.4% (31/90) of right central group LN (rCLN) metastasis, 33.3% (18/54) of lateral compartment LN (LLN) metastasis, 25.7% (9/35) of

local recurrent patients respectively. The ultrasound suspected metastatic LNs, tumor diameter, tumor number, tumor location, and numbers of metastatic Delphian LNs, central group LNs (CLNs), rCLNs, and LLNs between patients with and without RPELN metastasis showed significant differences in univariate analysis (P < 0.05). In multivariate analysis, number of metastatic rCLNs (1-2: OR 13.6, 95% CI, 2.7-67.5; >==3: OR39.4, 95% CI, 7.7-200.9), right side tumor (OR 6.4, 95% CI, 1.1-35.6), and three or more metastatic LLNs (OR 3.5, 95% CI, 1.2-10.2) were independent risk factors for RPELN metastasis. CONCLUSIONS: PTC patients with right lobe lesions, especially with potential rCLN metastasis, are at considerable risk of RPELN metastasis. RPELN dissection should be considered in these patients.
PubMed-ID: 26615455
http://dx.doi.org/10.1016/j.ejso.2015.10.011

Stage II differentiated thyroid cancer: A mixed bag.
J Surg Oncol, 113(1):94-7.
K. A. Pathak, T. C. Klonisch and R. W. Nason. 2016.
BACKGROUND AND OBJECTIVES: AJCC-TNM Stage II well-differentiated thyroid cancer (WDTC) comprises T2N0M0 tumors in patients >/=45 years of age or metastatic WDTC in patients younger than 45 years. The objectives of this study were to assess the oncological outcome of stage II WDTC and to compare the oncological outcome of metastatic WDTC in patient younger (stage II) and older (stage IVC) than 45 years. METHODS: This study involved review of clinical presentation and oncological outcome of population cohort of 2,128 consecutive WDTC, diagnosed during 1970-2010 that includes 215 Stage II WDTC and 61 metastatic WDTC. Cox proportional hazard model was used to assess independent impact of prognostic factors on disease-specific survival (DSS) and disease-free survival (DFS) as calculated by Kaplan-Meier method. RESULTS: Metastatic and non-metastatic stage II WDTC had a 15-year DSS of 41.7% and 96.7%, respectively (P < 0.001). Multivariable analysis showed a 52 times higher risk of death in metastatic stage II WDTC and the DSS of metastatic stage II WDTC was not statistically different from that of stage IVC WDTC. CONCLUSION: Metastatic stage II WDTC is very different from non-metastatic stage II WDTC with oncological outcome similar to stage IVC WDTC.
PubMed-ID: 26628095
http://dx.doi.org/10.1002/jso.24089

Macrocalcitonin Is a Novel Pitfall in the Routine of Serum Calcitonin Immunoassay.
J Clin Endocrinol Metab, 101(2):653-8.
T. G. Alves, T. S. Kasamatsu, J. H. Yang, M. C. Meneghetti, A. Mendes, I. S. Kunii, S. C. Lindsey, C. P. Camacho, M. R. Dias da Silva, R. M. Maciel, J. G. Vieira and J. R. Martins. 2016.
CONTEXT: Calcitonin (CT) is a sensitive marker of medullary thyroid carcinoma (MTC) and is used for primary diagnosis and follow-up after thyroidectomy. However, persistently elevated CT is observed even after complete surgical removal without evidence of a recurrent or persistent tumor. OBJECTIVE: To investigate the presence of assay interference in the serum CT of MTC patients who are apparently without a structural disease. PATIENTS AND METHODS: We studied three index MTC cases for CT assay interference and 14 patients with metastatic MTC. The CT level was measured using an immunofluorometric assay. Screening for assay interference was performed by determination of CT levels before and after serum treatment with polyethylene glycol. Additionally, samples were analyzed by chromatography on ultra-performance liquid chromatography and protein A-Sepharose. RESULTS: Patients with biochemical and structural disease showed CT mean recovery of 84.1% after polyethylene glycol treatment, whereas patients suspected of interference showed recovery from 2-7%. The elution profile on UPLC showed that the immunometric CT from these three patients behaved like a high molecular mass aggregate (>300 kDa). Additionally, when these samples were applied to the protein A-Sepharose, CT immunoreactivity was retained on the column and was only released after lowering the pH. CONCLUSIONS: For the first time, our results show the presence of a novel pitfall in the CT immunoassay: "macrocalcitonin." Its etiology, frequency, and meaning remain to be defined, but its recognition is of interest and can help clinicians avoid unnecessary diagnostic investigations and treatment during the follow-up of MTC.
PubMed-ID: 26647152
http://dx.doi.org/10.1210/jc.2015-3137

The Role of Core-Needle Biopsy as a First-Line Diagnostic Tool for Initially Detected Thyroid Nodules.
Thyroid, 26(3):395-403.
C. H. Suh, J. H. Baek, J. H. Lee, Y. J. Choi, J. K. Kim, T. Y. Sung, J. H. Yoon and Y. K. Shong. 2016.
BACKGROUND: The aim of this study was to evaluate the role of core-needle biopsy (CNB) as a first-line diagnostic tool for initially detected thyroid nodules. METHODS: This observational study evaluated 632 initially detected thyroid nodules in 632 consecutive patients who underwent CNB between October 2008 and

December 2011. CNB results were categorized into the six categories of the Bethesda System. A final diagnosis of malignancy was based on surgery or CNB, whereas a final diagnosis of benign nodules was based on surgery, two benign biopsy results, or benign cytology of stable size after one year. The rates of Bethesda category 1 and inconclusive results, diagnostic performance, unnecessary surgery, and complications were evaluated. Subgroup analysis based on nodule size was performed. Risk factors for inconclusive results were evaluated by multivariate logistic regression analysis. RESULTS: The rates of Bethesda category 1 and inconclusive results by CNB were 1.3% and 5.9%, respectively. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of malignancy were 97.6%, 90.0%, 100%, 100%, and 92.3%, respectively. The rate of unnecessary surgery was 0.5%, and the complications rate was 0.2%. Based on subgroup analysis, the diagnostic performance was not significantly associated with nodule size. There were no independent risk factors associated with inconclusive results. CONCLUSION: CNB showed low rates of Bethesda category 1 and inconclusive results and a high diagnostic accuracy. CNB also minimized unnecessary surgery. CNB seems to be a promising diagnostic tool for patients with initially detected thyroid nodules.
PubMed-ID: 26651390
http://dx.doi.org/10.1089/thy.2015.0404

Socioeconomic Factors Affect Outcomes in Well-Differentiated Thyroid Cancer.
Otolaryngol Head Neck Surg, 154(3):440-5.
W. C. Swegal, M. Singer, E. Peterson, H. S. Feigelson, S. A. Kono, S. Snyder, T. A. Melvin, G. Calzada, N. R. Ghai, D. M. Saman and S. S. Chang. 2016.
OBJECTIVES: The effects of socioeconomic status (SES) on the incidence of well-differentiated thyroid cancer (WDTC) are well researched. However, the association between SES and outcomes is not delineated. Our objective was to determine if SES affected outcomes of WDTC. STUDY DESIGNS: Retrospective database review. SETTING: Tertiary care medical center. SUBJECTS AND METHODS: The Henry Ford Virtual Data Warehouse Tumor Registry was used to identify cases of WDTC. Socioeconomic data were obtained through the 2010 US Census: median household income, percentage below poverty line, median household size, percentage rent versus own property, and general demographics. Survival was the primary outcome. Disease-specific survival was also calculated. Cox proportional hazards were calculated and a multivariate analysis performed. RESULTS: There were 1317 patients with WDTC. In multivariable analysis, median household income (hazard ratio [HR]: 0.85, 95% confidence interval [95% CI]: 0.79-0.91), household size (HR: 1.49, 95% CI: 1.09-2.14), younger age (HR: 1.97, 95% CI: 1.74-2.23), and female sex (HR: 0.50, 95% CI: 0.37-0.69) were significantly associated with survival. Controlling for stage revealed percentage below poverty line (stage I, HR: 0.51, 95% CI: 1.34-1.78; stage IV, HR: 1.28, 95% CI: 1.04-1.57) and median household income (HR: 0.84, 95% CI: 0.71-0.99) to be significant factors in survival. Median household income was a statistically significant variable for disease-related death (HR: 0.82, 95% CI: 0.69-0.96) CONCLUSIONS: Along with effects on incidence, lower SES correlates with worse survival in WDTC. This suggests that a patient's economic background, with younger age and female sex, influences one's outcomes with regard to both overall and disease-specific death.
PubMed-ID: 26671905
http://dx.doi.org/10.1177/0194599815620778

Phase 2 clinical trial of sunitinib as adjunctive treatment in patients with advanced differentiated thyroid cancer.
Eur J Endocrinol, 174(3):373-80.
A. Bikas, P. Kundra, S. Desale, M. Mete, K. O'Keefe, B. G. Clark, L. Wray, R. Gandhi, C. Barett, J. S. Jelinek, J. A. Wexler, L. Wartofsky and K. D. Burman. 2016.
OBJECTIVE: Our objective was to evaluate the efficacy and safety of sunitinib following at least one course of radioactive iodine treatment in patients with advanced differentiated thyroid cancer (DTC). The study endpoints included best response rate (including best objective response rate) and progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, measurement of serum thyroglobulin (Tg), and toxicity evaluation. DESIGN AND METHODS: This was a single center, nonrandomized, open-label, phase 2 clinical trial. In total, 23 patients were enrolled and were treated with a starting daily, oral dose of 37.5 mg sunitinib. Patients were evaluated with imaging, laboratory tests, and physical examination periodically per protocol. RESULTS: The mean best response was a decrease of 17.2% (S.D. 22.8) in tumor sum from baseline. Six (26%) patients achieved a partial response (PR), and 13 (57%) had stable disease (SD) for a clinical benefit rate (PR+SD) of 83%. The overall median PFS was 241 days (interquartile limits, 114-518). No statistically significant difference was observed between the medians of the baseline and post-treatment Tg values (P=0.24). The most common adverse events included grades 1 and 2 decreases in blood cell counts (especially

leukocytes), diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, and hypertension. CONCLUSIONS: These data demonstrate that sunitinib exhibits significant anti-tumor activity in patients with advanced DTC. Since sunitinib was relatively well-tolerated, there is the potential for clinical benefit in these patients, and further investigation of this agent is warranted.
PubMed-ID: 26671977
http://dx.doi.org/10.1530/EJE-15-0930

EBSLN and Factors Influencing its Identification and its Safety in Patients Undergoing Total Thyroidectomy: A Study of 456 Cases.
World J Surg, 40(3):545-50.
K. Ravikumar, D. Sadacharan, S. Muthukumar, G. Mohanpriya, Z. Hussain and R. V. Suresh. 2016.
BACKGROUND: The external branch of the superior laryngeal nerve (EBSLN) is at surgical risk during superior thyroid pole ligation during thyroidectomy. Majority of studies have addressed the identification of these nerves and its reported incidence. Very few studies have addressed the relationship of these nerves with the volume of the thyroid gland and presence of toxicity. MATERIALS AND METHODS: A retrospective evaluation of 456 patients who underwent total thyroidectomy were analysed from the prospectively maintained database. The EBSLN was diligently identified and preserved before individual ligation of the superior thyroid pedicle. The nerve was graded as per the Cernea classification (type I, IIa and IIb). Goitres are classified into toxic & non-toxic based on hyperthyroidism, further sub classified as large (>50 cc) and small (</=50 cc) based on volume of each lobe. The grading of EBSLN was correlated with hyperthyroidism and volume of each lobe. RESULTS: In 456 patients (912 nerves), EBSLN was identified in 849/912(93.09%), type I in 156/912(17.1%), type IIa in 522/912(57.23%) and type IIb in 171/912(18.75%). The prevalence of large goitres was 180/912(19.73%).Type IIb nerve was predominantly seen in 161/180(89.4%) of large goitres. Type IIb nerves was more common in toxic 141/372(37.9%) than non-toxic lobes 25/540(5.46%). CONCLUSION: Large goitres are not uncommon in toxic cases. The EBSLN is at highest risk of injury in this subgroup of patients and surgical expertise is essential to identify this entity of EBSLN to perform a safe thyroidectomy.
PubMed-ID: 26675930
http://dx.doi.org/10.1007/s00268-015-3383-z

Impact of EMG Changes in Continuous Vagal Nerve Monitoring in High-Risk Endocrine Neck Surgery.
World J Surg, 40(3):672-80.
K. Brauckhoff, R. Vik, L. Sandvik, J. H. Heimdal, T. Aas, M. Biermann and M. Brauckhoff. 2016.
BACKGROUND: Continuous vagal intraoperative neuromonitoring (CIONM) of the recurrent laryngeal nerve (RLN) may reduce the risk of RLN lesions during high-risk endocrine neck surgery such as operation for large goiter potentially requiring transsternal surgery, advanced thyroid cancer, and recurrence. METHODS: Fifty-five consecutive patients (41 female, median age 61 years, 87 nerves at risk) underwent high-risk endocrine neck surgery. CIONM was performed using the commercially available NIM-Response 3.0 nerve monitoring system with automatic periodic stimulation (APS) and matching endotracheal tube electrodes (Medtronic Inc.). All CIONM events (decreased amplitude/increased latency) were recorded. RESULTS: APS malfunction occurred on three sides (3%). A total of 138 CIONM events were registered on 61 sides. Of 138, 47 (34%) events were assessed as imminent (13 events) or potentially imminent (34 events) lesions, whereas 91 (66%) were classified as artifacts. Loss of signal was observed in seven patients. Actions to restore the CIONM baseline were undertaken in 58/138 (42%) events with a median 60 s required per action. Four RLN palsies (3 transient, 1 permanent) occurred: one in case of CIONM malfunction, two sudden without any significant previous CIONM event, and one without any CIONM event. The APS vagus electrode led to temporary damage to the vagus nerve in two patients. CONCLUSIONS: CIONM may prevent RLN palsies by timely recognition of imminent nerve lesions. In high-risk endocrine neck surgery, CIONM may, however, be limited in its utility by system malfunction, direct harm to the vagus nerve, and particularly, inability to indicate RLN lesions ahead in time.
PubMed-ID: 26678490
http://dx.doi.org/10.1007/s00268-015-3368-y

[Bilateral vocal cord paresis after total thyroidectomy].
Chirurg, 87(1):65-8.
H. Dralle, J. Neu, T. J. Musholt and C. Nies. 2016.
A 66-year-old female patient complained of hoarseness and dyspnea under exertion following total thyroidectomy. Due to a faulty operating technique both nerves to the vocal cords were damaged. From the operation report it emerged that the dissection was carried out by protecting the border lamellae but the recurrent laryngeal nerve could not be found on both sides. This article presents the external expert opinion, the decision of the arbitration board and the assessment of the case by two specialist physicians.

PubMed-ID: 26683653
http://dx.doi.org/10.1007/s00104-015-0125-6

The HABP2 G534E variant is an unlikely cause of familial non-medullary thyroid cancer.
J Clin Endocrinol Metab:jc20153928.
R. Sahasrabudhe, J. Stultz, J. Williamson, P. Lott, A. Estrada, M. Bohorquez, C. Palles, G. Polanco-Echeverry, E. Jaeger, L. Martin, M. Magdalena Echeverry, I. Tomlinson and L. G. Carvajal-Carmona. 2015.
CONTEXT: A recent study reported the non-synonymous G534E (rs7080536, allele A) variant in the HABP2 gene as causal in familial non-medullary thyroid cancer (NMTC). OBJECTIVE: The objective of this study was to evaluate the causality of HABP2 G534E in the TCUKIN study, a multi-center population based study of NMTC cases from the British Isles. DESIGN AND SETTING: A case-control analysis of rs7080536 genotypes was performed using 2,105 TCUKIN cases and 5,172 UK controls. PARTICIPANTS: Cases comprised 2,105 NMTC cases. Patients sub-groups with papillary (N=1,056), follicular (N=691) and Hurthle cell (N=86) TC cases were studied separately. Controls comprised 5,172 individuals from the 1958 Birth Cohort (58C) and the National Blood Donor Service (NBS) study. The controls had previously been genotyped using genome-wide SNP arrays by the Wellcome Trust Case Control Consortium study. OUTCOME: Measures: Association between HABP2 G534E (rs7080536A) and NMTC risk was evaluated using logistic regression. RESULTS: The frequency of HABP2 G534E was 4.2% in cases and 4.6% in controls. We did not detect an association between this variant and NMTC risk (OR=0.896, 95% CI: 0.746-1.071, P=0.233). We also failed to detect an association between HABP2 G534E and cases with papillary (1056 cases, G534E frequency= 3.5%, OR=0.74, P=0.017), follicular (691 cases, G534E frequency= 4.7%, OR=1.00, P=1.000) or Hurthle cell (86 cases, G534E frequency= 6.3%, OR=1.40, P=0.279) histology. CONCLUSIONS: We found that HABP2 G534E is a low-to-moderate frequency variant in the British Isles and failed to detect an association with NMTC risk, independent of histological type. Hence, our study does not implicate HABP2 G534E or a correlated polymorphism in familial NMTC and additional data are required before using this variant in NMTC risk assessment.
PubMed-ID: 26691890
http://dx.doi.org/10.1210/jc.2015-3928

Clinical Analysis of Familial Nonmedullary Thyroid Carcinoma.
World J Surg, 40(3):570-3.
Q. Zhang, S. Yang, X. Y. Meng, G. Chen and R. Z. Pang. 2016.
OBJECTIVE: To analyze the clinical characteristics of familial nonmedullary thyroid carcinoma (FNMTC), in order to provide evidence for early diagnosis and treatment. METHODS: We retrospectively investigated the inpatients between September 2006 and September 2013 in the First Bethune Hospital of Jilin University, in which 78 patients with FNMTC from 31 families were analyzed by a comparison with 3445 control cases from the patients with sporadic nonmedullary thyroid carcinoma (SNMTC). RESULTS: There was no significant difference in gender, age, and tumor size between FNMTC and SNMTC patients. However, the characteristics of disease in multifoci, neck lymph node metastasis, invasion to the surrounding tissues, and coexistence with Hashimoto disease in two types of cancer patients show significant difference. They are: multifoci: 71.8% (56/78) in FNMTC versus 46.3% (1595/3445) in SNMTC; neck lymph node metastasis: 52.6% (41/78) in FNMTC versus 33.3% (1148/3445) in SNMTC; surrounding tissue invasion: 64.1% (50/78) in FNMTC versus 48.5% (1670/3445) in SNMTC; coexistence with Hashimoto disease: 30.8% (24/78) in FNMTC versus 20.0% (689/3445) in SNMTC. CONCLUSION: Lymph node metastasis, multifoci, invasion to the surrounding tissues, and combination with chronic lymphocytic thyroiditis are the main features of FNMTC, which suggests the extent of the operation for FNMTC patients should be amplified properly.
PubMed-ID: 26711636
http://dx.doi.org/10.1007/s00268-015-3342-8

Cost-Effectiveness of Diagnostic Lobectomy Versus Observation for Thyroid Nodules >4 cm.
Thyroid, 26(2):271-9.
L. Lee, E. J. Mitmaker, J. A. Chabot, J. A. Lee and J. H. Kuo. 2016.
BACKGROUND: The management of thyroid nodules >4 cm with benign cytology after fine-needle aspiration biopsy (FNAB) is controversial. FNAB is associated with a high false-negative rate in this setting, and may result in a delayed diagnosis and management of thyroid cancer. However, the majority of these nodules are benign. Therefore, the objective of this study was to determine the cost-utility of observation versus surgical management for thyroid nodules >4 cm with benign cytology after FNAB. METHODS: A microsimulation model comparing routine thyroid lobectomy with observation for low-risk patients with >4 cm thyroid nodules with benign FNAB cytology was constructed. Costs, quality-adjusted life-years (QALYs), and life-years gained were calculated over a lifetime time horizon from a U.S. Medicare perspective. RESULTS: The proportion of patients

undergoing thyroid lobectomy for benign final pathology was 40% in the observation strategy versus 66% in the surgical strategy (p < 0.001). Overall, the surgical strategy was associated with higher lifetime costs compared with the observation strategy (incremental difference: + US$12,992 [confidence interval (CI) 13,042-13,524]), but also more QALYs (+0.12 QALYs [CI 0.02-0.24]) and longer life expectancy (+1.67 years [CI 1.00-2.41]). Incremental lifetime costs were lower for patients <55 years compared with those >/=55 years (+11,181 vs. +14,811, p < 0.001). The probability of cost-effectiveness of the surgical strategy was 49% at a $100k/QALY threshold or 65% at a $100k/life-year gained threshold. CONCLUSIONS: Routine thyroid lobectomy is associated with improved outcomes at an acceptable cost compared with observation for thyroid nodules >4 cm with benign cytology after FNAB. Surgical resection may be a cost-effective strategy to rule out malignancy in these nodules.
PubMed-ID: 26715288
http://dx.doi.org/10.1089/thy.2015.0300

Mounting Evidence of the Potential Perils Associated with Continuous Intraoperative Neuromonitoring: Reply.
World J Surg, 40(3):770-1.
D. J. Terris, K. Chaung and W. S. Duke. 2016.
PubMed-ID: 26728889
http://dx.doi.org/10.1007/s00268-015-3384-y

Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid.
World J Surg, 40(3):516-22.
A. Miyauchi. 2016.
BACKGROUND: The incidence of thyroid cancer is increasing globally. This is mainly due to the increase in the detection of small papillary carcinomas, including papillary microcarcinomas (PMC) 1 cm or smaller. It was suggested recently that PMCs are overdiagnosed and overtreated. METHODS: In 1993, the author proposed a clinical trial to compare surgery and observation for low-risk PMC at doctors' meeting in Kuma Hospital, which was approved and the trial started in the same year. Patients choose immediate surgery or observation. This paper shares our 22-year experience with the active surveillance of more than 2000 patients with low-risk PMC and compares the outcomes of immediate surgery with that of active observation. RESULTS: The oncological outcomes of these management groups were similarly excellent. In our active surveillance trial on 1235 patients, 8% of patients showed tumor enlargement by 3 mm or more at 10 years of observation, and 3.8% of the patients showed novel appearance of lymph node metastasis at 10 years. Patients 40 years or younger tended to show progression of the disease. Patients with these slight progressions of the disease were successfully treated with a rescue surgery. None of the patients in both study groups died of the disease. However, incidences of unfavorable events, such as temporary vocal cord paralysis (VCP) and temporary and permanent hypoparathyroidism, were significantly higher in the immediate surgery group than in the observation group (4.1 vs. 0.6%, p < 0.0001; 16.7 vs. 2.8%, p < 0.0001; and 1.6 vs. 0.08%, p < 0.0001, respectively). Permanent VCP occurred in two of the surgery group. CONCLUSIONS: As a result, although we still offer two options, immediate surgery or observation, to patients with low-risk PMC at Kuma Hospital, we now strongly recommend observation as the best choice.
PubMed-ID: 26744340
http://dx.doi.org/10.1007/s00268-015-3392-y

Transcutaneous Ultrasonography in Early Postoperative Diagnosis of Vocal Cord Palsy After Total Thyroidectomy.
World J Surg, 40(3):665-71.
F. Borel, A. S. Delemazure, F. Espitalier, A. Spiers, E. Mirallie and C. Blanchard. 2016.
PURPOSE: This study evaluated the efficiency of transcutaneous laryngeal ultrasonography (TLUS) as an alternative to direct flexible laryngoscopy (DFL) in the early postoperative screening of vocal cord palsy (VCP) after total thyroidectomy, performed for benign and non-extensive malignant disease. METHODS: A prospective study was performed on patients who underwent total thyroidectomy between October 2013 and January 2015 at the Nantes University Hospital (France). Patients underwent DFL on postoperative day 1 performed by an otolaryngologist, followed by TLUS performed by a radiologist on postoperative day 1 or 2. RESULTS: One hundred and three (103) patients were included in this study, 17.5% were male and 82.5% were female, with a mean age of 51 +/- 12 years. Nine patients (9.5%) were diagnosed with postoperative VCP using DFL of these cases 2 were not completely resolved at 3 months postoperatively. Three cases of VCP (33%) were diagnosed using TLUS. TLUS had a sensitivity of 33% and a negative predictive value (NPV) of 95% for the diagnosis of postoperative VCP. Vocal cords (VC) were unassessable in 27.2% of patients. Unassessable VC were

significantly associated with male gender (p = 0.0001), age (p = 0.0001), weight (p = 0.002), operating time (p = 0.032), postoperative drainage (p = 0.001), and thyroid weight (p = 0.001). Independent risk factors in the multivariate analysis were male gender (p = 0.0001) and age (p = 0.0001). In the group of women under 50-year old, TLUS had a sensitivity of 50% and a NPV of 97.4%. CONCLUSION: TLUS sensitivity is insufficient in early postoperative screening of VCP after thyroid surgery. Ultrasonographic VCP diagnosis should be confirmed with DFL.
PubMed-ID: 26744341
http://dx.doi.org/10.1007/s00268-015-3393-x

Comparison of Bilateral Axillo-Breast Approach Robotic Thyroidectomy with Open Thyroidectomy for Graves' Disease.
World J Surg, 40(3):498-504.
H. Kwon, J. W. Yi, R. Y. Song, Y. J. Chai, S. J. Kim, J. Y. Choi and K. E. Lee. 2016.
BACKGROUND: There is an ongoing debate about whether robotic thyroidectomy (RT) is appropriate for Graves' disease. The aim of this study was to compare the safety of bilateral axillo-breast approach (BABA) RT with that of open thyroidectomy (OT) in patients with Graves' disease. METHODS: From January 2008 to June 2014, 189 (44 BABA RT and 145 OT) patients underwent total thyroidectomy for Graves' disease. Recurrence of Graves' disease, intraoperative blood loss, hospital stay, and complication rates including recurrent laryngeal nerve (RLN) palsy and hypoparathyroidism were analyzed between BABA RT and OT groups, after propensity score matching according to age, gender, body mass index, surgical indication, the extent of operation, excised thyroid weight, and follow-up period. RESULTS: No patient experienced recurrence of Graves' disease after median follow-up of 35.0 months. Intraoperative blood loss (151.8 +/- 165.4 mL vs. 134.5 +/- 75.4 mL; p = 0.534) and hospital stay (3.4 +/- 0.7 day vs. 3.3 +/- 0.7 day; p = 0.564) were not different between BABA RT and OT groups. Complication rates including transient RLN palsy (11.4 vs. 11.4%; p = 1.000), transient hypoparathyroidism (18.2 vs. 20.5%; p = 0.787), permanent RLN palsy (0 vs. 2.3%; p = 0.315), and permanent hypoparathyroidism (2.3 vs. 2.3%; p = 1.000) were also comparable between groups. CONCLUSIONS: BABA RT for Graves' disease showed comparable surgical completeness and complications to conventional OT. BABA RT can be recommended as an alternative surgical option for patients with Graves' disease who are concerned about cosmesis.
PubMed-ID: 26754077
http://dx.doi.org/10.1007/s00268-016-3403-7

Long-Term Outcome of Follicular Thyroid Carcinoma in Patients Undergoing Surgical Intervention for Skeletal Metastases.
World J Surg, 40(3):562-9.
A. Mishra, C. Kumar, G. Chand, G. Agarwal, A. Agarwal, A. K. Verma and S. K. Mishra. 2016.
BACKGROUND: A large proportion of follicular thyroid carcinoma (FTC) patients in developing countries present with overt skeletal metastases (SM). These patients often require surgical interventions for prevention of morbidity, palliation of symptoms, and facilitation of radioiodine therapy (RAIT). Scarce literature is available about the long-term outcome of such patients. The aim of this study was to evaluate the long-term outcome of FTC patients undergoing surgical intervention for SM. METHODS: We retrospectively reviewed the data of FTC patients with SM (January 1990-December 2011). Out of 91 patients with SM, 32 had surgical interventions for SM. All had total thyroidectomy performed. RESULTS: The mean age of the patients was 48.5 years (M:F = 1:2). Majority (93.7%) had synchronous metastases and 22% had multiple SM. The surgical interventions for SM included: laminectomy (50%), resection of skull metastases (18.8%), resection of manubrium sterni (18.8%), partial clavicle excision (9.4%), and hemimandibulectomy (3.1%). The main intents were palliation (50%) and facilitation of RAIT (37.5%). 84% patients received RAIT. Median follow-up was 52 months (mean = 50 +/- 37). Five- (56 vs 63%) and 10-year (28 vs 23%) overall survival (OS) did not differ significantly (p = 0.968) from those not having interventions for SM. On univariate analysis tumor invasion (p = 0.006) and synchronous presentation of SM (p = 0.043) were significant risk factors for OS, whereas on multivariate analysis tumor invasion (p = 0.006) was significant. CONCLUSIONS: Surgical interventions directed at SM in FTC patients with overt multiple SM might not result in improve OS. However, considering reasonable long-term survival, interventions should be considered for desired palliation and preservation of body function.
PubMed-ID: 26757717
http://dx.doi.org/10.1007/s00268-016-3402-8

Prognosis After Brain Metastasis from Differentiated Thyroid Carcinoma.
World J Surg, 40(3):574-81.
F. Saito, T. Uruno, H. Shibuya, W. Kitagawa, M. Nagahama, K. Sugino and K. Ito. 2016.
BACKGROUND: In patients with differentiated thyroid carcinoma (DTC), lung and bone metastasis sometimes occur. However, brain metastasis (BM) is extremely rare. Because most previous reports about BM from DTC included a relatively small number of cases, the clinical characteristics and outcomes of BM are still unclear. PATIENTS AND METHODS: Between 1965 and 2013, among 961 patients who had died because of DTC, 24 patients were diagnosed with BM from DTC. One patient with BM from DTC is still alive. To identify the prognostic factors for longer survival after BM, the medical records of these 25 patients were retrospectively reviewed. RESULTS: The median age at BM diagnosis was 66 years. Typical symptoms associated with BM had appeared in 20 patients (80%). The Karnofsky Performance Status (KPS) was good (>/=70) in 10 patients and poor (</=60) in 15 patients. Seven patients had a single intracranial lesion of BM, 6 patients had 2 or 3 lesions, and 9 patients had 4 or more. Eleven patients did not receive any treatment for BM, and 14 patients underwent surgical resection, radiation therapy, or both. One-year and 5-year disease-specific survival rates were 28 and 10.6%, respectively. Good KPS (>/=70), small number of intracranial lesions (</=3), and treatment for BM were prognostic factors for long survival on univariate analysis ($p < 0.05$). On multivariate analysis, only treatment for BM was significant. CONCLUSION: Treatment of BM from DTC is indicated in patients who have a good KPS and fewer intracranial lesions, and some of them may achieve long survival.
PubMed-ID: 26762631
http://dx.doi.org/10.1007/s00268-016-3405-5

Completion thyroidectomy and total thyroidectomy for differentiated thyroid cancer: Comparison and prediction of postoperative hypoparathyroidism.
J Surg Oncol, 113(5):522-5.
X. Wang, T. Xing, T. Wei and J. Zhu. 2016.
BACKGROUND: Consensus regarding the difference of postoperative hypoparathyroidism following completion thyroidectomy (CT) and total thyroidectomy (TT) has yet to be reached. We compare the occurrence of postoperative hypoparathyroidism between CT and TT for differentiated thyroid cancer (DTC), and explore the predictive factors for postoperative hypoparathyroidism. METHODS: We retrospectively reviewed 221 consecutive patients underwent CT or TT for DTC between February 2012 and March 2014. Patients' demographic and clinical data of the two groups were analyzed. RESULTS: There were 57 CTs and 164 TTs. Temporary hypoparathyroidism occurred in 12.3% (7 of 57) and 28.0% (46 of 164) of patients in the CT and TT groups, respectively. In univariate analysis, type of surgical procedure (CT or TT) and extent of central lymph node dissection (CND) (unilateral or bilateral) were significantly associated with the postoperative temporary hypoparathyroidism ($P < 0.05$). Multivariate analysis showed that only the extent of CND was an independent risk factor for temporary hypoparathyroidism. CONCLUSIONS: Although temporary hypoparathyroidism was lower in the CT group, our analysis indicates the difference is due to the extent of CND rather than type of surgical procedure (CT vs. TT). Only bilateral CND is an independent risk factor for temporary hypoparathyroidism after thyroidectomy. J. Surg. Oncol. 2016;113:522-525. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 26776666
http://dx.doi.org/10.1002/jso.24159

Continuous Vagal Nerve Monitoring: Too Much of a Good Thing?
World J Surg, 40(3):681-2.
D. J. Terris. 2016.
PubMed-ID: 26787176
http://dx.doi.org/10.1007/s00268-016-3406-4

Preablative Stimulated Thyroglobulin Correlates to New Therapy Response System in Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 101(3):1307-13.
X. Yang, J. Liang, T. Li, T. Zhao and Y. Lin. 2016.
CONTEXT: Studies suggested a potential value of preablative stimulated thyroglobulin (ps-Tg) on predicting the recurrent and persistent diseases of differentiated thyroid cancer, whereas its correlations with therapeutic response remain uncertain. OBJECTIVE: To establish the correlation between ps-Tg and therapeutic response proposed in 2015 American Thyroid Association guidelines, and calculate a cutoff ps-Tg threshold for predicting a poor response. DESIGN/SETTING: Patients who underwent total thyroidectomy and radioactive iodine therapy in a university hospital participated in this retrospective study. PATIENTS: Totally, 452 patients with differentiated thyroid cancer were followed for a median of 38 months and were divided into three groups in

terms of ps-Tg level: group 1, less than 1 ng/ml (n = 82); group 2, 1-10 ng/ml (n = 173); and group 3, at least 10 ng/ml (n = 197). MAIN OUTCOME MEASURE: Clinical outcomes were assessed based on response to therapy restaging system, dividing responses into excellent, indeterminate, biomedical incomplete, and structural incomplete (SIR). RESULTS: Therapeutic responses could be obviously distinguished by different ps-Tg strata. SIR was identified in none of group 1, 1.73% of group 2, and 42.74% of group 3, respectively (chi(2) = 123.037, P < .001). A cutoff value of ps-Tg at 26.75 ng/ml was obtained by receiver operating characteristic curve for differentiating SIR from either excellent, indeterminate, or biomedical incomplete responses. The area under curve was 0.947 and negative predictive value was 96.99%. Ps-Tg was an independent predictive variable of SIR (odds ratio, 42.312; P < .001). CONCLUSIONS: Ps-Tg has a great performance in predicting therapeutic response and providing incremental value for decision making of radioactive iodine therapy, especially for patients with high ps-Tg level.
PubMed-ID: 26789779
http://dx.doi.org/10.1210/jc.2015-4016

