EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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

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

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Journals covered

Journal	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

Factitious Graves' Disease Due to Biotin Immunoassay Interference-A Case and Review of the Literature.
J Clin Endocrinol Metab, 101(9):3251-5.
M. S. Elston, S. Sehgal, S. Du Toit, T. Yarndley and J. V. Conaglen. 2016.
CONTEXT: Biotin (vitamin B7) is an essential co-factor for four carboxylases involved in fatty acid metabolism, leucine degradation, and gluconeogenesis. The recommended daily intake (RDI) of biotin is approximately 30 mug per day. Low-moderate dose biotin is a common component of multivitamin preparations, and high-dose biotin (10 000 times RDI) has been reported to improve clinical outcomes and quality of life in patients with progressive multiple sclerosis. Biotin is also a component of immunoassays, and supplementation may cause interference in both thyroid and non-thyroid immunoassays. OBJECTIVE: To assess whether biotin ingestion caused abnormal thyroid function tests (TFTs) in a patient through assay interference. DESIGN: We report a patient with biotin-associated abnormal TFTs and a systematic review of the literature. SETTING: A tertiary endocrine service in Hamilton, New Zealand. RESULTS: The patient had markedly abnormal TFTs that did not match the clinical context. After biotin cessation, TFTs normalized far more rapidly than possible given the half-life of T4, consistent with assay interference by biotin. Multiple other analytes also tested abnormal in the presence of biotin. CONCLUSION: Biotin ingested in moderate to high doses can cause immunoassay interference. Depending on the assay format, biotin interference can result in either falsely high or low values. Interference is not limited to thyroid tests and has the potential to affect a wide range of analytes. It is important for clinicians to be aware of this interaction to prevent misdiagnosis and inappropriate treatment.
PubMed-ID: 27362288
http://dx.doi.org/10.1210/jc.2016-1971

Intraoperative Neuromonitoring in Thyroid Surgery: A Systematic Review.
World J Surg, 40(8):2051-8.
R. Malik and D. Linos. 2016.
This study aimed to assess the efficacy of intraoperative neurophysiologic monitoring (IONM) in preventing recurrent laryngeal nerve palsy (RLNP) during thyroid surgery. When IONM results in false positives, it seeks to evaluate contributing factors. A systematic review was conducted gauging the predictive power of neuromonitoring in determining RLN function intraoperatively, its reductions of temporary and permanent RLNP rates, and surgeons' response to the technology. MEDLINE, EMBASE, and PubMed were searched for RLN monitoring in thyroid surgery following a set of inclusion/exclusion criteria. Seventeen studies comparing thyroid surgery with and without IONM were reviewed, including 30,926 patients. Selected studies were pooled to gage the predictive power. Mean specificity of IONM in identifying functional nerves was 90.24 % among 7366 nerves at risk (NAR). However, mean positive predictive power (PPP) was low, and both specificity and PPP varied substantially when stratified by risk levels. Among the pooled studies focusing on IONM efficacy-there were 44,575 NAR, of which (57.98 %) were operated on with IONM and 18,732 (42.02 %) without (control). The rates of overall RLNP per NAR were 3.18 and 3.83 % for the IONM group and control, respectively. There is no statistically significant difference between IONM and control, a conclusion supported by qualitative analysis from many individual studies. IONM is not recommended as the standard of care for thyroidectomies. Low PPP of IONM and complications associated with IONM-assisted thyroidectomies may be attributed to either the absence of a standardized negative-signal cutoff value or injury from intubation.
PubMed-ID: 27329143
http://dx.doi.org/10.1007/s00268-016-3594-y

Diagnostic accuracy of thyroid nodule growth to predict malignancy in thyroid nodules with benign cytology: systematic review and meta-analysis.
Clin Endocrinol (Oxf), 85(1):122-31.
N. Singh Ospina, S. Maraka, A. Espinosa DeYcaza, D. O'Keeffe, J. P. Brito, M. R. Gionfriddo, M. R. Castro, J. C. Morris, P. Erwin and V. M. Montori. 2016.
BACKGROUND: Thyroid ultrasound to assess for nodular growth is commonly performed during the follow-up of patients with benign thyroid nodules, with the goal of identifying patients with a missed diagnosis of thyroid cancer. The objective of this study was to summarize the evidence regarding the diagnostic accuracy of growth during follow-up of benign thyroid nodules for thyroid cancer. METHODS: We searched multiple electronic databases using a search strategy designed by an experienced medical librarian from inception to March 2015.

Eligible studies included patients with benign thyroid nodules assessed for growth during follow-up and evaluated for thyroid cancer either by surgical histology or a repeat fine needle aspiration biopsy. Reviewers working independently and in duplicate recorded data and assessed each study. RESULTS: The seven eligible studies lacked safeguards against bias and generated results that were imprecise with wide confidence intervals and inconsistent across studies. This warrants very low confidence in these results. The odds of nodule growth in patients with thyroid cancer on histopathology over these odds in patients without thyroid cancer (diagnostic odds ratio) was 0.58 (95% CI: 0.26-1.3); the diagnostic odds ratio was 2.2 (95% CI: 0.26-18) when an abnormal repeat biopsy was the reference standard. CONCLUSION: The body of evidence linking nodule growth with thyroid cancer during the follow-up of benign nodules warrants very low confidence. In the era of high-value health care, the commonplace practice of following benign thyroid nodules with serial ultrasound assessment of growth to diagnose cancer can be questioned, calling for imminent evaluation.
PubMed-ID: 26562828
http://dx.doi.org/10.1111/cen.12975

Systematic Review of Trends in the Incidence Rates of Thyroid Cancer.
Thyroid, 26(11):1541-52.
J. J. Wiltshire, T. M. Drake, L. Uttley and S. P. Balasubramanian. 2016.
BACKGROUND: A large proportion of global increase in thyroid cancer (TC) incidence has been attributed to increased detection of papillary thyroid cancer (PTC). Nonetheless, some reports support a real increase in incidence. This study aimed to perform a systematic review to evaluate the changing trends in TC incidence and summarize potential risk factors predisposing to this trend. METHODS: Literature published in the English language between 1980 and August 2014 was searched via PubMed (MEDLINE) and OvidSP (EMBASE). Original studies on changes in TC incidence in defined geographic areas that described clear methods of case selection and population estimates were included. Data on incidence rates and risk factors were collected. RESULTS: Of 4719 manuscripts, 60 studies were included, of which 31 were from Europe, 13 from North America, and the rest from Asia (n = 9), Oceania (n = 4), and South America (n = 3). Fifty-three articles reported a significant increase in incidence (highest was a 10-fold increase in South Korea), six reported stable rates, and one noted a decrease. PTC was the commonest type reported to have increased in incidence (in 10 studies with relevant data). Follicular TC increased in incidence (in four studies), albeit at a lower rate compared with PTC. Data on risk factors were sparse; factors discussed included ionizing radiation, iodine deficiency, and supplementation. CONCLUSION: This systematic review strongly supports a widespread and persistent increase in TC incidence. Evidence for over-detection of PTC as the predominant influence includes increased numbers of smaller size tumors and improved or unchanged survival.
PubMed-ID: 27571228
http://dx.doi.org/10.1089/thy.2016.0100

Meta-analysis of radiofrequency ablation for treating the local recurrence of thyroid cancers.
J Endocrinol Invest, 39(8):909-16.
Q. Zhao, G. Tian, D. Kong and T. Jiang. 2016.
OBJECTIVES: Our aim was to evaluate the efficacy of ultrasound-guided radiofrequency ablation (RFA) for localized recurrent thyroid cancers. METHODS: We did a systematic review and meta-analysis of the scientific literature by searching the PubMed, Embase, Web of Science,Scopus and the Cochrane Library up to November 26, 2015. We assessed the pooled standard mean difference (SMD) of nodule volume, largest diameter and serum thyroglobulin (Tg) level by comparing pre-RFA with post-RFA using fixed or random-effects model. The Newcastle-Ottawa Scale was used to evaluate the methodological quality of the included studies, risk of bias in the selective populations, comparability of groups and exposure. RESULTS: We finally identified nine articles including 189 patients (male: 54 and female: 135) with 255 tumor lesions, who underwent ultrasound (US)-guided RFA beyond the mean 6 months of follow-up. The results showed that tumor volume (SWD: 0.77, 95 % CI: 0.57-0.97, I (2) = 25.9 %, p = 0.231), largest diameter (SWD: 1.56, 95 % CI: 0.94-2.17, I (2) = 82.6 %, p < 0.001) and Tg level (SWD: 0.52, 95 % CI: 0.30-0.73, I (2) = 0 %, p = 0.493) were decreased and no significant publication bias was detectable. CONCLUSIONS: The pooled data indicated that the prognosis improved for patients with localized recurrent thyroid cancers and RFA is a promising treatment for these patients with infeasible surgery.
PubMed-ID: 26980591
http://dx.doi.org/10.1007/s40618-016-0450-8

Randomized controlled trials

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

Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer.
J Clin Endocrinol Metab, 101(11):4103-9.
B. Robinson, M. Schlumberger, L. J. Wirth, C. E. Dutcus, J. Song, M. H. Taylor, S. B. Kim, M. K. Krzyzanowska, J. Capdevila, S. I. Sherman and M. Tahara. 2016.
CONTEXT: Lenvatinib improved the progression-free survival (PFS) and overall response rate of patients with radioiodine-refractory differentiated thyroid cancer vs placebo in the Phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT). OBJECTIVE: The objective of the study was to characterize tumor size changes with lenvatinib treatment. DESIGN: SELECT was a phase 3, randomized, double-blind, multicenter study. SETTING: In this clinical trial, tumor assessments of lenvatinib (n = 261) and placebo-treated (n = 131) patients were performed by independent radiological review per Response Evaluation Criteria in Solid Tumors version, 1.1 at 8-week intervals. PATIENTS: Patients with complete or partial response were defined as responders to lenvatinib (n = 169). Of the 92 nonresponders, 76 had at least one postbaseline tumor assessment and were included in this analysis. INTERVENTIONS: Lenvatinib (24 mg once daily) or placebo in 28-day cycles until unacceptable toxicity, disease progression, or death. MAIN OUTCOME MEASURES: This was an exploratory analysis of key end points from SELECT, including PFS, overall response rate, and tumor reduction. RESULTS: The median maximum percentage change in tumor size was -42.9% for patients receiving lenvatinib (responders, -51.9%; nonresponders, -20.2%). Tumor size reduction was most pronounced at first assessment (median, -24.7% at 8 wk after randomization); thereafter, the rate of change was slower but continuous (-1.3% per mo). In a multivariate model, percentage change in tumor size at the first assessment was a marginally significant positive predictor for PFS (P = .06). CONCLUSIONS: The change in tumor size conferred by lenvatinib was characterized by two phases: an initial, rapid decline, followed by slower, continuous shrinkage.
PubMed-ID: 27548104
http://dx.doi.org/10.1210/jc.2015-3989