Impact of microscopic extra-nodal extension (ENE) on locoregional recurrence following curative surgery for papillary thyroid carcinoma.
J Surg Oncol, 113(5):526-31.
B. H. Lang, T. W. Shek and K. Y. Wan. 2016.
BACKGROUND: The presence of microscopic extra-nodal extension (ENE) may increase locoregional recurrence (LRR) in papillary thyroid carcinoma (PTC). We aimed to evaluate the association between microscopic ENE, response to initial therapy and LRR risk following total thyroidectomy, therapeutic neck dissection, and radioactive iodine (RAI) ablation in PTC. METHODS: Of the 369 eligible PTC patients, 264 (71.5%) did not have microscopic ENE (group I) while 105 (28.5%) did (group II). All presented with clinical nodal metastasis (cN1) and underwent therapeutic neck dissection and RAI ablation. Biochemical incompleteness meant post-ablation stimulated thyroglobulin (sTg) >10 ng/ml. Multivariate analyses were conducted to identify independent factors for LRR. RESULTS: Biochemical incompleteness was significantly more common group II (43.8% vs. 17.4%, P < 0.05). The 10-year locoregional free-survival was significantly worse in group II than I (52.0% vs. 86.2%, P = 0.005). After adjusting for other significant factors, age <45 (P < 0.05), multifocality (P < 0.05), presence of ENE (P = 0.027) were independent risk factors of LRR. The number and size of positive lymph nodes were not independent factors. CONCLUSIONS: Patients with microscopic ENE were significantly more likely to have biochemical incompleteness after initial therapy. After adjusting for other significant primary and nodal characteristics, microscopic ENE was an independent factor for LRR in patients with cN1. J. Surg. Oncol. 2016;113:526-531. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 26792294
http://dx.doi.org/10.1002/jso.24180

Changing trends in the clinicopathological features and clinical outcomes of medullary thyroid carcinoma.
J Surg Oncol, 113(2):152-8.
H. Kwon, W. G. Kim, T. Y. Sung, M. J. Jeon, D. E. Song, Y. M. Lee, 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. 2016.
BACKGROUND: The early detection of papillary thyroid cancer has contributed to the increase in the incidence and improved clinical outcomes. However, recent changes of medullary thyroid carcinoma (MTC) over time remain unclear. We evaluated changes of the clinicopathological characteristics and clinical outcomes in patients with MTC in recent years. METHODS: A total of 109 MTC patients were classified based on the year of initial surgery: 1996-2000 (n = 14), 2001-2006 (n = 39), and 2007-2011 (n = 56). RESULTS: The primary tumor size significantly decreased and the proportion of microMTCs (size </=1 cm) increased over time (P = 0.002 and P < 0.001, respectively). The proportion of patients with cervical lymph node (LN) metastasis significantly decreased (P = 0.037), and the ratio of metastatic LNs significantly decreased (P = 0.011). Disease-free survival (DFS) rate of patients was significantly improved over time (P = 0.007). There was no significant difference in DFS between microMTC and macroMTC patients. However, more advanced LN stage patients demonstrated more recurrences (P < 0.001). Especially, there were significantly more recurrences in patients with N1b diseases in comparison with patients without cervical LN metastases (P < 0.001). CONCLUSIONS: The prognosis of MTC patients has significantly improved in recent years. These changes could be associated with the early diagnosis before development of lateral and extensive cervical LN metastases. J. Surg. Oncol. 2016;113:152-158. (c) 2015 Wiley Periodicals, Inc.
PubMed-ID: 26799259
http://dx.doi.org/10.1002/jso.24126

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

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

Predictors for papillary thyroid cancer persistence and recurrence: a retrospective analysis with a 10-year follow-up cohort study.
Clin Endocrinol (Oxf),
T. P. de Castro, W. Waissmann, T. C. Simoes, R. C. de Mello and D. P. Carvalho. 2016.
OBJECTIVE: We aimed to determine outcome predictors of papillary thyroid cancer (PTC) persistence and recurrence, separately. CONTEXT: The factors contributing to either persistence or recurrence of PTC are poorly defined, since both outcomes are usually evaluated together. DESIGN AND PATIENTS: In this 10-year follow-up cohort study, 190 PTC patients were evaluated (18-85 years old; registered from 01/01/1990 to 12/31/1999 at a Brazilian Cancer Care referral Hospital). After initial surgery, we examined persistence (disease detected up to 1 year), recurrence (disease detected after 1 year) and PTC-free status (disease absence during

follow-up). MEASUREMENTS: Outcome predictors were modeled using multinomial logit regression analysis. RESULTS: The univariate analysis showed that persistence and recurrence were significantly associated with lymph node metastasis (OR=12.33; OR=2.84, respectively), local aggressiveness (OR=5.22; OR=3.35), and extrathyroidal extension (OR=5.07; OR=7.11). Persistence was associated with male sex (OR=3.49), age above 45 years old at diagnosis (OR=1.03), macroscopic lymph node metastasis (OR=5.85), local aggressiveness (OR=5.22), each 1-cm tumor size increase (OR=1.34), a cancer care referral hospital as the place of initial surgery (OR=2.3), thyroidectomy or near total-thyroidectomy) OR=3.03) and neck dissection (OR=3.19). Recurrence was associated with the time of radioactive iodine (131 I) therapy (OR=3.71). After data modeling, persistence was associated with macroscopic lymph node metastasis (OR=6.17), 1-cm increases in tumor size (OR=1.30), and thyroidectomy or near total-thyroidectomy (OR=3.82); while recurrence was associated with surgery at referral hospital (OR=3.79). CONCLUSIONS: The best predictors of persistence were tumor size and macroscopic lymph node metastasis; when the initial surgery is of quality, the recurrence depends more on tumor's biology aspects. This article is protected by copyright. All rights reserved.
PubMed-ID: 26834009
http://dx.doi.org/10.1111/cen.13032

Subclonality for BRAF Mutation in Papillary Thyroid Carcinoma Is Associated With Earlier Disease Stage.
J Clin Endocrinol Metab, 101(4):1407-13.
A. Finkel, L. Liba, E. Simon, T. Bick, E. Prinz, E. Sabo, O. Ben-Izhak and D. Hershkovitz. 2016.
Papillary thyroid carcinoma samples were analyzed for the presence of BRAF mutation status subclonality using computerized morphometry and molecular tools. BRAF mutation subclonality was associated with earlier disease stage.
PubMed-ID: 26835544
http://dx.doi.org/10.1210/jc.2015-4031

Apparently intrathyroid papillary thyroid carcinoma >1 and </=4 cm: is the need for completion thyroidectomy common among patients submitted to lobectomy?
Clin Endocrinol (Oxf), 85(1):150-1.
P. W. Rosario, G. F. Mourao and M. R. Calsolari. 2016.
PubMed-ID: 26840381
http://dx.doi.org/10.1111/cen.13034

Innervation of the human cricopharyngeal muscle by the recurrent laryngeal nerve and external branch of the superior laryngeal nerve.
Langenbecks Arch Surg,
M. Uludag, N. Aygun and A. Isgor. 2016.
PURPOSE: The major component of the upper esophageal sphincter is the cricopharyngeal muscle (CPM). We assessed the contribution of the laryngeal nerves to motor innervation of the CPM. METHODS: We performed an intraoperative electromyographic study of 27 patients. The recurrent laryngeal nerve (RLN), vagus nerve, external branch of the superior laryngeal nerve (EBSLN), and pharyngeal plexus (PP) were stimulated. Responses were evaluated by visual observation of CPM contractions and electromyographic examination via insertion of needle electrodes into the CPM. RESULTS: In total, 46 CPMs (24 right, 22 left) were evaluated. PP stimulation produced both positive visual contractions and electromyographic (EMG) responses in 42 CPMs (2080 +/- 1583 muV). EBSLN stimulation produced visual contractions of 28 CPMs and positive EMG responses in 35 CPMs (686 +/- 630 muV). Stimulation of 45 RLNs produced visible contractions of 37 CPMs and positive EMG activity in 41 CPMs (337 +/- 280 muV). Stimulation of 42 vagal nerves resulted in visible contractions of 36 CPMs and positive EMG responses in 37 CPMs (292 +/- 229 muV). Motor activity was noted in 32 CPMs by both RLN and EBSLN stimulation, 9 CPMs by RLN stimulation, and 3 CPMs by EBSLN stimulation; 2 CPMs exhibited no response. CONCLUSIONS: This is the first study to show that the EBSLN contributes to motor innervation of the human CPM. The RLN, EBSLN, or both of the nerves innervate the 90, 75, and 70 % of the CPMs ipsilaterally, respectively.
PubMed-ID: 26843022
http://dx.doi.org/10.1007/s00423-016-1376-5

Does microscopically involved margin increase disease recurrence after curative surgery in papillary thyroid carcinoma?
J Surg Oncol, 113(6):635-9.
B. H. Lang, T. W. Shek and K. Y. Wan. 2016.
BACKGROUND: The prognostic significance of microscopically involved margin in papillary thyroid carcinoma (PTC) following curative surgery remains unclear. We aimed to evaluate the impact of an involved margin and its location (anterior vs. posterior) on disease recurrence. METHODS: Of the 638 eligible patients, 538 (85.9%) did not have an involved margin (group I) while 100 (14.1%) did (group II). The latter group was further classified according to its location relative to the surface of the thyroid gland (anterior or posterior). A multivariate analysis was conducted to identify independent factors for recurrence risk. RESULTS: After a mean of 130.1 +/- 93.5 months, 22 patients had disease recurrence. The 10-year disease-free survival (DFS) was significantly worse in group II (95.0% vs. 97.0%, P = 0.011). After adjusting other significant factors, involved margin was not an independent risk factor for disease recurrence (P = 0.358). Compared to a negative margin, an anterior involved margin did not pose increased recurrence risk (HR = 1.21, 95%CI = 0.93-500.00, P = 0.368), whereas a posterior involved margin had almost 23 times higher recurrence risk (HR = 22.95; 95%CI = 4.33-121.70, P < 0.001). CONCLUSIONS: Overall, a microscopically involved margin was not an independent factor for DFS. However, although an anterior involved margin itself did not increase disease recurrence, a posterior involved margin did. J. Surg. Oncol. 2016;113:635-639. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 26843438
http://dx.doi.org/10.1002/jso.24194

Predicting the Risk of Recurrence Before the Start of Antithyroid Drug Therapy in Patients With Graves' Hyperthyroidism.
J Clin Endocrinol Metab, 101(4):1381-9.
X. G. Vos, E. Endert, A. H. Zwinderman, J. G. Tijssen and W. M. Wiersinga. 2016.
Genotyping increases the accuracy of a clinical score (based on pretreatment age, goiter size, FT4, TBII) for predicting recurrence of Graves' hyperthyroidism after a course of antithyroid drugs: a prospective study.
PubMed-ID: 26863422
http://dx.doi.org/10.1210/jc.2015-3644

Parathyroid gland angiography with indocyanine green fluorescence to predict parathyroid function after thyroid surgery.
Br J Surg, 103(5):537-43.
J. Vidal Fortuny, V. Belfontali, S. M. Sadowski, W. Karenovics, S. Guigard and F. Triponez. 2016.
BACKGROUND: Postoperative hypoparathyroidism remains the most common complication following thyroidectomy. The aim of this pilot study was to evaluate the use of intraoperative parathyroid gland angiography in predicting normal parathyroid gland function after thyroid surgery. METHODS: Angiography with the fluorescent dye indocyanine green (ICG) was performed in patients undergoing total thyroidectomy, to visualize vascularization of identified parathyroid glands. RESULTS: Some 36 patients underwent ICG angiography during thyroidectomy. All patients received standard calcium and vitamin D supplementation. At least one well vascularized parathyroid gland was demonstrated by ICG angiography in 30 patients. All 30 patients had parathyroid hormone (PTH) levels in the normal range on postoperative day (POD) 1 and 10, and only one patient exhibited asymptomatic hypocalcaemia on POD 1. Mean(s.d.) PTH and calcium levels in these patients were 3.3(1.4) pmol/l and 2.27(0.10) mmol/l respectively on POD 1, and 4.0(1.6) pmol/l and 2.32(0.08) mmol/l on POD 10. Two of the six patients in whom no well vascularized parathyroid gland could be demonstrated developed transient hypoparathyroidism. None of the 36 patients presented symptomatic hypocalcaemia, and none received treatment for hypoparathyroidism. CONCLUSION: PTH levels on POD 1 were normal in all patients who had at least one well vascularized parathyroid gland demonstrated during surgery by ICG angiography, and none required treatment for hypoparathyroidism.
PubMed-ID: 26864909
http://dx.doi.org/10.1002/bjs.10101

Clinical Relationship Between IgG4-Positive Hashimoto's Thyroiditis and Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 101(4):1516-24.
Y. Yu, J. Zhang, G. Lu, T. Li, Y. Zhang, N. Yu, Y. Gao, Y. Gao and X. Guo. 2016.
PTC may be facilitated by preexisting autoimmune inflammation of IgG4-positive HT. IgG4-positive HT with PTC cases may have worse clinical outcomes. The high levels of TgAb IgG4 might present a risk factor for PTC.
PubMed-ID: 26866571
http://dx.doi.org/10.1210/jc.2015-3783

Management of patients with Graves' orbitopathy: initial assessment, management outside specialized centres and referral pathways.
Clin Endocrinol (Oxf), 84(5):662-3.
J. Orgiazzi. 2016.
PubMed-ID: 26866718
http://dx.doi.org/10.1111/cen.13039

Time Course and Predictors of Structural Disease Progression in Pulmonary Metastases Arising from Follicular Cell-Derived Thyroid Cancer.
Thyroid, 26(4):518-24.
M. M. Sabra, R. Ghossein and R. M. Tuttle. 2016.
BACKGROUND: With the advent of molecular targeted therapy for the management of radioactive iodine (RAI) refractory, progressive metastatic thyroid cancer, it becomes important to define the time course and risk factors for structural disease progression in follicular cell-derived thyroid cancer (FCDTC) patients. This will help in defining the optimal time to start these therapies and better define their impact on structural disease progression. OBJECTIVES: This retrospective review of 199 consecutive patients with FCDTC presenting with lung metastasis examined the progression-free survival (PFS) in thyroid cancer patients with lung metastasis treated with surgery and RAI, and who had not received molecular targeted therapy or chemotherapy. RESULTS: The median overall survival (OS) was 10.45 years, while the median PFS was 3.65 years. A strong correlation was found between OS and PFS. PFS is shorter in patients with RAI refractory disease, poorly differentiated/Hurthle cell histologies, male sex, fluorodeoxyglucose-avid metastatic foci, older age (>45 years), and pulmonary metastases >1 cm. At final follow-up (a median of 6.9 years from lung metastasis diagnosis), 68% of the patients had progressed and 46% had died. CONCLUSIONS: With the exception of younger patients with low disease burden, most patients presenting with lung metastasis from FCDTC (RAI avid and RAI refractory) using standard-of-care approaches will have disease progression on long-term follow-up. Additional studies are needed to identify novel therapies that would improve the PFS of such patients.
PubMed-ID: 26872102
http://dx.doi.org/10.1089/thy.2015.0395

Recurrent laryngeal nerve injury with incomplete loss of electromyography signal during monitored thyroidectomy-evaluation and outcome.
Langenbecks Arch Surg,
C. W. Wu, M. Hao, M. Tian, G. Dionigi, R. P. Tufano, H. Y. Kim, K. Y. Jung, X. Liu, H. Sun, I. C. Lu, P. Y. Chang and F. Y. Chiang. 2016.
PURPOSE: During monitored thyroidectomy, a partially or completely disrupted point of nerve conduction on the exposed recurrent laryngeal nerve (RLN) indicates true electrophysiologic nerve injury. Complete loss of signal (LOS; absolute threshold value <100 muV) at the end of operation often indicates a postoperative vocal cord (VC) palsy. However, the evaluation for the injured RLN with incomplete LOS and its functional outcome has not been well described. METHODS: Three hundred twenty-three patients with 522 RLNs at risk who underwent standardized monitored thyroidectomy were enrolled. The RLN was routinely stimulated at the most proximal (R2p signal) and distal (R2d signal) ends of exposure after thyroid resection to determine if there was an injured point on the RLN. Pre- and postoperative VC function was routinely examined. RESULTS: Twenty-nine RLNs (5.6 %) were detected with an injury point. Five nerves had complete LOS and other 24 nerves had incomplete LOS where the R2p/R2d reduction (% of amplitude reduction compared with proximal to distal RLN stimulation) ranged from 22 to 79 %. Postoperative temporary VC palsy was noted in those five RLNs with complete LOS (final vagal signal, V2 < 100 muV) and four RLNs with incomplete LOS (R2p/R2d reduction 62-79 %; V2 181-490 muV). In the remaining 20 nerves with R2p/R2d reduction </=53 % (V2 373-1623 muV), all showed normal VC mobility. Overall, false negative results were found in two RLNs (0.4 %) featuring unchanged V2 and R2p/R2d but developed VC palsy. CONCLUSIONS: Testing and comparing the R2p/R2d signal is a simple and useful procedure to evaluate RLN injury after its dissection and predict functional outcome. When the relative threshold value R2p/R2d reduction reaches over 60 %, surgeon should consider the possibility of postoperative VC palsy.
PubMed-ID: 26886281
http://dx.doi.org/10.1007/s00423-016-1381-8

Visualizing fewer parathyroid glands may be associated with lower hypoparathyroidism following total thyroidectomy.
Langenbecks Arch Surg, 401(2):231-8.
B. H. Lang, D. T. Chan and F. C. Chow. 2016.
BACKGROUND: It remains uncertain whether the number of parathyroid glands (PGs) seen during extra-capsular dissection impacts short- and long-term hypoparathyroidism. Our study aimed to address this by analyzing patients who underwent total thyroidectomy for benign disease. METHODS: Consecutive patients undergoing total thyroidectomy were analyzed. The extra-capsular dissection technique was performed throughout the study period. The number of PGs identified, auto-transplanted and found on excised specimen was recorded prospectively. The number of PGs in situ was equaled to four minus the number of PGs auto-transplanted and PGs found on specimen. Temporary hypoparathyroidism was defined as serum adjusted calcium <2.00 mol/L 24 h after surgery and/or need for oral supplements while protracted hypoparathyroidism meant subnormal PTH (<1.2 pmol/L) at 4-6 weeks and/or need for >6-week oral supplements. Permanent hypoparathyroidism was defined as need for oral supplements for >/=1 year. RESULTS: Five-hundred and sixty-nine patients were eligible for analysis. After adjusting for other significant parameters, greater number of PGs identified was an independent risk factor for temporary ($p < 0.001$) and protracted hypoparathyroidism ($p = 0.007$). Mean recovery time from protracted hypoparathyroidism for identifying </=three PGs was significantly shorter than identifying all four PGs (2.8 vs. 7.8 months, $p < 0.001$). Chance of having all four PGs in situ decreased with greater number of PGs identified ($p < 0.001$). CONCLUSIONS: When the extra-capsular technique was adopted during total thyroidectomy, identifying fewer PGs in their orthotopic positions not only lowered risk of temporary and protracted hypoparathyroidism but also shortened recovery from protracted hypoparathyroidism.
PubMed-ID: 26892668
http://dx.doi.org/10.1007/s00423-016-1386-3

The Impact of Metastatic Lymph Nodes on Risk Stratification in Differentiated Thyroid Cancer: Have We Reached a Higher Level of Understanding?
Thyroid, 26(4):481-8.
M. L. Urken, G. C. Haser, I. Likhterov and B. M. Wenig. 2016.
BACKGROUND: The revised American Thyroid Association (ATA) management guidelines for differentiated thyroid cancer emphasize a variety of clinicopathologic features of metastatic lymph nodes in determining the risk of recurrence. The mere presence of a positive node is not sufficient to confer reliable prognostic significance. The number and size of lymph nodes, as well as the presence of extranodal extension (ENE), impact risk stratification. Moreover, the presence of clinically evident lymph nodes is important for determining risk of recurrence. A patient's place on the risk spectrum has ramifications for the management of differentiated thyroid cancer. However, there are inherent inconsistencies in the identification and characterization of metastatic lymph nodes. Moreover, the significance of ENE must be clarified. SUMMARY: There are many obstacles to the consistent reporting of metastatic lymph nodes. What constitutes a "clinically evident" lymph node has not been well defined, lacks precision, and varies depending on clinical context, as well as the experience of the surgeon and the ultrasonographer. The number of lymph nodes sampled by surgeons and reported by pathologists may vary from institution to institution. The literature on ENE has been limited by the fact that the definition of ENE has not been standardized. Nevertheless, 17/19 manuscripts reviewed herein suggest that ENE confers a worse prognosis. The ATA risk stratification for metastatic lymph nodes published in the 2015 guidelines combines clinicopathological features that are variably identified and reported across institutions. This review brings into question the significance of the number of nodes with ENE, a factor that is used as an important stratifying variable in the latest guidelines. CONCLUSIONS: Metastatic lymph nodes do not all carry the same prognostic significance, but a risk assignment based on the ATA guidelines is limited by a lack of standardization in clinical and pathologic definitions, lymph node sampling, and reporting. This study reviews the limitations of prior studies on ENE and concludes that the body of the evidence reported in those studies suggests that ENE increases the risk of recurrence. The impact of ENE in lymph nodes in thyroid cancer risk stratification should be reconsidered.
PubMed-ID: 26892765
http://dx.doi.org/10.1089/thy.2015.0544

Effects of Dosimetrically Guided I-131 Therapy on Hematopoiesis in Patients With Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 101(4):1762-9.
A. Bikas, M. Schneider, S. Desale, F. Atkins, M. Mete, K. D. Burman, L. Wartofsky and D. Van Nostrand. 2016.
A retrospective analysis was performed to evaluate the effects of dosimetrically-guided I-131 treatment on

hematopoiesis. Statistically significant decreases in CBC parameters following a specific time-pattern were shown.
PubMed-ID: 26900639
http://dx.doi.org/10.1210/jc.2015-3544

Hypothyroidism Following Hemithyroidectomy: Incidence, Risk Factors, and Clinical Characteristics.
J Clin Endocrinol Metab, 101(4):1429-36.
D. Ahn, J. H. Sohn and J. H. Jeon. 2016.
We conducted a retrospective cohort study involving 405 patients to evaluate characteristics of hypothyroidism following hemithyroidectomy, suggesting an appropriate follow-up strategy after thyroid-conserving surgery.
PubMed-ID: 26900643
http://dx.doi.org/10.1210/jc.2015-3997

Diagnosis of Metastasis to the Thyroid Gland: Comparison of Core-Needle Biopsy and Fine-Needle Aspiration.
Otolaryngol Head Neck Surg, 154(4):618-25.
S. H. Choi, J. H. Baek, E. J. Ha, Y. J. Choi, D. E. Song, J. K. Kim, K. W. Chung, T. Y. Kim and J. H. Lee. 2016.
OBJECTIVES: Early detection and diagnosis of metastasis to the thyroid gland is important. This study aims to evaluate the clinical value of core-needle biopsy (CNB) by comparing the results of CNB and fine-needle aspiration (FNA) in patients with clinically suspected metastasis to the thyroid gland. STUDY DESIGN: Case series with chart review. SETTING: Tertiary referral practice. SUBJECTS: Fifty-two thyroid nodules from 52 patients with clinically suspected metastasis to the thyroid gland (mean age, 62.8 years). METHODS: Of these 52 patients, FNA was initially used in 41 patients and CNB in 20 patients (11 patients as the initial approach and 9 patients after inconclusive FNA results). Ultrasound features of metastasis to the thyroid gland were evaluated. The diagnostic performance, repeated diagnostic examination rate, and diagnostic surgery rate were evaluated for FNA and CNB. RESULTS: Among these 52 patients, 46 were diagnosed with thyroid metastases and 6 were diagnosed with primary thyroid cancer. Common ultrasound features were an ovoid to round shape (58.7%), ill-defined margin (56.5%), hypoechogenicity (65.2%), and no calcifications (87.0%). Core-needle biopsy achieved a significantly higher sensitivity than FNA (100.0% vs 58.6%, P = .008) without any false-negative results. Both the repeated diagnostic examination rate and the diagnostic surgery rate were significantly lower in CNB than in FNA (5.0% vs 46.3%, P = .001, and 5.0% vs 34.1%, P = .013, respectively). CONCLUSIONS: In cases of known rare primary malignancy, nontypical ultrasound features of primary thyroid malignancy, and need for an additional immunohistochemical analysis, CNB may be primarily considered.
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http://dx.doi.org/10.1177/0194599816629632

Education in thyroid surgery: a matched-pair analysis comparing residents and board-certified surgeons.
Langenbecks Arch Surg, 401(2):239-47.
A. Reinisch, P. Malkomes, J. Liese, T. Schreckenbach, K. Holzer, W. O. Bechstein and N. Habbe. 2016.
PURPOSE: Resident participation in operative procedures is mandatory in educational residency programs but remains controversial, especially in the context of patient safety. This study compared the surgical quality and outcomes of thyroidectomies performed by surgical residents (RESs) and board-certified surgeons (BCSs). METHODS: This retrospective matched-pair study included patients undergoing thyroidectomies for multinodular goiter, Grave's disease and early-stage thyroid cancer that were performed by a RES with BCS supervision between 2006 and 2014. The intraoperative and postoperative course, complication rates and handling of the recurrent laryngeal nerve (RLN) and parathyroid glands were analyzed. RESULTS: In total, 112 thyroidectomies that were performed by a RES fulfilled the inclusion criteria and were matched 1:1 with BCS patients. We included 88 hemithyroidectomies, 80 subtotal thyroidectomies and 56 total thyroidectomies. No significant differences in the handling of the RLN or parathyroid glands, the rates of postoperative RLN palsies or the rates of hypocalcaemia were found. No intraoperative complications led to the replacement of the RES as the surgeon-in-charge. Three RES and two BCS patients experienced postoperative haemorrhages (p = 0.205), and three surgical site infections (p = 1.000) occurred in each group. The mean operative time and the length of stay did not differ significantly between the two groups. CONCLUSIONS: Major aspects of patient safety in thyroid surgery are not affected by resident participation. Thyroidectomies performed by RES are not significantly longer and reveal no differences in length of stay or complication rates. The economic burden of resident involvement is modest.
PubMed-ID: 26931517
http://dx.doi.org/10.1007/s00423-016-1390-7

Can the follow-up of patients with papillary thyroid carcinoma of low and intermediate risk and excellent response to initial therapy be simplified using second-generation thyroglobulin assays?
Clin Endocrinol (Oxf),
P. W. Rosario, G. F. Mourao and M. R. Calsolari. 2016.
OBJECTIVE: In view of the low probability of recurrence, the cost-effective follow-up of patients with papillary thyroid carcinoma (PTC) of low or intermediate risk and excellent response to initial therapy represents a challenge. This study evaluated the cases of structural recurrence among these patients. PATIENTS: The sample comprised 578 patients with PTC of low or intermediate risk, who were submitted to total thyroidectomy with or without 131 I therapy and exhibited an excellent response to initial therapy defined based on nonstimulated thyroglobulin (Tg) </= 0.2 ng/ml and negative neck ultrasonography (US). RESULTS: Twelve patients (2%) showed structural recurrence. At the time when recurrence was "confirmed", Tg elevation had not occurred in only two patients, one with lymph node metastases < 1 cm detected by US and the other with pulmonary metastases. Antithyroglobulin antibodies (TgAb) were undetectable in both patients. The first alteration observed in patients with recurrence was Tg elevation in six patients, Tg elevation associated with suspicious US in three, and suspicious US in two. An increase in TgAb was not the first alteration in any of the patients. Among the 560 patients who continued to have Tg </= 0.2 ng/ml, US permitted the detection of only one neck recurrence. Measurement of TgAb did not detect any recurrence. CONCLUSION: Our results confirm that in patients with PTC of low or intermediate risk an excellent response to initial therapy can be defined based on nonstimulated Tg </= 0.2 ng/ml. Follow-up consisting only of clinical examination and periodic measurement of Tg with a second-generation assay may be sufficient. This article is protected by copyright. All rights reserved.
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http://dx.doi.org/10.1111/cen.13053

Association of BRAF(V600E) Mutation and MicroRNA Expression with Central Lymph Node Metastases in Papillary Thyroid Cancer: A Prospective Study from Four Endocrine Surgery Centers.
Thyroid, 26(4):532-42.
P. Aragon Han, H. S. Kim, S. Cho, R. Fazeli, A. Najafian, H. Khawaja, M. McAlexander, B. Dy, M. Sorensen, A. Aronova, T. J. Sebo, T. J. Giordano, T. J. Fahey, 3rd, G. B. Thompson, P. G. Gauger, H. Somervell, J. A. Bishop, J. R. Eshleman, E. B. Schneider, K. W. Witwer, C. B. Umbricht and M. A. Zeiger. 2016.
BACKGROUND: Studies have demonstrated an association of the BRAF(V600E) mutation and microRNA (miR) expression with aggressive clinicopathologic features in papillary thyroid cancer (PTC). Analysis of BRAF(V600E) mutations with miR expression data may improve perioperative decision making for patients with PTC, specifically in identifying patients harboring central lymph node metastases (CLNM). METHODS: Between January 2012 and June 2013, 237 consecutive patients underwent total thyroidectomy and prophylactic central lymph node dissection (CLND) at four endocrine surgery centers. All tumors were tested for the presence of the BRAF(V600E) mutation and miR-21, miR-146b-3p, miR-146b-5p, miR-204, miR-221, miR-222, and miR-375 expression. Bivariate and multivariable analyses were performed to examine associations between molecular markers and aggressive clinicopathologic features of PTC. RESULTS: Multivariable logistic regression analysis of all clinicopathologic features found miR-146b-3p and miR-146b-5p to be independent predictors of CLNM, while the presence of BRAF(V600E) almost reached significance. Multivariable logistic regression analysis limited to only predictors available preoperatively (molecular markers, age, sex, and tumor size) found miR-146b-3p, miR-146b-5p, miR-222, and BRAF(V600E) mutation to predict CLNM independently. While BRAF(V600E) was found to be associated with CLNM (48% mutated in node-positive cases vs. 28% mutated in node-negative cases), its positive and negative predictive values (48% and 72%, respectively) limit its clinical utility as a stand-alone marker. In the subgroup analysis focusing on only classical variant of PTC cases (CVPTC), undergoing prophylactic lymph node dissection, multivariable logistic regression analysis found only miR-146b-5p and miR-222 to be independent predictors of CLNM, while BRAF(V600E) was not significantly associated with CLNM. CONCLUSION: In the patients undergoing prophylactic CLNDs, miR-146b-3p, miR-146b-5p, and miR-222 were found to be predictive of CLNM preoperatively. However, there was significant overlap in expression of these miRs in the two outcome groups. The BRAF(V600E) mutation, while being a marker of CLNM when considering only preoperative variables among all histological subtypes, is likely not a useful stand-alone marker clinically because the difference between node-positive and node-negative cases was small. Furthermore, it lost significance when examining only CVPTC. Overall, our results speak to the concept and interpretation of statistical significance versus actual applicability of molecular markers, raising questions about their clinical usefulness as individual prognostic markers.
PubMed-ID: 26950846
http://dx.doi.org/10.1089/thy.2015.0378

Does the T1 subdivision correlate with the risk of recurrence of papillary thyroid cancer?
Langenbecks Arch Surg, 401(2):223-30.
N. Chereau, C. Tresallet, S. Noullet, G. Godiris-Petit, F. Tissier, L. Leenhardt and F. Menegaux. 2016.
BACKGROUND: Based on the AJCC seventh TNM classification, T1 intraglandular tumors are subdivided into T1a (</=10 mm) and T1b (11-20 mm), but the differences in prognosis remain controversial. The present study aimed to determine the clinicopathological features and outcomes of T1a and T1b patients. METHODS: A retrospective study of 2518 T1 patients, including 1840 T1a (73 %) and 678 (27 %) T1b patients who underwent surgery for PTC from 1978 to 2014, was conducted. In patients with a preoperative or operative diagnosis of PTC, a total thyroidectomy (TT) with prophylactic (macroscopically N0) or therapeutic (evident N1) lymph node dissection (LND) was performed. Other patients had a TT or partial thyroidectomy without LND. The mean follow-up time was 8.9 +/- 8.8 years (median, 6.5 years; range, 1-36.4 years). RESULTS: A TT was performed in 2273 patients (90 %), including 1184 (52 %) with LND. Other patients (n = 245) had a single lobectomy with isthmectomy. Multifocality, bilaterality, number of tumors, sum of the largest size of all foci, vascular invasion, and (in patients with LND) LN metastases were significantly more frequent in T1b than in T1a patients. Of the 1184 patients with LND, 278 had LN metastases (N1, 23 %), including 136/680 T1a (20 %) and 142/504 (28 %) T1b patients (p = 0.002). These LN metastases were diagnosed after a prophylactic LND in 86/609 T1a (14 %) and 93/440 T1b (21 %) patients (p = 0.001). Recurrences were more frequent in T1b (n = 26, 3.8 %) than in T1a patients (n = 35, 1.9 %, p = 0.005). In the multivariate analysis, independent prognostic factors for recurrence in both groups were the number of tumors, the sum of the largest size of all foci and, in patients who had LND, LN metastases and extranodal extension. For N0-x patients, the recurrence rate was significantly higher in the T1b than in the T1a group (2.4 vs. 0.9 %, respectively, p = 0.005), although this rate was similar in N1 patients (16.2 % for T1a and 9.2 % for T1b patients, p = 0.1). The 5-year disease-free survival rates for T1a and T1b patients were 98.3 and 96.6 %, respectively (p = 0.01). CONCLUSION: For PTC patients, T1b had poorer clinicopathological features and increased risk of recurrence than T1a.
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http://dx.doi.org/10.1007/s00423-016-1399-y