Consensus Statements/Guidelines

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis.
Thyroid, 26(10):1343-421.
D. S. Ross, H. B. Burch, D. S. Cooper, M. C. Greenlee, P. Laurberg, A. L. Maia, S. A. Rivkees, M. Samuels, J. A. Sosa, M. N. Stan and M. A. Walter. 2016.
BACKGROUND: Thyrotoxicosis has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference. This document describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspecialty physicians and others providing care for patients with this condition. METHODS: The American Thyroid Association (ATA) previously cosponsored guidelines for the management of thyrotoxicosis that were published in 2011. Considerable new literature has been published since then, and the ATA felt updated evidence-based guidelines were needed. The association assembled a task force of expert clinicians who authored this report. They examined relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to update the 2011 text and recommendations. The strength of the recommendations and the quality of evidence supporting them were rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group. RESULTS: Clinical topics addressed include the initial evaluation and management of thyrotoxicosis; management of Graves' hyperthyroidism using radioactive iodine, antithyroid drugs, or surgery; management of toxic multinodular goiter or toxic adenoma using radioactive iodine or surgery; Graves' disease in children, adolescents, or pregnant patients; subclinical hyperthyroidism; hyperthyroidism in patients with Graves' orbitopathy; and management of other miscellaneous causes of thyrotoxicosis. New paradigms since publication of the 2011 guidelines are presented for the evaluation of the etiology of thyrotoxicosis, the management of Graves' hyperthyroidism with antithyroid drugs, the management of pregnant hyperthyroid patients, and the preparation of patients for thyroid surgery. The sections on less common causes of thyrotoxicosis have been expanded. CONCLUSIONS: One hundred twenty-four evidence-based recommendations were developed to aid in the care of patients with thyrotoxicosis and to share what the task force believes is current, rational, and optimal medical practice.
PubMed-ID: 27521067
http://dx.doi.org/10.1089/thy.2016.0229

Laryngeal examination in thyroid and parathyroid surgery: An American Head and Neck Society consensus statement: AHNS Consensus Statement.
Head Neck, 38(6):811-9.
C. F. Sinclair, J. M. Bumpous, B. R. Haugen, A. Chala, D. Meltzer, B. S. Miller, N. S. Tolley, J. J. Shin, G. Woodson and G. W. Randolph. 2016.
This American Head and Neck Society (AHNS) consensus statement discusses the techniques of laryngeal examination for patients undergoing thyroidectomy and parathyroidectomy. It is intended to help guide all clinicians who diagnose or manage adult patients with thyroid disease for whom surgery is indicated, contemplated, or has been performed. This consensus statement concludes that flexible transnasal laryngoscopy is the optimal laryngeal examination technique, with other techniques including laryngeal ultrasound and stroboscopy being useful in selected scenarios. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 811-819, 2016.
PubMed-ID: 26970554
http://dx.doi.org/10.1002/hed.24409

Other Articles

Tuberculosis cervical lymphadenopathy mimics lateral neck metastasis from papillary thyroid carcinoma.
ANZ J Surg, 86(6):495-8.
S. M. Kim, H. H. Jun, H. J. Chang, K. W. Chun, B. W. Kim, Y. S. Lee, H. S. Chang and C. S. Park. 2016.
BACKGROUND: Tuberculosis (TB) lymphadenitis is a frequent cause of lymphadenopathy in areas in which TB is endemic. Cervical lymphadenopathy in TB can mimic lateral neck metastasis (LNM) from papillary thyroid carcinoma (PTC). This study evaluated the clinicopathological features of patients with PTC and TB lateral neck

lymphadenopathy. METHODS: Of the 9098 thyroid cancer patients who underwent thyroid cancer surgery at the Thyroid Cancer Center of Gangnam Severance Hospital between January 2009 and April 2013, 28 had PTC and showed TB lymphadenopathy of the lateral neck node. The clinicopathological features of these 28 patients were evaluated. RESULTS: Preoperatively, all 28 patients were diagnosed with PTC and showed cervical lymphadenopathy. All had radiological characteristics suspicious of metastasis in lateral neck nodes. Based upon the results from intraoperative frozen sections, lymph node dissection (LND) was not performed on 19 patients. Seven of eight patients who underwent LND had metastasis combined with tuberculous lymphadenopathy, with the remaining patient negative for LNM. CONCLUSIONS: Intraoperative sampling and frozen sectioning of lymph nodes suspicious of metastasis can help avoid unnecessary LND for tuberculous lymphadenopathy.
PubMed-ID: 24981703
http://dx.doi.org/10.1111/ans.12727

Ultrasound-guided percutaneous laser ablation in treating symptomatic solid benign thyroid nodules: Our experience in 45 patients.
Head Neck, 38(5):677-82.
G. Achille, S. Zizzi, E. Di Stasio, A. Grammatica and L. Grammatica. 2016.
BACKGROUND: Laser ablation may be useful in debulking of benign thyroid nodules. METHODS: In order to retrospectively evaluate the effectiveness and safety of laser ablation, 45 patients with benign solid thyroid nodules, with a fluid component </=20%, were included in our series between October 2009 and January 2011. All reported pressure and/or cosmetic complaints. Nd:YAG laser at 1064 nm was used, with a fix-power (3W), changing the application time. All patients were evaluated at baseline, 6 months, and 12 months and any complications were recorded. RESULTS: Mean nodule volume reduction decreased from 24.2 mL +/- 19.4 to 4.5 +/- 5.2 at 12 months ($p < .001$). Mean nodule volume reduction was 84% +/- 13. Cosmetic signs were completely resolved in 87%, reduced in 9%, unchanged in 2%, and pressure symptoms were resolved in 88%. One patient experienced transient dysphonia. CONCLUSION: Ultrasound-guided laser ablation is an effective tool for treatment of symptomatic benign thyroid nodules in patients not eligible for surgery.
PubMed-ID: 25522303
http://dx.doi.org/10.1002/hed.23957

Thyroid thyrothymic extension: An anatomic study in a surgical series.
Head Neck, 38(5):732-5.
P. Sheahan and F. O'Duffy. 2016.
BACKGROUND: The thyrothymic extension (TTE) is a variable projection from the inferior thyroid pole along the course of the thyrothymic ligament. Awareness of the TTE is critical to ensure complete total thyroidectomy. However, there is little mention of the TTE in the literature. The purpose of the present study was to investigate the frequency of the TTE in our surgical series. METHODS: We conducted a prospective cohort study of 284 thyroid and parathyroid surgeries performed by a single surgeon. RESULTS: A TTE was present in 138 of 414 evaluable thyroid lobes (33.3%), with no predilection for left or right. The TTE was bilateral in 57% of cases. In 5 cases, there was significant nodular enlargement of the TTE. The inferior parathyroid gland was closely associated with 8% of TTEs. CONCLUSION: The TTE is a commonly encountered projection from the inferior thyroid pole. Awareness of the TTE is important to ensure complete total thyroidectomy.
PubMed-ID: 25524573
http://dx.doi.org/10.1002/hed.23954

Carbon nanoparticle-guided central lymph node dissection in clinically node-negative patients with papillary thyroid carcinoma.
Head Neck, 38(6):840-5.
Y. Zhu, X. Chen, H. Zhang, L. Chen, S. Zhou, K. Wu, Z. Wang, L. Kong and H. Zhuang. 2016.
BACKGROUND: Distinguishing the involved lymph nodes from other tissues during surgery is critical for lymph node dissection. The purpose of this study was to assess the feasibility by using carbon nanoparticles as guidance for lymph node dissection in patients with papillary thyroid carcinoma (PTC). METHODS: Eighty-one patients were injected with carbon nanoparticles (carbon nanoparticle group), whereas the other 81 patients were not (control group). Routine pathological examination was performed. RESULTS: The lymph node dissection and metastatic lymph node dissection rates of the carbon nanoparticle group were significantly higher than that of the control group. In the carbon nanoparticle group, the number of mistakenly dissected parathyroid gland, the case number of postoperative hypocalcemia, the case number of postoperative hypoparathyroidism, and the recovery time from hypocalcemia were 4, 6, 8, and 2.33 +/- 0.58 weeks, respectively, significantly less than 14, 17, 20, 3, and 3.8 +/- 0.92 weeks in the control group ($p < .05$). CONCLUSION: Carbon nanoparticles

can be applied to more accurately guide the dissection of lymph nodes during thyroidectomy in patients with PTC. (c) 2015 Wiley Periodicals, Inc. Head Neck 38: 840-845, 2016.
PubMed-ID: 25832013
http://dx.doi.org/10.1002/hed.24060

Treatment options in the young patient with Graves' disease.
Clin Endocrinol (Oxf), 85(2):161-4.
T. Cheetham and R. Bliss. 2016.
The treatment options in the young patient with Graves' disease are the same as in adults, namely antithyroid drug (ATD), surgery (partial or total thyroidectomy) and radioiodine. However, the emphasis and expectation is different in the young person, reflecting a range of considerations including age, pubertal status, disease natural history, likely impact of ATD on disease course and the implications of radiation exposure. New therapeutic strategies that could increase the likelihood of long-term remission are being explored.
PubMed-ID: 26252256
http://dx.doi.org/10.1111/cen.12871