Pediatric Differentiated Thyroid Carcinoma in The Netherlands: A Nationwide Follow-Up Study.
J Clin Endocrinol Metab, 101(5):2031-9.
M. S. Klein Hesselink, M. Nies, G. Bocca, A. H. Brouwers, J. G. Burgerhof, E. W. van Dam, B. Havekes, M. M. van den Heuvel-Eibrink, E. P. Corssmit, L. C. Kremer, R. T. Netea-Maier, H. J. van der Pal, R. P. Peeters, K. W. Schmid, J. W. Smit, G. R. Williams, J. T. Plukker, C. M. Ronckers, H. M. van Santen, W. J. Tissing and T. P. Links. 2016.
INTRODUCTION: Treatment for differentiated thyroid carcinoma (DTC) in pediatric patients is based mainly on evidence from adult series due to lack of data from pediatric cohorts. Our objective was to evaluate presentation, treatment-related complications, and long-term outcome in patients with pediatric DTC in The Netherlands. PATIENTS AND METHODS: In this nationwide study, presentation, complications, and outcome of patients with pediatric DTC (age at diagnosis </=18 y) treated in The Netherlands between 1970 and 2013 were assessed using medical records. RESULTS: We identified 170 patients. Overall survival was 99.4% after a median follow-up of 13.5 years (range 0.3-44.7 y). Extensive follow-up data were available for 105 patients (83.8% women), treated in 39 hospitals. Median age at diagnosis was 15.6 years (range 5.8-18.9 y). At initial diagnosis, 43.8% of the patients had cervical lymph node metastases; 13.3% had distant metastases. All patients underwent total thyroidectomy. Radioiodine was administered to 97.1%, with a median cumulative activity of 5.66 GBq (range 0.74-35.15 GBq). Life-long postoperative complications (permanent hypoparathyroidism and/or recurrent laryngeal nerve injury) were present in 32.4% of the patients. At last known follow-up, 8.6% of the patients had persistent disease and 7.6% experienced a recurrence. TSH suppression was not associated with recurrences (odds ratio 2.00, 95% confidence interval 0.78-5.17, P = .152). CONCLUSIONS: Survival of pediatric DTC is excellent. Therefore, minimizing treatment-related morbidity takes major priority. Our study shows a frequent occurrence of life-long postoperative complications. Adverse effects may be reduced by the centralization of care, which is crucial for children with DTC.
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http://dx.doi.org/10.1210/jc.2015-3290

Thyroid Stimulating Antibodies Are Highly Prevalent in Hashimoto's Thyroiditis and Associated Orbitopathy.
J Clin Endocrinol Metab, 101(5):1998-2004.
G. J. Kahaly, T. Diana, J. Glang, M. Kanitz, S. Pitz and J. Konig. 2016.
CONTEXT: Thyroid-associated orbitopathy (TAO) rarely occurs in patients with Hashimoto's thyroiditis (HT). OBJECTIVE: There is evidence that TSH receptor stimulating antibodies (TSAb) play a role in the pathogenesis

of TAO. In this report, the prevalence of TSAb in HT patients with and without TAO was studied. DESIGN: This is a longitudinal observational study. SETTING: The study took place in an academic joint thyroid-eye clinic. SUBJECTS: A total of 1055 subjects were included. METHODS: TSAb was measured with a Food and Drug Administration-cleared bioassay that uses Chinese hamster ovary cells expressing a chimeric TSH receptor and a cAMP response element-dependent luciferase. Results of TSAb activity were reported as percentage of specimen-to-reference ratio (SRR%, cutoff >140%). MAIN OUTCOME MEASURE: We measured the association of TSAb with the risk of TAO in patients with HT. RESULTS: Of 700 consecutive and unselected patients with HT, 44 (6%) had overt TAO. Patients with HT+TAO were older (P < .001), heavier smokers (P = .032), and clustered less with autoimmune diseases (P = .005). All healthy controls were TSAb negative. In contrast, serum was TSAb positive in 30/44 (68.2%) and 36/656 (5.5%, P < .001) patients with HT+TAO and HT, respectively. Compared to patients with HT only, serum TSAb levels were higher in HT+TAO (median SRR%, 25th and 75th percentiles): 45, 35-65 vs 192.5, 115-455.3, P < .001. Highest TSAb values were noted in patients with active and severe TAO vs those with mild and inactive TAO: 486, 392-592 vs 142, 73-192.5; P < .001. The odds ratio of TSAb positivity for the risk of TAO adjusted for gender and age was 55.9 (95% confidence interval [CI], 24.6-127, P < .0001), whereas the odds ratio per 10-fold change in TSAb SRR% (quantitative TSAb) was 133 (95% CI, 45-390, P < .0001). The area under the receiver operating characteristic curve for qualitative and quantitative TSAb was 87.2% (95% CI, 80.6-93.8) and 89.4% (95% CI, 84.1-94.7), respectively. CONCLUSIONS: TSAb is strongly associated with TAO in HT and TSAb may contribute to the pathophysiology of TAO.
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Thyroid nodules with indeterminate cytology: prospective comparison between 18F-FDG-PET/CT, multiparametric neck ultrasonography, 99mTc-MIBI scintigraphy and histology.
Eur J Endocrinol, 174(5):693-703.
A. Piccardo, M. Puntoni, G. Treglia, L. Foppiani, F. Bertagna, F. Paparo, M. Massollo, B. Dib, G. Paone, A. Arlandini, U. Catrambone, S. Casazza, A. Pastorino, M. Cabria and L. Giovanella. 2016.
PURPOSE: To evaluate the role of (18)F-flurodeoxiglucose positron emission tomography/computed tomography ((18)F-FDG-PET/CT) in predicting malignancy of thyroid nodules with indeterminate cytology. PATIENTS AND METHODS: We analysed 87 patients who have been scheduled to undergo surgery for thyroid nodule with indeterminate cytology. All patients underwent (18)F-FDG-PET/CT, multiparametric neck ultrasonography (MPUS), and (99m)Tc-methoxyisobutylisonitrile scintigraphy ((99m)Tc-MIBI-scan). Histopathology was the standard of reference. We compared the sensitivity (SE), specificity (SP), accuracy (AC), positive (PPV) and negative predictive (NPV) values of (18)F-FDG-PET/CT with those of (99m)Tc-MIBI-scan and MPUS in detecting cancer. Univariate and multivariate analyses evaluated the association between each diagnostic tool and histopathology. RESULTS: On histopathology, 69 out of 87 nodules were found to be benign and 18 to be malignant. The SE, SP, AC, PPV and NPV of (18)F-FDG-PET/CT were 94, 58, 66, 37 and 98% respectively. The SE, AC and NPV of (18)F-FDG-PET/CT were significantly higher than those of MPUS and (99m)Tc-MIBI-scan. The association of both positive (18)F-FDG-PET/CT and MPUS (FDG+/MPUS+) showed significantly lower SE (61% vs 94%) and NPV (88% vs 98%) than (18)F-FDG-PET/CT alone, but significantly higher SP (77% vs 58%). On univariate analysis, (18)F-FDG-PET/CT and the combination of FDG+/MPUS+ and of FDG+/MIBI- were all significantly associated with histopathology. On multivariate analysis, only FDG+/MIBI- was significantly associated with histopathology. CONCLUSION: The AC of (18)F-FDG-PET /CT in detecting thyroid malignancy is higher than that of (99m)Tc-MIBI-scan and MPUS. A negative (18)F-FDG-PET/CT correctly predicts benign findings on histopathology. The association of FDG+/MPS+ is significantly more specific than (18)F-FDG-PET/CT alone in identifying differentiated thyroid cancer. A positive (18)F-FDG-PET/CT is significantly associated with malignancy when qualitative (99m)Tc-MIBI-scan is rated as negative.
PubMed-ID: 26966173
http://dx.doi.org/10.1530/EJE-15-1199

Motor function of the recurrent laryngeal nerve: Sometimes motor fibers are also located in the posterior branch.
Surgery, 160(1):153-60.
M. Uludag, N. Aygun and A. Isgor. 2016.
BACKGROUND: The function of the extralaryngeal branches of the recurrent laryngeal nerve (RLN) has yet to be described precisely. The goal of this study was to evaluate the incidence and motor function of the extralaryngeal branches of the RLN. METHODS: Our study group consisted of 335 consecutive patients undergoing thyroid and parathyroid operations in whom the branches of the RLNs (n = 200) were evaluated with intraoperative nerve monitoring and by measuring the distance from the point of branching of the RLN into

anterior and posterior branches and the entry of the individual branches into the larynx-defined as the branching distance. Anterior and posterior branches of the RLN were assessed separately by electromyography (using a standard electromyography endotracheal tube) for adduction and by finger palpation for abduction. The RLNs were classified as having motor function only in the anterior branches (Group 1) or function both in the anterior and posterior branches (Group 2). RESULTS: There were 185 RLNs in Group 1 and 15 RLNs in Group 2, assessed by intraoperative nerve monitoring. Motor function was detected in all anterior branches of the RLN (100%) and in 8% of the posterior branches. The mean branching distance was greater in Group 2 compared with Group 1 (24.1 +/- 13.6 mm, 17.3 +/- 8.5 mm, respectively, P = .045). CONCLUSION: Although the anterior branch of RLN always has motor function, the posterior branch also has motor function in about 8% of patients. The probability of detecting motor function in the posterior branch was greater among early branching RLNs, which have a greater branching distance. The surgeon should remember that posterior branches may contain motor fibers and protect these branches to avoid postoperative vocal cord dysfunction.
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Epigenetic Alterations and Canonical Pathway Disruption in Papillary Thyroid Cancer: A Genome-wide Methylation Analysis.
Ann Surg Oncol, 23(7):2302-9.
M. G. White, S. Nagar, B. Aschebrook-Kilfoy, F. Jasmine, M. G. Kibriya, H. Ahsan, P. Angelos, E. L. Kaplan and R. H. Grogan. 2016.
BACKGROUND: Alterations in DNA methylation have been demonstrated in a variety of malignancies, including papillary thyroid cancer (PTC). The full extent of dysregulation in PTC and the downstream affected pathways remains unclear. Here we report a genome-wide analysis of PTC methylation, the dysregulation of various canonical pathways, and assess its potential as a diagnostic test. METHODS: A discovery set utilized 49 PTCs and matched normal controls from The Cancer Genome Atlas. Another set of 16 PTCs and 13 normal controls were used as a replication set. Genome-wide methylation analysis was done using Illumina 450 K methylation chips. Differentially methylated loci (DML) were identified by comparing PTC and matched normal tissues. DML were defined as false-discovery rate p < 0.05 and absolute Deltabeta >/= 0.2. DML were then analyzed for pathway and disease commonalities using Qiagen Ingenuity Pathway Analysis. RESULTS: Of 485,577 CpG sites analyzed, 1226 DML were identified in our discovery and replication sets, and 1061 (86.5 %) DML showed hypomethylation when comparing tumor with normal tissue. Support vector machine classification was able to differentiate benign from malignant tissue in 107 (94.7 %) of 113 tested samples, including 15 (83.3 %) of 18 samples lacking a clearly deleterious mutation. Statistically significant associations with multiple canonical pathways, diseases, and biofunctions were observed including PI3K, PTEN, wnt/beta-catenin, and p53. CONCLUSIONS: Epigenetic dysregulation of multiple canonical pathways are associated with the development of PTC. This methylation signature shows promise as a future adjunctive screening test for thyroid nodules.
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http://dx.doi.org/10.1245/s10434-016-5185-4

Pattern of neck recurrence after lateral neck dissection for cervical metastases in papillary thyroid cancer.
Surgery, 159(6):1565-71.
W. F. McNamara, L. Y. Wang, F. L. Palmer, I. J. Nixon, J. P. Shah, S. G. Patel and I. Ganly. 2016.
BACKGROUND: The objective of this study was to determine the rate and pattern of nodal recurrence in patients who underwent a therapeutic, lateral neck dissection (LND) for papillary thyroid cancer (PTC) with clinically evident cervical metastases and to determine if there was any correlation between the extent of initial dissection and the rate and pattern of neck recurrence. METHODS: A total of 3,664 patients with PTC treated between 1986 and 2010 at Memorial Sloan Kettering Cancer Center were identified from our institutional database. Tumor factors, patient demographics, extent of initial LND, and adjuvant therapy were recorded. Patterns of recurrent lateral neck metastases by level involvement were recorded and outcomes calculated using the Kaplan-Meier method. RESULTS: A total of 484 patients had an LND for cervical metastases; 364 (75%) had a comprehensive LND (CLND) and 120 (25%) had a selective neck dissection (SND). The median duration of follow-up was 63.5 months. As expected, patients with CLND had a greater number of nodes removed as well as a greater number of positive nodes (P < .001). There was no difference in overall lateral neck recurrence-free status (CLND 94.4% vs SND 89.4%, P = .158), but in the dissected neck, the ipsilateral lateral neck recurrence-free status was superior in the CLND patients (97.7% vs 89.4%, P < .001). CONCLUSION: Patients with clinically evident neck metastases from PTC managed by CLND have lesser rates of recurrence in the dissected neck compared with patients managed by SND. SND should only be done in highly selected cases with small volume disease.

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http://dx.doi.org/10.1016/j.surg.2016.02.005

Characteristics of contralateral carcinomas in patients with differentiated thyroid cancer larger than 1 cm.
Langenbecks Arch Surg, 401(3):365-73.
L. Lodewijk, W. P. Kluijfhout, J. W. Kist, I. Stegeman, J. T. Plukker, E. J. Nieveen van Dijkum, H. J. Bonjer, N. D. Bouvy, A. Schepers, J. H. de Wilt, R. T. Netea-Maier, J. A. van der Hage, J. W. Burger, G. Ho, W. S. Lee, W. T. Shen, A. Aronova, R. Zarnegar, C. Benay, E. J. Mitmaker, M. S. Sywak, A. M. Aniss, S. Kruijff, B. James, R. H. Grogan, L. Brunaud, G. Hoch, C. Pandolfi, D. T. Ruan, M. D. Jones, M. A. Guerrero, G. D. Valk, I. H. Borel Rinkes and M. R. Vriens. 2016.
PURPOSE: Traditionally, total thyroidectomy has been advocated for patients with tumors larger than 1 cm. However, according to the ATA and NCCN guidelines (2015, USA), patients with tumors up to 4 cm are now eligible for lobectomy. A rationale for adhering to total thyroidectomy might be the presence of contralateral carcinomas. The purpose of this study was to describe the characteristics of contralateral carcinomas in patients with differentiated thyroid cancer (DTC) larger than 1 cm. METHODS: A retrospective study was performed including patients from 17 centers in 5 countries. Adults diagnosed with DTC stage T1b-T3 N0-1a M0 who all underwent a total thyroidectomy were included. The primary endpoint was the presence of a contralateral carcinoma. RESULTS: A total of 1313 patients were included, of whom 426 (32 %) had a contralateral carcinoma. The contralateral carcinomas consisted of 288 (67 %) papillary thyroid carcinomas (PTC), 124 (30 %) follicular variant of a papillary thyroid carcinoma (FvPTC), 5 (1 %) follicular thyroid carcinomas (FTC), and 3 (1 %) Hurthle cell carcinomas (HTC). Ipsilateral multifocality was strongly associated with the presence of contralateral carcinomas (OR 2.62). Of all contralateral carcinomas, 82 % were </=10 mm and of those 99 % were PTC or FvPTC. Even if the primary tumor was a FTC or HTC, the contralateral carcinoma was (Fv)PTC in 92 % of cases. CONCLUSIONS: This international multicenter study performed on patients with DTC larger than 1 cm shows that contralateral carcinomas occur in one third of patients and, independently of primary tumor subtype, predominantly consist of microPTC.
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http://dx.doi.org/10.1007/s00423-016-1393-4

Single-session radiofrequency ablation on benign thyroid nodules: a prospective single center study : Radiofrequency ablation on thyroid.
Langenbecks Arch Surg, 401(3):357-63.
E. Aysan, U. O. Idiz, H. Akbulut and L. Elmas. 2016.
PURPOSE: The activity of the application of single-session ultrasonography (US)-guided percutaneous radio frequency ablation (RFA) in benign thyroid nodules was investigated in this prospective clinical study. METHODS: RFA treatment was applied to 100 nodules in 100 patients (78 women, 22 men; average age 44.5 years old; age range 18-71) who had euthyroid condition, nodule size larger than 1 cm in the ultrasonography, proven to be benign by fine needle aspiration cytology. The nodules were separated into three groups according to the content: solid, cystic and mixed. In first 73 cases, the process performed under local anesthesia and the other 27 cases were performed under general anesthesia. RFA process was standardized to 70 W in all of the patients, and a moving shot technique was used. The results acquired in the third and sixth months of the controls were evaluated, and the volume of the nodules was screened. RESULTS: No differences between the thyroid function tests performed before and after RFA were detected ($p > 0.05$). The mean volume of the nodules before the process, in the third month after the process, and in the sixth month were 16.8, 4.8, and 2.6 ml, respectively ($p < 0.001$). The decrease in cystic nodules was greater than solid and mixed structures. Temporary hoarseness occurred in one case and skin edema was detected in a patient at the isthmus. CONCLUSIONS: RFA is an option for treatment, with minimal invasiveness and a low complication rate, and it is effective primarily in cases with benign nodules and nodular goiter. In cases with good compliance, the likelihood of success is greater. General anesthesia can be a good option for anxious cases to gather better results.
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http://dx.doi.org/10.1007/s00423-016-1408-1

A 2015 Survey of Clinical Practice Patterns in the Management of Thyroid Nodules.
J Clin Endocrinol Metab:jc20161155.
H. B. Burch, K. D. Burman, D. S. Cooper, J. V. Hennessey and N. O. Vietor. 2016.
CONTEXT: The management of thyroid nodules has changed dramatically over the past two decades. In the interim, technological advances including high-resolution ultrasound (US), and molecular testing of thyroid nodules have been introduced. OBJECTIVE: We sought to document current practices in the management

thyroid nodules and assess the extent to which technological advances have been incorporated into current practice. We further sought to compare current practice to recommendations made in a recently updated American Thyroid Association (ATA) clinical practice guideline (CPG), and to examine differences in thyroid nodule management among international members of U.S.-based endocrine societies. METHODS: Members of The Endocrine Society (TES), ATA, and American Association of Clinical Endocrinologists (AACE) were invited to participate in a web-based survey dealing with testing, treatment preference, and modulating factors in patients with thyroid nodules. RESULTS: A total of 897 respondents participated in the survey, including 661 TES members, 454 AACE members, and 365 ATA members. Thyroid fine-needle aspiration (FNA) in 2015 is generally performed by endocrinologists (56.6%) and radiologists (31.9%), most frequently utilizing ultrasound guidance (83.3%). Respondents in general have a lower threshold for FNA of thyroid nodules than that recommended in the updated ATA CPG. Management depends on the FNA result, with follicular lesion of undetermined significance/ atypia of undetermined significance (FLUS/ AUS) resulting in molecular testing (38.8% of respondents), repeat FNA cytology (31.5%), or immediate referral for thyroid surgery (24.4%). Nodules showing follicular neoplasm (FN) by FNA are referred for thyroid surgery by 61.2% of respondents (46.6 % lobectomy, 14.6 % total thyroidectomy), or molecular testing (29.0 %). Nodules found suspicious but not conclusive for malignancy (Bethesda category V), are referred for thyroid surgery (86.0%) and rarely undergo molecular testing (9.5%). During pregnancy, only 47.6% of respondents would perform FNA in the absence of nodular growth, with most respondents deferring FNA until after pregnancy. Endocrinologists are 64.2% less likely to perform FNA in an octogenarian than a younger patient with a comparable thyroid nodule. Striking international differences were identified in the routine measurement of calcitonin and in the use of molecular testing of thyroid nodules. CONCLUSIONS: In summary, our survey of clinical endocrinologists on the management of thyroid nodules documents current practice patterns and demonstrates both concordance and focal discordance with recently updated CPGs. Both international differences and a change in practice patterns over the past two decades are demonstrated.
PubMed-ID: 27014951
http://dx.doi.org/10.1210/jc.2016-1155

Dynamic Risk Stratification in Differentiated Thyroid Cancer Patients Treated without Radioactive Iodine.
J Clin Endocrinol Metab:jc20154290.
D. P. Momesso, F. Vaisman, S. P. Yang, D. A. Bulzico, R. Corbo, M. Vaisman and R. M. Tuttle. 2016.
CONTEXT: While response to therapy assessment is a validated tool for dynamic risk stratification in differentiated thyroid cancer (DTC) patients treated with total thyroidectomy (TT) and radioactive iodine therapy (RAI), it has not been well studied in patients treated with lobectomy (L) or TT without RAI. Because these response to therapy definitions are heavily dependent on serum thyroglobulin (Tg) levels, modifications of the original definitions were needed to appropriately classify patients treated without RAI. OBJECTIVES: To validate the response to therapy assessment in DTC patients treated with L or TT without RAI. DESIGN: Retrospective study, median follow-up period of 100.5 months Settings: Referral center Patients: 507 adults with DTC treated with L (n=187) or TT (n=320) without RAI; median age of 43.7 years; 88% were female; 85.4% low and 14.6% intermediate risk. MAIN OUTCOME MEASURE: Recurrent/persistent structural disease (SD). RESULTS: Recurrent/persistent SD was observed in: 0% of the patients with excellent response to therapy (nonstimulated Tg for TT <0.2 ng/ml and for L <30 ng/ml, undetectable Tg antibodies- TgAb and negative imaging; n=326); 1.3% with indeterminate response (nonstimulated Tg for TT 0.2-5 ng/ml, stable or declining TgAb and/or non-specific imaging findings; n=2/152); 31.6% of the patients with biochemical incomplete response (nonstimulated Tg for TT >5 ng/ml and for L >30 ng/ml and/or increasing Tg with similar TSH levels and/or increasing TgAb and negative imaging; n=6/19) and all (100%) patients with structural incomplete response (n=10/10) (p<0-0001). Initial ATA risk estimates were significantly modified based on response to therapy assessment. CONCLUSIONS: Our data validates the newly proposed response to therapy assessment in DTC patients treated with L or TT without RAI as an effective tool to modify initial risk estimates of recurrent/persistent SD and better tailor follow-up and future therapeutic approaches. This study provides further evidence to support a selective use of RAI in DTC.
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http://dx.doi.org/10.1210/jc.2015-4290

Racial Disparities in Initial Presentation of Benign Thyroid Disease for Resection.
Ann Surg Oncol,
L. E. Kuo, K. D. Simmons, H. Wachtel, S. Zaheer, G. C. Karakousis, D. L. Fraker and R. R. Kelz. 2016.
BACKGROUND: Racial disparities exist in thyroidectomy outcomes. One contributing factor may be the disease state upon presentation to a surgeon. Minorities with thyroid cancer present at a later disease stage and with larger tumors. This relationship has not been examined for benign thyroid disease. We sought to examine the

association between race, referral patterns, and disease severity for benign thyroid conditions. METHODS: We analyzed all patients receiving a thyroidectomy for benign disease in our institutional endocrine surgery registry. Patient demographics, disease history, disease severity, and postoperative outcomes were investigated. Univariate analysis compared black and white patients. Multivariable linear regression examined the relationship between race and time to surgical referral. RESULTS: Of the 1189 patients studied, the majority (86.0 %) were white. Black and white patients differed in median income and reason for referral. When compared with white patients, black patients more commonly presented with compressive symptoms (black: 45.0 % vs. white: 21.2 %, p < .01) and dysphagia (19.0 % vs. 10.1 %, p < .01), and after a longer disease duration [black: median 0 years (interquartile ratio, IQR, 0-5) vs. white: 0 years (IQR, 0-2)]. Blacks also had larger glands than white [median 71 grams (IQR, 33.5-155.3) vs. 24.3 grams (IQR, 15.0-50.2)]. With the exception of reintubation rate, there were no differences in postoperative outcomes. CONCLUSIONS: Black patients with benign thyroid conditions have a longer time to surgical referral and present for surgical evaluation with more severe disease than white patients. Identification of these disparities is the first step in eliminating differences in patient care.
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http://dx.doi.org/10.1245/s10434-016-5199-y

TSH/IGF-1 Receptor Cross Talk in Graves' Ophthalmopathy Pathogenesis.
J Clin Endocrinol Metab, 101(6):2340-7.
C. C. Krieger, R. F. Place, C. Bevilacqua, B. Marcus-Samuels, B. S. Abel, M. C. Skarulis, G. J. Kahaly, S. Neumann and M. C. Gershengorn. 2016.
CONTEXT: The TSH receptor (TSHR) is considered the main target of stimulatory autoantibodies in the pathogenesis of Graves' ophthalmopathy (GO); however, it has been suggested that stimulatory IGF-1 receptor (IGF-1R) autoantibodies also play a role. OBJECTIVE: We previously demonstrated that a monoclonal stimulatory TSHR antibody, M22, activates TSHR/IGF-1R cross talk in orbital fibroblasts/preadipocytes obtained from patients with GO (GO fibroblasts [GOFs]). We show that cross talk between TSHR and IGF-1R, not direct IGF-1R activation, is involved in the mediation of GO pathogenesis stimulated by Graves' autoantibodies. DESIGN/SETTING/PARTICIPANTS: Immunoglobulins were purified from the sera of 57 GO patients (GO-Igs) and tested for their ability to activate TSHR and/or IGF-1R directly and TSHR/IGF-1R cross talk in primary cultures of GOFs. Cells were treated with M22 or GO-Igs with or without IGF-1R inhibitory antibodies or linsitinib, an IGF-1R kinase inhibitor. MAIN OUTCOME MEASURES: Hyaluronan (hyaluronic acid [HA]) secretion was measured as a major biological response for GOF stimulation. IGF-1R autophosphorylation was used as a measure of direct IGF-1R activation. TSHR activation was determined through cAMP production. RESULTS: A total of 42 out of 57 GO-Ig samples stimulated HA secretion. None of the GO-Ig samples exhibited evidence for IGF-1R autophosphorylation. Both anti-IGF-1R antibodies completely inhibited IGF-1 stimulation of HA secretion. By contrast, only 1 IGF-1R antibody partially blocked HA secretion stimulated by M22 or GO-Igs in a manner similar to linsitinib, whereas the other IGF-1R antibody had no effect on M22 or GO-Ig stimulation. These findings show that the IGF-1R is involved in GO-Igs stimulation of HA secretion without direct activation of IGF-1R. CONCLUSIONS: IGF-1R activation by GO-Igs occurs via TSHR/IGF-1R cross talk rather than direct binding to IGF-1R, and this cross talk is important in the pathogenesis of GO.
PubMed-ID: 27043163
http://dx.doi.org/10.1210/jc.2016-1315

Risk factors for Graves' Orbitopathy; the Australian Thyroid-associated Orbitopathy Research (ATOR) Study.
J Clin Endocrinol Metab:jc20154294.
J. J. Khong, S. Finch, C. De Silva, S. Rylander, J. E. Craig, D. Selva and P. R. Ebeling. 2016.
CONTEXT: Previous association studies suggest the development of Graves' orbitopathy (GO) is variably influenced by environmental risk factors. OBJECTIVE: To determine the risk factors and predict odds for developing GO in Graves' hyperthyroidism (GH). DESIGN: Case-control study Setting: Multi-centre Australian Thyroid-associated Orbitopathy Research (ATOR) group consisting of tertiary endocrinology and ophthalmology outpatients and related private practices. PATIENTS OR OTHER PARTICIPANTS: 1042 participants with GH were designated as cases if they had GO (n=604) and controls if they did not have GO (n=438). MAIN OUTCOME MEASURES: Primary outcome was GO risk factors and secondary outcome was dysthyroid optic neuropathy (DON) with the effects of risk factors measured by odds ratio (OR) using multiple logistic regression, adjusted for known risk factors and exploratory variables. RESULTS: The odds of GO increased by 17% for each decade increase in the age of onset of GH (OR 1.17, CI: 1.06-1.29, p = 0.002) and by 7% for each year increase in the duration of GH (OR 1.07, CI:1.05-1.10, p<0.001)). Smoking increased the odds for GO by 2.22 for current smoker and 2.07 for ex-smoker (p<0.001), compared with never smoking. The odds of GO are 86% less in Graves' patients using anti-thyroid medication than those not (OR 0.14, CI 0.06-0.34, p<0.001).

Predictors for DON were older age, oculomotility restriction, strabismus, reduced palpebral aperture and active GO. CONCLUSIONS: This study identified increase age of onset, duration of GH and smoking as risk factors for GO. Usage of anti-thyroid medication was negatively related to GO. Older patients with restricted ocular motility, strabismus and active GO are at higher risk of DON and may benefit from early medical intervention.
PubMed-ID: 27055083
http://dx.doi.org/10.1210/jc.2015-4294

Cervical hematoma following an endocrine surgical procedure: The MD Anderson experience.
Surgery,
I. A. Christakis, E. Potylchansky, A. M. Silva, J. P. Nates, P. A. Prieto, P. H. Graham, E. G. Grubbs, J. E. Lee and N. D. Perrier. 2016.
BACKGROUND: Airway compromise from postoperative neck hematoma remains the most feared complication after cervical endocrine operative procedures. Events are rare and potentially lethal, and clear multidisciplinary guidelines for management of these patients are lacking. The aim of our study was to review the experience of a tertiary cancer center in this scenario. METHODS: Data prospectively collected over a 10-year period, between 2005 and 2014, were retrospectively analyzed. We included all adult patients who had had a neck operation and needed reoperation for postoperative neck hematoma after an endocrine procedure. We excluded pediatric patients and cases with incomplete records. RESULTS: The inclusion criteria were met for 21 patients (21/2,930; 0.7%). The median age at operation was 56.2 years (SD: 16.7). The M:F ratio was 1:2. All 21 patients presented with a neck swelling at the time of reoperation. Eight of 21 patients (38%) underwent emergency bedside clot evacuation. Presentation was within 6 hours for two thirds (14/21) of the patients; the remaining one third of the patients had the hematoma develop during the evening/night (from 1700-0500). The mean estimated hematoma size was 98 cc (SD: 58). A source of bleeding was identified in 12 of 21 cases (57%). A total of 15.8% of patients had an airway classified as difficult/awkward under the American Society of Anesthesiologists classification for their wound re-exploration. CONCLUSION: Postoperation, increased vigilance is needed for the first 6 hours to detect patients with neck swelling. Emergency drainage by the bedside was performed in 38% of patients. A difficult airway was uncommon in our series.
PubMed-ID: 27063343
http://dx.doi.org/10.1016/j.surg.2016.02.024

Incidence of Permanent Hypocalcaemia after Total Thyroidectomy with or without Central Neck Dissection for Thyroid Carcinoma: A Nationwide Claim Study.
Clin Endocrinol (Oxf),
G. H. Seo, Y. J. Chai, H. J. Choi and K. E. Lee. 2016.
OBJECTIVE: Permanent hypocalcaemia is the most common and serious complication after total thyroidectomy (TT). This study examined the impact of central neck dissection (CND) and institutional volume on rates of permanent hypocalcaemia by analysing data held in the nationwide claim database of South Korea. DESIGN: Data from patients who underwent TT due to thyroid carcinoma from 2007-2013 were obtained from the Health Insurance Review and Assessment Service database. Of these, patients prescribed more than 1,000 mg of elemental calcium for more than 288 days during the first 360 days post-surgery were defined as having permanent hypocalcaemia. RESULTS: In total, 192,333 patients (32,988 male and 159,345 female) were eligible for analysis. Of these, 52,707 (27.4%) underwent TT alone and 139,626 (72.6%) underwent TT plus CND. The incidence of permanent hypocalcaemia was greater in the TT plus CND group than in the TT alone group (5.4% vs. 4.6%, p<0.001). The age- and sex-adjusted risk for permanent hypocalcaemia in the TT plus CND group was 1.20 (p < 0.001). CND did not raise the rates of permanent hypocalcaemia in institutes with a low volume of annual cases (<200), whereas permanent hypocalcaemia was more common in the TT plus CND group than in the TT alone group (3.5% vs. 2.9%, p=0.002) in institutes with a large volume of annual cases (>/=800). CONCLUSIONS: TT plus CND was associated with a greater risk of permanent hypocalcaemia than TT alone. Surgeons should consider the risk of permanent hypocalcaemia when deciding whether to perform CND. This article is protected by copyright. All rights reserved.
PubMed-ID: 27063793
http://dx.doi.org/10.1111/cen.13082

Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma.
Ann Surg Oncol,
S. K. Kim, I. Park, J. W. Woo, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
BACKGROUND: Because lymph node (LN) metastasis has been proven to be a predictor for locoregional recurrence (LRR) in papillary thyroid microcarcinoma (PTMC), better knowledge about the predictors for LN metastasis in PTMC is required. METHODS: We retrospectively reviewed 5656 PTMC patients who underwent

total thyroidectomy and central neck dissection and/or lateral neck dissection between January 1997 and June 2015. RESULTS: Male gender (adjusted odds ratio [OR] 2.332), conventional variant (adjusted OR 4.266), tumor size >0.5 cm (adjusted OR 1.753), multiplicity (adjusted OR 1.168), bilaterality (adjusted OR 1.177), and extrathyroidal extension (ETE) (adjusted OR 1.448) were independent predictors for high prevalence of central LN metastasis (CLNM), whereas per 10-year age increment (adjusted OR 0.760) and chronic lymphocytic thyroiditis (adjusted OR 0.791) were independent predictors for low prevalence of CLNM. In addition, male gender (adjusted OR 1.489), tumor size >0.5 cm (adjusted OR 1.295), multiplicity (adjusted OR 1.801), ETE (adjusted OR 1.659), and CLNM (adjusted OR 4.359) were independent predictors for high prevalence of lateral LN metastasis (LLNM), whereas per 10-year age increment (adjusted OR 0.838) was an independent predictor for low prevalence of LLNM. There was a statistically significant difference in LRR with regard to nodal stage ($p < 0.001$). CONCLUSIONS: Meticulous perioperative evaluation of LN metastasis is required for PTMC patients with the above predictors.
PubMed-ID: 27075321
http://dx.doi.org/10.1245/s10434-016-5225-0

EMG changes during continuous intraoperative neuromonitoring with sustained recurrent laryngeal nerve traction in a porcine model.
Langenbecks Arch Surg,
K. Brauckhoff, T. Aas, M. Biermann and P. Husby. 2016.
PURPOSE: Traction is the most common cause of injury to the recurrent laryngeal nerve (RLN) in endocrine neck surgery. The purpose of this study was to evaluate specific alterations to the electromyogram (EMG) and verify safe alarm limits in a porcine model of sustained traction of the RLN using continuous intraoperative neuromonitoring (C-IONM). METHODS: Sixteen Norwegian Landrace pigs were anesthetized and intubated with a tracheal tube with a stick-on laryngeal electrode. EMG was recorded at baseline (BL) and during sustained traction applied to each RLN until 70 % amplitude decrease from BL, and during 30-min recovery. RESULTS: In 29 nerves at risk (NAR), BL amplitude and latency values were 1098 +/- 418 (586-2255) muV (mean +/- SD (range)) (right vagus) and 845 +/- 289 (522-1634) muV (left vagus), and 4.7 +/- 0.5 (4.1-5.9) ms and 7.9 +/- 0.8 (6.7-9.6) ms, respectively. At 50 % amplitude decrease, latency increased by 14.0 +/- 5.7 % (right side) and 14.5 +/- 9.1 % (left side) compared with BL. Corresponding values for 70 % amplitude depression were 17.9 +/- 6.1 % and 17.3 +/- 12.8 %. Traction time to 50 and 70 % amplitude decrease ranged from 3 to 133 min and 3.9-141 min, respectively. In 16 NAR (55 %), time from 50 to 70 % reduction in amplitude was </=5 min, but in six NAR (21 %) </=1 min. In only 11 (38 %) of 29 nerves, the amplitude recovered to more than 50 % of BL. CONCLUSIONS: Latency increase may be the first warning of RLN stretch injury. Given the short interval between 50 and 70 % amplitude reduction of the EMG, amplitude reduction by 50 % can be taken as an appropriate alert limit.
PubMed-ID: 27086308
http://dx.doi.org/10.1007/s00423-016-1419-y

Thyroid lobectomy is an effective option for unilateral benign nodular disease.
Clin Endocrinol (Oxf),
M. Lytrivi, A. Kyrilli, A. Burniat, M. Ruiz Patino, Y. Sokolow and B. Corvilain. 2016.
OBJECTIVE: The use of thyroid lobectomy in the treatment of unilateral, benign nodules is limited by the potential of nodular recurrence in the remaining lobe. This study aimed to assess the rate and clinical impact of nodular recurrence in the contralateral lobe after thyroid lobectomy and to identify predictive factors of recurrence. DESIGN: Single-center retrospective study. PATIENTS: Records of patients that underwent lobectomy for unilateral thyroid nodules between 1991 and 2010 were reviewed and 270 patients were included. Exclusion criteria were: presence of contralateral nodule(s) >/= 5 mm on preoperative ultrasound, diagnosis of cancer necessitating completion thyroidectomy or pseudonodules. Recurrence was defined as the occurrence of nodule(s) >/= 5mm in the remaining lobe on at least one postoperative ultrasound. A set of clinical, imaging, histological and biochemical parameters was tested as predictors of recurrence using logistic regression. RESULTS: After a median follow-up of 78 months (range, 12-277 months), the global recurrence rate was 42% and recurrence of nodules of a size >/= 1 cm occurred in 19%. Reoperation rate was 1.1%. 90% of patients were treated postoperatively by levothyroxine. Median time to nodular recurrence was 4 years. Preoperative contralateral lobe volume and resected thyroid weight were identified as significant predictors of recurrence ($p=0.045$ and $p=0.03$ respectively). CONCLUSIONS: Thyroid lobectomy is an effective therapeutic strategy for unilateral, benign nodules, resulting in a low rate of clinically relevant nodular relapse in a mildly iodine-deficient area. Patients with uninodular disease and a contralateral lobe of normal size are particularly good candidates for lobectomy. This article is protected by copyright. All rights reserved.