Benign thyroid nodules with RAS mutation grow faster.
Clin Endocrinol (Oxf), 84(5):736-40.
A. Puzziello, A. Guerra, A. Murino, G. Izzo, M. Carrano, E. Angrisani, P. Zeppa, V. Marotta, A. Faggiano and M. Vitale. 2016.
CONTEXT: The management of a benign thyroid nodule includes follow-up until its size requires a surgical or alternative treatment. To date, it is difficult or impossible to predict the size changes of a benign nodule in a given patient because no specific growth parameters exist. RAS mutations have been described in thyroid adenomas and hyperplastic benign nodules. OBJECTIVE: The aim of this study was to establish whether the volume changes of benign nodules are associated with the presence of RAS mutation. PATIENTS AND METHODS: Genomic DNA obtained by fine-needle aspiration of 78 thyroid nodules with benign cytology was analysed by pyrosequencing for the presence of NRAS(61) and KRAS(13) mutations. Ultrasonographic features were obtained. The volume of nodules at baseline and their changes after a mean follow-up of 25 months were evaluated according to the presence of RAS mutation. RESULTS: A RAS mutation was found in 24 thyroid aspirates (30.8%, 8 NRAS(61) and 16 KRAS(13)). RAS mutation was not associated with ultrasonographic features, but was significantly associated with a larger size at baseline (P = 0.017). After a 25-month mean follow-up, RAS mutation-positive nodules displayed faster growth (RAS mutation-positive vs RAS mutation-negative % annual growth 27.6% +/-32.2% vs 1.0% +/-17.0%, P < 0.001). CONCLUSIONS: Benign thyroid nodules bearing RAS mutation grow more rapidly than those with wild-type RAS. Searching for RAS mutations in thyroid nodules with benign cytology might be useful to the clinician in choosing a more appropriate and timely surgical management.
PubMed-ID: 26260959
http://dx.doi.org/10.1111/cen.12875

Concomitant high expression of BRAFV600E, P-cadherin and cadherin 6 is associated with High TNM stage and lymph node metastasis in conventional papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 84(5):748-55.
L. Zhao, R. Jiang, M. Xu, P. Zhu, X. M. Mo, N. Wang, G. G. Chen and Z. M. Liu. 2016.
CONTEXT AND OBJECTIVE: BRAFV600E mutation is the most common activating mutation associated with aggressive behaviours in human tumours including conventional papillary thyroid carcinoma (cPTC). P-cadherin and cadherin 6 have been shown to be mesenchymal-associated cadherins and promote cancer cell invasion and metastasis. The purpose of this study was to examine BRAFV600E, P-cadherin and cadherin 6 expressions in cPTC and to assess the association of their expression with clinicopathological indicators. METHODS: BRAFV600E, P-cadherin and cadherin 6 protein expressions in 80 cPTCs, 61 nodular hyperplasia and 76 normal thyroid tissues were examined by immunohistochemistry. The correlation of their protein expression with clinicopathological indicators of cPTC was statistically analysed. RESULTS: Protein expression of BRAFV600E, P-cadherin and cadherin 6 was upregulated in cPTC. High protein expression of BRAFV600E, P-cadherin and cadherin 6 was significantly correlated with high TNM stage and lymph node metastasis (LNM) (P < 0.001). Furthermore, BRAFV600E, P-cadherin and cadherin 6 protein expressions were correlated with one another. BRAFV600E high expression combined with both P-cadherin and cadherin-6 high expressions had stronger correlation with high TNM stage and LNM when compared with BRAFV600E high expression combined with either P-cadherin or cadherin-6 high expression (P = 0.042, 0.017 for TNM stage and P = 0.003, 0.006 for LNM, respectively) and only BRAFV600E high expression (P < 0.001 for both TNM stage and LNM). CONCLUSIONS: Concomitant high expression of BRAFV600E, P-cadherin and cadherin 6 is strongly associated with high TNM

stage and LNM in cPTC.
PubMed-ID: 26285159
http://dx.doi.org/10.1111/cen.12878

Minimally invasive video-assisted thyroidectomy: reflections after more than 2400 cases performed.
Surg Endosc, 30(6):2489-95.
P. Miccoli, M. Biricotti, V. Matteucci, C. E. Ambrosini, J. Wu and G. Materazzi. 2016.
BACKGROUND: The minimally invasive video-assisted approach was developed for primary hyperparathyroidism in 1997 and the year after for thyroid disease. Since then, the technique has been adopted worldwide, and indications moved from the initial benign disease to low-risk and intermediate-risk carcinoma, demonstrating a level of oncologic radicality comparable to the conventional open approach when inclusion criteria are strictly respected. METHODS: Between 1998 and 2014, 2412 minimally invasive video-assisted thyroidectomies (MIVAT) were performed in our department. The indication for surgery in 825 patients (34.3 %) was a malignant tumor, in particular, a papillary carcinoma in 800 patients. Among them, 528 patients operated on between 2000 and 2009 had a mean complete follow-up of 7.5 (standard deviation, 2.3) years. RESULTS: A total thyroidectomy was performed in 1788 patients (74.1 %) and a hemithyroidectomy in 564 (23.4 %). Also performed was central compartment lymphadenectomy in 31 patients (1.3 %) and parathyroidectomy for the presence of a solitary parathyroid adenoma in 29 (1.2 %). Mean duration of the procedure was 41 (standard deviation, 14) minutes. After a mean follow-up of 7. 5 years, 528 patients who underwent MIVAT for low-risk or intermediate-risk papillary carcinoma presented a cure rate of 85 % (undetectable thyroglobulin), comparable with the 80 % rate reported in patients who had undergone open thyroidectomy during the same period. CONCLUSIONS: After a long experience and a considerable number of procedures performed in a single center, MIVAT is confirmed as a safe operation, with a complication rate comparable with open thyroidectomy. MIVAT offers a cure rate for the treatment of low-risk and intermediate-risk malignancies that is comparable with an open procedure when inclusion criteria are strictly respected.
PubMed-ID: 26335076
http://dx.doi.org/10.1007/s00464-015-4503-4

Post-thyroidectomy complications. The role of the device: bipolar vs ultrasonic device: Collection of data from 1,846 consecutive patients undergoing thyroidectomy.
Am J Surg, 212(1):116-21.
M. De Palma, L. Rosato, F. Zingone, G. Orlando, A. Antonino, M. Vitale and A. Puzziello. 2016.
BACKGROUND: Specific complications after thyroid surgery, such as recurrent laryngeal nerve injury (RLN) or hypoparathyroidism, are feared because they may give rise to a lifelong disability for the patient. The aim of this study was to evaluate the possible association between the types of device used (bipolar vs ultrasound-based harmonic scalpel defined Harmonic Focus) and major postoperative complications. METHODS: During a 1-year period, between October 2010 and October 2011, Italian Endocrine Surgery Units affiliated with the Italian Endocrine Surgery Units Association collected data on all consecutive patients older than 18 years who had undergone primary total thyroidectomy, near total thyroidectomy, and completion thyroidectomy. The data were included in a dataset, listing demographic variables, details on the surgical procedure, and 2 major complications of the thyroid surgery: postoperative RLN palsy/hypomobility and hypocalcemia. RESULTS: Our population comprised 1,846 subjects (78.6% women, median age 52 years). Six hundred four (32.7%) subjects underwent thyroidectomy by bipolar forceps and 1,242 (67.3%) by ultrasonic device. The risk of hypocalcemia in subjects undergoing thyroidectomy by ultrasonic device was similar to those undergoing thyroidectomy by bipolar after adjusting for sex, type of thyroidectomy, and central lymphadenectomy (odds ratio .94, 95% confidence interval .76 to 1.17). Subjects who underwent thyroidectomy by ultrasonic device had a lower risk of RLN paralysis compared with those undergoing thyroidectomy by bipolar forceps also after adjusting for central lymphadenectomy (odds ratio .39, 95% confidence interval .2 to .7). CONCLUSION: This multicenter study acknowledges the value of the ultrasonic device as a protective factor only for RLN palsy, confirming nodal dissection as a risk factor for postoperative hypocalcemia and vocal folds disorders.
PubMed-ID: 26349585
http://dx.doi.org/10.1016/j.amjsurg.2015.05.024

Assessing perioperative body weight changes in patients thyroidectomized for a benign nontoxic nodular goitre.
Clin Endocrinol (Oxf), 84(6):882-8.
B. H. Lang, H. Zhi and B. J. Cowling. 2016.
BACKGROUND: Following thyroidectomy, patients often complain of weight gain. Our study aimed to evaluate the extent of weight change in patients thyroidectomized for a nontoxic benign goitre after adjusting for patient

demographics and pre-operative weight changes. METHODS: Three different patient groups were studied. The first comprised 898 patients who underwent thyroidectomy for benign nontoxic nodular goitre (group I). The second comprised 179 patients who had benign nontoxic goitre but did not undergo thyroidectomy (group II), and the third comprised 80 patients who underwent a simple excision of a parathyroid adenoma (group III). All patients were weighed 12 months preceding baseline, at baseline and 6 months after baseline. RESULTS: Baseline characteristics were comparable between groups. Patients in Group I who gained the least weight in the year leading to surgery gained the most weight 12 months after surgery (P = 0.030). After adjusting for demographics and pre-operative weight changes, Group I gained significantly more weight at post 6 and 12 months (0.71 (95% CI=0.46-0.95) kg and 1.21 (95% CI = 0.96-1.46) kg, respectively). Weight gain at post 12 months appeared similar between hemithyroidectomy and total thyroidectomy (1.32 vs 1.16 kg, P = 0.197). Younger age (ss coefficient -0.100, 95% CI = -0.030 to 0.003, P = 0.015) and higher baseline thyroid stimulating hormone (ss coefficient -0.315, 95% CI = -1.468 to 0.134, P = 0.020) were significant factors for weight gain at post 12 months. CONCLUSIONS: Compared to nonthyroidectomized patients, thyroidectomized patients experienced significant weight increases at post 6 and 12 months. The extent of thyroidectomy did not affect the extent of weight gain. Younger age and higher baseline thyroid stimulating hormone were significant factors of weight gain at post 12 months.
PubMed-ID: 26384591
http://dx.doi.org/10.1111/cen.12945

Innervation of the cricothyroid muscle by extralaryngeal branches of the recurrent laryngeal nerve.
Laryngoscope, 126(5):1157-62.
A. Miyauchi, H. Masuoka, A. Nakayama and T. Higashiyama. 2016.
OBJECTIVES/HYPOTHESIS: A major concern in thyroid surgery is possible changes in the patient's voice due to dysfunction of the laryngeal muscles. The classical understanding of the anatomy is that the cricothyroid muscle (CTM) is innervated solely by the external branch of the superior laryngeal nerve (EBSLN), and the endolaryngeal muscles are covered only by the recurrent laryngeal nerve (RLN). Meticulous anatomical studies found communication between these nerves. Recent neurophysiological studies revealed cross-innervations among these nerve-muscle sets. Here, we report innervation of the CTM by extralaryngeal branches of the RLN. STUDY DESIGN: Clinical observation during thyroid surgery at a hospital center for thyroid diseases. METHODS: During thyroid cancer surgeries, we encountered four adult Japanese patients who had an extralaryngeal branch of the RLN, the electrical stimulation of which showed contraction of the CTM. The EBSLN and RLN were electrically stimulated. Responses were evaluated by visual observation of contraction of the CTM and palpable laryngeal twitch of the endolaryngeal muscles. Electromyographic studies were also performed in two patients. RESULTS: Five of the seven RLNs examined showed contraction of the CTM on stimulation. Four of these five RLNs had an extralaryngeal branch that showed contraction of the CTM on stimulation. Stimulation of the RLN proximal to the branch yielded contraction of the CTM and laryngeal twitch, whereas stimulation of the RLN distal to the branch yielded only laryngeal twitch. CONCLUSIONS: Extralaryngeal branches of the RLN innervated the CTM in four patients. This phenomenon might influence voice changes following thyroid surgery. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:1157-1162, 2016.
PubMed-ID: 26509739
http://dx.doi.org/10.1002/lary.25691