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http://dx.doi.org/10.1111/cen.13088

Prophylactic Central Neck Dissection Might Not Be Necessary in Papillary Thyroid Carcinoma: Analysis of 11,569 Cases from a Single Institution.
J Am Coll Surg, 222(5):853-64.
S. K. Kim, J. W. Woo, J. H. Lee, I. Park, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
BACKGROUND: The benefits of prophylactic central neck dissection (pCND) remain controversial in clinically node-negative (cN0) papillary thyroid carcinoma (PTC). The purpose of this study was to investigate the clinical impact of pCND with a large group of cN0 PTC patients. STUDY DESIGN: A total of 11,569 cN0 PTC patients who underwent thyroidectomy between January 1997 and June 2015 were investigated. Using Cox multivariate analysis, the prognostic impact of pCND was assessed using subset analyses according to various clinicopathologic conditions. Using propensity score matching, various surgical morbidities were assessed under adjusted conditions. RESULTS: Of 11,569 cN0 PTC patients, 8,735 (75.5%) underwent pCND. Prophylactic CND did not significantly decrease the risk of locoregional recurrence in cN0 PTC patients (adjusted hazard ratio [HR] = 0.874; p = 0.392). In addition, pCND did not significantly decrease the risk of locoregional recurrence in various surgical extents (lobectomy and ipsilateral pCND [adjusted HR = 0.636; p = 0.131], total thyroidectomy and ipsilateral pCND [adjusted HR = 0.775; p = 0.164], and total thyroidectomy and bilateral pCND [adjusted HR = 1.041; p = 0.821]). However, surgical morbidities, such as temporary vocal cord palsy (5.6% vs 2.5%; p = 0.001), temporary hypoparathyroidism (30.8% vs 16.7%; p < 0.001), and permanent hypoparathyroidism (3.5% vs 1.7%; p < 0.001) were significantly more frequent in the pCND(+) group. CONCLUSIONS: Given the lack of proven benefits and the clear evidence of morbidities, pCND cannot be recommended as a routine procedure. We suggest that CND be reserved for therapeutic situations.
PubMed-ID: 27113516
http://dx.doi.org/10.1016/j.jamcollsurg.2016.02.001

Impact of central node dissection on postoperative morbidity in pediatric patients with suspected or proven thyroid cancer.
Surgery,
A. Machens, M. Elwerr, P. N. Thanh, K. Lorenz, R. Schneider and H. Dralle. 2016.
BACKGROUND: Pediatric risk factors for postoperative morbidity after central node dissection are ill-defined. METHODS: This outcome study aimed to evaluate operative morbidity in patients aged </=18 years after total thyroidectomy with or without central node dissection for suspected or proven thyroid cancer. RESULTS: Included were 102 patients with hereditary C-cell hyperplasia, 66 patients with medullary, 60 patients with papillary, and 2 patients with follicular thyroid cancer. In all 230 patients, 131 of whom underwent central node dissection, transient recurrent laryngeal nerve palsy was significantly associated only with central node dissection (100% vs 55%; P = .010). Transient and permanent hypoparathyroidism were significantly associated with age (means of 11.9 years versus 7.8 years, and 12.9 years versus 8.5 years; P </= .002); central node dissection (80% vs 50%, and 100% vs 54%; P </= .001); and the number of central lymph nodes cleared (means of 12.2 nodes versus 5.4 nodes, and 26.9 nodes versus 5.8 nodes, P < .001). These effects were stronger for permanent than transient hypoparathyroidism. Correlations between permanent hypoparathyroidism and the number of nodes cleared on central node dissection (r = 0.35) were closer than those between permanent hypoparathyroidism and age (r = 0.15), but similar for transient hypoparathyroidism (r = 0.22 and r = 0.25). CONCLUSION: Owing to the incremental morbidity from central node dissection, the extent of a neck operation, in experienced hands, should be tailored to the extent of the underlying disease regardless of the child's age. The notion that the experience of the center and surgeons may be more important than the age of the child requires validation in independent series across different health care settings.
PubMed-ID: 27117577
http://dx.doi.org/10.1016/j.surg.2016.03.007

Parathyroids

Meta-Analyses

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

Randomized controlled trials

- None -

Consensus Statements/Guidelines

Management of Hypoparathyroidism: Summary Statement and Guidelines.
J Clin Endocrinol Metab, 101(6):2273-83.
M. L. Brandi, J. P. Bilezikian, D. Shoback, R. Bouillon, B. L. Clarke, R. V. Thakker, A. A. Khan and J. T. Potts, Jr. 2016.
OBJECTIVE: Hypoparathyroidism is a rare disorder characterized by hypocalcemia and absent or deficient PTH. This report presents a summary of current information about epidemiology, presentation, diagnosis, clinical features, and management and proposes guidelines to help clinicians diagnose, evaluate, and manage this disorder. PARTICIPANTS: Participants in the First International Conference on the Management of Hypoparathyroidism represented a worldwide constituency with acknowledged interest and expertise in key basic, translational, and clinical aspects of hypoparathyroidism. Three Workshop Panels were constituted to address questions for presentation and discussion at the Conference held in Florence, Italy, May 7-9, 2015. At that time, a series of presentations were made, followed by in-depth discussions in an open forum. Each Workshop Panel also met in closed sessions to formulate the three evidence-based reports that accompany this summary statement. An Expert Panel then considered this information, developed summaries, guidelines, and a research agenda that constitutes this summary statement. EVIDENCE: Preceding the conference, each Workshop Panel conducted an extensive literature search as noted in the individual manuscripts accompanying this report. All presentations were based upon the best peer-reviewed information taking into account the historical and current literature. CONSENSUS PROCESS: This report represents the Expert Panel's synthesis of the conference material placed in a context designed to be relevant to clinicians and those engaged in cutting-

edge studies of hypoparathyroidism. CONCLUSIONS: This document not only provides a summary of our current knowledge but also places recent advances in its management into a context that should enhance future advances in our understanding of hypoparathyroidism.
PubMed-ID: 26943719
http://dx.doi.org/10.1210/jc.2015-3907

Other Articles

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

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

FGF23, metabolic risk factors, and blood pressure in patients with primary hyperparathyroidism undergoing parathyroid adenomectomy.
Surgery, 159(1):211-7.
I. L. Nilsson, S. Norenstedt, F. Granath, J. Zedenius, Y. Pernow and T. E. Larsson. 2016.
BACKGROUND: Fibroblast growth factor-23 (FGF23), a regulator of secretion of parathyroid hormone (PTH), is implicated in the development of cardiovascular disease. The role of FGF23 in primary hyperparathyroidism (pHPT) is unclear. METHODS: A total of 150 consecutive patients with pHPT were examined with ambulatory blood pressure monitoring ((24h)ABP) before parathyroid adenomectomy (PTX). Blood samples were collected 6 +/- 2 weeks before and 6 +/- 2 weeks after PTX. RESULTS: Plasma FGF23 levels decreased after PTX from a

median of 45.2 pg/mL (interquartile range 37.6-54.8) to 36.8 pg/mL (26.7-48.7); P < .001. This postoperative decrease correlated with the decrease in ionized calcium (r = 0.24; P < .01). Greater FGF23 concentrations at baseline were associated with a greater weight of the adenoma and PTH levels, as well as with body mass index, triglycerides, and insulin levels and greater postoperative decreases in FGF23, ionized calcium, insulin growth-like factor 1, and insulin. FGF23 and PTH both correlated with greater blood pressures on (24h)ABP, especially at nighttime (r = 0.31 and r = 0.28; P </= .01), whereas after multivariate adjustment, only PTH remained independently associated with (24)ABP. CONCLUSION: Circulating FGF23 is increased in pHPT and is associated independently with the metabolic risk profile. The long-term benefit of decreasing FGF23 in pHPT after PTX remains to be established.
PubMed-ID: 26435425
http://dx.doi.org/10.1016/j.surg.2015.06.057

A Prospective Comparative Study of Parathyroid Dual-Phase Scintigraphy, Dual-Isotope Subtraction Scintigraphy, 4D-CT, and Ultrasonography in Primary Hyperparathyroidism.
Clin Nucl Med, 41(2):93-100.
M. Krakauer, B. Wieslander, P. S. Myschetzky, A. Lundstrom, T. Bacher, C. H. Sorensen, W. Trolle, B. Nygaard and F. N. Bennedbaek. 2016.
PURPOSE: Preoperative localization of the diseased parathyroid gland(s) in primary hyperparathyroidism allows for minimally invasive surgery. This study was designed to establish the optimal first-line preoperative imaging modality. PATIENTS AND METHODS: Ninety-one patients were studied consecutively in a prospective head-to-head comparison of dual isotope (Tc-MIBI vs I) subtraction parathyroid scintigraphy (PS), dual-phase PS, 4-dimensional (4D) CT, and ultrasonography (US). Surgery, histological confirmation, and postoperative normalization of Ca and parathyroid hormone were the reference standard. RESULTS: Ninety-seven hyperfunctioning parathyroid glands (HPGs) were identified by the reference standard. Sensitivity and specificity for subtraction PS, dual-phase PS, 4D-CT, and US were 93%, 65%, 58%, and 57% as well as 99%, 99.6%, 86%, and 95%, respectively. Interrater agreement was excellent for subtraction PS (kappa = 0.96) while only fair for 4D-CT (kappa = 0.34). Pinhole imaging and subtraction of delayed images (the latter especially in case of a nodular thyroid gland) increased the sensitivity of subtraction PS. SPECT/low-dose CT did not increase sensitivity but aided in the exact localization of the HPGs. Of 7 negative subtraction PS studies, 4D-CT and US were able to locate 3 and 1 additional HPGs, respectively. CONCLUSIONS: Dual isotope pinhole subtraction PS has higher diagnostic accuracy compared with dual-phase PS, 4D-CT, and US as a first-line imaging study in primary hyperparathyroidism. In case of a negative scintigraphy or suspicion of multiglandular disease, 4D-CT and/or US is recommended as a second-line modality. However, diagnostic algorithms should be adapted in accordance with local availability and expertise.
PubMed-ID: 26447369
http://dx.doi.org/10.1097/RLU.0000000000000988

Establishing the clinical utility of autofluorescence spectroscopy for parathyroid detection.
Surgery, 159(1):193-202.
M. A. McWade, M. E. Sanders, J. T. Broome, C. C. Solorzano and A. Mahadevan-Jansen. 2016.
BACKGROUND: The inability of surgeons to identify parathyroid glands accurately during cervical endocrine surgery hinders patients from achieving postoperative normocalcemia. An intrinsic, near-infrared fluorescence method was developed for real-time parathyroid identification with high accuracy. This study assesses the clinical utility of this approach. METHODS: Autofluorescence measurements were obtained from 137 patients (264 parathyroid glands) undergoing parathyroidectomy and/or thyroidectomy. Measurements were correlated to disease state, calcium levels, parathyroid hormone, vitamin D levels, age, sex, ethnicity, and body mass index. Statistical analysis identified which factors affect parathyroid detection. RESULTS: High parathyroid fluorescence was detected consistently and showed wide variability across patients. Near-infrared fluorescence was used to identify 256 of 264 (97%) of glands correctly. The technique showed high accuracy over a wide variety of disease states, although patients with secondary hyperparathyroidism demonstrated confounding results. Analysis revealed body mass index (P < .01), disease state (P < .01), vitamin D (P < .05), and calcium levels (P < .05) account greatly for variability in signal intensity. Age, sex, parathyroid hormone, and ethnicity had no effect. CONCLUSION: This intrinsic fluorescence-based intraoperative technique can detect nearly all parathyroid glands accurately in real time. Its discrimination capacity is largely unlimited by patient variables, but several factors affect signal intensity. These results demonstrate potential clinical utility of optical guidance for parathyroid detection.
PubMed-ID: 26454675
http://dx.doi.org/10.1016/j.surg.2015.06.047

Minimal impact of calcimimetics on the management of hyperparathyroidism in chronic dialysis.
Surgery, 159(1):183-91.
L. Brunaud, W. Ngueyon Sime, P. Filipozzi, C. Nomine-Criqui, A. Aronova, R. Zarnegar, M. Kessler, L. Frimat and C. Ayav. 2016.
BACKGROUND: The calcimimetic drug cinacalcet has changed the prescription patterns in patients with secondary hyperparathyroidism, despite the lack of randomized studies that compare cinacalcet with conventional treatment, including parathyroidectomy. The aim of this study was to evaluate current management of patients on chronic dialysis with incidental and parathyroid hormone (PTH) levels >/= 500 ng/L. METHODS: Prospective pharmacoepidemiologic study of chronic dialysis patients with PTH level >/= 500 ng/L. RESULTS: We studied 269 patients. Among the 186 patients who had 2-year follow-up, 125 (67%) were managed using cinacalcet. At 2 years, when comparing the cinacalet with the noncinacalet groups, we found that mean PTH values were 400 +/- 318 versus 388 +/- 251 ng/L (P = ns) and the percentage of patients following 2009 PTH Kidney Disease Improving Global Outcomes (KDIGO) guidelines were 79 versus 85% (P = ns). Eight patients (4%) underwent parathyroidectomy. On multivariate analysis, the use of cinacalcet was not a predictor for PTH within KDIGO guidelines at 2-year follow-up. CONCLUSION: Cinacalcet was used in the majority (67%) of patients on chronic dialysis with secondary hyperparathyroidism, but the use of cinacalcet did not affect mean PTH values nor the proportion of patients following KDIGO guidelines compared with patients not using calcimimetics.
PubMed-ID: 26476826
http://dx.doi.org/10.1016/j.surg.2015.06.058

Does impotence improve after parathyroidectomy in men with primary hyperparathyroidism?
Surgery, 159(1):204-10.
J. Y. Yoo, L. Yip, M. J. Armstrong, S. E. Carty, M. L. Kelley, M. T. Stang and K. L. McCoy. 2016.
BACKGROUND: Erectile dysfunction (ED) is a common diagnosis associated with age, hypertension, cardiovascular disease, and diabetes. Primary hyperparathyroidism (PHP) is also seen with these comorbidities, but its association with ED has yet to be studied. We evaluated the rate and resolution of impotence after curative surgery for PHP. METHODS: Prospectively collected data, including a self-reported questionnaire of symptoms, were reviewed for men who had curative parathyroid exploration for sporadic PHP from July 2010 to January 2014. Data were compared with an age-matched cohort of men who had thyroidectomy during the same period. RESULTS: Among 160 men with PHP and mean age of 60 years (range, 19-88), preoperative ED was reported by 13%, and this group was older than patients without ED (mean age, 70 vs 58 years, P < .01). Self-reported resolution of ED after parathyroidectomy occurred in 67% compared with 43% of patients in a thyroidectomy cohort. Preoperative mean arterial blood pressure was less in men with postoperative resolution of ED (96.6 vs 105.4 mm Hg, P = .03). Among 3 of 21 men on specific ED medications, 2 no longer required them postoperatively. CONCLUSION: Impotence is reported often by men undergoing parathyroidectomy for PHP. After curative surgery, 67% of those affected may self-report ED resolution, which may be more pronounced in those patients with a lesser preoperative mean arterial blood pressure.
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http://dx.doi.org/10.1016/j.surg.2015.06.055

Long-Term Surveillance of Treated Hyperparathyroidism for Multiple Endocrine Neoplasia Type 1: Recurrence or Hypoparathyroidism?
World J Surg, 40(3):615-21.
E. Fyrsten, O. Norlen, O. Hessman, P. Stalberg and P. Hellman. 2016.
BACKGROUND: Primary hyperparathyroidism (HPT) in multiple endocrine neoplasia type 1 (MEN1) is surgically treated with either a subtotal parathyroidectomy removing 3 or 3,5 glands (SPX), less than 3 glands (LSPX), or a total parathyroidectomy with autotransplantation (TPX). Previous studies with shorter follow-up have shown that LSPX and SPX are associated with recurrent HPT, and TPX with hypocalcemia and substitution therapy. We examined the situation after long-term follow-up (median 20,6 years). METHODS: Sixty-nine patients with MEN1 HPT underwent 110 operations, the first operation being 31 LSPX, 30 SPX, and 8 TPX. Thirty patients underwent reoperative surgery in median 120 months later, as completion to TPX (n = 12), completion of LSPX to SPX (n = 9), extirpation of single glands (n = 3) still resulting in LSPX, and resection of forearm grafts (n = 3). Nine patients underwent a second, and 2 a third reoperation. In 24 patients genetic testing confirmed MEN1, and in the remaining heredity and phenotype led to the diagnosis. RESULTS: TPX had higher risk for hypoparathyroidism necessitating substitution therapy, at latest follow-up 50%, compared to SPX (16% after 3-6 months; none at latest follow-up). Recurrent HPT was common after LSPX, leading to 24 reoperations in 17 patients. No need for substitution therapy after SPX indicated forthcoming recurrent disease. Not having hypocalcemia in the postoperative period and less radical surgery than TPX were significantly associated to risk

for recurrence. Further, mutation in exon 3 in the MEN1 gene may eventually be linked to risk of recurrence. CONCLUSION: LSPX is highly associated with recurrence and TPX with continuous hypoparathyroidism, also after long-term follow-up. SPX should be the chosen method in the majority of patients with MEN1 HPT.
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http://dx.doi.org/10.1007/s00268-015-3297-9

Limited Parathyroidectomy in Multiple Endocrine Neoplasia Type 1-Associated Primary Hyperparathyroidism: A Setup for Failure.
Ann Surg Oncol, 23(2):416-23.
N. Nilubol, L. S. Weinstein, W. F. Simonds, R. T. Jensen, S. J. Marx and E. Kebebew. 2016.
BACKGROUND: Recently, some surgeons have suggested that minimally invasive parathyroidectomy guided by preoperative localizing studies of patients with multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) provides an acceptable outcome while minimizing the risk of hypoparathyroidism. This study aimed to evaluate the outcome for MEN1 patients who underwent limited parathyroidectomy compared with subtotal parathyroidectomy. METHODS: The authors performed a retrospective analysis of 99 patients with MEN1-associated pHPT who underwent at least one parathyroid operation at their institution. Preoperative imaging studies, intraoperative findings, and clinical outcomes for patients were compared. RESULTS: A total of 99 patients underwent 146 operations. Persistent pHPT was significantly higher in patients whose initial operations involved removal of 1 or 2 glands (69 %) or 2.5 to 3 glands (20 %) compared with those who had 3.5 or more glands removed (6 %) ($P < 0.01$). Persistent pHPT occurred in 5 % of all operations that cumulatively removed 3.5 or more parathyroid glands compared with 40 % of operations that removed 3 or fewer glands ($P < 0.01$). The single largest parathyroid gland was correctly identified preoperatively in 69 % (22/32) of the patients. However, preoperative localizing studies missed enlarged contralateral parathyroid glands in 86 % (19/22) of these patients. Preoperative localizing studies missed the largest contralateral parathyroid gland in 16 % (5/32) of the patients. CONCLUSIONS: Limited parathyroidectomy in MEN1 is associated with a high failure rate and should not be performed. Preoperative identification of a single enlarged parathyroid gland in MEN1 is not reliable enough to justify unilateral neck exploration because additional enlarged contralateral parathyroid glands are frequently missed.
PubMed-ID: 26542588
http://dx.doi.org/10.1245/s10434-015-4865-9

Characteristics of Persistent Hyperparathyroidism After Renal Transplantation.
World J Surg, 40(3):600-6.
T. Yamamoto, Y. Tominaga, M. Okada, T. Hiramitsu, M. Tsujita, N. Goto, S. Narumi and Y. Watarai. 2016.
BACKGROUND: Persistent hyperparathyroidism (HPT) after renal transplantation (RTx), termed tertiary HPT (THPT), is not uncommon. However, risk factors and appropriate operative procedures for THPT are poorly understood. METHODS: A retrospective study of patients who underwent RTx without pre-transplant parathyroidectomy (PTx) was performed at our hospital between January 2001 and March 2011. Risk factors for the development of THPT were investigated by comparing THPT and non-THPT groups. We retrospectively analyzed patients with THPT who underwent total PTx with forearm autograft. Pre- and postoperative (1 year after PTx) laboratory results were analyzed for PTx efficacy. RESULTS: Data for 520 patients were analyzed. On multivariate analysis, long dialysis duration ($p = 0.009$, hazard ratio (HR) 1.01), large maximum parathyroid gland size before RTx ($p = 0.003$, HR 1.23), pre-RTx high intact parathyroid hormone (iPTH) ($p = 0.041$, HR 1.01), post-RTx (<2 weeks) high calcium (Ca) ($p < 0.001$, HR 25.04), and post-RTx high alkaline phosphatase (ALP) ($p = 0.027$, HR 0.99) were identified as risk factors for THPT. Patients who underwent PTx showed significant improvement compared with baseline for serum Ca, phosphorus, iPTH, and ALP. Serum creatinine showed no significant difference. CONCLUSIONS: Several risk factors for THPT development were identified. PTx for patients with THPT significantly improved serum Ca, iPTH, ALP, and phosphorous levels. There was no significant difference in renal function after PTx. Therefore, total PTx with forearm autograft may be an appropriate surgical approach for patients with THPT.
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http://dx.doi.org/10.1007/s00268-015-3314-z

Location Frequency of Missed Parathyroid Glands After Parathyroidectomy in Patients with Persistent or Recurrent Secondary Hyperparathyroidism.
World J Surg, 40(3):595-9.
M. Okada, Y. Tominaga, T. Yamamoto, T. Hiramitsu, S. Narumi and Y. Watarai. 2016.
BACKGROUND: Reoperative parathyroidectomy (RPTX) because parathyroid glands have been missed is frequently required in patients with secondary hyperparathyroidism (SHPT). The usual locations of these missed

glands in patients with SHPT are yet to be fully elucidated. METHODS: We retrospectively investigated the locations of missed glands in 165 patients who underwent RPTX for persistent or recurrent SHPT at our institution from August 1982 to July 2014. At our institution, total parathyroidectomy with forearm autograft is the routine operative procedure for SHPT. We also routinely resect the thymic tongue. RESULTS: Of 165 patients, 82 underwent initial parathyroidectomy at our institution (Group A), and the remaining 83 underwent initial parathyroidectomy at other institutions (Group B). A total of 239 parathyroid glands were resected (Group A, 93; Group B, 146). Missed glands were most commonly located in the mediastinum (Group A, 22/93) and the thymic tongue (Group B, 31/146). CONCLUSIONS: In patients with persistent or recurrent SHPT, ectopic parathyroid glands are frequently located in the mediastinum and thymic tongue. Therefore, resecting the thymic tongue during the initial operation may reduce the need for RPTX.
PubMed-ID: 26563219
http://dx.doi.org/10.1007/s00268-015-3312-1

Presentation and Outcomes After Surgery for Primary Hyperparathyroidism During an 18-Year Period.
World J Surg, 40(2):356-64.
M. Thier, E. Nordenstrom, A. Bergenfelz and M. Almquist. 2016.
PURPOSE: The objective of this study is to analyze whether the trend towards operating on patients with less severe primary hyperparathyroidism (pHPT) than earlier is reflected in a change of preoperative presentation and surgical outcome. METHODS: In this longitudinal cohort study, patients with pHPT subjected to first time surgery were compared in three time periods: 1989-1994, 1995-2000, and 2001-2006 in this longitudinal cohort study. RESULTS: There were 404 patients. Median levels of preoperative ionized calcium were lower in 2001-2006 compared to 1989-1994; 1.45 versus 1.50 versus 1.45 mmol/L; p < 0.001. Preoperative parathyroid hormone levels in patients with parathyroid adenoma were lower in 2001-2006 than in 1989-1994; 10.0 versus 11.6 pmol/L; p 0.04. Median preoperative bone mineral density, BMD, in the whole cohort did not differ between time periods. Median pre- and postoperative glomeruli filtration rate, GFR, and 25-hydroxy-vitamin D3 remained unchanged between period 1 and period 3. Adenoma weight was lower in 2001-2006 than 1989-1994; 0.70 versus 0.50 g; p 0.04. Cure rate did not change during observation time. There was no evidence for differences in change of BMD (femoral neck) after surgery between period 2 and 3 1995-2000 and 2001-2006, 0.798 versus 0.795 g/cm(2); p 0.67. GFR did not change significantly between 1989-1994 and 2001-2006, 74 versus 77 mL/min; p 0.43. CONCLUSIONS: A significant change towards operating patients with smaller adenomas and lower preoperative calcium levels was evident throughout the observation period, but this did not correlate with differences in preoperative renal or skeletal function. We found no evidence for a change of postoperative renal function or skeletal function during observation time.
PubMed-ID: 26578321
http://dx.doi.org/10.1007/s00268-015-3329-5

4D MRI for the Localization of Parathyroid Adenoma: A Novel Method in Evolution.
Otolaryngol Head Neck Surg, 154(3):446-8.
S. Merchavy, J. Luckman, M. Guindy, Y. Segev and A. Khafif. 2016.
The sestamibi scan (MIBI) and ultrasound (US) are used for preoperative localization of parathyroid adenoma (PTA), with sensitivity as high as 90%. We developed 4-dimensional magnetic resonance imaging (4D MRI) as a novel tool for identifying PTAs. Eleven patients with PTA were enrolled. 4D MRI from the mandible to the aortic arch was used. Optimization of the timing of image acquisition was obtained by changing dynamic and static sequences. PTAs were identified in all except 1 patient. In 9 patients, there was a complete match between the 4D MRI and the US and MIBI, as well as with the operative finding. In 1 patient, the adenoma was correctly localized by 4D MRI, in contrast to the US and MIBI scan. The sensitivity of the 4D MRI was 90% and after optimization, 100%. Specificity was 100%. We concluded that 4D MRI is a reliable technique for identification of PTAs, although more studies are needed.
PubMed-ID: 26598499
http://dx.doi.org/10.1177/0194599815618199

Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation.
Surgery, 159(1):172-9.
I. Lou, D. F. Schneider, G. Leverson, D. Foley, R. Sippel and H. Chen. 2016.
BACKGROUND: Parathyroidectomy (PTX) is the only curative treatment for tertiary hyperparathyroidism (3HPT). With the introduction of calcimimetics (cinacalcet), PTX can sometimes be delayed or avoided. The purpose of this study was to determine the current incidence of utilization of PTX in patients with posttransplant 3HPT with the advent of cinacalcet. METHODS: We evaluated renal transplant patients between January 1,

2004, and June 30, 2012, with a minimum of 24 months follow-up who had persistent allograft function. Patients with an increased serum level of parathyroid hormone (PTH) at 1 year after successful renal transplantation with normocalcemia or hypercalcemia were defined as having 3HPT. A multivariate logistic regression model was constructed to determine factors associated with undergoing PTX. RESULTS: We identified 618 patients with 3HPT, only 41 (6.6%) of whom underwent PTX. Patients with higher levels of serum calcium (P < .001) and PTH (P = .002) posttransplant were more likely to be referred for PTX. Importantly, those who underwent PTX had serum calcium and PTH values distributed more closely to the normal range on most recent follow-up. PTX was not associated with rejection (P = .400) or with worsened allograft function (P = .163). CONCLUSION: PTX seems to be underused in patients with 3HPT at our institution. PTX is associated with high cure rates, improved serum calcium and PTH levels, and is not associated with rejection.
PubMed-ID: 26603850
http://dx.doi.org/10.1016/j.surg.2015.08.039

Reoperative Parathyroidectomy: Overly Descended Superior Adenoma.
Otolaryngol Head Neck Surg, 154(2):268-71.
W. S. Duke, H. M. Vernon and D. J. Terris. 2016.
OBJECTIVES: To identify the importance of the ectopic, overly descended superior parathyroid adenoma variant and its prevalence in primary and reoperative parathyroid surgery and the implications for successful initial parathyroidectomy. STUDY DESIGN: Case series with planned data collection. SETTING: Tertiary endocrine surgery practice in an academic medical center. SUBJECTS AND METHODS: An analysis was undertaken of 561 consecutive patients undergoing parathyroid surgery in a tertiary endocrine surgery practice from March 2004 to April 2013. There were 270 patients who had curative primary or reoperative surgery for single-gland parathyroid adenomas during this time. Clinical records, imaging studies, operative reports, and pathology findings were evaluated, and cases from a subset of patients who had an ectopic, overly descended superior parathyroid adenoma were further analyzed. The prevalence of this entity in primary and revision surgeries was calculated. RESULTS: Among the 270 patients with single-gland parathyroid adenomas, there were 251 primary operations and 19 reoperative procedures referred from outside institutions. An ectopic, overly descended superior parathyroid adenoma was present in 23 (9.2%) primary cases and 4 (21.1%) reoperative cases. CONCLUSION: An overly descended superior parathyroid adenoma is frequently encountered during primary parathyroid surgery. It is more than twice as common in reoperative parathyroidectomy, reflecting the propensity to be missed at the first exploration. Recognition and proper treatment of this entity at the initial operation will reduce the need for revision surgery.
PubMed-ID: 26607282
http://dx.doi.org/10.1177/0194599815619625

Evaluation of malignant parathyroid tumours in two European cohorts of patients with sporadic primary hyperparathyroidism.
Langenbecks Arch Surg,
A. Ozolins, Z. Narbuts, A. Vanags, Z. Simtniece, Z. Visnevska, A. Akca, D. Wirowski, J. Gardovskis, I. Strumfa and P. E. Goretzki. 2015.
PURPOSE: Parathyroid carcinoma (PC) is remarkable for its rare occurrence and challenging diagnostics. PC accounts for 0.1-5 % cases of primary hyperparathyroidism (PHPT). The differentiation from benign tumours is difficult even by morphological criteria. To address these issues, we assessed the PC frequency in two separate European PHPT cohorts and evaluated the demographic, clinical, morphological and molecular background. METHODS: A retrospective study was carried out, using continuously maintained database (2005-2014) of PHPT patients from two tertiary referral university hospitals in Europe. The demographic, clinical data and frequency of PC among surgically treated PHPT was detected. Immunohistochemistry (IHC) was performed to detect parafibromin, representing protein product of HRPT2 gene and proliferation marker Ki-67. RESULTS: Both PHPT cohorts were characterised by close mean age values (58.6 and 58.0 years) and female predominance. The frequency of PC differed significantly between the cohorts: 2.1 vs. 0.3 %; p = 0.004. PC was characterised by invariable complete loss of parafibromin contrasting with parathyroid adenomas. The proliferation fraction was similar in both PC cohorts (10.6 and 11.0 %). PC showed significantly higher proliferation fraction than typical parathyroid adenomas (1.6 %), atypical adenomas (1.6 %) or adenomas featuring focal loss of parafibromin (2.2 %). CONCLUSIONS: PC frequency can range significantly between the two European cohorts. The differences can be attributable to selection bias of patients referred for surgery and are not caused by discordant definition of malignant parathyroid histology. Diffuse loss of parafibromin and increased proliferation fraction by Ki-67 are valuable adjuncts in PC diagnostics due to significant differences with various clinical and morphological subtypes of adenoma.