Comparison of conventional thyroidectomy and endoscopic thyroidectomy via axillo-bilateral breast approach in papillary thyroid carcinoma patients.
Surg Endosc, 30(8):3419-25.
S. K. Kim, S. Y. Kang, H. J. Youn and S. H. Jung. 2016.
BACKGROUND: Endoscopic thyroidectomy has been applied to solve the cosmetic problems that resulted from conventional thyroidectomy. The aim of this study was to evaluate and compare the surgical outcomes of conventional and endoscopic thyroidectomies via axillo-bilateral-breast approach (ABBA) in patients with papillary thyroid carcinoma (PTC). METHODS: Between May 2007 and February 2011, 1003 patients with PTC underwent thyroidectomies. The eight hundred and thirty patients underwent conventional thyroidectomy and 173 patients underwent endoscopic thyroidectomy via ABBA. Clinicopathologic characteristics, complications, and surgical completeness were analyzed. RESULTS: The mean age was 49.53 years who received a conventional thyroidectomy and 38.90 years in endoscopic thyroidectomy (P < 0.0001). The conventional thyroidectomy group underwent more extensive surgery than the endoscopic thyroidectomy group but the operation time was longer in the endoscopic thyroidectomy group (P < 0.0001). The mean hospitalization length was 6.98 days following open thyroidectomy and 6.40 days after endoscopic thyroidectomy (P = 0.003). The tumor size was larger in the conventional thyroidectomy group than the endoscopic thyroidectomy group and a lesser number of lymph nodes were retrieved in the endoscopic thyroidectomy group compared to the

conventional thyroidectomy group (P < 0.0001). The postoperative complications and thyroglobulin levels in both groups were not significantly different. CONCLUSION: These results suggest that conventional and endoscopic thyroidectomy via ABBA has similar surgical outcomes in PTC patients. Therefore, endoscopic thyroidectomy via ABBA may be an appropriate surgical alternative to conventional thyroidectomy for treating PTC in selected patients.
PubMed-ID: 26511120
http://dx.doi.org/10.1007/s00464-015-4624-9

Long-term oncologic outcome of robotic versus open total thyroidectomy in PTC: a case-matched retrospective study.
Surg Endosc, 30(8):3474-9.
S. G. Lee, J. Lee, M. J. Kim, J. B. Choi, T. H. Kim, E. J. Ban, C. R. Lee, S. W. Kang, J. J. Jeong, K. H. Nam, Y. S. Jo and W. Y. Chung. 2016.
PURPOSE: The role of the robot in thyroid surgery remains uncertain, and it is unclear whether robotic total thyroidectomy (R-TT) can be justified as a standard treatment for patients with thyroid cancer. This study compared the long-term operative results and oncologic outcomes of R-TT and conventional open TT (O-TT) after propensity score matching of the cohorts. METHODS: This study retrospectively evaluated patients with papillary thyroid cancer (PTC) who underwent TT with central compartment node dissection (CCND) by a single surgeon in tertiary medical center. Of the 833 patients, 94 (11.3 %) were lost to follow-up. 245 (33.2 %) underwent R-TT, and 494 (66.8 %) underwent O-TT. The mean follow-up duration was 74 (range 61-91) months. Propensity score matching in age, gender, tumor size, extrathyroidal invasion, multiplicity, bilaterality, and TNM stage identified 206 pairs of patients. The long-term oncologic outcomes were assessed in the R-TT and O-TT groups before and after adjustment for baseline covariates. RESULTS: After adjustment for baseline covariates, serum thyroglobulin (Tg) (p = 0.746) and anti-thyroglobulin antibody (TgAb) (p = 0.394) concentrations were similar in the two groups 5 years after surgery. Nine patients experienced locoregional recurrence, six in the O-TT and three in the R-TT group, with all recurrences in regional LNs. Disease-free survival (DFS) was similar in the R-TT and O-TT groups before matching (p = 0.890) and after adjustment for baseline covariates (p = 0.882). CONCLUSION: This represents the first report of 5-year surgical outcomes in patients who underwent R-TT for thyroid cancer. Long-term oncologic quality was similar after R-TT and O-TT.
PubMed-ID: 26514137
http://dx.doi.org/10.1007/s00464-015-4632-9

Symptoms of thyrotoxicosis, bone metabolism and occult atrial fibrillation in older women with mild endogenous subclinical hyperthyroidism.
Clin Endocrinol (Oxf), 85(1):132-6.
P. W. Rosario, M. Carvalho and M. R. Calsolari. 2016.
OBJECTIVE: The objective of this study was to evaluate symptoms of thyrotoxicosis, bone turnover, bone mineral density (BMD) and occult atrial fibrillation (AF) in women >/=65 years with mild endogenous subclinical hyperthyroidism (SCH). DESIGN: Cross-sectional and case-control study. PATIENTS: Signs and symptoms of thyrotoxicosis, serum carboxyterminal telopeptide (CTx) and procollagen type I N-terminal propeptide (PINP), BMD, resting electrocardiogram (ECG) and 72-h ECG monitoring were evaluated in 180 women >/=65 years, including 90 with mild SCH (TSH between 0.1 and 0.4 mIU/l) and 90 euthyroid controls matched for age and body mass index. RESULTS: Symptom Rating Scale scores did not differ between patients and controls. None of the patients with SCH scored 20 points, a score compatible with clinical thyrotoxicosis. Eighty patients with SCH (89%) obtained seven or fewer points, a score compatible with euthyroidism. No difference in serum CTx or PINP concentrations was observed between patients and controls. There was also no correlation between these markers and TSH, free T4 or total T3 levels. Finally, no difference in femoral neck or lumbar spine BMD was observed between patients with SCH and controls. Three patients with SCH (3.3%) and two euthyroid women (2.2%) had known AF or AF in the resting ECG. ECG monitoring for 72 h revealed episodes of occult AF in 1/87 patients with SCH and in 1/88 euthyroid women (1.1%). CONCLUSIONS: Mild endogenous SCH (TSH between 0.1 and 0.4 mIU/l) was not associated with symptoms of thyrotoxicosis, altered bone metabolism or a higher prevalence of occult AF in women >/=65 years.
PubMed-ID: 26587960
http://dx.doi.org/10.1111/cen.12979

124I PET/CT to Predict the Outcome of Blind 131I Treatment in Patients with Biochemical Recurrence of Differentiated Thyroid Cancer: Results of a Multicenter Diagnostic Cohort Study (THYROPET).
J Nucl Med, 57(5):701-7.
J. W. Kist, B. de Keizer, M. van der Vlies, A. H. Brouwers, D. A. Huysmans, F. M. van der Zant, R. Hermsen, M.

P. Stokkel, O. S. Hoekstra and W. V. Vogel. 2016.
Patients with suspected recurrence from differentiated thyroid carcinoma, based on an increased thyroglobulin (Tg) level and negative neck ultrasound (US), pose a clinical dilemma. Because standard imaging has a low yield identifying potential recurrence, blind (131)I treatment is often applied. However, a tumor-negative (131)I whole-body scintigraphy (WBS) prevails in 38%-50% of patients. We performed a prospective multicenter observational cohort study to test the hypothesis that (124)I PET/CT can identify the patients with a tumor-negative posttherapy (131)I WBS. METHODS: Our study was designed to include 100 patients with detectable Tg and a negative neck US, who were planned for blind (131)I therapy. All patients underwent (124)I PET/CT after administration of recombinant human thyroid-stimulating hormone. Subsequently, after 4-6 wk of thyroid hormone withdrawal patients were treated with 5.5-7.4 GBq of (131)I, followed by WBS a week later. The primary endpoint was the number of (131)I therapies that could have been omitted using the predicted outcome of the (124)I PET/CT, operationalized as the concordance of tumor detection by (124)I PET/CT, using post-(131)I therapy WBS as the reference test. The study would be terminated if 3 patients had a negative (124)I PET/CT and a positive posttherapy (131)I scan. RESULTS: After inclusion of 17 patients, we terminated the study preliminarily because the stopping rule had been met. Median Tg level at (131)I therapy was 28 mug/L (interquartile range, 129). Eight posttherapy WBS were negative (47%), all of which were correctly predicted by negative (124)I PET/CT. Nine posttherapy WBS showed iodine-avid tumor, of which 4 also had positive (124)I PET/CT findings. Sensitivity, specificity, negative predictive value, and positive predictive value of (124)I PET/CT were 44% (confidence interval [CI], 14%-79%), 100% (CI, 63%-100%), 62% (CI, 32%-86%), and 100% (CI, 40%-100%), respectively. Implementation of (124)I PET in this setting would have led to 47% (8/17) less futile (131)I treatments, but 29% of patients (5/17) would have been denied potentially effective therapy. CONCLUSION: In patients with biochemical evidence of recurrent differentiated thyroid carcinoma and a tumor-negative neck US, the high false-negative rate of (124)I PET/CT after recombinant human thyroid-stimulating hormone (124)I PET/CT as implemented in this study precludes its use as a scouting procedure to prevent futile blind (131)I therapy.
PubMed-ID: 26609180
http://dx.doi.org/10.2967/jnumed.115.168138