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http://dx.doi.org/10.1007/s00423-015-1361-4

Results of a Fifteen-Year Follow-up Program in Patients Operated with Unilateral Neck Exploration for Primary Hyperparathyroidism.
World J Surg, 40(3):582-8.
M. Thier, E. Nordenstrom, M. Almquist and A. Bergenfelz. 2016.
BACKGROUND: Since the introduction of unilateral parathyroidectomy for primary hyperparathyroidism (pHPT) it has been debated wherever this approach is associated with greater long-term risk for recurrence compared to bilateral neck exploration. METHODS: This is a prospective study based on a structured 15-year follow-up program in patients with non-hereditary, sporadic pHPT, undergoing first time surgery with unilateral or focused neck exploration (unilateral procedures), with the use of intraoperative PTH (iOPTH) between 1989 and 2010. RESULTS: 292 patients were analyzed. The median age of the patients was 66 years [interquartile range (IQR) 57-75], and 234 (80.4%) were female. The median preoperative level of total calcium was 2.74 mmol/L (IQR 2.63-2.85 mmol/L) and the median PTH level was 10 pmol/L (IQR 7.4-14 pmol/L). The median follow-up time was 5 years (IQR 1-10 years). Some 275 patients were followed for 1 year (94.2%/275 person-years/5 patients deceased), 164 for 5 years (56.2%/820 person-years/31 patients deceased), 70 for 10 years (24.0%/700 patient-years/57 patients deceased) and 51 (17.5%/765 patient-years/69 patients deceased) for 15 years after surgery. Three patients (1.1%) had signs of persistent disease. One patient recurred in pHPT at 5 years postoperatively during 15 years of follow-up. Histopathology indicated solitary parathyroid adenoma at primary surgery. CONCLUSION: Patients with pHPT operated with unilateral procedures and iOPTH, had a low risk for long-term recurrence during a 15 years follow-up program.
PubMed-ID: 26661636
http://dx.doi.org/10.1007/s00268-015-3360-6

[Optimal timing of parathyroidectomy after renal transplantation].
Chirurg, 87(1):69.
H. Dralle. 2016.
PubMed-ID: 26666443
http://dx.doi.org/10.1007/s00104-015-0129-2

Molecular Characteristics of Large Parathyroid Adenomas.
World J Surg, 40(3):607-14.
A. Agarwal, R. Pradhan, N. Kumari, N. Krishnani, P. Shukla, S. K. Gupta, G. Chand, A. Mishra, G. Agarwal, A. K. Verma and S. K. Mishra. 2016.
INTRODUCTION: The clinical entity of large parathyroid adenomas (LPTAs) has not been well defined. It is speculated that LPTAs would have biochemical, histological, and molecular characteristics different from small adenomas. Our study aimed to find out occurrence of atypia and carcinomas in large parathyroid lesions and the presence of distinct molecular abnormalities in LPTAs. MATERIALS AND METHODS: We divided the parathyroid lesions into large (>7 g, i.e., LPTAs) and small (<7 g) adenomas. We performed parafibromin, APC (adenomatous polyposis coli), galectin 3, and PGP9.5 (protein gene product 9.5) analysis by immunohistochemistry in adenomas without atypia, atypical adenomas, and carcinomas. RESULTS: Mean serum calcium, alkaline phosphatase, and intact PTH were significantly higher in large parathyroid tumor group. The presence of both atypical adenoma and carcinoma was higher in large parathyroid tumor group. There was higher percentage of atypia in patients with LPTAs >10 g (33%), and 68% of tumors showed at least one marker suggestive of malignancy in this group. Detailed analysis of immunohistochemical features of LPTA >10 g revealed that six patients showed complete loss of parafibromin immunoreactivity (out of these four showed atypia), while seven showed partial loss. In histopathologically proven malignancy (n = 9), six patients showed complete loss of parafibromin staining, 5 (55%) APC negativity, and 45% showed both galectin 3 and PGP9.5 positivity. Three out of these showed all IHC markers s/o malignancy, and all of them had evidence of metastases or recurrence. 32% of atypical adenoma and 13% of atypical adenoma showed complete loss of parafibromin staining, however none developed metastases or recurrence in follow-up (median follow-up 40 months). Loss of parafibromin staining (complete or partial) was higher in LPTA group (56%) than that in small adenoma (39%); however, it was not statistically significant. APC, galectin 3, and PGP9.5 markers suggestive were higher in LPTA group but were not significant. CONCLUSION: LPTAs may show some morphological and immunohistochemical features suggestive of malignancy and can be considered a separate entity. However, the immunohistochemical markers are unable to clearly segregate those LPTAs that may show premalignant potential. Further, we would like to recommend that LPTAs showing complete parafibromin loss together with atypia should be kept under close follow-up.

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http://dx.doi.org/10.1007/s00268-015-3380-2

Compliance with recommendations on surgery for primary hyperparathyroidism-from guidelines to real practice: results from an Iberian survey.
Langenbecks Arch Surg,
J. Villar-Del-Moral, J. Capela-Costa, A. Jimenez-Garcia, A. Sitges-Serra, D. Casanova-Rituerto, J. Rocha, J. M. Martos-Martinez, A. de la Quintana-Basarrate, J. Rosa-Santos, X. Guirao-Garriga, J. M. Bravo-de-Lifante, O. Vidal-Perez, A. Moral-Duarte and J. Polonia. 2015.
PURPOSE: Knowledge about compliance with recommendations derived from the positional statement of the European Society of Endocrine Surgeons on modern techniques in primary hyperparathyroidism surgery and the Third International Workshop on management of asymptomatic primary hyperparathyroidism is scarce. Our purpose was to check it on a bi-national basis and determine whether management differences may have impact on surgical outcomes. METHODS: An online survey including questions about indications, preoperative workup, surgical approach, intraoperative adjuncts, and outcomes was sent to institutions affiliated to the endocrine surgery divisions of the National Surgical Societies from Spain and Portugal. A descriptive evaluation of the responses was performed. Finally, we assessed the correlation between the different types of management with the achievement of optimal results, defined as a cure rate equal or greater than the median of all interviewed institutions. RESULTS: Fifty-seven hospitals (41 Spanish, 16 Portuguese) answered the survey. First-ordered imaging tests were neck ultrasound and sestamibi scan. Facing negative or non-concordant results, 44 % of surgeons ordered additional tests before first-time surgery, and 84 % before reoperations. When indicated, selective parathyroidectomy was an acceptable option for 95 % of institutions as first-time surgery and for 51 % in reoperations. Intraoperative parathormone measurements were used by 92 % of departments. The surgical outcomes were good in most institutions (median cure rate 97 %) and were influenced mostly by the presence of an endocrine surgery unit in the surgical department (p = 0.038). CONCLUSIONS: Practice of Iberian endocrine surgeons is consistent with current recommendations on surgery for primary hyperparathyroidism, with variability in some areas.
PubMed-ID: 26686853
http://dx.doi.org/10.1007/s00423-015-1362-3

A Multimodal Imaging Protocol, (123)I/(99)Tc-Sestamibi, SPECT, and SPECT/CT, in Primary Hyperparathyroidism Adds Limited Benefit for Preoperative Localization.
World J Surg, 40(3):589-94.
G. S. Lee, T. J. McKenzie, B. P. Mullan, D. R. Farley, G. B. Thompson and M. L. Richards. 2016.
INTRODUCTION: Focused parathyroidectomy in primary hyperparathyroidism (1 degrees HPT) is possible with accurate preoperative localization and intraoperative PTH monitoring (IOPTH). The added benefit of multimodal imaging techniques for operative success is unknown. METHOD: Patients with 1 degrees HPT, who underwent parathyroidectomy in 2012-2014 at a single institution, were retrospectively reviewed. Only the patients who underwent the standardized multimodal imaging workup consisting of (123)I/(99)Tc-sestamibi subtraction scintigraphy, SPECT, and SPECT/CT were assessed. RESULTS: Of 360 patients who were identified, a curative operation was performed in 96%, using pre-operative imaging and IOPTH. Imaging analysis showed that (123)I/(99)Tc-sestamibi had a sensitivity of 86% (95% CI 82-90%), positive predictive value (PPV) 93%, and accuracy 81%, based on correct lateralization. SPECT had a sensitivity of 77% (95% CI 72-82%), PPV 92% and accuracy 72%. SPECT/CT had a sensitivity of 75% (95% CI 70-80%), PPV of 94%, and accuracy 71%. There were 3 of 45 (7%) patients with negative sestamibi imaging that had an accurate SPECT and SPECT/CT. Of 312 patients (87%) with positive uptake on sestamibi (93% true positive, 7% false positive), concordant findings were present in 86% SPECT and 84% SPECT/CT. In cases where imaging modalities were discordant, but at least one method was true-positive, (123)I/(99)Tc-sestamibi was significantly better than both SPECT and SPECT/CT (p < 0.001). The inclusion of SPECT and SPECT/CT in 1 degrees HPT imaging protocol increases patient cost up to 2.4-fold. CONCLUSION: (123)I/(99)Tc-sestamibi subtraction imaging is highly sensitive for preoperative localization in 1 degrees HPT. SPECT and SPECT/CT are commonly concordant with (123)I/(99)Tc-sestamibi and rarely increase the sensitivity. Routine inclusion of multimodality imaging technique adds minimal clinical benefit but increases cost to patient in high-volume setting.
PubMed-ID: 26732668
http://dx.doi.org/10.1007/s00268-015-3389-6

Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms.
J Endocrinol Invest, 39(5):567-76.

A. Trombetti, E. R. Christ, C. Henzen, G. Gold, M. Brandle, F. R. Herrmann, C. Torriani, F. Triponez, M. Kraenzlin, R. Rizzoli and C. Meier. 2016.
PURPOSE: To describe the clinical and biochemical profile of patients with primary hyperparathyroidism (PHPT) of the Swiss Hyperparathyroidism Cohort, with a focus on neurobehavioral and cognitive symptoms and on their changes in response to parathyroidectomy. METHODS: From June 2007 to September 2012, 332 patients were enrolled in the Swiss PHPT Cohort Study, a nationwide prospective and non-interventional project collecting clinical, biochemical, and outcome data in newly diagnosed patients. Neuro-behavioral and cognitive status were evaluated annually using the Mini-Mental State Examination, the Hospital Anxiety and Depression Scale, and the Clock Drawing tests. Follow-up data were recorded every 6 months. Patients with parathyroidectomy had one follow-up visit 3-6 months' postoperatively. RESULTS: Symptomatic PHPT was present in 43 % of patients. Among asymptomatic patients, 69 % (131/189) had at least one of the US National Institutes for Health criteria for surgery, leaving thus a small number of patients with cognitive dysfunction or neuropsychological symptoms, but without any other indication for surgery. At baseline, a large proportion showed elevated depression and anxiety scores and cognitive dysfunction, but with no association between biochemical manifestations of the disease and test scores. In the 153 (46 %) patients who underwent parathyroidectomy, we observed an improvement in the Mini-Mental State Examination (P = 0.01), anxiety (P = 0.05) and depression (P = 0.05) scores. CONCLUSION: PHPT patients often present elevated depression and anxiety scores and cognitive dysfunction, but rarely as isolated manifestations. These alterations may be relieved upon treatment by parathyroidectomy.
PubMed-ID: 26742935
http://dx.doi.org/10.1007/s40618-015-0423-3

Thiazide-Associated Hypercalcemia: Incidence and Association With Primary Hyperparathyroidism Over Two Decades.
J Clin Endocrinol Metab, 101(3):1166-73.
M. L. Griebeler, A. E. Kearns, E. Ryu, P. Thapa, M. A. Hathcock, L. J. Melton, 3rd and R. A. Wermers. 2016.
CONTEXT: Thiazide diuretics, the antihypertensive agent prescribed most frequently worldwide, are commonly associated with hypercalcemia. However, the epidemiology and clinical features are poorly understood. OBJECTIVE: To update the incidence of thiazide-associated hypercalcemia and clarify its clinical features. PATIENTS AND METHODS: In a population-based descriptive study, Olmsted County, Minnesota, residents with thiazide-associated hypercalcemia were identified through the Rochester Epidemiology Project and the Mayo Clinic Laboratory Information System from 2002-2010 and were added to the historical cohort beginning in 1992. MAIN OUTCOME: Incidence rates were adjusted to the 2010 United States white population. RESULTS: Overall, 221 Olmsted County residents were identified with thiazide-associated hypercalcemia an average of 5.2 years after initiation of treatment. Subjects were older (mean age, 67 years) and primarily women (86.4%). The incidence of thiazide-associated hypercalcemia increased after 1997 and peaked in 2006 with an annual incidence of 20 per 100 000, compared to an overall rate of 12 per 100 000 in 1992-2010. Severe hypercalcemia was not observed in the cohort despite continuation of thiazide treatment in 62.4%. Of patients discontinuing thiazides, 71% continued to have hypercalcemia. Primary hyperparathyroidism was diagnosed in 53 patients (24%), including five patients who underwent parathyroidectomy without thiazide discontinuation. CONCLUSIONS: Many patients with thiazide-associated hypercalcemia have underlying primary hyperparathyroidism. Additionally, a sharp rise in thiazide-associated hypercalcemia incidence began in 1998, paralleling the increase observed in primary hyperparathyroidism in this community. Case ascertainment bias from targeted osteoporosis screening is the most likely explanation.
PubMed-ID: 26751196
http://dx.doi.org/10.1210/jc.2015-3964

Physical Activity and the Risk of Primary Hyperparathyroidism.
J Clin Endocrinol Metab, 101(4):1590-7.
A. Vaidya, G. C. Curhan, J. M. Paik, M. Wang and E. N. Taylor. 2016.
In this large prospective cohort study of women, higher weekly physical activity was associated with a significantly lower risk of developing incident primary hyperparathyroidism.
PubMed-ID: 26812691
http://dx.doi.org/10.1210/jc.2015-3836

Parathyroid Surgery: Getting It Right the First Time.
Otolaryngol Head Neck Surg, 154(2):396.
D. J. Terris and B. C. Stack, Jr. 2016.
PubMed-ID: 26833647
http://dx.doi.org/10.1177/0194599815619601

Management of Hypoparathyroidism: Present and Future.
J Clin Endocrinol Metab, 101(6):2313-24.
J. P. Bilezikian, M. L. Brandi, N. E. Cusano, M. Mannstadt, L. Rejnmark, R. Rizzoli, M. R. Rubin, K. K. Winer, U. A. Liberman and J. T. Potts, Jr. 2016.
CONTEXT: Conventional management of hypoparathyroidism has focused upon maintaining the serum calcium with oral calcium and active vitamin D, often requiring high doses and giving rise to concerns about long-term consequences including renal and brain calcifications. Replacement therapy with PTH has recently become available. This paper summarizes the results of the findings and recommendations of the Working Group on Management of Hypoparathyroidism. EVIDENCE ACQUISITION: Contributing authors reviewed the literature regarding physiology, pathophysiology, and nutritional aspects of hypoparathyroidism, management of acute hypocalcemia, clinical aspects of chronic management, and replacement therapy of hypoparathyroidism with PTH peptides. PubMed and other literature search engines were utilized. EVIDENCE SYNTHESIS: Under normal circumstances, interactions between PTH and active vitamin D along with the dynamics of calcium and phosphorus absorption, renal tubular handing of those ions, and skeletal responsiveness help to maintain calcium homeostasis and skeletal health. In the absence of PTH, the gastrointestinal tract, kidneys, and skeleton are all affected, leading to hypocalcemia, hyperphosphatemia, reduced bone remodeling, and an inability to conserve filtered calcium. Acute hypocalcemia can be a medical emergency presenting with neuromuscular irritability. The recent availability of recombinant human PTH (1-84) has given hope that management of hypoparathyroidism with the missing hormone in this disorder will provide better control and reduced needs for calcium and vitamin D. CONCLUSIONS: Hypoparathyroidism is associated with abnormal calcium and skeletal homeostasis. Control with calcium and active vitamin D can be a challenge. The availability of PTH (1-84) replacement therapy may usher new opportunities for better control with reduced supplementation requirements.
PubMed-ID: 26938200
http://dx.doi.org/10.1210/jc.2015-3910

Preoperative diagnosis and prognosis in 40 Parathyroid Carcinoma Patients.
Clin Endocrinol (Oxf), 85(1):29-36.
S. Xue, H. Chen, C. Lv, X. Shen, J. Ding, J. Liu and X. Chen. 2016.
OBJECTIVE: Parathyroid carcinoma (PC) is a rare disease which is difficult to diagnose preoperatively and predict prognosis. The goal of this study was to analyse the preoperative predictive factors and prognostic factors in PC patients and to evaluate the possibility of diagnosing PC preoperatively. DESIGN, SETTING AND PATIENTS: This is a retrospective study from Jan 2000 to Aug 2015 conducted in Shanghai Ruijin Hospital. MEASUREMENTS: Comparisons were made between 40 parathyroid carcinoma patients and 282 patients with benign parathyroid lesions during the same period. All patients underwent parathyroid surgery, and the results were certified by paraffin pathology. Prognostic factors were analysed in the 40 PC patients. RESULTS: Patients with higher levels of intact parathyroid hormone (P < 0.001, OR = 1.001, CI: 1.000-1.002), calcium (P = 0.008, OR = 3.395, CI: 1.382-8.341) and a larger parathyroid volume (P = 0.001, OR = 2.023, CI: 1.333-3.071) were more likely to have PC. Local excision (P = 0.008, OR = 4.992, CI: 1.533-16.252), stage III in the Schulte staging system (P = 0.039, OR = 9.600, CI: 1.12-82.322), high risk in the Schulte Risk Classification (P = 0.012, OR = 5.466, CI: 1.448-20.628) and first surgery by other medical teams (P = 0.008, OR = 4.992, CI: 1.496-15.037) were associated with PC recurrence. Calcium (P = 0.01, OR = 7.270, CI: 1.611-32.812), intact parathyroid hormone (P = 0.037, OR = 1.001, CI: 1.000-1.001), local excision (P = 0.009, OR = 6.875, CI: 1.633-28.936) and recurrence (P = 0.014, OR = 7.762, CI: 1.504-40.055) were associated with death. CONCLUSIONS: A preoperative diagnostic system may provide a new method to distinguish PC from benign parathyroid lesions before surgery. For PC patients who did not undergo en-bloc resection at first operation, timely further surgery may offer a second chance of cure. Early diagnosis and surgery are pivotal to reduce mortality in PC patients.
PubMed-ID: 26939543
http://dx.doi.org/10.1111/cen.13055

Elevated PTH with normal serum calcium level: a structured approach.
Clin Endocrinol (Oxf), 84(6):809-13.
R. K. Crowley and N. J. Gittoes. 2016.
Normocalcaemic hyperparathyroidism is a common biochemical finding, usually identified during an assessment

of bone or renal health. Hypercalcaemia must be considered by calculation of adjusted calcium, and a careful history taken to assess dietary calcium intake and for the possibility of a malabsorption syndrome. 25-hydroxyvitamin D (25OHD) should be measured and replaced if indicated. The management plan for the patient is influenced by the context in which calcium and PTH were measured. In this brief review we describe the assessment of a patient with normocalcaemic hyperparathyroidism.
PubMed-ID: 26939669
http://dx.doi.org/10.1111/cen.13056

Epidemiology and Diagnosis of Hypoparathyroidism.
J Clin Endocrinol Metab, 101(6):2284-99.
B. L. Clarke, E. M. Brown, M. T. Collins, H. Juppner, P. Lakatos, M. A. Levine, M. M. Mannstadt, J. P. Bilezikian, A. F. Romanischen and R. V. Thakker. 2016.
CONTEXT: Hypoparathyroidism is a disorder characterized by hypocalcemia due to insufficient secretion of PTH. Pseudohypoparathyroidism is a less common disorder due to target organ resistance to PTH. This report summarizes the results of the findings and recommendations of the Working Group on Epidemiology and Diagnosis of Hypoparathyroidism. EVIDENCE ACQUISITION: Each contributing author reviewed the recent published literature regarding epidemiology and diagnosis of hypoparathyroidism using PubMed and other medical literature search engines. EVIDENCE SYNTHESIS: The prevalence of hypoparathyroidism is an estimated 37 per 100 000 person-years in the United States and 22 per 100 000 person-years in Denmark. The incidence in Denmark is approximately 0.8 per 100 000 person-years. Estimates of prevalence and incidence of hypoparathyroidism are currently lacking in most other countries. Hypoparathyroidism increases the risk of renal insufficiency, kidney stones, posterior subcapsular cataracts, and intracerebral calcifications, but it does not appear to increase overall mortality, cardiovascular disease, fractures, or malignancy. The diagnosis depends upon accurate measurement of PTH by second- and third-generation assays. The most common etiology is postsurgical hypoparathyroidism, followed by autoimmune disorders and rarely genetic disorders. Even more rare are etiologies including parathyroid gland infiltration, external radiation treatment, and radioactive iodine therapy for thyroid disease. Differentiation between these different etiologies is aided by the clinical presentation, serum biochemistries, and in some cases, genetic testing. CONCLUSIONS: Hypoparathyroidism is often associated with complications and comorbidities. It is important for endocrinologists and other physicians who care for these patients to be aware of recent advances in the epidemiology, diagnosis, and genetics of this disorder.
PubMed-ID: 26943720
http://dx.doi.org/10.1210/jc.2015-3908

Presentation of Hypoparathyroidism: Etiologies and Clinical Features.
J Clin Endocrinol Metab, 101(6):2300-12.
D. M. Shoback, J. P. Bilezikian, A. G. Costa, D. Dempster, H. Dralle, A. A. Khan, M. Peacock, M. Raffaelli, B. C. Silva, R. V. Thakker, T. Vokes and R. Bouillon. 2016.
CONTEXT: Understanding the etiology, diagnosis, and symptoms of hypoparathyroidism may help to improve quality of life and long-term disease outcomes. This paper summarizes the results of the findings and recommendations of the Working Group on Presentation of Hypoparathyroidism. EVIDENCE ACQUISITION: Experts convened in Florence, Italy, in May 2015 and evaluated the literature and recent data on the presentation and long-term outcomes of patients with hypoparathyroidism. EVIDENCE SYNTHESIS: The most frequent etiology is surgical removal or loss of viability of parathyroid glands. Despite precautions and expertise, about 20-30% of patients develop transient and 1-7% develop permanent postsurgical hypoparathyroidism after total thyroidectomy. Autoimmune destruction is the main reason for nonsurgical hypoparathyroidism. Severe magnesium deficiency is an uncommon but correctable cause of hypoparathyroidism. Several genetic etiologies can result in the loss of parathyroid function or action causing isolated hypoparathyroidism or a complex syndrome with other symptoms apart from those of hypoparathyroidism or pseudohypoparathyroidism. Neuromuscular signs or symptoms due to hypocalcemia are the main characteristics of the disease. Hyperphosphatemia can contribute to major long-term complications such as ectopic calcifications in the kidney, brain, eye, or vasculature. Bone turnover is decreased, and bone mass is increased. Reduced quality of life and higher risk of renal stones, renal calcifications, and renal failure are seen. The risk of seizures and silent or symptomatic calcifications of basal ganglia is also increased. CONCLUSIONS: Increased awareness of the etiology and presentation of the disease and new research efforts addressing specific questions formulated during the meeting should improve the diagnosis, care, and long-term outcome for patients.
PubMed-ID: 26943721
http://dx.doi.org/10.1210/jc.2015-3909

Familial Hypocalciuric Hypercalcemia Types 1 and 3 and Primary Hyperparathyroidism: Similarities and Differences.
J Clin Endocrinol Metab, 101(5):2185-95.
R. Vargas-Poussou, L. Mansour-Hendili, S. Baron, J. P. Bertocchio, C. Travers, C. Simian, C. Treard, V. Baudouin, S. Beltran, F. Broux, O. Camard, S. Cloarec, C. Cormier, X. Debussche, E. Dubosclard, C. Eid, J. P. Haymann, S. R. Kiando, J. M. Kuhn, G. Lefort, A. Linglart, B. Lucas-Pouliquen, M. A. Macher, G. Maruani, S. Ouzounian, M. Polak, E. Requeda, D. Robier, C. Silve, J. C. Souberbielle, I. Tack, D. Vezzosi, X. Jeunemaitre and P. Houillier. 2016.
CONTEXT: Familial hypocalciuric hypercalcemia (FHH) is a genetically heterogeneous condition resembling primary hyperparathyroidism (PHPT) but not curable by surgery; FHH types 1, 2, and 3 are due to loss-of-function mutations of the CASR, GNA11, or AP2S1 genes, respectively. OBJECTIVE: This study aimed to compare the phenotypes of patients with genetically proven FHH types 1 or 3 or PHPT. DESIGN, SETTING, AND PATIENTS: This was a mutation analysis in a large cohort, a cross-sectional comparison of 52 patients with FHH type 1, 22 patients with FHH type 3, 60 with PHPT, and 24 normal adults. INTERVENTION: There were no interventions. MAIN OUTCOME MEASURES: Abnormalities of the CASR, GNA11, and AP2S1 genes, blood calcium, phosphate, and PTH concentrations, urinary calcium excretion were measured. RESULTS: In 133 families, we detected 101 mutations in the CASR gene, 68 of which were previously unknown, and in 19 families, the three recurrent AP2S1 mutations. No mutation was detected in the GNA11 gene. Patients with FHH type 3 had higher plasma calcium concentrations than patients with FHH type 1, despite having similar PTH concentrations and urinary calcium excretion. Renal tubular calcium reabsorption levels were higher in patients with FHH type 3 than in those with FHH type 1. Plasma calcium concentration was higher whereas PTH concentration and urinary calcium excretion were lower in FHH patients than in PHPT patients. In patients with FHH or PHPT, all data groups partially overlapped. CONCLUSION: In our population, AP2S1 mutations affect calcium homeostasis more severely than CASR mutations. Due to overlap, the risk of confusion between FHH and PHPT is high.
PubMed-ID: 26963950
http://dx.doi.org/10.1210/jc.2015-3442

Delayed Calcium Normalization After Presumed Curative Parathyroidectomy is Not Associated with the Development of Persistent or Recurrent Primary Hyperparathyroidism.
Ann Surg Oncol, 23(7):2310-4.
V. Lai, T. W. Yen, K. Doffek, A. A. Carr, T. B. Carroll, G. G. Fareau, D. B. Evans and T. S. Wang. 2016.
BACKGROUND: Following parathyroidectomy for primary hyperparathyroidism (pHPT), serum calcium levels typically normalize relatively quickly. The purpose of this study was to identify potential factors associated with delayed normalization of calcium levels despite meeting intraoperative parathyroid hormone (IOPTH) criteria and to determine whether this phenomenon is associated with higher rates of persistent pHPT. METHODS: This was a retrospective review of 554 patients who underwent parathyroidectomy for sporadic pHPT from January 2009 to July 2013. Patients who underwent presumed curative parathyroidectomy and had elevated POD0 calcium levels (>10.2 mg/dL) were matched 1:2 for age and gender to control patients with normal POD0 calcium levels. RESULTS: Of the 554 patients, 52 (9 %) had an elevated POD0 Ca (median 10.7, range 10.3-12.2). Compared with the control group, these patients had higher preoperative calcium (12 vs. 11.1, $p < 0.001$) and PTH (144 vs. 110 pg/mL, $p = 0.004$) levels and lower 25OH vitamin D levels (26 vs. 31 pg/mL; $p = 0.024$). Calcium normalization occurred in 64, 90, and 96 % of patients by postoperative days (POD) 1, 14, and 30, respectively. There was no difference in rates of single-gland disease or cure rates between the groups. CONCLUSIONS: After presumed curative parathyroidectomy, nearly 10 % of patients had transiently persistent hypercalcemia. Most of these patients had normal serum calcium levels within the first 2 weeks and did not have increased rates of persistent pHPT. Immediate postoperative calcium levels do not predict the presence of persistent pHPT, and these patients may not require more stringent follow-up.
PubMed-ID: 27006125
http://dx.doi.org/10.1245/s10434-016-5190-7

The utility of indocyanine green near infrared fluorescent imaging in the identification of parathyroid glands during surgery for primary hyperparathyroidism.
J Surg Oncol, 113(7):771-4.
N. Zaidi, E. Bucak, A. Okoh, P. Yazici, H. Yigitbas and E. Berber. 2016.
BACKGROUND AND OBJECTIVES: Intraoperative adjuncts for the localization of parathyroid glands in parathyroid surgery are limited. The aim of this study is to assess the usefulness of indocyanine green (ICG) near-infrared (NIR) fluorescent imaging in patients undergoing surgery for primary hyperparathyroidism (PHPT). METHODS: ICG imaging was performed in 33 patients undergoing parathyroidectomy (PTX). Thyroid and

parathyroid ICG uptake were assessed and independently verified on a grading scale. Clinical variables were recorded and analyzed for factors associated with ICG uptake. RESULTS: Of 112 glands identified by naked eye, 104 (92.9%) demonstrated ICG uptake. Concomitant ICG fluorescence was identified in the thyroid in all patients. There was a trend toward increased ICG fluorescence in patients <60 years of age (P = 0.05). A higher degree of fluorescence was seen in patients presenting with pre-operative calcium values >11 mg/dl (P = 0.04) and in those parathyroids larger than 10 mm (P < 0.01). All patients had biochemically proven cure. No patients who underwent subtotal PTX (n = 6) developed postoperative hypoparathyroidism. CONCLUSION: ICG can reliably localize parathyroid glands during PTX and additionally allow for assessment of parathyroid perfusion in patients undergoing subtotal resection. Concomitant fluorescence of the thyroid gland limits ICG's usefulness in directing the course of PTX. J. Surg. Oncol. 2016;113:771-774. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 27039880
http://dx.doi.org/10.1002/jso.24240

The feasibility of indocyanine green fluorescence imaging for identifying and assessing the perfusion of parathyroid glands during total thyroidectomy.
J Surg Oncol, 113(7):775-8.
N. Zaidi, E. Bucak, P. Yazici, S. Soundararajan, A. Okoh, H. Yigitbas, C. Dural and E. Berber. 2016.
BACKGROUND: There are limited adjuncts available for identifying and assessing the viability of parathyroid glands (PGs) during total thyroidectomy (TT). The aim of this study is to determine the feasibility of indocyanine green (ICG) imaging in identifying and assessing perfusion of PGs during TT. METHODS: ICG was administered in patients undergoing TT and fluorescence of PGs was assessed. A grading scale was developed for assessing degree of ICG uptake. Patients were evaluated for hypocalcemia and hypoparathyroidism on post-operative day (POD) #1. RESULTS: Twenty-seven patients underwent TT with ICG imaging for multinodular goiter (n = 13), thyroid cancer (n = 10), and Graves' disease (n = 4). Eight-five PGs were identified visually, 71 (84%) of which showed ICG fluorescence. False negative rate was 6%. Post-operatively, three patients (11%) had a serum calcium value <8 mg/dl. ICG uptake after TT correlated with post-operative PTH levels: mean POD#1 PTH of those patients with at least two PGs exhibiting <30% fluorescence was 9 pg/ml; whereas those with fewer than two demonstrating <30% fluorescence had a POD#1 PTH of 19.5 pg/ml (P = 0.05). CONCLUSION: ICG imaging of PGs during TT is feasible. ICG might be a useful adjunct in identifying those patients at risk for post-thyroidectomy hypoparathyroidism. J. Surg. Oncol. 2016;113:775-778. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 27041628
http://dx.doi.org/10.1002/jso.24237

Forearm Dxa Increases the Rate of Patients with Asymptomatic Primary Hyperparathyroidism Meeting Surgical Criteria.
J Clin Endocrinol Metab:jc20161513.
E. Castellano, R. Attanasio, L. Gianotti, F. Cesario, F. Tassone and G. Borretta. 2016.
INTRODUCTION: A reduction in bone mineral density (BMD) is common in primary hyperparathyroidism (PHPT), above all at cortical sites. Guidelines for the management of asymptomatic PHPT (aPHPT) recommend a BMD evaluation at the lumbar spine, hip, and forearm. Surgery is recommended for patients with a T-score </=-2.5 at any of these sites. However, a BMD evaluation at the forearm is not routinely performed Aim: To evaluate the impact of measuring forearm BMD in the clinical management of aPHPT. SUBJECTS AND METHODS: We retrospectively reviewed a prospective database of 172 patients with aPHPT, selecting the 116 patients in whom a dual x-ray absorptiometry (DXA) scan had been performed at all three sites. RESULTS: Seventy-four out of 116 patients had a densitometric diagnosis of osteoporosis (OP) at any site, and the forearm was the only site involved in 13/74 (group A, 17.6% of osteoporotic patients and 11.2% of the whole aPHPT cohort). Patients belonging to group A were significantly older than the other aPHPT patients, while no difference was found in biochemical measurements. Six out of 13 patients belonging to group A (5.2% of the whole aPHPT cohort) fulfilled surgical criteria based only on a forearm T-score. CONCLUSIONS: DXA at three sites revealed OP at the forearm, but not at the other sites, in 11.2% of aPHPT patients. Half of these cases met surgical criteria based on this one factor alone. These patients did not show any clinical (except age) or biochemical differences from the other patients. The implementation of forearm DXA increases the rate of patients with aPHPT meeting surgical criteria.
PubMed-ID: 27070376
http://dx.doi.org/10.1210/jc.2016-1513

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

Adrenals

Meta-Analyses

MANAGEMENT OF ENDOCRINE DISEASE: Recurrence or new tumors after complete resection of phaeochromocytomas and paragangliomas. A systematic review and meta-analysis.
Eur J Endocrinol,
L. Amar, C. Lussey-Lepoutre, J. Lenders, J. Djadi-Prat, P. F. Plouin and O. Steichen. 2016.
OBJECTIVES: To systematically review the incidence and factors associated with recurrences or new tumors after apparent complete resection of phaeochromocytoma or thoraco-abdomino-pelvic paraganglioma. DESIGN: Systematic review and meta-analysis. METHODS: Pubmed and Embase from 1980 to 2012 were searched for studies published in English on patients with: non-metastatic phaeochromocytoma or thoraco-abdomino-pelvic paraganglioma; complete tumor resection; postoperative follow-up exceeding one month; recurrence or new tumor documented by pathology, hormonal dosages, or imaging tests. Incidence rates of new events after curative surgery were calculated for each study that had sufficient information and pooled using random effect meta-analysis. RESULTS: Thirty-eight studies were selected from 3518 references, of which 36 reported retrospective cohorts from the USA, Europe and Asia. Patient follow-up was neither standardized nor exhaustive in the included studies. A clear description of patient retrieval methods was available for nine studies, and the follow-up protocol and patient flow for four studies. Only two studies used multivariable methods to assess potential predictors of postoperative events.The overall rate of recurrent disease from 34 studies was 0.98 events/100 person-years (95% confidence interval 0.71, 1.25). Syndromic diseases and paragangliomas were consistently associated with a higher risk of a new event in individual studies and in meta-regression analysis. CONCLUSIONS: The risk of recurrent disease after complete resection of phaeochromocytoma may be lower than previously thought, although late events occur. Risk stratification is required to tailor the follow-up protocol after complete resection of a phaeochromocytoma or paraganglioma. Large multicentric studies are needed to this end.
PubMed-ID: 27080352
http://dx.doi.org/10.1530/EJE-16-0189

Open Versus Laparoscopic Adrenalectomy for Adrenocortical Carcinoma: A Meta-analysis of Surgical and Oncological Outcomes.
Ann Surg Oncol, 23(4):1195-202.
R. Autorino, P. Bove, M. De Sio, R. Miano, S. Micali, L. Cindolo, F. Greco, J. Nicholas, C. Fiori, G. Bianchi, F. J. Kim and F. Porpiglia. 2016.
PURPOSE: This study was designed to determine the role of laparoscopic adrenalectomy (LA) in the surgical management of adrenocortical carcinoma (ACC). METHODS: A systematic literature review was performed on January 2, 2015 using PubMed. Article selection proceeded according to PRISMA criteria. Studies comparing open adrenalectomy (OA) to LA for ACC and including at least 10 cases per each surgical approach were included. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. Pooled estimates were calculated with the fixed-effect model, if no significant heterogeneity was identified; alternatively, the random-effect model was used when significant heterogeneity was detected. Main demographics, surgical outcomes, and oncological outcomes were analyzed. RESULTS: Nine studies published between 2010 and 2014 were deemed eligible and included in the analysis, all of them being retrospective case-control studies. Overall, they included 240 LA and 557 OA cases. Tumors treated with laparoscopy were significantly smaller in size (WMD -3.41 cm; confidence interval [CI] -4.91, -1.91; $p < 0.001$), and a higher proportion of them (80.8 %) more at a localized (I-II) stage compared with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2; $p < 0.001$). Hospitalization time was in favor of laparoscopy, with a WMD of -2.5 days (CI -3.3, -1.7; $p < 0.001$). There was no difference in the overall recurrence rate between LA and OA (relative risk [RR] 1.09; CI 0.83, 1.43; $p = 0.53$), whereas development of peritoneal carcinomatosis was higher for LA (RR 2.39; CI 1.41, 4.04; $p = 0.001$). No difference could be found for time to recurrence (WMD -8.2 months; CI -18.2, 1.7; $p = 0.11$), as well as for cancer specific mortality (OR 0.68; CI 0.44, 1.05; $p = 0.08$). CONCLUSIONS: OA should still be considered the standard surgical management of ACC. LA can offer a shorter hospital stay and possibly a faster recovery. Therefore, this minimally invasive approach can certainly play a role in this setting, but it should be only offered in carefully selected cases to avoid jeopardizing the oncological outcome.
PubMed-ID: 26480850
http://dx.doi.org/10.1245/s10434-015-4900-x

ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis.
J Clin Endocrinol Metab, 101(2):427-34.
N. S. Ospina, A. Al Nofal, I. Bancos, A. Javed, K. Benkhadra, E. Kapoor, A. N. Lteif, N. Natt and M. H. Murad. 2016.
CONTEXT: The diagnosis of adrenal insufficiency is clinically challenging and often requires ACTH stimulation tests. OBJECTIVE: To determine the diagnostic accuracy of the high- (250 mcg) and low- (1 mcg) dose ACTH stimulation tests in the diagnosis of adrenal insufficiency. METHODS: We searched six databases through February 2014. Pairs of independent reviewers selected studies and appraised the risk of bias. Diagnostic association measures were pooled across studies using a bivariate model. DATA SYNTHESIS: For secondary adrenal insufficiency, we included 30 studies enrolling 1209 adults and 228 children. High- and low-dose ACTH stimulation tests had similar diagnostic accuracy in adults and children using different peak serum cortisol cutoffs. In general, both tests had low sensitivity and high specificity resulting in reasonable likelihood ratios for a positive test (adults: high dose, 9.1; low dose, 5.9; children: high dose, 43.5; low dose, 7.7), but a fairly suboptimal likelihood ratio for a negative test (adults: high dose, 0.39; low dose, 0.19; children: high dose, 0.65; low dose, 0.34). For primary adrenal insufficiency, we included five studies enrolling 100 patients. Data were only available to estimate the sensitivity of high dose ACTH stimulation test (92%; 95% confidence interval, 81-97%). CONCLUSION: Both high- and low-dose ACTH stimulation tests had similar diagnostic accuracy. Both tests are adequate to rule in, but not rule out, secondary adrenal insufficiency. Our confidence in these estimates is low to moderate because of the likely risk of bias, heterogeneity, and imprecision.
PubMed-ID: 26649617
http://dx.doi.org/10.1210/jc.2015-1700

Randomized controlled trials

- None –

Consensus Statements/Guidelines

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline.
J Clin Endocrinol Metab, 101(5):1889-916.
J. W. Funder, R. M. Carey, F. Mantero, M. H. Murad, M. Reincke, H. Shibata, M. Stowasser and W. F. Young, Jr. 2016.
OBJECTIVE: To develop clinical practice guidelines for the management of patients with primary aldosteronism. PARTICIPANTS: The Task Force included a chair, selected by the Clinical Guidelines Subcommittee of the Endocrine Society, six additional experts, a methodologist, and a medical writer. The guideline was cosponsored by American Heart Association, American Association of Endocrine Surgeons, European Society of Endocrinology, European Society of Hypertension, International Association of Endocrine Surgeons, International Society of Endocrinology, International Society of Hypertension, Japan Endocrine Society, and The Japanese Society of Hypertension. The Task Force received no corporate funding or remuneration. EVIDENCE: We searched for systematic reviews and primary studies to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation group criteria to describe both the quality of evidence and the strength of recommendations. We used "recommend" for strong recommendations and "suggest" for weak recommendations. CONSENSUS PROCESS: We achieved consensus by collecting the best available evidence and conducting one group meeting, several conference calls, and multiple e-mail communications. With the help of a medical writer, the Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and Council successfully reviewed the drafts prepared by the Task Force. We placed the version approved by the Clinical Guidelines Subcommittee and Clinical Affairs Core Committee on the Endocrine Society's website for comments by members. At each stage of review, the Task Force received written comments and incorporated necessary changes. CONCLUSIONS: For high-risk groups of hypertensive patients and those with hypokalemia, we recommend case detection of primary aldosteronism by determining the aldosterone-renin ratio under standard conditions and recommend that a commonly used confirmatory test should confirm/exclude the condition. We recommend that all patients with

primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adrenocortical carcinoma. We recommend that an experienced radiologist should establish/exclude unilateral primary aldosteronism using bilateral adrenal venous sampling, and if confirmed, this should optimally be treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia or those unsuitable for surgery should be treated primarily with a mineralocorticoid receptor antagonist.
PubMed-ID: 26934393
http://dx.doi.org/10.1210/jc.2015-4061

Other Articles

Curative Resection of Adrenocortical Carcinoma: Rates and Patterns of Postoperative Recurrence.
Ann Surg Oncol, 23(1):126-33.
N. Amini, G. A. Margonis, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2016.
BACKGROUND: Adrenocortical carcinoma (ACC) is a rare malignancy. The aim of this study was to determine the incidence and patterns of recurrence after curative-intent surgery for ACC. METHODS: Patients who underwent curative-intent resection for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the United States ACC study group. Patients with metastasis or an R2 margin were excluded. Patterns and rates of recurrence were determined and classified as locoregional and distant recurrence. RESULTS: A total of 180 patients with a median age of 52 years (interquartile range 43-61) were identified. Most patients underwent open surgery (n = 111, 64.5 %) and had an R0 resection margin (n = 117, 75.0 %). At last follow-up, 116 patients (64.4 %) had experienced recurrence (locoregional only, n = 41, 36.3 %; distant only, n = 51, 45.1 %; locoregional and distant, n = 21, 18.6 %). Median time to recurrence was 18.8 months. Several factors were associated with locoregional recurrence, including left-sided ACC location (odds ratio [OR] 2.71, 95 % confidence interval [CI] 1.06-6.89) and T3/T4 disease (reference T1/T2, OR 3.04, 95 % CI 1.19-7.80) (both $p < 0.05$). Distant recurrence was associated with larger tumor size (OR 1.11, 95 % CI 1.01-1.24) and T3/T4 disease (reference T1/T2, OR 5.23, 95 % CI 1.70-16.10) (both $p < 0.05$). Patients with combined locoregional and distant recurrence had worse survival (3- and 5-year survival: 39.5, 19.7 %) versus patients with distant-only (3- and 5-year survival 55.1, 43.3 %) or locoregional-only recurrence (3- and 5-year survival 81.4, 64.1 %) ($p = 0.01$). CONCLUSIONS: Nearly two-thirds of patients experienced disease recurrence after resection of ACC. Although a subset of patients experienced recurrence with locoregional disease only, many patients experienced recurrence with distant disease as a component of recurrence and had a poor prognosis.
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http://dx.doi.org/10.1245/s10434-015-4810-y

MANAGEMENT OF ENDOCRINE DISEASE: Outcome of adrenal sparing surgery in heritable pheochromocytoma.
Eur J Endocrinol, 174(1):R9-18.
F. Castinetti, D. Taieb, J. F. Henry, M. Walz, C. Guerin, T. Brue, B. Conte-Devolx, H. P. Neumann and F. Sebag. 2016.
The management of hereditary pheochromocytoma has drastically evolved in the last 20 years. Bilateral pheochromocytoma does not increase mortality in MEN2 or von Hippel-Lindau (VHL) mutation carriers who are followed regularly, but these mutations induce major morbidities if total bilateral adrenalectomy is performed. Cortical sparing adrenal surgery may be proposed to avoid definitive adrenal insufficiency. The surgical goal is to leave sufficient cortical tissue to avoid glucocorticoid replacement therapy. This approach was achieved by the progressive experience of minimally invasive surgery via the transperitoneal or retroperitoneal route. Cortical sparing adrenal surgery exhibits <5% significant recurrence after 10 years of follow-up and normal glucocorticoid function in more than 50% of the cases. Therefore, cortical sparing adrenal surgery should be systematically considered in the management of all patients with MEN2 or VHL hereditary pheochromocytoma. Hereditary pheochromocytoma is a rare disease, and a randomized trial comparing cortical sparing vs classical adrenalectomy is probably not possible. This lack of data most likely explains why cortical sparing surgery has not been adopted in most expert centers that perform at least 20 procedures per year for the treatment of this disease. This review examined recent data to provide insight into the technique, its indications, and the results

and subsequent follow-up in the management of patients with hereditary pheochromocytoma with a special emphasis on MEN2.
PubMed-ID: 26297495
http://dx.doi.org/10.1530/EJE-15-0549

Long-term outcome after adrenalectomy for incidentally diagnosed subclinical cortisol-secreting adenomas.
Surgery,
B. de La Villeon, S. Bonnet, H. Gouya, L. Groussin, F. Tenenbaum, S. Gaujoux and B. Dousset. 2016.
BACKGROUND: The management of subclinical cortisol-secreting adenomas (SCSAs) is controversial, and available evidence to assess the superiority of an operative versus a nonoperative approach is lacking. The aim of this work was to report the postoperative results and the long-term outcomes for patients with incidentally diagnosed SCSAs and to compare the results with those of patients who underwent an operation for cortisol-secreting adenomas (CSAs). METHODS: From 1994-2011, 107 consecutive patients underwent laparoscopic unilateral adrenalectomy for either an SCSA (n = 39) or a CSA (n = 68). Preoperatively, all patients underwent standardized clinical, hormonal, and imaging assessments. Patients were followed up for >/=2 years with serial assessments of body weight, blood pressure, and glycated hemoglobin, HbA1c. RESULTS: Operative resection of SCSAs and CSAs did not significantly differ regarding operative time, conversion rate, overall operative and medical morbidity, and duration of stay. For SCSAs, the comparison between preoperative status and 2-year assessment showed a median weight loss of 6% (P < .001), a decrease in the median HbA1c of 15% (P < .001), and an improvement or normalization of blood pressure in 50% of the patients. The same significant beneficial metabolic effects of the operation with even greater improvement were observed in patients with CSAs. CONCLUSION: Laparoscopic unilateral adrenalectomy for SCSA is associated with low morbidity, no mortality, and significant improvement of various aspects of metabolic syndrome. Until additional evidence from prospective randomized controlled studies is obtained, laparoscopic unilateral adrenalectomy should be considered a valid option in the care of patients with SCSA.
PubMed-ID: 27129933
http://dx.doi.org/10.1016/j.surg.2016.03.008

Basal and Post-ACTH Aldosterone and Its Ratios Are Useful During Adrenal Vein Sampling in Primary Aldosteronism.
J Clin Endocrinol Metab, 101(4):1826-35.
N. El Ghorayeb, T. L. Mazzuco, I. Bourdeau, J. P. Mailhot, P. S. Zhu, E. Therasse and A. Lacroix. 2016.
ACTH improves selectivity, but can modify lateralization. Basal and post-ACTH ratios are important for surgical indication. Basal aldosterone contralateral suppression predicts residual hyperplasia and post-operative outcomes.
PubMed-ID: 26918291
http://dx.doi.org/10.1210/jc.2015-3915

ENDOCRINE TUMOURS: The genomics of adrenocortical tumors.
Eur J Endocrinol, 174(6):R249-65.
S. Faillot and G. Assie. 2016.
The last decade witnessed the emergence of genomics, a set of high-throughput molecular measurements in biological samples. These pan-genomic and agnostic approaches have revolutionized the molecular biology and genetics of malignant and benign tumors. These techniques have been applied successfully to adrenocortical tumors. Exome sequencing identified new major drivers in all tumor types, including KCNJ5, ATP1A1, ATP2B3 and CACNA1D mutations in aldosterone-producing adenomas (APA), PRKACA mutations in cortisol-producing adenomas (CPA), ARMC5 mutations in primary bilateral macronodular adrenocortical hyperplasia (PBMAH) and ZNRF3 mutations in adrenocortical carcinomas (ACC). Moreover, the various genomic approaches - including exome sequencing, transcriptome, miRNome, genome and methylome - converge into a single molecular classification of adrenocortical tumors. Especially for ACC, two main molecular groups have emerged, showing major differences in outcomes. These ACC groups differ by their gene expression profiles, but also by recurrent mutations and specific DNA hypermethylation patterns in the subgroup of poor outcome. The clinical impact of these findings is just starting. The main altered signaling pathways now become therapeutic targets. The molecular groups of diseases individualize robust subtypes within diseases such as APA, CPA, PBMAH and ACC. A revised nosology of adrenocortical tumors should impact the clinical research. Obvious consequences also include genetic counseling for the new genetic diseases such as ARMC5 mutations in PBMAH, and a better prognostication of ACC based on targeted measurements of a few discriminant molecular alterations. Identifying the main molecular groups of adrenocortical tumors by extensively gathering the molecular variations is a

significant step forward towards precision medicine.
PubMed-ID: 26739091
http://dx.doi.org/10.1530/EJE-15-1118

Management of suspected adrenal metastases at 2 academic medical centers.
Am J Surg, 211(4):664-70.
J. A. Glenn, C. M. Kiernan, T. W. Yen, C. C. Solorzano, A. A. Carr, D. B. Evans and T. S. Wang. 2016.
BACKGROUND: The optimal management of suspected adrenal metastases remains controversial. METHODS: This is a retrospective bi-institutional review of 37 patients who underwent adrenalectomy for suspected adrenal metastasis between 2001 and 2014. RESULTS: Three (8%) patients had benign adenomas on final pathology. At a median follow-up of 21 months, 7 (32%) patients were alive with no evidence of disease and 7 (32%) were alive with recurrent disease. Recurrence-free survival (RFS) was 8 months; decreased RFS was associated with positive margins and size >/=6 cm. Overall survival (OS) was 29 months; decreased OS was associated with capsular disruption. There were no differences in RFS or OS by surgical approach. CONCLUSIONS: The favorable OS supports adrenalectomy in select patients with suspected adrenal metastases. Minimally invasive adrenalectomy is safe and effective, but the surgical approach should be based on the ability to achieve a margin-negative resection with avoidance of capsular disruption.
PubMed-ID: 26822269
http://dx.doi.org/10.1016/j.amjsurg.2015.11.019

Pheochromocytoma and Paraganglioma: Diagnosis, Genetics, and Treatment.
Surg Oncol Clin N Am, 25(1):119-38.
C. M. Kiernan and C. C. Solorzano. 2016.
This article highlights the epidemiology and pathophysiology of pheochromocytomas and paragangliomas. The current management of pheochromocytoma and paragangliomas, including utilization and interpretation of biochemical testing, preoperative imaging, and genetic screening are discussed. Furthermore, perioperative surgical management, outcomes, and recommended follow-up are reviewed.
PubMed-ID: 26610778
http://dx.doi.org/10.1016/j.soc.2015.08.006

Novel targeted therapies in adrenocortical carcinoma.
Curr Opin Endocrinol Diabetes Obes, 23(3):233-41.
B. Konda and L. S. Kirschner. 2016.
PURPOSE OF REVIEW: Adrenocortical carcinoma is a rare cancer, but one that carries a poor prognosis due to its aggressive nature and unresponsiveness to conventional chemotherapeutic strategies. Over the past 12 years, there has been renewed interest in developing new therapies for this cancer, including identifying key signaling nodes responsible for cell proliferation. RECENT FINDINGS: Clinical trials of tyrosine kinase inhibitors as monotherapy have generally been disappointing, although the identification of exceptional responders may lead to the identification of targeted therapies that may produce responses in subsets of patients. Agents targeted to the Wnt signaling pathway, a known player in adrenal carcinogenesis, have been developed, although they have not yet been used specifically for adrenal cancer. There is current excitement about inhibitors of acetyl-coA cholesterol acetyl transferase 1, an enzyme required for intracellular cholesterol handling, although trials are still underway. Tools to target other proteins such as Steroidogenic Factor 1 and mechanistic target of rapamycin have been developed and are moving towards clinical application. SUMMARY: Progress is being made in the fight against adrenocortical carcinoma with the identification of new therapeutic targets and new means by which to attack them. Continued improvement in the prognosis for patients with adrenal cancer is expected as this research continues.
PubMed-ID: 27119750
http://dx.doi.org/10.1097/MED.0000000000000247

Incidence of Perioperative Complications Following Resection of Adrenocortical Carcinoma and Its Association with Long-Term Survival.
World J Surg, 40(3):706-14.
G. A. Margonis, N. Amini, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. E. Moses, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2016.
BACKGROUND: The association of postoperative complications with long-term oncologic outcomes remains unclear. We sought to determine the incidence of complications among patients who underwent surgery for

adrenocortical carcinoma (ACC) and define the relationship of morbidity with long-term survival. METHODS: Patients who underwent surgery for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the US ACC group study. The incidence and type of the postoperative complications, the factors associated with them as well their association with long-term survival were analyzed. RESULTS: A total of 265 patients with median age of 52 years (IQR 44-63) were identified; at surgery, the majority of patients underwent an open abdominal procedure (n = 169, 66.8%). A postoperative complication occurred in 99 patients for a morbidity of 37.4%; five patients (1.9%) died in hospital. Factors associated with morbidity included a thoraco-abdominal operative approach (reference: open abdominal; OR 2.85, 95% CI 1.00-8.18), and a hormonally functional tumor (OR 3.56, 95% CI 1.65-7.69) (all P < 0.05). Presence of any complication was associated with a worse long-term outcome (median survival: no complication, 58.9 months vs. any complication, 25.1 months; P = 0.009). In multivariate analysis, after adjusting for patient- and disease-related factors postoperative infectious complications independently predicted shorter overall survival (hazard ratio (HR) 5.56, 95% CI 2.24-13.80; P < 0.001). CONCLUSION: Postoperative complications were independently associated with decreased long-term survival after resection for ACC. The prevention of complications may be important from an oncologic perspective.
PubMed-ID: 26546184
http://dx.doi.org/10.1007/s00268-015-3307-y

Clinical predictors of prolonged postresection hypotension after laparoscopic adrenalectomy for pheochromocytoma.
Surgery, 159(3):763-70.
T. Namekawa, T. Utsumi, K. Kawamura, N. Kamiya, T. Imamoto, T. Takiguchi, N. Hashimoto, T. Tanaka, Y. Naya, H. Suzuki and T. Ichikawa. 2016.
BACKGROUND: Although the perioperative management of patients with pheochromocytoma has been improving recently, severe hypotensive episodes can occur that require postoperative catecholamine support and are challenging to manage. Our aim was to identify the clinical factors that predict prolonged postresection hypotension in patients after laparoscopic adrenalectomy for pheochromocytoma. METHODS: The records of 73 Japanese patients who underwent unilateral laparoscopic adrenalectomy for pheochromocytoma were surveyed retrospectively. Patients were divided into 2 groups according to whether catecholamine support was needed after postoperatively. Clinical and biochemical data were evaluated at baseline and after operation. RESULTS: Thirty-four of 73 patients (47%) required continuous infusion of catecholamine to maintain systolic blood pressure >90 mm Hg at the end of the operation. The median duration of postoperative catecholamine support was 17 hours (range, 3-130) in these 34 patients. On multivariate analysis, tumor size >60 mm, urinary epinephrine levels >200 mug/day, and urinary norepinephrine levels >600 mug/day were independent predictors of prolonged hypotension requiring postoperative catecholamine support. Tumor size and urinary norepinephrine levels were significantly correlated with the duration of postoperative catecholamine support. CONCLUSION: Larger tumor size and greater values of urinary epinephrine and norepinephrine levels were significant predictors of prolonged hypotension requiring postoperative catecholamine support. Moreover, tumor size and urinary norepinephrine levels were positively correlated with the duration of postoperative catecholamine support. Clinicians can identify and manage patients more effectively with a greater risk of prolonged hypotension after tumor resection using these preoperative clinical variables.
PubMed-ID: 26477475
http://dx.doi.org/10.1016/j.surg.2015.09.016

Cosyntropin stimulation testing on postoperative day 1 allows for selective glucocorticoid replacement therapy after adrenalectomy for hypercortisolism: Results of a novel, multidisciplinary institutional protocol.
Surgery, 159(1):259-65.
D. I. Ortiz, J. W. Findling, T. B. Carroll, B. R. Javorsky, A. A. Carr, D. B. Evans, T. W. Yen and T. S. Wang. 2016.
BACKGROUND: Secondary adrenal insufficiency (AI) can occur after unilateral adrenalectomy for adrenal-dependent hypercortisolism. Postoperative glucocorticoid replacement (GR), although given routinely, may not be necessary. We sought to identify factors that, in combination with postoperative day 1 cosyntropin stimulation testing (POD1-CST), would predict the need for GR. METHODS: We reviewed 31 consecutive patients who underwent unilateral adrenalectomy for hypercortisolism (study patients) or hyperaldosteronism (control patients). A standard POD1-CST protocol was used. Hydrocortisone was started for clinical evidence of AI, basal plasma cortisol </= 5 (mug/dL), or a stimulated plasma cortisol <18. RESULTS: A normal POD1-CST was found in all nine control patients and 11 of 22 patients (50%) with Cushing's syndrome; the other 11 study patients (50%) received GR based on the POD1-CST. These patients were younger (51 vs 62 years; P = .017), had a higher body mass index (BMI; 31 vs 29 kg/m(2)), and smaller adrenal neoplasms (16.9 vs 33.0 g; P = .009) than

non-GR study patients. CONCLUSION: After unilateral adrenalectomy for hypercortisolism, only 50% of patients received GR. No preoperative biochemical characteristics were associated with postoperative AI, although patients who received GR were younger, and tended to have a higher BMI and smaller adrenal nodules. Use of this novel protocol for postoperative dynamic adrenal function testing prevented unnecessary GR in 50% of patients and allowed for individualized patient care.
PubMed-ID: 26422766
http://dx.doi.org/10.1016/j.surg.2015.05.034

Management of adrenal incidentaloma by laparoscopic transperitoneal anterior and submesocolic approach.
Langenbecks Arch Surg, 401(1):71-9.
A. M. Paganini, M. Guerrieri, A. Balla, S. Quaresima, A. M. Isidori, F. Iafrate, G. D'Ambrosio, G. Lezoche and E. Lezoche. 2016.
PURPOSE: Laparoscopic adrenalectomy (LA) is becoming the main approach for incidentally discovered adrenal masses (adrenal incidentaloma (AI)). The aim of this study was to evaluate the results of LA with a transperitoneal anterior approach for right adrenal lesions and either a transperitoneal anterior or transperitoneal anterior submesocolic approach for the left-sided lesions. METHODS: The study is a retrospective analysis of prospectively collected data. From January 1994 to December 2012, 393 patients underwent LA, 117 of these for an AI. Sixty-seven (57.26 %) and 50 (42.73 %) patients underwent right and left adrenalectomy, respectively. The transperitoneal anterior approach was used in all 67 patients with right lesions (57.26 %) (group A) and in 13 patients with left-sided lesions (11.11 %) (group B). The transperitoneal anterior submesocolic approach was used in the remaining 37 left-sided lesions (31.62 %) (group C). RESULTS: Mean operative time in groups A, B, and C was 104.6 min (range 35-255), 148.9 min (range 80-210), and 82.7 min (range 45-230), respectively. One right and one left anterior LA (1.7 %) were converted to open surgery. There were one major and one minor complications (1.7 %). The mean lesion size was 4.73 cm (range 1-10 cm). Mean hospital stay was 3.6 days. CONCLUSIONS: With adequate experience, LA with a transperitoneal anterior approach for AI is a safe and effective procedure. Early control of the adrenal vein with minimal gland manipulation and limited surgical dissection are its major advantages. In case of left LA, the submesocolic approach reduces the operative time significantly.
PubMed-ID: 26683612
http://dx.doi.org/10.1007/s00423-015-1367-y

Adrenal surgery in England: better outcomes in high-volume practices.
Clin Endocrinol (Oxf), 85(1):17-20.
F. Palazzo, A. Dickinson, B. Phillips, A. Sahdev, R. Bliss, A. Rasheed, Z. Krukowski and J. Newell-Price. 2016.
AIMS AND BACKGROUND: Adrenal surgery is performed by a variety of surgical specialities in differing environments and volumes. International data suggest that there is a correlation between adrenal surgery volume and outcomes but there are no UK data to support this or UK surgical guidelines. A multidisciplinary team representing the stakeholders in adrenal disease is preparing a national guidance on adrenal surgery. A review of the outcomes for adrenal surgery in England was performed to correlate outcomes with the volume of surgeon practice. METHODS: Hospital Episode Statistics (HES) data for the National Health Service (NHS) in England in the tax year 2013-2014 were examined for adrenal surgery. Length of hospital stay and rate of postoperative readmission were assessed as surrogate quality markers and a comparison made between 'high-' and 'low-' volume surgeons. RESULTS: A total of 795 adult adrenalectomies were performed by 222 different surgeons with a range of between 1 and 34 adrenalectomies performed per surgeon. Only thirty-six (16%) adrenal surgeons performed 6 or more adrenalectomies. A total of 186 surgeons (84%) performed a median of one adrenalectomy a year. Length of stay and readmission rate within thirty days of operation was 60% longer and 47% higher, respectively, when performed by low-volume surgeons. CONCLUSION: The current provision of adrenal surgery in the UK is not in the best interests of patients and is not cost-effective for the NHS. Adrenal surgery is best performed by higher volume surgeons in centres with dedicated adrenal multidisciplinary teams expert in all aspects of care of the adrenal patient.
PubMed-ID: 26776382
http://dx.doi.org/10.1111/cen.13021

FDG PET/CT Scan and Functional Adrenal Tumors: A Pilot Study for Lateralization.
World J Surg, 40(3):683-9.
D. Patel, S. K. Gara, R. J. Ellis, M. Boufraqech, N. Nilubol, C. Millo, C. A. Stratakis and E. Kebebew. 2016.
BACKGROUND: Patients with Cushing's Syndrome (CS) and Conn's Syndrome with bilateral adrenal masses pose a dilemma. Uptake of 18F-FDG by hyperfunctioning adrenal glands has not been previously reported and

may help lateralize. The aim was to determine if 18F-FDG PET/CT scan could identify hyperfunctioning adrenal masses and determine a biological basis for uptake. METHODS: Patients with nonfunctional adenomas (n = 9), CS (n = 11), and Conn's syndrome (n = 4) underwent an 18F-FDG PET/CT scan with a volume of interest circumscribing each mass to obtain a maximal standardized uptake value (SUVmax). Thirty-two adrenal masses were analyzed. Genome-wide expression data from an independent cohort were analyzed in nonfunctioning adenomas (n = 20), Conn's syndrome (n = 29), and CS (n = 24) focusing on GLUT genes. For genes differentially expressed, immunohistochemistry was performed on tissue samples. RESULTS: Cortisol-secreting masses (n = 16) had a higher average SUVmax of 5.9 compared to nonfunctioning masses (n = 11, average SUVmax 4.2) and aldosterone-hypersecreting masses (n = 5, average SUVmax 3.2) (p = 0.007). SUVmax cut-off of 5.33 had 50.0% sensitivity and 81.8% specificity in localizing a cortisol-secreting mass. GLUT3 expression was 2.19-fold higher in patients with CS compared to patients with nonfunctioning adenomas (p = 0.003) and 2.16-fold higher in patients with CS compared to Conn's syndrome (p = 0.006). GLUT3 immunohistochemistry showed 2.2-fold higher staining in CS tumor samples compared to nonfunctioning adenomas. CONCLUSIONS: Differential 18F-FDG PET/CT uptake was observed in patients with nonfunctioning, aldosterone-hypersecreting, and cortisol-secreting masses. GLUT3 overexpression in cortisol-secreting tumor likely accounts for the differential uptake. Future larger cohort studies will need to be conducted to determine if 18F-FDG PET/CT uptake can lateralize cortisol-secreting adrenal masses in patients with bilateral adrenal masses.
PubMed-ID: 26324161
http://dx.doi.org/10.1007/s00268-015-3242-y

Total 18F-FDG PET/CT Metabolic Tumor Volume Is Associated With Postoperative Biochemical Response in Patients With Metastatic Pheochromocytomas and Paragangliomas.
Ann Surg, 263(3):582-7.
D. Patel, A. Mehta, N. Nilubol, W. Dieckmann, K. Pacak and E. Kebebew. 2016.
OBJECTIVE: The aim of this pilot study was to determine if metabolic tumor volume (MTV) and total lesion glycolysis (TLG) could serve as predictors of biochemical remission and pharmacotherapy-free interval in patients with metastatic pheochromocytomas (PCCs) and paragangliomas (PGLs). BACKGROUND: Patients with metastatic PCCs/PGLs have a high rate of biochemical recurrence, which can be associated with increased cardiovascular morbidity. Predictors of biochemical response are needed to guide and select patients who may benefit from therapy. METHODS: Whole body MTV and TLG was calculated from preoperative 18F-FDG PET/CT scans and analyzed as marker of biochemical response and pharmacotherapy-free interval. RESULTS: Seventeen patients underwent a total of 19 procedures, with a median follow-up time of 26.4 months. Whole body MTV of patients with biochemical recurrence (n = 13, mean 73.8 mL) was higher than those who had a biochemical response (n = 6, mean 14.7 mL, P = 0.05). Patients with low MTV (<37.2 mL) had an improved durable partial biochemical response (P < 0.05), and a statistical trend for complete biochemical remission (P = 0.07) and pharmacotherapy-free interval (P = 0.06). In 8 patients with metastatic disease outside the abdomen, 4 patients had less than 35% of their disease burden outside the abdomen and these patients had a more durable partial biochemical response compared to patients with greater than 35% of their disease burden outside the abdomen (P < 0.05). CONCLUSIONS: Whole body MTV and TLG represents novel and valuable predictors of biochemical response for patients with metastatic PCCs and PGLs. A larger prospective study should be performed to validate these findings.
PubMed-ID: 25405562
http://dx.doi.org/10.1097/SLA.0000000000001018

Outcomes of Adjuvant Mitotane after Resection of Adrenocortical Carcinoma: A 13-Institution Study by the US Adrenocortical Carcinoma Group.
J Am Coll Surg, 222(4):480-90.
L. M. Postlewait, C. G. Ethun, T. B. Tran, J. D. Prescott, T. M. Pawlik, T. S. Wang, J. Glenn, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, C. A. Staley, G. A. Poultsides and S. K. Maithel. 2016.
BACKGROUND: Current treatment guidelines recommend adjuvant mitotane after resection of adrenocortical carcinoma with high-risk features (eg, tumor rupture, positive margins, positive lymph nodes, high grade, elevated mitotic index, and advanced stage). Limited data exist on the outcomes associated with these practice guidelines. STUDY DESIGN: Patients who underwent resection of adrenocortical carcinoma from 1993 to 2014 at the 13 academic institutions of the US Adrenocortical Carcinoma Group were included. Factors associated with mitotane administration were determined. Primary end points were recurrence-free survival (RFS) and overall survival (OS). RESULTS: Of 207 patients, 88 (43%) received adjuvant mitotane. Receipt of mitotane was associated with hormonal secretion (58% vs 32%; p = 0.001), advanced TNM stage (stage IV: 42% vs 23%; p =

0.021), adjuvant chemotherapy (37% vs 5%; p < 0.001), and adjuvant radiation (17% vs 5%; p = 0.01), but was not associated with tumor rupture, margin status, or N-stage. Median follow-up was 44 months. Adjuvant mitotane was associated with decreased RFS (10.0 vs 27.9 months; p = 0.007) and OS (31.7 vs 58.9 months; p = 0.006). On multivariable analysis, mitotane was not independently associated with RFS or OS, and margin status, advanced TNM stage, and receipt of chemotherapy were associated with survival. After excluding all patients who received chemotherapy, adjuvant mitotane remained associated with decreased RFS and similar OS; multivariable analyses again showed no association with recurrence or survival. Stage-specific analyses in both cohorts revealed no association between adjuvant mitotane and improved RFS or OS. CONCLUSIONS: When accounting for stage and adverse tumor and treatment-related factors, adjuvant mitotane after resection of adrenocortical carcinoma is not associated with improved RFS or OS. Current guidelines should be revisited and prospective trials are needed.
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http://dx.doi.org/10.1016/j.jamcollsurg.2015.12.013