Microscopic Positive Tumor Margin Does Not Increase the Risk of Recurrence in Patients with T1-T2 Well-Differentiated Thyroid Cancer.
Ann Surg Oncol, 23(5):1446-51.
W. P. Kluijfhout, J. D. Pasternak, J. S. Kwon, J. Lim, W. T. Shen, J. E. Gosnell, E. Khanafshar, Q. Y. Duh and I. Suh. 2016.
BACKGROUND: Incomplete surgical resection with gross positive tumor margin increases the risk of recurrence in patients with well-differentiated thyroid cancer (WDTC); however, it is not clear whether a microscopic positive margin found only on final pathology has similar implications on patient outcomes. METHODS: We conducted a single-institution retrospective review of all patients undergoing total thyroidectomy for T1-T2 WDTC (January 2000-January 2010). Factors that may influence the risk of locoregional recurrence or distant metastasis were evaluated by univariate and multivariate analysis. RESULTS: Of 1000 consecutive patients undergoing surgical resection for WDTC, 684 T1-T2 cancers were included. Mean age was 46 years and 81 % were women. Of this total cohort, 78 (11 %) patients had microscopic positive margins. Radioactive iodine (RAI) was administered in 47/78 (60 %) patients with positive margins versus 312/606 (51 %) patients without positive margins. After a mean follow-up of 46 months, 53 (8 %) patients developed recurrent disease (1 local and 52 nodal). On multivariate analysis, nodal metastases (N1, odds ratio [OR] 7.7) and contralateral multifocality (OR 3.7) were independent risk factors for recurrent disease. A microscopic positive margin was not a risk factor for recurrence. CONCLUSIONS: A microscopic positive margin found only on final pathological analysis does not increase the risk of recurrence in T1-T2 WDTC. Clinicians should interpret such pathology findings accordingly when considering further surveillance and treatment decisions such as the use of RAI ablation.
PubMed-ID: 26628431
http://dx.doi.org/10.1245/s10434-015-4998-x

An Evaluation of Postoperative Complications and Cost After Short-Stay Thyroid Operations.
Ann Surg Oncol, 23(5):1440-5.
S. Narayanan, D. Arumugam, S. Mennona, M. Wang, T. Davidov and S. Z. Trooskin. 2016.
BACKGROUND: Concern for postoperative complications causing airway compromise has limited widespread acceptance of ambulatory thyroid surgery. We evaluated differences in outcomes and hospital costs in those monitored for a short stay of 6 h (SS), inpatient observation of 6-23 h (IO), or inpatient admission of >23 h (IA). METHODS: We retrospectively reviewed all patients undergoing thyroidectomy from 2006 to 2012. The incidence of postoperative hemorrhage, nerve dysfunction, and hypocalcemia were evaluated, as well as cost

data comparing the SS and IO groups. RESULTS: Of 1447 thyroidectomies, 880 (60.8 %) were performed as SS, 401 (27.7 %) as IO, and 166 (11.5 %) as IA. Fewer patients in the SS group (59 %) underwent total thyroidectomy than IO (73 %) and IA (71 %; $p < 0.01$), and SS patients had smaller thyroid weights (27.9 g) compared with IO and IA (47.2 and 98.9 g, respectively; $p < 0.01$). Ten (0.69 %) patients developed hematomas requiring reoperation, five of the ten patients received antiplatelet or anticoagulant therapy perioperatively. Only one patient in the IA group bled within the 6- to 23-h period, and no patients with bleeding who were discharged at 6 h would have benefitted from 23-h observation. Twenty-four (1.66 %) recurrent laryngeal nerve injuries were identified, 16 with temporary neuropraxias. In addition, 24 (1.66 %) patients had symptomatic hypocalcemia, which was transient in 17 individuals. Financial data showed higher payments and lower costs associated with SS compared with IO. CONCLUSIONS: Selective SS thyroidectomy can be safe and cost effective, with few overall complications in patients undergoing more complex operations involving larger thyroids who were admitted to hospital.
PubMed-ID: 26628433
http://dx.doi.org/10.1245/s10434-015-5004-3

Prospective study of vocal fold function after loss of the neuromonitoring signal in thyroid surgery: The International Neural Monitoring Study Group's POLT study.
Laryngoscope, 126(5):1260-6.
R. Schneider, G. Randolph, G. Dionigi, M. Barczynski, F. Y. Chiang, F. Triponez, K. Vamvakidis, K. Brauckhoff, T. J. Musholt, M. Almquist, N. Innaro, A. Jimenez-Garcia, J. L. Kraimps, A. Miyauchi, B. Wojtczak, G. Donatini, D. Lombardi, U. Muller, L. Pezzullo, T. Ratia, S. Van Slycke, P. Nguyen Thanh, K. Lorenz, C. Sekulla, A. Machens and H. Dralle. 2016.
OBJECTIVES/HYPOTHESIS: Intraoperative neuromonitoring identifies recurrent laryngeal nerve (RLN) injury and gives prognostic information regarding postoperative glottic function. Loss of the neuromonitoring signal (LOS) signifies segmental type 1 or global type 2 RLN injury. This study aimed at identifying risk factors for RLN injury and determining vocal fold (VF) function initially and 6 months after definitive LOS. STUDY DESIGN: Prospective study encompassing 21 hospitals from 13 countries. METHODS: Included in this study were patients with persistent intraoperative LOS. RESULTS: At first postoperative laryngoscopy, early VF palsy was present in 94 of all 115 patients with LOS (81.7%): in 53 of 56 patients (94.6%) with type 1 injury and 41 of 59 patients (69.5%) with type 2 injury. In LOS type 1, women outnumbered men >5-fold. Traction produced LOS type 1 in 38 of 56 patients (67.9%) and LOS type 2 in 54 of 59 patients (91.5%). Course of the RLN posterior and/or anterior to the inferior thyroid artery, extralaryngeal branching, or tuberculum of Zuckerkandl did not increase VF palsy rates. Permanent VF palsy rates were also lower ($P = .661$) after LOS type 2 than after LOS type 1: 6.8% (four of 59 patients) versus 10.7% (six of 56 patients). Intraoperative administration of steroids did not diminish postoperative VF palsy rates. CONCLUSIONS: LOS type 1 entails more severe nerve damage than LOS type 2, affecting women disproportionately. Both LOS types, being primarily associated with traction injury, are unaffected by variant neck anatomy in expert hands and unresponsive to steroids. LEVEL OF EVIDENCE: 2b Laryngoscope, 126:1260-1266, 2016.
PubMed-ID: 26667156
http://dx.doi.org/10.1002/lary.25807

Upper neck papillary thyroid cancer (UPTC): A new proposed term for the composite of thyroglossal duct cyst-associated papillary thyroid cancer, pyramidal lobe papillary thyroid cancer, and Delphian node papillary thyroid cancer metastasis.
Laryngoscope, 126(7):1709-14.
M. Zizic, W. Faquin, A. E. Stephen, D. Kamani, R. Nehme, C. M. Slough and G. W. Randolph. 2016.
OBJECTIVES/HYPOTHESIS: Thyroglossal duct cyst (TGDC) is a common congenital anomaly, but TGDC carcinoma is rare. Thyroglossal duct cyst carcinoma management is controversial, especially that of the orthotopic thyroid gland. We aim to provide an insight into the pathologic basis of this management controversy through the review of 28 TGDC cancer cases, thus far the largest such series to our knowledge. STUDY DESIGN: Retrospective. METHODS: Twenty-eight cases recorded as TGDC cancer in the hospital database were reviewed; their initial clinical diagnosis from medical chart review (DX1) and final pathological review diagnosis (DX2) through pathology slides review by our pathologist (blinded to DX1) were compared. The thyroid gland management and pathology were evaluated. RESULTS: In the 28 TGDC carcinoma (hospital-recorded diagnosis) patients, DX1 and DX2 were respectively reported as 53% and 14% TGDC carcinoma, 11% and 29% as pyramidal lobe primary, and 4% and 25% as metastatic Delphian node. Thirty-two percent of cases were in the indeterminate category, in both DX1 and DX2, but included different patients. Thyroidectomy was performed in 54% of the cases, papillary thyroid cancer (PTC) was reported in 37% of these thyroid glands. Concurrent thyroid gland malignancy was reported in all Delphian node and pyramidal lobe PTC patients. CONCLUSION:

The diagnosis of TGDC cancer comprises a heterogeneous group that includes true TGDC cancer, pyramidal lobe primary, Delphian node metastasis, and indeterminate cases. We propose a new terminology of upper neck papillary thyroid carcinoma (UPTC) to denote this heterogeneous group and recommend a rational algorithm for management. Correct pathologic subcategory and thyroid ultrasonography are essential for optimal management of thyroid gland in UPTC cases. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:1709-1714, 2016.
PubMed-ID: 26691539
http://dx.doi.org/10.1002/lary.25824

Severity of Recurrent Laryngeal Nerve Injuries in Thyroid Surgery.
World J Surg, 40(6):1373-81.
G. Dionigi, C. W. Wu, H. Y. Kim, S. Rausei, L. Boni and F. Y. Chiang. 2016.
BACKGROUND: Few studies in the literature have reported recovery data for different types of recurrent laryngeal nerve injuries (RLNIs). This study is the first attempt to classify RLNIs and rank them by severity. METHODS: This prospective clinical study analyzed 281 RLNIs in which a true loss of signal was identified by intraoperative neuromonitoring (IONM), and vocal cord palsy (VCP) was confirmed by a postoperative laryngoscope. For each injury type, the prevalence of VCP, the time of VCP recovery, and physical changes on nerves were analyzed. Additionally, different RLNI types were experimentally induced in a porcine model to compare morphological change. RESULTS: The overall VCP rate in at-risk patients/nerves was 8.9/4.6 %, respectively. The distribution of RLNI types, in order of frequency, was traction (71 %), thermal (17 %), compression (4.2 %), clamping (3.4 %), ligature entrapment (1.6 %), suction (1.4 %), and nerve transection (1.4 %). Complete recovery from VCP was documented in 91 % of RLNIs. Recovery time was significantly faster in the traction group compared to the other groups ($p < 0.001$). The rates of temporary and permanent VCP were 98.6 and 1.4 % for traction lesion, 72 and 28 % for thermal injury, 100 and 0 % for compression injury, 50 and 50 % for clamping injury, 100 and 0 % for ligature entrapment, 100 and 0 % for suction injury, and 0 and 100 % for nerve transection, respectively. Physical changes were noted in 14 % of RLNIs in which 56 % of VCP was permanent. However, among the remaining 86 % IONM-detectable RLNIs without physical changes, only 1.2 % of VCP was permanent. A porcine model of traction lesion showed only distorted outer nerve structure, whereas the thermal lesion showed severe damage in the inner endoneurium. CONCLUSIONS: Different RNLIs induce different morphological alterations and have different recovery outcomes. Permanent VCP is rare in lesions that are visually undetectable but detectable by IONM. By enabling early detection of RLNI and prediction of outcome, IONM can help clinicians plan intra- and postoperative treatment.
PubMed-ID: 26817650
http://dx.doi.org/10.1007/s00268-016-3415-3

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

Treatment and survival of patients with insular thyroid carcinoma: 508 cases from the National Cancer Data Base.
Head Neck, 38(6):906-12.
T. A. Pezzi, V. C. Sandulache, C. M. Pezzi, A. E. Turkeltaub, L. Feng, M. E. Cabanillas, M. D. Williams and S. Y. Lai. 2016.
BACKGROUND: Insular thyroid carcinoma (ITC) is a rare but aggressive thyroid malignancy. METHODS: Patients with ITC (n = 508) reported to the National Cancer Data Base from 1998 to 2012 were evaluated for patient, tumor, and treatment characteristics and outcomes. RESULTS: Compared to papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), patients with ITC cancer were older, more often were men, had larger tumors, were more likely to present with distant metastasis, were less likely to have an R0 resection, more likely to receive external beam radiation and chemotherapy, and had significantly worse survival. Multivariate Cox regression identified age >65 years (hazard ratio [HR] = 1.53), presence of at least 1 comorbidity (HR = 1.80), positive lymph nodes (HR = 1.67), the presence of metastasis (HR = 2.73), positive margins (HR = 2.48), and radioactive iodine therapy (HR = 0.63) as significant and independent predictors of survival in ITC. CONCLUSION: Treatment recommendations should incorporate the use of radioactive iodine after complete surgical resection and clearance of involved nodal basins. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 906-912, 2016.