Genotype-Phenotype Correlation in Indian Patients with MEN2-Associated Pheochromocytoma and Comparison of Clinico-Pathological Attributes with Apparently Sporadic Adrenal Pheochromocytoma.
World J Surg, 40(3):690-6.
S. Rajan, G. Zaidi, G. Agarwal, A. Mishra, A. Agarwal, S. K. Mishra and E. Bhatia. 2016.
INTRODUCTION: Pheochromocytoma (PCC) manifests in up to 50% of MEN2 patients. We correlated the clinico-pathological features of MEN2-associated PCC (MEN-PCC) with RET mutations and compared them with non-MEN adrenal-PCCs. METHODS: In this retrospective single institution study on a large PCC database (n = 208, 1997-2014) 24 MEN-PCC patients with known RET mutations were reviewed. Excluding 7 with incomplete data, the study cohort of 17 MEN-PCC patients from 11 kindreds (M:F::7:10) was identified. Clinical, biochemical, pathological attributes, and outcomes in the MEN-PCC group were correlated with the genotype, and further compared with non-MEN, apparently sporadic adrenal-PCCs (n = 132, excluding 37 extra-adrenal and 15 VHL/NF1/SDH-associated PCC). RESULTS: Components of MEN2 encountered included MTC in 13(76.5%), Marfanoid habitus in 2, and PHPT, cutaneous lichen amyloidosis and mucosal neuromas in 1 patient each. In 11(64.7%), PCC was the first detected MEN2 component (Symptomatic:8, Incidentaloma:3). Four (23.5%) were normotensive; 8(47.1%) had bilateral PCC (7 synchronous, 1 metachronous). Surgery for PCC included laparoscopic adrenalectomy in 12; and cortical-sparing adrenalectomy in 2 of 8 bilateral PCC patients. Mean MEN-PCC tumor size was 6.9 +/- 3.9 cm, and 6(35%) had additional adrenal medullary hyperplasia. Four different genotypes were encountered, commonest involving codon 634, others being 804 and 918. Mean age in MEN-PCC (27.7 +/- 12.2 years) was lower than non-MEN PCC (39.4 +/- 15.7, p = 0.018). Proportion of pediatric patients (35.3% in MEN-PCC vs. 12.9% in non-MEN-PCC, p = 0.007), bilateral tumors (47.1% in MEN-PCC, 4.5% in non-MEN-PCC, p < 0.001), and adrenal medullary hyperplasia (35.2% in MEN-PCC, 0.7% in non-MEN-PCC, p < 0.001) were different. Median 24-hour urinary metanephrines was significantly higher in index MEN-PCC patients, than non-MEN-PCC (634 vs. 214 mcg/24 h, p value = 0.006), but was non-significantly higher in non-index MEN-PCC patients. Mean tumor sizes were comparable in the two groups. None of MEN-PCC patients had malignant PCC, compared to 7(5.3%) in non-MEN-PCC. CONCLUSIONS: In this cohort of MEN-PCC from India, the commonest causative RET mutations for MEN-PCC involved codon 634. MEN-PCC patients were younger, and more frequently had bilateral PCC than non-MEN disease. MEN-PCC patients in India are diagnosed with large tumors and extremely high catecholamine/metanephrine levels.
PubMed-ID: 26438242
http://dx.doi.org/10.1007/s00268-015-3255-6

Chromosome 19 amplification correlates with advanced disease in adrenocortical carcinoma.
Surgery, 159(1):296-301.
J. C. Rubinstein, T. C. Brown, G. Goh, C. C. Juhlin, A. Stenman, R. Korah and T. Carling. 2016.
BACKGROUND: Familial syndromes with specific genetic drivers account for a subset of adrenocortical carcinomas (ACCs), but the genomic underpinnings of sporadic cases remain poorly understood. Recent advances in copy number variation (CNV) prediction from exome sequencing are facilitating exploration of genomic rearrangements common to these carcinomas. METHODS: ACC and matched, nontumor samples underwent exome sequencing. CNVs were predicted using coverage-depth comparison. Clinicopathologic characteristics of amplification- and deletion-dominant samples were compared and pathway enrichment analysis performed for regions with significant variation. RESULTS: CNVs are distributed broadly across the ACC genome. Individual signatures demonstrate amplification or deletion dominance. Areas of recurrent amplification include chromosomes 5, 12, 19, and 20, whereas chromosomes 1, 10, 18, and 22 are deletion prone. Large-scale amplification of chromosome 19 occurred in 12 of 19 cases (63%), including 6 of 8 amplification-dominant samples (75%) and was associated with stage III/IV disease (P = .002). Genes within this

amplified region are overrepresented among the adrenal hyperplasia and steroid biosynthesis pathways (P = 4.2(-5) and 2.5(-5), respectively). CONCLUSION: CNV detection via exome sequencing allows high-resolution cataloging of structural variations in ACC. Large-scale, recurrent amplifications encompassing known adrenal-specific gene pathways correlate with tumor stage. Further functional analysis of individual genes within these regions could provide mechanistic insight into specific drivers underlying pathogenesis and progression of ACC.
PubMed-ID: 26453132
http://dx.doi.org/10.1016/j.surg.2015.09.001

Mitotane treatment in patients with adrenocortical cancer causes central hypothyroidism.
Clin Endocrinol (Oxf), 84(4):614-9.
M. Russo, C. Scollo, G. Pellegriti, O. R. Cotta, S. Squatrito, F. Frasca, S. Cannavo and D. Gullo. 2016.
INTRODUCTION: Mitotane, a steroidogenesis inhibitor with adrenolytic properties used to treat adrenocortical cancer (ACC), can affect thyroid function. A reduction of FT4 levels with normal FT3 and TSH has been described in these patients. Using an in vitro murine model, the secretory capacity of thyrotrophic cells has been shown to be inhibited by mitotane. OBJECTIVE: To investigate the pathogenesis of thyroid abnormalities in mitotane-treated patients with ACC. PATIENTS AND METHODS: In five female patients with ACC (median age 47; range 31-65) treated with mitotane (dosage 1.5 g/day; 1.0-3.0), we analysed the pattern of TSH and thyroid function index (FT4, FT3 and FT3/FT4 ratio) compared to an age- and gender-matched control group. The in vivo secretory activity of the thyrotrophic cells was evaluated using a standard TRH test (200 mug), and the response was compared to both a group of age-matched female controls (n = 10) and central hypothyroid patients (n = 10). RESULTS: Basal TSH (median 1.54 mU/l; range 1.20-2.17) was normal and scattered around our median reference value, FT3 levels (median 3.80 pmol/l; 3.30-4.29) were normal but below the median reference value of 4.37 pmol/l and FT4 levels were below the normal range in all patients (median 8.40 pmol/l; 7.6-9.9). FT3/FT4 ratio was in the upper range in 4 patients and higher than normal in one patient. A blunted TSH response to TRH was observed in mitotane-treated patients. DeltaTSH (absolute TSH response, peak TSH minus basal TSH) was 3.65 (range 3.53-5.26), 12.37 (range 7.55-19.97) and 1.32 mU/l (range 0.52-4.66) in mitotane-treated patients, controls and central hypothyroid patients, respectively. PRL secretion was normal. CONCLUSIONS: Mitotane-treated patients with ACC showed low FT4, normal FT3 and TSH and impaired TSH response to TRH, characteristic of central hypothyroidism. Furthermore, the elevated FT3/FT4 ratio of these subjects reflects an enhanced T4 to T3 conversion rate, a compensatory mechanism characteristic of thyroid function changes observed in hypothyroid conditions. This finding thus confirms in vitro studies and may have a therapeutic implication for treatment with thyroid hormones, as suggested by current guidelines for this specific condition.
PubMed-ID: 26221968
http://dx.doi.org/10.1111/cen.12868

Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism.
Eur J Endocrinol, 174(3):261-9.
A. S. Salcuni, V. Morelli, C. Eller Vainicher, S. Palmieri, E. Cairoli, A. Spada, A. Scillitani and I. Chiodini. 2016.
OBJECTIVE: Subclinical hypercortisolism (SH) is associated with increased risk of vertebral fractures (VFx). The effect on bone following recovery from SH is unknown. DESIGN: Of the 605 subjects consecutively referred for monolateral adrenal incidentalomas (AIs) to our outpatient clinics, 55 SH patients (recruited on the basis of the exclusion criteria) were enrolled. We suggested to all patients to undergo adrenalectomy, which was accepted by 32 patients (surgical group, age 61.3+/-8.1 years) and refused by 23 patients, who were followed with a conservative management (non-surgical group, age 65.4+/-7.1 years). METHODS: We diagnosed SH in patients with serum cortisol after 1 mg dexamethasone suppression test (1 mg-DST) >5.0 mug/dl or with greater than or equal to two criteria among 1 mg-DST >3.0 mug/dl, urinary free cortisol >70 mug/24 h and ACTH <10 pg/ml. We assessed: bone mineral density (BMD) at lumbar spine (LS) and femoral neck (as Z-score) by dual-energy X-ray absorptiometry and the VFx presence by X-ray at baseline and at the end of follow up (surgical group 39.9+/-20.9 months and non-surgical group 27.7+/-11.1 months). RESULTS: The LS Z-score (DeltaZ-score/year) tended to increase in the surgical group (0.10+/-0.20) compared with the non-surgical group (-0.01+/-0.27, P=0.08) and in the former, the percentage of patients with new VFx was lower (9.4%) than in the latter (52.2%, P<0.0001). Surgery in AI patients with SH was associated with a 30% VFx risk reduction (odds ratio 0.7, 95% CI 0.01-0.05, P=0.008) regardless of age, gender, follow up duration, 1 mg-DST, LS BMD, and presence of VFx at baseline. CONCLUSION: In patients with monolateral AI and SH, adrenalectomy reduces the risk of VFx.
PubMed-ID: 26630908
http://dx.doi.org/10.1530/EJE-15-0977

Synthetic high-density lipoprotein nanoparticles: A novel therapeutic strategy for adrenocortical carcinomas.
Surgery, 159(1):284-94.
C. Subramanian, R. Kuai, Q. Zhu, P. White, J. J. Moon, A. Schwendeman and M. S. Cohen. 2016.
BACKGROUND: Chemotherapeutic strategies for adrenocortical carcinoma (ACC) carry substantial toxicities. Cholesterol is critical for ACC cell growth and steroidogenesis, and ACC cells overexpress scavenger receptor BI, which uptakes cholesterol from circulating high-density lipoprotein (HDL) cholesterol. We hypothesize that cholesterol-free synthetic-HDL nanoparticles (sHDL) will deplete cholesterol and synergize with chemotherapeutics to achieve enhanced anticancer effects at lesser (less toxic) drug levels. METHODS: The antiproliferative efficacy of ACC cells for the combinations of sHDL with chemotherapeutics was tested by Cell-Titer Glo. Cortisol levels were measured from the culture media. Effects on steroidogenesis was measured by real-time polymerase chain reaction (RT-PCR). Induction of apoptosis was evaluated by flow cytometry. RESULTS: Combination Index (CI) for sHDL and either etoposide (E), cisplatin (P), or mitotane (M) demonstrated synergy (CI < 1) for antiproliferation. Alone or in combination with the chemotherapy drugs, sHDL was able to decrease cortisol production by 70-90% compared with P alone or controls (P < .01). RT-PCR indicated inhibition of steroidogenic enzymes for sHDL (P < .01 vs no sHDL). Combination therapy with sHDL increased apoptosis by 30-50% compared with drug or sHDL alone (P < .03), confirmed by a decrease in the mitochondrial potential. CONCLUSION: sHDL can act synergistically and lessen the amount of M/E/P needed for anticancer efficacy in ACC in part owing to cholesterol starvation. This novel treatment strategy warrants further investigation translationally.
PubMed-ID: 26582501
http://dx.doi.org/10.1016/j.surg.2015.08.023

Role of adrenal vein sampling in primary aldosteronism: Impact of imaging, localization, and age.
J Surg Oncol, 113(5):532-7.
H. Wachtel, S. Zaheer, P. K. Shah, S. O. Trerotola, G. C. Karakousis, R. E. Roses, D. L. Cohen and D. L. Fraker. 2016.
BACKGROUND: The role of adrenal vein sampling (AVS) has been debated, with some authorities advocating selective use in younger patients (</=40 years), and those localized by preoperative imaging. We examined our experience to determine the impact of AVS in patients who routinely underwent AVS with a high success rate. METHODS: A retrospective cohort study was performed using a prospectively maintained database of patients referred for evaluation of PA (1997-2013). Patients were classified as localized (L) if a unilateral mass was identified on imaging, and non-localized (NL) otherwise. RESULTS: Of 367 patients, 94% (n = 345) underwent successful AVS. Seventy-two percent (n = 265) were L; AVS was lateralizing 58% (n = 214). AVS changed management in 43% of patients (n = 158). In patients </=40 years, AVS changed management in 30% (n = 15). In patients </=40 years with a >/=1 cm adrenal mass, 12% (n = 3) would have undergone unnecessary surgery based on imaging results alone; in patients >40 years with a >/=1 cm adrenal mass, 3% (n = 5) would have undergone wrong-side surgery, and 30% (n = 50) would have undergone unnecessary surgery based on imaging. CONCLUSION: AVS changed management in a significant minority of patients regardless of age and imaging findings. AVS should be routinely recommended in all patients with PA, to direct operative therapy. J. Surg. Oncol. 2016;113:532-537. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 26792453
http://dx.doi.org/10.1002/jso.24182

PTH Is a Promising Auxiliary Index for the Clinical Diagnosis of Aldosterone-Producing Adenoma.
Am J Hypertens, 29(5):575-81.
L. X. Zhang, W. J. Gu, Y. J. Li, Y. Wang, W. B. Wang, A. P. Wang, L. Shen, L. Zang, G. Q. Yang, Z. H. Lu, J. T. Dou and Y. M. Mu. 2016.
BACKGROUND: Parathyroid hormone (PTH) stimulates aldosterone secretion in human adrenocortex and is regulated by the renin-angiotensin-aldosterone system. We speculated that measurement of PTH may be a valuable aid in the diagnosis of aldosterone-producing adenoma (APA). METHODS: To test this hypothesis, we recruited 142 patients with adrenal adenoma, of whom 84 had an APA and 58 had a nonfunctioning adrenal adenoma (NFA). Plasma levels of intact PTH, serum potassium, sodium, calcium, phosphate, 25(OH) vitamin D, plasma aldosterone concentration (PAC), plasma renin activity (PRA), and aldosterone to renin ratio (ARR) were measured in every patient. Computed tomography (CT) scanning of the adrenal gland and adrenal hormone levels was used to evaluate the function of the adrenal adenoma. We also evaluated the impact of renin-angiotensin-aldosterone system (RAAS) components on PTH from the recumbent-upright test in 15 patients with APA and 30 patients with NFA. RESULTS: Compared with NFA, PTH levels were significantly increased in patients with APA, and serum calcium and phosphate were significantly decreased. When position was changed

from supine to upright, the variation in PTH levels was significantly higher in APA patients compared with NFA patients. Receiver operator characteristic (ROC) curves identified the Youden index, which corresponded to the best tradeoff of combined marker (ARR and PTH) with a sensitivity and specificity of 89.3% and 93.1%, respectively. CONCLUSIONS: The baseline and positional variation of serum PTH levels were significant in APA, thus PTH may be a promising auxiliary index for the clinical diagnosis of APA.
PubMed-ID: 26304960
http://dx.doi.org/10.1093/ajh/hpv146

NET

Meta-Analyses

Postoperative Complications, In-Hospital Mortality and 5-Year Survival After Surgical Resection for Patients with a Pancreatic Neuroendocrine Tumor: A Systematic Review.
World J Surg, 40(3):729-48.
A. P. Jilesen, C. H. van Eijck, K. H. in't Hof, S. van Dieren, D. J. Gouma and E. J. van Dijkum. 2016.
Studies on postoperative complications and survival in patients with pancreatic neuroendocrine tumors (pNET) are sparse and randomized controlled trials are not available. We reviewed all studies on postoperative complications and survival after resection of pNET. A systematic search was performed in the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from 2000-2013. Inclusion criteria were studies of resected pNET, which described postoperative complications separately for each surgical procedure and/or 5-year survival after resection. Prospective and retrospective studies were pooled separately and overall pooled if heterogeneity was below 75%. The random-effect model was used. Overall, 2643 studies were identified and after full-text analysis 62 studies were included. Pancreatic fistula (PF) rate of the prospective studies after tumor enucleation was 45%; PF-rates after distal pancreatectomy, pancreatoduodenectomy, or central pancreatectomy were, respectively, 14-14-58%. Delayed gastric emptying rates were, respectively, 5-5-18-16%. Postoperative hemorrhage rates were, respectively, 6-1-7-4%. In-hospital mortality rates were, respectively, 3-4-6-4%. The 5-year overall survival (OS) and disease-specific survival (DSS) of resected pNET without synchronous resected liver metastases were, respectively, 85-93%. Heterogeneity between included studies on 5-year OS in patients with synchronous resected liver metastases was too high to pool all studies. The 5-year DSS in patients with liver metastases was 80%. Morbidity after pancreatic resection for pNET was mainly caused by PF. Liver resection in patients with liver metastases seems to have a positive effect on DSS. To reduce heterogeneity, ISGPS criteria and uniform patient groups should be used in the analysis of postoperative outcome and survival.
PubMed-ID: 26661846
http://dx.doi.org/10.1007/s00268-015-3328-6

Meta-analysis of Liver Resection Versus Nonsurgical Treatments for Pancreatic Neuroendocrine Tumors with Liver Metastases.
Ann Surg Oncol, 23(1):244-9.
C. H. Yuan, J. Wang, D. R. Xiu, M. Tao, Z. L. Ma, B. Jiang, Z. F. Li, L. Li, L. Wang, H. Wang and T. L. Zhang. 2016.
PURPOSE: Studies have reported limited evidence of the benefits and harms of various regimens, such as liver resection and medical therapy, for the treatment of pancreatic neuroendocrine tumors (pNETs) with liver metastases. This meta-analysis aimed to evaluate the efficacy of liver resection versus nonsurgical treatments in patients with pNET. METHODS: Relevant studies published in English were retrieved from the computerized databases Medline, Embase, and Cochrane. A meta-analysis was performed to investigate the differences in the efficacy of liver resection and nonsurgical treatments based on the evaluation of 30-day mortality, symptom relief rate, median survival time, and 2-, 3-, or 5-year survival using a random-effects model. Studies were independently reviewed by two investigators. Data from eligible studies were extracted, and the meta-analysis was performed using the comprehensive meta-analysis program version 2. RESULTS: A total of seven studies were included in the analysis. The results demonstrated that liver resection was significantly associated with a higher rate of symptom relief, longer median survival time, higher 2- or 3-year survival rates, as well as a higher 5-year survival rate. There was no significant difference in 30-day mortality among patients with pNETs who were treated by liver resection and nonsurgical therapy or survival between functional and nonfunctional pNETs. No publication bias was detected. CONCLUSIONS: Liver resection has a favorable prognostic outcome in terms of higher postoperative symptom relief rates and longer survival rates. Further randomized, controlled trials with longer follow-up periods are required to confirm the advantages of liver resection for pNETs.
PubMed-ID: 26111625
http://dx.doi.org/10.1245/s10434-015-4654-5

Randomized controlled trials

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

Consensus Statements/Guidelines

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids.
Ann Oncol, 26(8):1604-20.
M. E. Caplin, E. Baudin, P. Ferolla, P. Filosso, M. Garcia-Yuste, E. Lim, K. Oberg, G. Pelosi, A. Perren, R. E. Rossi and W. D. Travis. 2015.
BACKGROUND: Pulmonary carcinoids (PCs) are rare tumors. As there is a paucity of randomized studies, this expert consensus document represents an initiative by the European Neuroendocrine Tumor Society to provide guidance on their management. PATIENTS AND METHODS: Bibliographical searches were carried out in PubMed for the terms 'pulmonary neuroendocrine tumors', 'bronchial neuroendocrine tumors', 'bronchial carcinoid tumors', 'pulmonary carcinoid', 'pulmonary typical/atypical carcinoid', and 'pulmonary carcinoid and diagnosis/treatment/epidemiology/prognosis'. A systematic review of the relevant literature was carried out, followed by expert review. RESULTS: PCs are well-differentiated neuroendocrine tumors and include low- and intermediate-grade malignant tumors, i.e. typical (TC) and atypical carcinoid (AC), respectively. Contrast CT scan is the diagnostic gold standard for PCs, but pathology examination is mandatory for their correct classification. Somatostatin receptor imaging may visualize nearly 80% of the primary tumors and is most sensitive for metastatic disease. Plasma chromogranin A can be increased in PCs. Surgery is the treatment of choice for PCs with the aim of removing the tumor and preserving as much lung tissue as possible. Resection of metastases should be considered whenever possible with curative intent. Somatostatin analogs are the first-line treatment of carcinoid syndrome and may be considered as first-line systemic antiproliferative treatment in unresectable PCs, particularly of low-grade TC and AC. Locoregional or radiotargeted therapies should be considered for metastatic disease. Systemic chemotherapy is used for progressive PCs, although cytotoxic regimens have demonstrated limited effects with etoposide and platinum combination the most commonly used, however, temozolomide has shown most clinical benefit. CONCLUSIONS: PCs are complex tumors which require a multidisciplinary approach and long-term follow-up.
PubMed-ID: 25646366
http://dx.doi.org/10.1093/annonc/mdv041

ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms.
Neuroendocrinology, 103(2):119-24.
G. Delle Fave, D. O'Toole, A. Sundin, B. Taal, P. Ferolla, J. K. Ramage, D. Ferone, T. Ito, W. Weber, Z. Zheng-Pei, W. W. De Herder, A. Pascher and P. Ruszniewski. 2016.
PubMed-ID: 26784901
http://dx.doi.org/10.1159/000443168

ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors.
Neuroendocrinology, 103(2):153-71.
M. Falconi, B. Eriksson, G. Kaltsas, D. K. Bartsch, J. Capdevila, M. Caplin, B. Kos-Kudla, D. Kwekkeboom, G. Rindi, G. Kloppel, N. Reed, R. Kianmanesh and R. T. Jensen. 2016.
PubMed-ID: 26742109
http://dx.doi.org/10.1159/000443171

ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas.
Neuroendocrinology, 103(2):186-94.
R. Garcia-Carbonero, H. Sorbye, E. Baudin, E. Raymond, B. Wiedenmann, B. Niederle, E. Sedlackova, C. Toumpanakis, M. Anlauf, J. B. Cwikla, M. Caplin, D. O'Toole and A. Perren. 2016.
PubMed-ID: 26731334
http://dx.doi.org/10.1159/000443172

ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum.
Neuroendocrinology, 103(2):125-38.
B. Niederle, U. F. Pape, F. Costa, D. Gross, F. Kelestimur, U. Knigge, K. Oberg, M. Pavel, A. Perren, C. Toumpanakis, J. O'Connor, D. O'Toole, E. Krenning, N. Reed and R. Kianmanesh. 2016.
PubMed-ID: 26758972
http://dx.doi.org/10.1159/000443170

ENETS 2016 Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: An Update.
Neuroendocrinology, 103(2):117-8.
D. O'Toole, R. Kianmanesh and M. Caplin. 2016.
PubMed-ID: 26731186
http://dx.doi.org/10.1159/000443169

ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas).
Neuroendocrinology, 103(2):144-52.
U. F. Pape, B. Niederle, F. Costa, D. Gross, F. Kelestimur, R. Kianmanesh, U. Knigge, K. Oberg, M. Pavel, A. Perren, C. Toumpanakis, J. O'Connor, E. Krenning, N. Reed and D. O'Toole. 2016.
PubMed-ID: 26730583
http://dx.doi.org/10.1159/000443165

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site.
Neuroendocrinology, 103(2):172-85.
M. Pavel, D. O'Toole, F. Costa, J. Capdevila, D. Gross, R. Kianmanesh, E. Krenning, U. Knigge, R. Salazar, U. F. Pape and K. Oberg. 2016.
PubMed-ID: 26731013
http://dx.doi.org/10.1159/000443167

ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms.
Neuroendocrinology, 103(2):139-43.
J. K. Ramage, W. W. De Herder, G. Delle Fave, P. Ferolla, D. Ferone, T. Ito, P. Ruszniewski, A. Sundin, W. Weber, Z. Zheng-Pei, B. Taal and A. Pascher. 2016.
PubMed-ID: 26730835
http://dx.doi.org/10.1159/000443166

Other Articles

Curative Resection of Adrenocortical Carcinoma: Rates and Patterns of Postoperative Recurrence.
Ann Surg Oncol, 23(1):126-33.
N. Amini, G. A. Margonis, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2016.
BACKGROUND: Adrenocortical carcinoma (ACC) is a rare malignancy. The aim of this study was to determine the incidence and patterns of recurrence after curative-intent surgery for ACC. METHODS: Patients who underwent curative-intent resection for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the United States ACC study group. Patients with metastasis or an R2 margin were excluded. Patterns and rates of recurrence were determined and classified as locoregional and distant recurrence. RESULTS: A total of 180 patients with a median age of 52 years (interquartile range 43-61) were identified. Most patients underwent open surgery (n = 111, 64.5 %) and had an R0 resection margin (n = 117, 75.0 %). At last follow-up, 116 patients (64.4 %) had experienced recurrence (locoregional only, n = 41, 36.3 %; distant only, n = 51, 45.1 %; locoregional and distant, n = 21, 18.6 %). Median time to recurrence was 18.8 months. Several factors were associated with locoregional recurrence, including left-sided ACC location (odds ratio [OR] 2.71, 95 % confidence interval [CI] 1.06-6.89) and T3/T4 disease (reference T1/T2, OR 3.04, 95 % CI 1.19-7.80) (both $p < 0.05$). Distant recurrence was associated with larger tumor size (OR 1.11, 95 % CI 1.01-1.24) and T3/T4 disease (reference T1/T2, OR 5.23, 95 % CI 1.70-16.10) (both $p < 0.05$). Patients with combined locoregional and distant recurrence had worse survival (3- and 5-year survival: 39.5, 19.7 %) versus patients with distant-only (3- and 5-year survival 55.1, 43.3 %) or locoregional-only recurrence (3- and 5-year survival 81.4, 64.1 %) ($p = 0.01$). CONCLUSIONS: Nearly two-thirds of patients experienced disease recurrence after resection of ACC. Although a subset of patients experienced recurrence with locoregional disease only, many patients experienced recurrence with distant disease as a component of recurrence and had a poor prognosis.
PubMed-ID: 26282907
http://dx.doi.org/10.1245/s10434-015-4810-y

MANAGEMENT OF ENDOCRINE DISEASE: Outcome of adrenal sparing surgery in heritable pheochromocytoma.
Eur J Endocrinol, 174(1):R9-18.
F. Castinetti, D. Taieb, J. F. Henry, M. Walz, C. Guerin, T. Brue, B. Conte-Devolx, H. P. Neumann and F. Sebag. 2016.
The management of hereditary pheochromocytoma has drastically evolved in the last 20 years. Bilateral pheochromocytoma does not increase mortality in MEN2 or von Hippel-Lindau (VHL) mutation carriers who are followed regularly, but these mutations induce major morbidities if total bilateral adrenalectomy is performed. Cortical sparing adrenal surgery may be proposed to avoid definitive adrenal insufficiency. The surgical goal is to leave sufficient cortical tissue to avoid glucocorticoid replacement therapy. This approach was achieved by the progressive experience of minimally invasive surgery via the transperitoneal or retroperitoneal route. Cortical sparing adrenal surgery exhibits <5% significant recurrence after 10 years of follow-up and normal glucocorticoid function in more than 50% of the cases. Therefore, cortical sparing adrenal surgery should be systematically considered in the management of all patients with MEN2 or VHL hereditary pheochromocytoma. Hereditary pheochromocytoma is a rare disease, and a randomized trial comparing cortical sparing vs classical adrenalectomy is probably not possible. This lack of data most likely explains why cortical sparing surgery has not been adopted in most expert centers that perform at least 20 procedures per year for the treatment of this disease. This review examined recent data to provide insight into the technique, its indications, and the results and subsequent follow-up in the management of patients with hereditary pheochromocytoma with a special emphasis on MEN2.
PubMed-ID: 26297495
http://dx.doi.org/10.1530/EJE-15-0549

Long-term outcome after adrenalectomy for incidentally diagnosed subclinical cortisol-secreting adenomas.
Surgery,
B. de La Villeon, S. Bonnet, H. Gouya, L. Groussin, F. Tenenbaum, S. Gaujoux and B. Dousset. 2016.
BACKGROUND: The management of subclinical cortisol-secreting adenomas (SCSAs) is controversial, and available evidence to assess the superiority of an operative versus a nonoperative approach is lacking. The aim of this work was to report the postoperative results and the long-term outcomes for patients with incidentally diagnosed SCSAs and to compare the results with those of patients who underwent an operation for cortisol-secreting adenomas (CSAs). METHODS: From 1994-2011, 107 consecutive patients underwent laparoscopic unilateral adrenalectomy for either an SCSA (n = 39) or a CSA (n = 68). Preoperatively, all patients underwent standardized clinical, hormonal, and imaging assessments. Patients were followed up for >/=2 years with serial assessments of body weight, blood pressure, and glycated hemoglobin, HbA1c. RESULTS: Operative resection of SCSAs and CSAs did not significantly differ regarding operative time, conversion rate, overall operative and medical morbidity, and duration of stay. For SCSAs, the comparison between preoperative status and 2-year assessment showed a median weight loss of 6% (P < .001), a decrease in the median HbA1c of 15% (P < .001), and an improvement or normalization of blood pressure in 50% of the patients. The same significant beneficial metabolic effects of the operation with even greater improvement were observed in patients with CSAs. CONCLUSION: Laparoscopic unilateral adrenalectomy for SCSA is associated with low morbidity, no mortality, and significant improvement of various aspects of metabolic syndrome. Until additional evidence from prospective randomized controlled studies is obtained, laparoscopic unilateral adrenalectomy should be considered a valid option in the care of patients with SCSA.
PubMed-ID: 27129933
http://dx.doi.org/10.1016/j.surg.2016.03.008

Basal and Post-ACTH Aldosterone and Its Ratios Are Useful During Adrenal Vein Sampling in Primary Aldosteronism.
J Clin Endocrinol Metab, 101(4):1826-35.
N. El Ghorayeb, T. L. Mazzuco, I. Bourdeau, J. P. Mailhot, P. S. Zhu, E. Therasse and A. Lacroix. 2016.
ACTH improves selectivity, but can modify lateralization. Basal and post-ACTH ratios are important for surgical indication. Basal aldosterone contralateral suppression predicts residual hyperplasia and post-operative outcomes.
PubMed-ID: 26918291
http://dx.doi.org/10.1210/jc.2015-3915

ENDOCRINE TUMOURS: The genomics of adrenocortical tumors.
Eur J Endocrinol, 174(6):R249-65.
S. Faillot and G. Assie. 2016.
The last decade witnessed the emergence of genomics, a set of high-throughput molecular measurements in biological samples. These pan-genomic and agnostic approaches have revolutionized the molecular biology and genetics of malignant and benign tumors. These techniques have been applied successfully to adrenocortical tumors. Exome sequencing identified new major drivers in all tumor types, including KCNJ5, ATP1A1, ATP2B3 and CACNA1D mutations in aldosterone-producing adenomas (APA), PRKACA mutations in cortisol-producing adenomas (CPA), ARMC5 mutations in primary bilateral macronodular adrenocortical hyperplasia (PBMAH) and ZNRF3 mutations in adrenocortical carcinomas (ACC). Moreover, the various genomic approaches - including exome sequencing, transcriptome, miRNome, genome and methylome - converge into a single molecular classification of adrenocortical tumors. Especially for ACC, two main molecular groups have emerged, showing major differences in outcomes. These ACC groups differ by their gene expression profiles, but also by recurrent mutations and specific DNA hypermethylation patterns in the subgroup of poor outcome. The clinical impact of these findings is just starting. The main altered signaling pathways now become therapeutic targets. The molecular groups of diseases individualize robust subtypes within diseases such as APA, CPA, PBMAH and ACC. A revised nosology of adrenocortical tumors should impact the clinical research. Obvious consequences also include genetic counseling for the new genetic diseases such as ARMC5 mutations in PBMAH, and a better prognostication of ACC based on targeted measurements of a few discriminant molecular alterations. Identifying the main molecular groups of adrenocortical tumors by extensively gathering the molecular variations is a significant step forward towards precision medicine.
PubMed-ID: 26739091
http://dx.doi.org/10.1530/EJE-15-1118

Management of suspected adrenal metastases at 2 academic medical centers.
Am J Surg, 211(4):664-70.
J. A. Glenn, C. M. Kiernan, T. W. Yen, C. C. Solorzano, A. A. Carr, D. B. Evans and T. S. Wang. 2016.
BACKGROUND: The optimal management of suspected adrenal metastases remains controversial. METHODS: This is a retrospective bi-institutional review of 37 patients who underwent adrenalectomy for suspected adrenal metastasis between 2001 and 2014. RESULTS: Three (8%) patients had benign adenomas on final pathology. At a median follow-up of 21 months, 7 (32%) patients were alive with no evidence of disease and 7 (32%) were alive with recurrent disease. Recurrence-free survival (RFS) was 8 months; decreased RFS was associated with positive margins and size >/=6 cm. Overall survival (OS) was 29 months; decreased OS was associated with capsular disruption. There were no differences in RFS or OS by surgical approach. CONCLUSIONS: The favorable OS supports adrenalectomy in select patients with suspected adrenal metastases. Minimally invasive adrenalectomy is safe and effective, but the surgical approach should be based on the ability to achieve a margin-negative resection with avoidance of capsular disruption.
PubMed-ID: 26822269
http://dx.doi.org/10.1016/j.amjsurg.2015.11.019

Pheochromocytoma and Paraganglioma: Diagnosis, Genetics, and Treatment.
Surg Oncol Clin N Am, 25(1):119-38.
C. M. Kiernan and C. C. Solorzano. 2016.
This article highlights the epidemiology and pathophysiology of pheochromocytomas and paragangliomas. The current management of pheochromocytoma and paragangliomas, including utilization and interpretation of biochemical testing, preoperative imaging, and genetic screening are discussed. Furthermore, perioperative surgical management, outcomes, and recommended follow-up are reviewed.
PubMed-ID: 26610778
http://dx.doi.org/10.1016/j.soc.2015.08.006

Novel targeted therapies in adrenocortical carcinoma.
Curr Opin Endocrinol Diabetes Obes, 23(3):233-41.
B. Konda and L. S. Kirschner. 2016.
PURPOSE OF REVIEW: Adrenocortical carcinoma is a rare cancer, but one that carries a poor prognosis due to its aggressive nature and unresponsiveness to conventional chemotherapeutic strategies. Over the past 12 years, there has been renewed interest in developing new therapies for this cancer, including identifying key signaling nodes responsible for cell proliferation. RECENT FINDINGS: Clinical trials of tyrosine kinase inhibitors as monotherapy have generally been disappointing, although the identification of exceptional responders may lead to the identification of targeted therapies that may produce responses in subsets of patients. Agents targeted to the Wnt signaling pathway, a known player in adrenal carcinogenesis, have been developed, although they have not yet been used specifically for adrenal cancer. There is current excitement about inhibitors of acetyl-coA cholesterol acetyl transferase 1, an enzyme required for intracellular cholesterol handling, although trials are still underway. Tools to target other proteins such as Steroidogenic Factor 1 and mechanistic target of rapamycin have been developed and are moving towards clinical application. SUMMARY: Progress is being made in the fight against adrenocortical carcinoma with the identification of new therapeutic targets and new means by which to attack them. Continued improvement in the prognosis for patients with adrenal cancer is expected as this research continues.
PubMed-ID: 27119750
http://dx.doi.org/10.1097/MED.0000000000000247

Incidence of Perioperative Complications Following Resection of Adrenocortical Carcinoma and Its Association with Long-Term Survival.
World J Surg, 40(3):706-14.
G. A. Margonis, N. Amini, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, D. B. Evans, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. E. Moses, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, G. A. Poultsides and T. M. Pawlik. 2016.
BACKGROUND: The association of postoperative complications with long-term oncologic outcomes remains unclear. We sought to determine the incidence of complications among patients who underwent surgery for adrenocortical carcinoma (ACC) and define the relationship of morbidity with long-term survival. METHODS: Patients who underwent surgery for ACC between 1993 and 2014 were identified from 13 academic institutions participating in the US ACC group study. The incidence and type of the postoperative complications, the factors associated with them as well their association with long-term survival were analyzed. RESULTS: A total of 265

patients with median age of 52 years (IQR 44-63) were identified; at surgery, the majority of patients underwent an open abdominal procedure (n = 169, 66.8%). A postoperative complication occurred in 99 patients for a morbidity of 37.4%; five patients (1.9%) died in hospital. Factors associated with morbidity included a thoraco-abdominal operative approach (reference: open abdominal; OR 2.85, 95% CI 1.00-8.18), and a hormonally functional tumor (OR 3.56, 95% CI 1.65-7.69) (all P < 0.05). Presence of any complication was associated with a worse long-term outcome (median survival: no complication, 58.9 months vs. any complication, 25.1 months; P = 0.009). In multivariate analysis, after adjusting for patient- and disease-related factors postoperative infectious complications independently predicted shorter overall survival (hazard ratio (HR) 5.56, 95% CI 2.24-13.80; P < 0.001). CONCLUSION: Postoperative complications were independently associated with decreased long-term survival after resection for ACC. The prevention of complications may be important from an oncologic perspective.
PubMed-ID: 26546184
http://dx.doi.org/10.1007/s00268-015-3307-y

Clinical predictors of prolonged postresection hypotension after laparoscopic adrenalectomy for pheochromocytoma.
Surgery, 159(3):763-70.
T. Namekawa, T. Utsumi, K. Kawamura, N. Kamiya, T. Imamoto, T. Takiguchi, N. Hashimoto, T. Tanaka, Y. Naya, H. Suzuki and T. Ichikawa. 2016.
BACKGROUND: Although the perioperative management of patients with pheochromocytoma has been improving recently, severe hypotensive episodes can occur that require postoperative catecholamine support and are challenging to manage. Our aim was to identify the clinical factors that predict prolonged postresection hypotension in patients after laparoscopic adrenalectomy for pheochromocytoma. METHODS: The records of 73 Japanese patients who underwent unilateral laparoscopic adrenalectomy for pheochromocytoma were surveyed retrospectively. Patients were divided into 2 groups according to whether catecholamine support was needed after postoperatively. Clinical and biochemical data were evaluated at baseline and after operation. RESULTS: Thirty-four of 73 patients (47%) required continuous infusion of catecholamine to maintain systolic blood pressure >90 mm Hg at the end of the operation. The median duration of postoperative catecholamine support was 17 hours (range, 3-130) in these 34 patients. On multivariate analysis, tumor size >60 mm, urinary epinephrine levels >200 mug/day, and urinary norepinephrine levels >600 mug/day were independent predictors of prolonged hypotension requiring postoperative catecholamine support. Tumor size and urinary norepinephrine levels were significantly correlated with the duration of postoperative catecholamine support. CONCLUSION: Larger tumor size and greater values of urinary epinephrine and norepinephrine levels were significant predictors of prolonged hypotension requiring postoperative catecholamine support. Moreover, tumor size and urinary norepinephrine levels were positively correlated with the duration of postoperative catecholamine support. Clinicians can identify and manage patients more effectively with a greater risk of prolonged hypotension after tumor resection using these preoperative clinical variables.
PubMed-ID: 26477475
http://dx.doi.org/10.1016/j.surg.2015.09.016

Cosyntropin stimulation testing on postoperative day 1 allows for selective glucocorticoid replacement therapy after adrenalectomy for hypercortisolism: Results of a novel, multidisciplinary institutional protocol.
Surgery, 159(1):259-65.
D. I. Ortiz, J. W. Findling, T. B. Carroll, B. R. Javorsky, A. A. Carr, D. B. Evans, T. W. Yen and T. S. Wang. 2016.
BACKGROUND: Secondary adrenal insufficiency (AI) can occur after unilateral adrenalectomy for adrenal-dependent hypercortisolism. Postoperative glucocorticoid replacement (GR), although given routinely, may not be necessary. We sought to identify factors that, in combination with postoperative day 1 cosyntropin stimulation testing (POD1-CST), would predict the need for GR. METHODS: We reviewed 31 consecutive patients who underwent unilateral adrenalectomy for hypercortisolism (study patients) or hyperaldosteronism (control patients). A standard POD1-CST protocol was used. Hydrocortisone was started for clinical evidence of AI, basal plasma cortisol </= 5 (mug/dL), or a stimulated plasma cortisol <18. RESULTS: A normal POD1-CST was found in all nine control patients and 11 of 22 patients (50%) with Cushing's syndrome; the other 11 study patients (50%) received GR based on the POD1-CST. These patients were younger (51 vs 62 years; P = .017), had a higher body mass index (BMI; 31 vs 29 kg/m(2)), and smaller adrenal neoplasms (16.9 vs 33.0 g; P = .009) than non-GR study patients. CONCLUSION: After unilateral adrenalectomy for hypercortisolism, only 50% of patients received GR. No preoperative biochemical characteristics were associated with postoperative AI, although patients who received GR were younger, and tended to have a higher BMI and smaller adrenal nodules. Use of this novel protocol for postoperative dynamic adrenal function testing prevented unnecessary GR in 50% of

patients and allowed for individualized patient care.
PubMed-ID: 26422766
http://dx.doi.org/10.1016/j.surg.2015.05.034

Management of adrenal incidentaloma by laparoscopic transperitoneal anterior and submesocolic approach.
Langenbecks Arch Surg, 401(1):71-9.
A. M. Paganini, M. Guerrieri, A. Balla, S. Quaresima, A. M. Isidori, F. Iafrate, G. D'Ambrosio, G. Lezoche and E. Lezoche. 2016.
PURPOSE: Laparoscopic adrenalectomy (LA) is becoming the main approach for incidentally discovered adrenal masses (adrenal incidentaloma (AI)). The aim of this study was to evaluate the results of LA with a transperitoneal anterior approach for right adrenal lesions and either a transperitoneal anterior or transperitoneal anterior submesocolic approach for the left-sided lesions. METHODS: The study is a retrospective analysis of prospectively collected data. From January 1994 to December 2012, 393 patients underwent LA, 117 of these for an AI. Sixty-seven (57.26 %) and 50 (42.73 %) patients underwent right and left adrenalectomy, respectively. The transperitoneal anterior approach was used in all 67 patients with right lesions (57.26 %) (group A) and in 13 patients with left-sided lesions (11.11 %) (group B). The transperitoneal anterior submesocolic approach was used in the remaining 37 left-sided lesions (31.62 %) (group C). RESULTS: Mean operative time in groups A, B, and C was 104.6 min (range 35-255), 148.9 min (range 80-210), and 82.7 min (range 45-230), respectively. One right and one left anterior LA (1.7 %) were converted to open surgery. There were one major and one minor complications (1.7 %). The mean lesion size was 4.73 cm (range 1-10 cm). Mean hospital stay was 3.6 days. CONCLUSIONS: With adequate experience, LA with a transperitoneal anterior approach for AI is a safe and effective procedure. Early control of the adrenal vein with minimal gland manipulation and limited surgical dissection are its major advantages. In case of left LA, the submesocolic approach reduces the operative time significantly.
PubMed-ID: 26683612
http://dx.doi.org/10.1007/s00423-015-1367-y

Adrenal surgery in England: better outcomes in high-volume practices.
Clin Endocrinol (Oxf), 85(1):17-20.
F. Palazzo, A. Dickinson, B. Phillips, A. Sahdev, R. Bliss, A. Rasheed, Z. Krukowski and J. Newell-Price. 2016.
AIMS AND BACKGROUND: Adrenal surgery is performed by a variety of surgical specialities in differing environments and volumes. International data suggest that there is a correlation between adrenal surgery volume and outcomes but there are no UK data to support this or UK surgical guidelines. A multidisciplinary team representing the stakeholders in adrenal disease is preparing a national guidance on adrenal surgery. A review of the outcomes for adrenal surgery in England was performed to correlate outcomes with the volume of surgeon practice. METHODS: Hospital Episode Statistics (HES) data for the National Health Service (NHS) in England in the tax year 2013-2014 were examined for adrenal surgery. Length of hospital stay and rate of postoperative readmission were assessed as surrogate quality markers and a comparison made between 'high-' and 'low-' volume surgeons. RESULTS: A total of 795 adult adrenalectomies were performed by 222 different surgeons with a range of between 1 and 34 adrenalectomies performed per surgeon. Only thirty-six (16%) adrenal surgeons performed 6 or more adrenalectomies. A total of 186 surgeons (84%) performed a median of one adrenalectomy a year. Length of stay and readmission rate within thirty days of operation was 60% longer and 47% higher, respectively, when performed by low-volume surgeons. CONCLUSION: The current provision of adrenal surgery in the UK is not in the best interests of patients and is not cost-effective for the NHS. Adrenal surgery is best performed by higher volume surgeons in centres with dedicated adrenal multidisciplinary teams expert in all aspects of care of the adrenal patient.
PubMed-ID: 26776382
http://dx.doi.org/10.1111/cen.13021

FDG PET/CT Scan and Functional Adrenal Tumors: A Pilot Study for Lateralization.
World J Surg, 40(3):683-9.
D. Patel, S. K. Gara, R. J. Ellis, M. Boufraqech, N. Nilubol, C. Millo, C. A. Stratakis and E. Kebebew. 2016.
BACKGROUND: Patients with Cushing's Syndrome (CS) and Conn's Syndrome with bilateral adrenal masses pose a dilemma. Uptake of 18F-FDG by hyperfunctioning adrenal glands has not been previously reported and may help lateralize. The aim was to determine if 18F-FDG PET/CT scan could identify hyperfunctioning adrenal masses and determine a biological basis for uptake. METHODS: Patients with nonfunctional adenomas (n = 9), CS (n = 11), and Conn's syndrome (n = 4) underwent an 18F-FDG PET/CT scan with a volume of interest circumscribing each mass to obtain a maximal standardized uptake value (SUVmax). Thirty-two adrenal masses

were analyzed. Genome-wide expression data from an independent cohort were analyzed in nonfunctioning adenomas (n = 20), Conn's syndrome (n = 29), and CS (n = 24) focusing on GLUT genes. For genes differentially expressed, immunohistochemistry was performed on tissue samples. RESULTS: Cortisol-secreting masses (n = 16) had a higher average SUVmax of 5.9 compared to nonfunctioning masses (n = 11, average SUVmax 4.2) and aldosterone-hypersecreting masses (n = 5, average SUVmax 3.2) (p = 0.007). SUVmax cut-off of 5.33 had 50.0% sensitivity and 81.8% specificity in localizing a cortisol-secreting mass. GLUT3 expression was 2.19-fold higher in patients with CS compared to patients with nonfunctioning adenomas (p = 0.003) and 2.16-fold higher in patients with CS compared to Conn's syndrome (p = 0.006). GLUT3 immunohistochemistry showed 2.2-fold higher staining in CS tumor samples compared to nonfunctioning adenomas. CONCLUSIONS: Differential 18F-FDG PET/CT uptake was observed in patients with nonfunctioning, aldosterone-hypersecreting, and cortisol-secreting masses. GLUT3 overexpression in cortisol-secreting tumor likely accounts for the differential uptake. Future larger cohort studies will need to be conducted to determine if 18F-FDG PET/CT uptake can lateralize cortisol-secreting adrenal masses in patients with bilateral adrenal masses.
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http://dx.doi.org/10.1007/s00268-015-3242-y

Total 18F-FDG PET/CT Metabolic Tumor Volume Is Associated With Postoperative Biochemical Response in Patients With Metastatic Pheochromocytomas and Paragangliomas.
Ann Surg, 263(3):582-7.
D. Patel, A. Mehta, N. Nilubol, W. Dieckmann, K. Pacak and E. Kebebew. 2016.
OBJECTIVE: The aim of this pilot study was to determine if metabolic tumor volume (MTV) and total lesion glycolysis (TLG) could serve as predictors of biochemical remission and pharmacotherapy-free interval in patients with metastatic pheochromocytomas (PCCs) and paragangliomas (PGLs). BACKGROUND: Patients with metastatic PCCs/PGLs have a high rate of biochemical recurrence, which can be associated with increased cardiovascular morbidity. Predictors of biochemical response are needed to guide and select patients who may benefit from therapy. METHODS: Whole body MTV and TLG was calculated from preoperative 18F-FDG PET/CT scans and analyzed as marker of biochemical response and pharmacotherapy-free interval. RESULTS: Seventeen patients underwent a total of 19 procedures, with a median follow-up time of 26.4 months. Whole body MTV of patients with biochemical recurrence (n = 13, mean 73.8 mL) was higher than those who had a biochemical response (n = 6, mean 14.7 mL, P = 0.05). Patients with low MTV (<37.2 mL) had an improved durable partial biochemical response (P < 0.05), and a statistical trend for complete biochemical remission (P = 0.07) and pharmacotherapy-free interval (P = 0.06). In 8 patients with metastatic disease outside the abdomen, 4 patients had less than 35% of their disease burden outside the abdomen and these patients had a more durable partial biochemical response compared to patients with greater than 35% of their disease burden outside the abdomen (P < 0.05). CONCLUSIONS: Whole body MTV and TLG represents novel and valuable predictors of biochemical response for patients with metastatic PCCs and PGLs. A larger prospective study should be performed to validate these findings.
PubMed-ID: 25405562
http://dx.doi.org/10.1097/SLA.0000000000001018

Outcomes of Adjuvant Mitotane after Resection of Adrenocortical Carcinoma: A 13-Institution Study by the US Adrenocortical Carcinoma Group.
J Am Coll Surg, 222(4):480-90.
L. M. Postlewait, C. G. Ethun, T. B. Tran, J. D. Prescott, T. M. Pawlik, T. S. Wang, J. Glenn, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, C. A. Staley, G. A. Poultsides and S. K. Maithel. 2016.
BACKGROUND: Current treatment guidelines recommend adjuvant mitotane after resection of adrenocortical carcinoma with high-risk features (eg, tumor rupture, positive margins, positive lymph nodes, high grade, elevated mitotic index, and advanced stage). Limited data exist on the outcomes associated with these practice guidelines. STUDY DESIGN: Patients who underwent resection of adrenocortical carcinoma from 1993 to 2014 at the 13 academic institutions of the US Adrenocortical Carcinoma Group were included. Factors associated with mitotane administration were determined. Primary end points were recurrence-free survival (RFS) and overall survival (OS). RESULTS: Of 207 patients, 88 (43%) received adjuvant mitotane. Receipt of mitotane was associated with hormonal secretion (58% vs 32%; p = 0.001), advanced TNM stage (stage IV: 42% vs 23%; p = 0.021), adjuvant chemotherapy (37% vs 5%; p < 0.001), and adjuvant radiation (17% vs 5%; p = 0.01), but was not associated with tumor rupture, margin status, or N-stage. Median follow-up was 44 months. Adjuvant mitotane was associated with decreased RFS (10.0 vs 27.9 months; p = 0.007) and OS (31.7 vs 58.9 months; p = 0.006). On multivariable analysis, mitotane was not independently associated with RFS or OS, and margin

status, advanced TNM stage, and receipt of chemotherapy were associated with survival. After excluding all patients who received chemotherapy, adjuvant mitotane remained associated with decreased RFS and similar OS; multivariable analyses again showed no association with recurrence or survival. Stage-specific analyses in both cohorts revealed no association between adjuvant mitotane and improved RFS or OS. CONCLUSIONS: When accounting for stage and adverse tumor and treatment-related factors, adjuvant mitotane after resection of adrenocortical carcinoma is not associated with improved RFS or OS. Current guidelines should be revisited and prospective trials are needed.
PubMed-ID: 26775162
http://dx.doi.org/10.1016/j.jamcollsurg.2015.12.013

Genotype-Phenotype Correlation in Indian Patients with MEN2-Associated Pheochromocytoma and Comparison of Clinico-Pathological Attributes with Apparently Sporadic Adrenal Pheochromocytoma.
World J Surg, 40(3):690-6.
S. Rajan, G. Zaidi, G. Agarwal, A. Mishra, A. Agarwal, S. K. Mishra and E. Bhatia. 2016.
INTRODUCTION: Pheochromocytoma (PCC) manifests in up to 50% of MEN2 patients. We correlated the clinico-pathological features of MEN2-associated PCC (MEN-PCC) with RET mutations and compared them with non-MEN adrenal-PCCs. METHODS: In this retrospective single institution study on a large PCC database (n = 208, 1997-2014) 24 MEN-PCC patients with known RET mutations were reviewed. Excluding 7 with incomplete data, the study cohort of 17 MEN-PCC patients from 11 kindreds (M:F::7:10) was identified. Clinical, biochemical, pathological attributes, and outcomes in the MEN-PCC group were correlated with the genotype, and further compared with non-MEN, apparently sporadic adrenal-PCCs (n = 132, excluding 37 extra-adrenal and 15 VHL/NF1/SDH-associated PCC). RESULTS: Components of MEN2 encountered included MTC in 13(76.5%), Marfanoid habitus in 2, and PHPT, cutaneous lichen amyloidosis and mucosal neuromas in 1 patient each. In 11(64.7%), PCC was the first detected MEN2 component (Symptomatic:8, Incidentaloma:3). Four (23.5%) were normotensive; 8(47.1%) had bilateral PCC (7 synchronous, 1 metachronous). Surgery for PCC included laparoscopic adrenalectomy in 12; and cortical-sparing adrenalectomy in 2 of 8 bilateral PCC patients. Mean MEN-PCC tumor size was 6.9 +/- 3.9 cm, and 6(35%) had additional adrenal medullary hyperplasia. Four different genotypes were encountered, commonest involving codon 634, others being 804 and 918. Mean age in MEN-PCC (27.7 +/- 12.2 years) was lower than non-MEN PCC (39.4 +/- 15.7, p = 0.018). Proportion of pediatric patients (35.3% in MEN-PCC vs. 12.9% in non-MEN-PCC, p = 0.007), bilateral tumors (47.1% in MEN-PCC, 4.5% in non-MEN-PCC, p < 0.001), and adrenal medullary hyperplasia (35.2% in MEN-PCC, 0.7% in non-MEN-PCC, p < 0.001) were different. Median 24-hour urinary metanephrines was significantly higher in index MEN-PCC patients, than non-MEN-PCC (634 vs. 214 mcg/24 h, p value = 0.006), but was non-significantly higher in non-index MEN-PCC patients. Mean tumor sizes were comparable in the two groups. None of MEN-PCC patients had malignant PCC, compared to 7(5.3%) in non-MEN-PCC. CONCLUSIONS: In this cohort of MEN-PCC from India, the commonest causative RET mutations for MEN-PCC involved codon 634. MEN-PCC patients were younger, and more frequently had bilateral PCC than non-MEN disease. MEN-PCC patients in India are diagnosed with large tumors and extremely high catecholamine/metanephrine levels.
PubMed-ID: 26438242
http://dx.doi.org/10.1007/s00268-015-3255-6

Chromosome 19 amplification correlates with advanced disease in adrenocortical carcinoma.
Surgery, 159(1):296-301.
J. C. Rubinstein, T. C. Brown, G. Goh, C. C. Juhlin, A. Stenman, R. Korah and T. Carling. 2016.
BACKGROUND: Familial syndromes with specific genetic drivers account for a subset of adrenocortical carcinomas (ACCs), but the genomic underpinnings of sporadic cases remain poorly understood. Recent advances in copy number variation (CNV) prediction from exome sequencing are facilitating exploration of genomic rearrangements common to these carcinomas. METHODS: ACC and matched, nontumor samples underwent exome sequencing. CNVs were predicted using coverage-depth comparison. Clinicopathologic characteristics of amplification- and deletion-dominant samples were compared and pathway enrichment analysis performed for regions with significant variation. RESULTS: CNVs are distributed broadly across the ACC genome. Individual signatures demonstrate amplification or deletion dominance. Areas of recurrent amplification include chromosomes 5, 12, 19, and 20, whereas chromosomes 1, 10, 18, and 22 are deletion prone. Large-scale amplification of chromosome 19 occurred in 12 of 19 cases (63%), including 6 of 8 amplification-dominant samples (75%) and was associated with stage III/IV disease (P = .002). Genes within this amplified region are overrepresented among the adrenal hyperplasia and steroid biosynthesis pathways (P = 4.2(-5) and 2.5(-5), respectively). CONCLUSION: CNV detection via exome sequencing allows high-resolution cataloging of structural variations in ACC. Large-scale, recurrent amplifications encompassing known adrenal-specific gene pathways correlate with tumor stage. Further functional analysis of individual genes within these

regions could provide mechanistic insight into specific drivers underlying pathogenesis and progression of ACC.
PubMed-ID: 26453132
http://dx.doi.org/10.1016/j.surg.2015.09.001

Mitotane treatment in patients with adrenocortical cancer causes central hypothyroidism.
Clin Endocrinol (Oxf), 84(4):614-9.
M. Russo, C. Scollo, G. Pellegriti, O. R. Cotta, S. Squatrito, F. Frasca, S. Cannavo and D. Gullo. 2016.
INTRODUCTION: Mitotane, a steroidogenesis inhibitor with adrenolytic properties used to treat adrenocortical cancer (ACC), can affect thyroid function. A reduction of FT4 levels with normal FT3 and TSH has been described in these patients. Using an in vitro murine model, the secretory capacity of thyrotrophic cells has been shown to be inhibited by mitotane. OBJECTIVE: To investigate the pathogenesis of thyroid abnormalities in mitotane-treated patients with ACC. PATIENTS AND METHODS: In five female patients with ACC (median age 47; range 31-65) treated with mitotane (dosage 1.5 g/day; 1.0-3.0), we analysed the pattern of TSH and thyroid function index (FT4, FT3 and FT3/FT4 ratio) compared to an age- and gender-matched control group. The in vivo secretory activity of the thyrotrophic cells was evaluated using a standard TRH test (200 mug), and the response was compared to both a group of age-matched female controls (n = 10) and central hypothyroid patients (n = 10). RESULTS: Basal TSH (median 1.54 mU/l; range 1.20-2.17) was normal and scattered around our median reference value, FT3 levels (median 3.80 pmol/l; 3.30-4.29) were normal but below the median reference value of 4.37 pmol/l and FT4 levels were below the normal range in all patients (median 8.40 pmol/l; 7.6-9.9). FT3/FT4 ratio was in the upper range in 4 patients and higher than normal in one patient. A blunted TSH response to TRH was observed in mitotane-treated patients. DeltaTSH (absolute TSH response, peak TSH minus basal TSH) was 3.65 (range 3.53-5.26), 12.37 (range 7.55-19.97) and 1.32 mU/l (range 0.52-4.66) in mitotane-treated patients, controls and central hypothyroid patients, respectively. PRL secretion was normal. CONCLUSIONS: Mitotane-treated patients with ACC showed low FT4, normal FT3 and TSH and impaired TSH response to TRH, characteristic of central hypothyroidism. Furthermore, the elevated FT3/FT4 ratio of these subjects reflects an enhanced T4 to T3 conversion rate, a compensatory mechanism characteristic of thyroid function changes observed in hypothyroid conditions. This finding thus confirms in vitro studies and may have a therapeutic implication for treatment with thyroid hormones, as suggested by current guidelines for this specific condition.
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http://dx.doi.org/10.1111/cen.12868

Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism.
Eur J Endocrinol, 174(3):261-9.
A. S. Salcuni, V. Morelli, C. Eller Vainicher, S. Palmieri, E. Cairoli, A. Spada, A. Scillitani and I. Chiodini. 2016.
OBJECTIVE: Subclinical hypercortisolism (SH) is associated with increased risk of vertebral fractures (VFx). The effect on bone following recovery from SH is unknown. DESIGN: Of the 605 subjects consecutively referred for monolateral adrenal incidentalomas (AIs) to our outpatient clinics, 55 SH patients (recruited on the basis of the exclusion criteria) were enrolled. We suggested to all patients to undergo adrenalectomy, which was accepted by 32 patients (surgical group, age 61.3+/-8.1 years) and refused by 23 patients, who were followed with a conservative management (non-surgical group, age 65.4+/-7.1 years). METHODS: We diagnosed SH in patients with serum cortisol after 1 mg dexamethasone suppression test (1 mg-DST) >5.0 mug/dl or with greater than or equal to two criteria among 1 mg-DST >3.0 mug/dl, urinary free cortisol >70 mug/24 h and ACTH <10 pg/ml. We assessed: bone mineral density (BMD) at lumbar spine (LS) and femoral neck (as Z-score) by dual-energy X-ray absorptiometry and the VFx presence by X-ray at baseline and at the end of follow up (surgical group 39.9+/-20.9 months and non-surgical group 27.7+/-11.1 months). RESULTS: The LS Z-score (DeltaZ-score/year) tended to increase in the surgical group (0.10+/-0.20) compared with the non-surgical group (-0.01+/-0.27, P=0.08) and in the former, the percentage of patients with new VFx was lower (9.4%) than in the latter (52.2%, P<0.0001). Surgery in AI patients with SH was associated with a 30% VFx risk reduction (odds ratio 0.7, 95% CI 0.01-0.05, P=0.008) regardless of age, gender, follow up duration, 1 mg-DST, LS BMD, and presence of VFx at baseline. CONCLUSION: In patients with monolateral AI and SH, adrenalectomy reduces the risk of VFx.
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http://dx.doi.org/10.1530/EJE-15-0977

Synthetic high-density lipoprotein nanoparticles: A novel therapeutic strategy for adrenocortical carcinomas.
Surgery, 159(1):284-94.
C. Subramanian, R. Kuai, Q. Zhu, P. White, J. J. Moon, A. Schwendeman and M. S. Cohen. 2016.
BACKGROUND: Chemotherapeutic strategies for adrenocortical carcinoma (ACC) carry substantial toxicities. Cholesterol is critical for ACC cell growth and steroidogenesis, and ACC cells overexpress scavenger receptor BI, which uptakes cholesterol from circulating high-density lipoprotein (HDL) cholesterol. We hypothesize that cholesterol-free synthetic-HDL nanoparticles (sHDL) will deplete cholesterol and synergize with chemotherapeutics to achieve enhanced anticancer effects at lesser (less toxic) drug levels. METHODS: The antiproliferative efficacy of ACC cells for the combinations of sHDL with chemotherapeutics was tested by Cell-Titer Glo. Cortisol levels were measured from the culture media. Effects on steroidogenesis was measured by real-time polymerase chain reaction (RT-PCR). Induction of apoptosis was evaluated by flow cytometry. RESULTS: Combination Index (CI) for sHDL and either etoposide (E), cisplatin (P), or mitotane (M) demonstrated synergy (CI < 1) for antiproliferation. Alone or in combination with the chemotherapy drugs, sHDL was able to decrease cortisol production by 70-90% compared with P alone or controls (P < .01). RT-PCR indicated inhibition of steroidogenic enzymes for sHDL (P < .01 vs no sHDL). Combination therapy with sHDL increased apoptosis by 30-50% compared with drug or sHDL alone (P < .03), confirmed by a decrease in the mitochondrial potential. CONCLUSION: sHDL can act synergistically and lessen the amount of M/E/P needed for anticancer efficacy in ACC in part owing to cholesterol starvation. This novel treatment strategy warrants further investigation translationally.
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http://dx.doi.org/10.1016/j.surg.2015.08.023

Role of adrenal vein sampling in primary aldosteronism: Impact of imaging, localization, and age.
J Surg Oncol, 113(5):532-7.
H. Wachtel, S. Zaheer, P. K. Shah, S. O. Trerotola, G. C. Karakousis, R. E. Roses, D. L. Cohen and D. L. Fraker. 2016.
BACKGROUND: The role of adrenal vein sampling (AVS) has been debated, with some authorities advocating selective use in younger patients (</=40 years), and those localized by preoperative imaging. We examined our experience to determine the impact of AVS in patients who routinely underwent AVS with a high success rate. METHODS: A retrospective cohort study was performed using a prospectively maintained database of patients referred for evaluation of PA (1997-2013). Patients were classified as localized (L) if a unilateral mass was identified on imaging, and non-localized (NL) otherwise. RESULTS: Of 367 patients, 94% (n = 345) underwent successful AVS. Seventy-two percent (n = 265) were L; AVS was lateralizing 58% (n = 214). AVS changed management in 43% of patients (n = 158). In patients </=40 years, AVS changed management in 30% (n = 15). In patients </=40 years with a >/=1 cm adrenal mass, 12% (n = 3) would have undergone unnecessary surgery based on imaging results alone; in patients >40 years with a >/=1 cm adrenal mass, 3% (n = 5) would have undergone wrong-side surgery, and 30% (n = 50) would have undergone unnecessary surgery based on imaging. CONCLUSION: AVS changed management in a significant minority of patients regardless of age and imaging findings. AVS should be routinely recommended in all patients with PA, to direct operative therapy. J. Surg. Oncol. 2016;113:532-537. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 26792453
http://dx.doi.org/10.1002/jso.24182

PTH Is a Promising Auxiliary Index for the Clinical Diagnosis of Aldosterone-Producing Adenoma.
Am J Hypertens, 29(5):575-81.
L. X. Zhang, W. J. Gu, Y. J. Li, Y. Wang, W. B. Wang, A. P. Wang, L. Shen, L. Zang, G. Q. Yang, Z. H. Lu, J. T. Dou and Y. M. Mu. 2016.
BACKGROUND: Parathyroid hormone (PTH) stimulates aldosterone secretion in human adrenocortex and is regulated by the renin-angiotensin-aldosterone system. We speculated that measurement of PTH may be a valuable aid in the diagnosis of aldosterone-producing adenoma (APA). METHODS: To test this hypothesis, we recruited 142 patients with adrenal adenoma, of whom 84 had an APA and 58 had a nonfunctioning adrenal adenoma (NFA). Plasma levels of intact PTH, serum potassium, sodium, calcium, phosphate, 25(OH) vitamin D, plasma aldosterone concentration (PAC), plasma renin activity (PRA), and aldosterone to renin ratio (ARR) were measured in every patient. Computed tomography (CT) scanning of the adrenal gland and adrenal hormone levels was used to evaluate the function of the adrenal adenoma. We also evaluated the impact of renin-angiotensin-aldosterone system (RAAS) components on PTH from the recumbent-upright test in 15 patients with APA and 30 patients with NFA. RESULTS: Compared with NFA, PTH levels were significantly increased in patients with APA, and serum calcium and phosphate were significantly decreased. When position was changed

from supine to upright, the variation in PTH levels was significantly higher in APA patients compared with NFA patients. Receiver operator characteristic (ROC) curves identified the Youden index, which corresponded to the best tradeoff of combined marker (ARR and PTH) with a sensitivity and specificity of 89.3% and 93.1%, respectively. CONCLUSIONS: The baseline and positional variation of serum PTH levels were significant in APA, thus PTH may be a promising auxiliary index for the clinical diagnosis of APA.
PubMed-ID: 26304960
http://dx.doi.org/10.1093/ajh/hpv146

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

When and how should patients with multiple endocrine neoplasia type 1 be screened for thymic and bronchial carcinoid tumours?
Clin Endocrinol (Oxf), 84(1):13-6.
N. Singh Ospina, S. Maraka, V. Montori, G. B. Thompson and W. F. Young, Jr. 2016.
Patients with multiple endocrine neoplasia type 1 (MEN1) are commonly evaluated for clinical manifestations of this syndrome with the rationale that early diagnosis and adequate treatment will result in improved survival and quality of life. Thymic and bronchial carcinoid tumours are uncommon but important manifestations of MEN1. Current practice guidelines recommend evaluation with computed tomography or magnetic resonance imaging scan of the chest every 1-2 years to detect these neoplasms. However, the certainty that patients will be better off (increased survival or quality of life) as a result of this case detection strategy is based on evidence at moderate-high risk of bias that yields only imprecise results of indirect relevance to these patients. In order to improve the care that patients with MEN1 receive, co-ordinated efforts from different stakeholders are required so that large, prospective, multicentre studies evaluating patient important outcomes are carried out.
PubMed-ID: 26562483
http://dx.doi.org/10.1111/cen.12972

Other Articles

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

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

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