PubMed-ID: 26843481
http://dx.doi.org/10.1002/hed.24342

BRAF V600E detection in cytological thyroid samples: A key component of the decision tree for surgical treatment of papillary thyroid carcinoma.
Head Neck, 38(7):1017-21.
J. F. Collet, R. Lacave, S. Hugonin, V. Poulot, M. Tassart and A. Fajac. 2016.
BACKGROUND: Whether preoperative knowledge of the BRAF mutation status would help to determine the extent of surgery for thyroid nodules is still under investigation. METHODS: We developed a method to state the V600E mutation before surgery on fine-needle aspiration (FNA) stained smears checked to contain tumor cells. We evaluated the interest of the preoperative assessment of the mutation for surgical strategy of nodules, diagnosed as malignant, suspicious for malignancy or follicular neoplasms. RESULTS: The mutation was found in 81% (79 of 97) malignant, 59% (20 of 34) suspicious nodules, and in none of follicular neoplasms (n = 29). Overall, the mutation was detected in 82% of papillary carcinomas. The sensitivity, specificity, and positive and negative predictive values for the diagnosis of malignancy were 75%, 100%, 100%, and 46%, respectively. CONCLUSION: The preoperative knowledge of the V600E mutation status is fundamental to plan total thyroidectomy with certainty and should be part of the decision tree for the management of thyroid nodules. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 1017-1021, 2016.
PubMed-ID: 26854757
http://dx.doi.org/10.1002/hed.24393

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

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

Correlating thyroid cytology and histopathology: Implications for molecular testing.
Head Neck, 38(7):1104-6.
M. J. Reed, S. M. Sperry, M. P. Gailey, C. S. Jensen, R. A. Robinson, G. F. Funk and N. A. Pagedar. 2016.
BACKGROUND: A gene expression classifier (GEC) has been advocated in management of some indeterminate nodules without surgery. We assessed the potential negative predictive value (NPV) of the GEC at our academic center. METHODS: Retrospectively, all cytologically indeterminate fine-needle aspirates (FNAs) diagnosed by University of Iowa cytopathologists over a 3-year period were identified. Histopathologic findings were recorded. Using published sensitivity and specificity, NPVs were calculated. RESULTS: Of 178 nodules (17, 135, and 26 in classes III, IV, and V, respectively), 71 (40%) were malignant. Prevalence of malignancy was

41%, 29%, and 96% for classes III, IV, and V, respectively. Using sensitivities and specificities for the GEC, NPVs were 91% for the cohort: 88%, 92%, and 26% for classes III, IV, and V, respectively. CONCLUSION: Molecular testing should be associated with an NPV no lower than that from clinical criteria alone. With the prevalences reported, GEC use may result in more missed cancer diagnoses. (c) 2016 Wiley Periodicals, Inc. Head Neck 38: 1104-1106, 2016.
PubMed-ID: 26900030
http://dx.doi.org/10.1002/hed.24410

HABP2 Gene Mutations Do Not Cause Familial or Sporadic Non-Medullary Thyroid Cancer in a Highly Inbred Middle Eastern Population.
Thyroid, 26(5):667-71.
A. S. Alzahrani, A. K. Murugan, E. Qasem and H. Al-Hindi. 2016.
BACKGROUND: Familial non-medullary thyroid cancer (NMTC) occurs either as part of known hereditary syndromes or as a non-syndromic isolated hereditary tumor. Although the genes underlying the syndromic type of NMTC have been identified in most syndromes, no clear underlying gene has been identified in the non-syndromic NMTC. Recently, a c.1601G>A, p.G534E mutation in the HABP2 gene was reported to be the underlying genetic defect in a family with seven members affected by NMTC. The G534E variant has also been reported to occur in about 4.7% of cases of the Thyroid Cancer Genome Atlas (TCGA) database. OBJECTIVES: The aim of this study was to explore whether the recent finding of G534E genetic variant can be replicated in a large sample of NMTC, including 11 members of four unrelated families with familial NMTC and 509 cases of sporadic pediatric (63 cases) and adult NMTC (446 cases). METHODS: All exons and exon-intron boundaries of HABP2 were screened in 11 members of four families with familial non-syndromic NMTC using DNA isolated from peripheral leucocytes, polymerase chain reaction, and direct sequencing. The G534E variant was also screened for specifically in 229 cases of sporadic NMTC using DNA isolated from peripheral leucocytes and an additional 217 cases of NMTC using DNA isolated from formalin-fixed paraffin-embedded tumor tissues. As a control cohort, 190 healthy individuals without known thyroid disease were also studied for the presence of the G534E variant using DNA isolated from peripheral leucocytes. RESULTS: None of the familial NMTC carried HABP2 mutations. Of 509 sporadic NMTC, only one case (0.2%) harbored the G534E variant. Similarly, only one case (0.5%) of the control group harbored the G534E variant. CONCLUSION: In this study, HABP2 mutations were not found in familial NMTC, and the G534E variant is not the underlying genetic defect in a large sample of sporadic NMTC from the Middle East.
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http://dx.doi.org/10.1089/thy.2015.0537

The Association of Discolored Parathyroid Glands and Hypoparathyroidism Following Total Thyroidectomy.
World J Surg, 40(7):1611-7.
B. H. Lang, D. T. Chan, F. C. Chow, K. P. Wong and R. Y. Chang. 2016.
BACKGROUND: It remains uncertain whether a parathyroid gland (PG) that appears darkened or severely bruised but still has an attached vascular pedicle should be left in situ or taken out and auto-transplanted following total thyroidectomy. Our study aimed to examine the impact of discolored PGs (DPGs) on short- and long-term hypoparathyroidism. METHODS: One hundred and three patients who underwent total thyroidectomy with 4 clearly identified PGs were analyzed. Location (superior/inferior) and color of each PG were recorded. Patients without DPG were grouped into I while those with 1-2 DPGs and >/=3 DPGs were grouped into II and III, respectively. Transient hypoparathyroidism meant adjusted Ca <2.00 mol/L 24 h after surgery and/or need for supplements. Protracted hypoparathyroidism meant a subnormal PTH at 4-6 weeks and/or supplements >6 weeks. Permanent hypoparathyroidism meant supplements >/=1 year. RESULTS: Relative to I, group III had greater adjusted Ca drop at postoperative 1-h ($p = 0.012$), 24-h ($p < 0.001$) and lower day-1 PTH ($p = 0.015$). Having >/=3 DPGs (OR 14.00, 95 % CI 1.575-124.474, $p = 0.018$) was an independent factor of transient hypoparathyroidism. However, permanent hypoparathyroidism rate was higher than in group I than II ($p = 0.019$). Eight patients (25.8 %) in group I had undetectable day-1 PTH, while none in group III had undetectable day-1 PTH. Graves' disease/toxic goiter (OR 15.166, 95 % CI 2.594-88.661, $p = 0.003$) and excised gland weight (OR 1.028, 95 % CI 1.010-1.046, $p = 0.003$) were independent factors of >/=3 DPGs. CONCLUSIONS: PG discoloration is associated with transient hypoparathyroidism while normal colored PG with seemingly adequate blood supply does not always imply functionally normal gland. These findings highlights the need for a real-time intraoperative method to assess PG viability.
PubMed-ID: 26908241
http://dx.doi.org/10.1007/s00268-016-3462-9

Radioactive iodine ablation may not decrease the risk of recurrence in intermediate-risk papillary thyroid carcinoma.
Endocr Relat Cancer, 23(5):367-76.
S. K. Kim, J. W. Woo, J. H. Lee, I. Park, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
The use of radioactive iodine (RAI) ablation in patients with intermediate-risk papillary thyroid carcinoma (PTC) who show microscopic extrathyroidal extension (ETE), regional lymph node (LN) metastasis, tumors with aggressive histology, or vascular invasion has been debated due to the lack of data regarding long-term prognosis in this risk group. Therefore, the purpose of this study was to resolve the controversy surrounding the prognostic benefit of RAI ablation, especially in intermediate-risk PTC patients. We retrospectively reviewed the medical records of 8297 intermediate-risk PTC patients who underwent primary total thyroidectomy with or without neck dissection at the Thyroid Cancer Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, between January 1997 and June 2015. Of these 8297 patients, 7483 (90.2%) received RAI ablation. After adjusting for clinicopathological characteristics, RAI ablation did not significantly decrease the risk of loco-regional recurrence (LRR) (adjusted hazard ratio (HR) 0.852, P 0.413). Moreover, RAI ablation did not decrease the risk of LRR even in intermediate-risk PTC patients with aggressive features such as BRAF positivity (adjusted HR 0.729, P 0.137), tumor size >1 cm (adjusted HR 0.762, P 0.228), multifocality (adjusted HR 1.032, P 0.926), ETE (adjusted HR 0.870, P 0.541), and regional LN metastasis (adjusted HR 0.804, P 0.349). Furthermore, high-dose RAI ablation (>100 mCi) did not significantly decrease the risk of LRR (adjusted HR 0.942, P 0.843). Therefore, RAI ablation in intermediate-risk PTC patients should be considered on the basis of tailored risk restratification.
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http://dx.doi.org/10.1530/ERC-15-0572

Impact of thyroidectomy on cardiac manifestations of Graves' disease.
Laryngoscope, 126(5):1256-9.
J. M. Gauthier, H. E. Mohamed, S. I. Noureldine, T. Z. Nazari-Shafti, T. K. Thethi and E. Kandil. 2016.
OBJECTIVES/HYPOTHESIS: Graves' disease (GD) has multiple adverse effects on the cardiovascular system. We aimed to examine the outcome of thyroidectomy in patients with cardiac manifestations of GD and evaluate their associated postoperative complications. STUDY DESIGN: Retrospective analysis using a prospectively collected database. METHODS: A retrospective analysis of our prospectively collected thyroid surgery database was performed. Forty patients with hyperthyroidism due to GD were identified, and each was appropriately age matched to a euthyroid patient with multinodular goiter (MNG). All patients underwent total thyroidectomy. Data relating to cardiac comorbidities were collected from preoperative and postoperative clinic notes, hospital admissions, electrocardiograms, echocardiograms, and blood work. Perioperative biochemical, cardiovascular, and postoperative outcomes were analyzed. RESULTS: Twenty-four (60%) GD patients and 14 (35.0%) MNG patients had cardiac manifestations (P = .001). Hypertension resolved in 41.7% of GD patients and 7.7% of MNG patients (P = .00002). Two of the three GD patients with congestive heart failure (CHF) had resolution of CHF with significant improvement in ejection fraction, whereas the one MNG patient with CHF saw no change. Additionally, the majority of GD patients saw a resolution of their tachycardia (68.8%) and atrial fibrillation (100%). Four postoperative complications occurred in both the GD and MNG groups (4/40, 10%). CONCLUSIONS: Surgical treatment of GD in patients with cardiac manifestations offers rapid clinical improvement of hypertension, impaired left ventricular systolic function, and arrhythmias. When performed by a high-volume surgeon, the complication rate is similar to thyroidectomy for other benign disease. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:1256-1259, 2016.
PubMed-ID: 26927707
http://dx.doi.org/10.1002/lary.25687

Elective central node dissection: Comparison of open to minimally invasive video-assisted approach.
Laryngoscope, 126(7):1715-8.
M. S. Hensler, M. Falciglia, A. Yaqub, H. Yang and D. L. Steward. 2016.
OBJECTIVES/HYPOTHESIS: Compare outcomes of concomitant primary thyroidectomy with elective central neck dissection (CND) by the standard open versus minimally invasive video-assisted (MIVA) approach. STUDY DESIGN: Case series chart review, single institution, tertiary referral center. METHODS: Current Procedural Terminology code 60252 was used to identify patients undergoing CND from February 2005 through June 2012. Therapeutic CND and revision cases were excluded. The MIVA approach was performed in patients with low-risk thyroid carcinoma (cT1 or 2, cN0). Primary outcomes included nodal yield and complications, and secondary outcomes included recurrence. RESULTS: Of 87 eligible patients, 38 were open and 49 were MIVA. The MIVA group was more likely female (88% vs. 68%, P = .03), but groups were similar in age (46.0 vs. 48.6 mean years, P = .37) and percentage of unilateral dissection (69.4% vs. 71.0%, P = .86). The MIVA group was more often

pT1 or 2 (86.9% vs. 76.4%, P = .02). Pathological node positivity was 40% overall and not significantly different between groups (43.5% vs. 35.3%, P = .46). Nodal yield was similar between groups (6.4 vs. 6.8, P = .73). Transient recurrent laryngeal nerve paralysis rates were similar (4.1% vs. 2.6%, P = .71). Transient hypoparathyroidism (postanesthesia care unit parathyroid hormone </=15 pg/mL) was lower in the MIVA group but not statistically significant (29.2% vs. 45.2%, P = .15). No patients experienced permanent hypoparathyroidism or developed clinically detectable structural recurrence. Rates of biochemical response were similar (any thyroglobulin >1 ng/dL) (13.8% vs. 8.0%, P = .86). CONCLUSIONS: Concomitant MIVA thyroidectomy with elective CND appears to be a safe and effective alternative to the open approach for low-risk thyroid carcinoma with similar nodal yield, complications, and recurrence. LEVEL OF EVIDENCE: 4 Laryngoscope, 126:1715-1718, 2016.
PubMed-ID: 26928077
http://dx.doi.org/10.1002/lary.25844

Pediatric Thyroid Cancer: Postoperative Classifications and Response to Initial Therapy as Prognostic Factors.
J Clin Endocrinol Metab, 101(5):1970-9.
L. Lazar, Y. Lebenthal, K. Segal, A. Steinmetz, Y. Strenov, M. Cohen, I. Yaniv, M. Yackobovitch-Gavan and M. Phillip. 2016.
CONTEXT: Prognostic factors for pediatric differentiated thyroid cancer (DTC) are not well established. OBJECTIVE: The objective of the study was to retrospectively compare the postoperative risk-stratification systems: American Thyroid Association (ATA) risk categories, Schneider Children's Medical Center of Israel (SCMCI) score, and the response to initial therapy as predictors for disease outcome. PATIENTS AND METHODS: Fifty-four DTC patients, median age at diagnosis 13.9 years (range 1.9-17 y), followed up for a median of 8.8 years (range 2.6-20.5 y) were stratified into prepubertal (n = 9), pubertal (n = 25), and postpubertal (n = 20) groups. All patients underwent total/near-total thyroidectomy; 48 received radioiodine therapy. The extent of DTC was evaluated by applying the ATA risk categories and the novel SCMCI score. Postoperative risk stratifications (low/intermediate/high) were determined using histopathological, laboratory, and imaging findings. Response to initial therapy (complete/acceptable/incomplete) was based on stimulated thyroglobulin and imaging results during the first 2 years of follow-up. RESULTS: The risk for recurrent/persistent disease, as assessed by the postoperative ATA risk-stratification system and the SCMCI score and by the response to initial therapy, was higher in the prepubertal group (P < .001, P = .002, and P = .02, respectively). Outcome prediction by the risk-stratification systems was applicable: ATA risk categories, P = .014, R(2) = 0.247, predictive ability 80.4%; SCMCI score, P < .001, R(2) = 0.435, predictive ability 86.3%; and response to initial therapy stratification, P < .001, R(2) = 0.789, predictive ability 96.1%. The proportion of variance explained by the ATA risk categories (0.25), SCMCI score (0.44), and response to initial therapy (0.79) indicated that the latter was the most precise predictor and that the SCMCI score reflected the disease outcome better than ATA risk categories. CONCLUSIONS: Our data confirm that the postoperative pediatric ATA stratification system and the novel SCMCI score are suitable for predicting the risk of recurrent/persistent disease in this population. The response to initial therapy classification performed 1-2 years after the initial therapy may be more appropriate for guiding surveillance recommendations.
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http://dx.doi.org/10.1210/jc.2015-3960

Postoperative Calcium Management in Same-Day Discharge Thyroid and Parathyroid Surgery.
Otolaryngol Head Neck Surg, 154(5):854-60.
K. L. Nelson, A. M. Hinson, B. R. Lawson, D. Middleton, D. L. Bodenner and B. C. Stack, Jr. 2016.
OBJECTIVE: To describe a safe and effective postoperative prophylactic calcium regimen for same-day discharge thyroid and parathyroid surgery. STUDY DESIGN: Case series with chart review. SETTING: Tertiary referral academic institution. SUBJECTS AND METHODS: In total, 162 adult patients who underwent total thyroidectomy, completion thyroidectomy, unilateral parathyroidectomy, parathyroidectomy with bilateral neck exploration, or revision parathyroidectomy were identified preoperatively to be candidates for same-day discharge. All patients in this study were successfully discharged the same day on our standard prophylactic calcium regimen. RESULTS: Less than 1% (1/162) of patients re-presented to the hospital within 30 days of surgery, and that patient was successfully discharged from the emergency department after negative workup for hypocalcemia. There was no significant difference between preoperative and postoperative calcium levels in the total/completion thyroidectomy groups (9.3 vs 9.2 mg/dL, respectively; P = .14). The average postoperative calcium level in the parathyroid group was well within normal limits (9.5 mg/dL), and the difference in postoperative calcium levels between revision and primary parathyroidectomy cases was not significantly different (P = .34). CONCLUSION: The reported calcium regimen demonstrates a safe, effective, and objective

means of postoperative calcium management in outpatient thyroid and parathyroid surgery in appropriately selected patients.
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http://dx.doi.org/10.1177/0194599816631732

Prognostic Value of the Number of Retrieved Lymph Nodes in Pathological Nx or N0 Classical Papillary Thyroid Carcinoma.
World J Surg, 40(8):2043-50.
T. Y. Sung, J. H. Yoon, D. E. Song, Y. M. Lee, T. Y. Kim, K. W. Chung, W. B. Kim, Y. K. Shong and S. J. Hong. 2016.
BACKGROUND: This study evaluated the clinical implications of the number of retrieved central lymph nodes (LN) for the recurrence and recurrence-free survival (RFS) outcomes in patients with pathological Nx (pNx) or N0 classical papillary thyroid carcinoma (PTC). METHODS: In total, 464 patients were enrolled following total thyroidectomy with central LN dissection. The risk factors related to recurrence and RFS were evaluated and compared between these groups. RESULTS: Age, primary tumor size, and number of retrieved central LNs were independent risk factors for recurrence according to multivariate analysis ($p < 0.05$). The cut-off value for the number of retrieved central LNs related to recurrence was 4.5. Group 2 (pN0; >/=5 nodes) demonstrated a significantly higher proportion of patients with an ablation-stimulated thyroglobulin (sTg) level <2.0 ng/mL (84.9 vs 61.1 %; $p < 0.050$) and control sTg level <1.0 ng/mL (92.1 vs 79.6 %; $p < 0.050$) in comparison with patients in group 1 (pNx or pN0; 1-4 nodes). Perioperative complication rates were comparable between groups. CONCLUSION: The number of retrieved central LNs is an independent risk factor for recurrence, even among patients with pNx or pN0 classical PTC. A thorough central LN dissection may therefore improve the long-term RFS rate.
PubMed-ID: 26952113
http://dx.doi.org/10.1007/s00268-016-3490-5

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.
PubMed-ID: 26964732
http://dx.doi.org/10.1210/jc.2016-1220

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.
PubMed-ID: 26979305
http://dx.doi.org/10.1245/s10434-016-5185-4

Genomic Alterations of Anaplastic Thyroid Carcinoma Detected by Targeted Massive Parallel Sequencing in a BRAF(V600E) Mutation-Prevalent Area.
Thyroid, 26(5):683-90.
M. J. Jeon, S. M. Chun, D. Kim, H. Kwon, E. K. Jang, T. Y. Kim, W. B. Kim, Y. K. Shong, S. J. Jang, D. E. Song and W. G. Kim. 2016.
BACKGROUND: Anaplastic thyroid carcinoma (ATC), the most aggressive type of thyroid cancer, has no effective therapy. Due to its dismal prognosis, it is vital to understand the genetic alterations of ATC and identify effective molecular targets. Targeted next-generation sequencing was performed to investigate the mutational profile of ATC using a massive parallel sequencing approach. METHODS: DNA from formalin-fixed, paraffin-embedded archival samples of 11 ATCs and normal matched pairs were used. A total of 48 genetic alterations were identified by targeted exome sequencing. These alterations were validated by mass spectrometric genotyping and direct Sanger sequencing. RESULTS: The most commonly mutated gene was BRAF, identified in 10 samples (91%), all showing the V600E point mutation. A KRAS point mutation was observed in the one sample (9%) without the BRAF(V600E) mutation. All 11 ATCs harbored BRAF or RAS mutations, reflecting the

possibility that differentiated thyroid carcinomas progress to ATCs after the accumulation of mutations. A loss of function mutation of TP53 was observed in eight samples (73%), a PIK3CA mutation was observed in two samples (18%), and a frameshift mutation of PTEN was observed in one sample (9%). Twenty-eight novel mutated genes were found that had not previously been associated with ATC. Of these, loss of function mutations of NF2, KMT2D, and PKHD1 were repeatedly seen in three samples (27%), two samples (18%), and two samples (18%), respectively. Using direct Sanger sequencing, two samples (18%) were also found with a RASAL1 mutation. KMT2D and RASAL1 mutations were significantly associated with shorter ATC patient survival. CONCLUSIONS: This comprehensive analysis of ATCs using targeted massive parallel sequencing identified several novel mutations in ATCs, such as loss of function mutations of NF2 or KMT2D. Future studies are needed to confirm the role of these novel mutations as independent drivers of ATC development.
PubMed-ID: 26980298
http://dx.doi.org/10.1089/thy.2015.0506

Comparison of Robotic versus Conventional Selective Neck Dissection and Total Thyroidectomy for Papillary Thyroid Carcinoma.
Otolaryngol Head Neck Surg, 154(6):1005-13.
C. M. Song, Y. B. Ji, E. S. Sung, D. S. Kim, H. R. Koo and K. Tae. 2016.
OBJECTIVE: To compare the surgical outcomes of robotic selective neck dissection (SND) with total thyroidectomy and conventional transcervical SND with total thyroidectomy. STUDY DESIGN: Case series with chart review. SETTING: University tertiary care facility. SUBJECT AND METHODS: We retrospectively analyzed 66 patients who underwent total thyroidectomy with SND (>/=3 levels of II-V) and bilateral central neck dissection for cN1b papillary thyroid carcinoma, of whom 41 underwent conventional SND and 25 of whom underwent robotic SND. Subjective pain, sensory change, and cosmetic satisfaction were evaluated regularly for 3 months with a questionnaire. RESULTS: Compared with the conventional group, patients in the robotic group were younger (mean, 36.7 vs 47.5 years; P = .003) and more female dominant (96.0% vs 73.2%; P = .023). Mean total operative time was longer in the robotic group than the conventional group (298 vs 236 minutes; P < .001). Anterior chest pain was higher in the robotic group at postoperative 1 day (pain score, 1.88 vs 0.62; P = .011), 1 week (1.30 vs 0.43; P = .036), and 1 month (0.90 vs 0.18; P = .029). Postoperative cosmetic satisfaction was significantly superior in the robotic group. CONCLUSION: Compared with conventional transcervical SND with total thyroidectomy, robotic SND with total thyroidectomy yields superior outcomes for cosmetic satisfaction, longer operative time, and higher chest pain in the short term. Further study with a larger number of patients is mandatory.
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http://dx.doi.org/10.1177/0194599816638084

Robotic Thyroidectomy: Comparison of a Postauricular Facelift Approach with a Gasless Unilateral Axillary Approach.
Otolaryngol Head Neck Surg, 154(6):997-1004.
E. S. Sung, Y. B. Ji, C. M. Song, B. R. Yun, W. S. Chung and K. Tae. 2016.
OBJECTIVES: Robotic thyroidectomy using remote access approaches has gained popularity with patients seeking to avoid neck scarring and enhanced cosmetic satisfaction. The aim of this study was to compare the efficacy and advantages of a postauricular facelift approach vs a gasless unilateral axillary (GUA) approach in robotic thyroidectomy. STUDY DESIGN: Case series with chart review. SETTING: University tertiary care hospital. SUBJECTS AND METHODS: We retrospectively analyzed the data of 65 patients who underwent robotic thyroidectomy with or without central neck dissection using a GUA approach (45 patients) or a postauricular facelift approach (20 patients) between September 2013 and December 2014. We excluded patients who underwent simultaneous lateral neck dissection or completion thyroidectomy. RESULTS: Robotic procedures were completed without being converted to an open procedure in all patients. There were no significant differences in terms of patient and tumor characteristics, extent of thyroidectomy and central neck dissection, operative time, complications, and postoperative pain between the 2 approaches, except the higher female ratio in the GUA approach group (female ratio, 95.6% vs 75%, P = .042). Cosmetic satisfaction evaluated by a questionnaire was not significantly different between the 2 groups, and most patients of both groups (85.7%) were satisfied with postoperative cosmesis. CONCLUSION: Both GUA and postauricular facelift approaches are feasible, with no significant adverse events in patients, and result in excellent cosmesis. However, a GUA approach seems to be superior when performing total thyroidectomy using a unilateral incision based on the preliminary result.
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http://dx.doi.org/10.1177/0194599816636366

Dual-energy computed tomography: a promising novel preoperative localization study for treatment of primary hyperparathyroidism.
Am J Surg, 211(5):839-45.
N. Seyednejad, C. Healy, P. Tiwari, P. Vos, G. Sexsmith, A. Melck, C. Hague and S. M. Wiseman. 2016.
BACKGROUND: The objective of this study was to evaluate dual-energy computed tomography (DE-CT) for preoperative parathyroid tumor (PT) localization in individuals undergoing parathyroidectomy for treatment of primary hyperparathyroidism (PHP). METHODS: DE-CT was evaluated by retrospective review of the clinical and biochemical characteristics, imaging, operative findings, and outcomes for PHP cases undergoing an initial operation at a single center. RESULTS: The accuracy of each preoperative imaging test, based on operative findings and pathological confirmation of removal of a PT from the localized site was: 58% for ultrasound, 75% Tc-99m sestamibi noncontrast single photon emission noncontrast CT, and 75% for DE-CT. DE-CT was able to correctly localize a PT in a 3rd of cases that were nonlocalized. All study patients had normalization of serum calcium and parathyroid hormone levels postoperatively. CONCLUSIONS: DE-CT shows promise for the preoperative PT localization, especially in nonlocalized PHP cases, and warrants further investigation.
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http://dx.doi.org/10.1016/j.amjsurg.2016.01.003

Safety of Outpatient Thyroid and Parathyroid Surgery: A Propensity Score-Matched Study.
Otolaryngol Head Neck Surg, 154(5):789-96.
C. Meltzer, M. Klau, D. Gurushanthaiah, J. Tsai, D. Meng, L. Radler and A. Sundang. 2016.
OBJECTIVE: To test our hypothesis that general and thyroid surgery-specific complications, mortality, and postdischarge utilization for patients undergoing outpatient and inpatient thyroid and parathyroid surgery would not differ when outpatient status was defined as discharge within 8 hours of surgery completion. STUDY DESIGN: Retrospective observational cohort, 2008 to 2013. SETTING: Kaiser Permanente Northern California and Kaiser Permanente Southern California. SUBJECTS AND METHODS: We used a robust set of variables and propensity score methods to match 2362 patients undergoing hemithyroidectomy, total thyroidectomy, or parathyroidectomy surgery as outpatients to 2362 patients undergoing the same procedures as inpatients. Outcomes assessed were 30-day rates of complications, emergency department visits, all-cause hospital readmissions, and mortality. RESULTS: After matching, no statistically significant differences between inpatients and outpatients were found for complication rates or postdischarge utilization. After matching, there was no statistically significant difference between inpatients and outpatients in hematoma rates, which were 0.55% in both groups. In the matched-pair groups, 2 deaths occurred among inpatients (0.09%) and none occurred among outpatients (0.00%), a difference that was not statistically significant. CONCLUSION: Discharge within 8 hours after completion of thyroid and parathyroid surgery is as safe as inpatient surgery.
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Thyroid Dysfunction in Children Exposed to Iodinated Contrast Media.
J Clin Endocrinol Metab, 101(6):2366-70.
M. L. Barr, H. K. Chiu, N. Li, M. W. Yeh, C. M. Rhee, J. Casillas, P. J. Iskander and A. M. Leung. 2016.
CONTEXT: Iodinated contrast media (ICM) is routinely used in imaging studies and contains several 100-fold the recommended daily allowance of iodine. OBJECTIVE: To determine whether children exposed to ICM have a higher risk of iodine-induced thyroid dysfunction. DESIGN: This was a single-institution case-control study, examining patients with incident thyroid dysfunction aged less than 18 years from 2001 to 2015. Cases were matched 1:1 to euthyroid controls by age, sex, and race. SETTING: This was a single-institution case-control study occurring at tertiary care center. PARTICIPANTS: Cases were defined as those with thyroid dysfunction (by International Classification of Diseases, Ninth Revision diagnosis codes and/or 2 consecutive abnormal serum TSH values <6 mo apart). We analyzed 870 cases matched to 870 controls (64% female, 51% White). MAIN OUTCOMES MEASURES: Using conditional logistic regression, the association between ICM exposure and the primary outcome, thyroid dysfunction, occurring within 2 years of exposure was assessed. RESULTS: Sixty-nine patients received ICM, including 53 (6%) among cases and 16 (2%) among controls. The risk of incident hypothyroidism was significantly higher after ICM exposure (odds ratio 2.60; 95% confidence interval, 1.43-4.72; P < .01). The median interval between exposure and onset of hypothyroidism was 10.8 months (interquartile range, 6.6-17.9). In hypothyroid cases, the median serum TSH concentration was 6.5 mIU/L (interquartile range, 5.8-9.6). CONCLUSIONS: ICM exposure increases the risk of incident hypothyroidism in pediatric patients. Children receiving ICM should be monitored for iodine-induced thyroid dysfunction, particularly during the first year after exposure.
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Family Screening in Familial Papillary Carcinoma: The Early Detection of Thyroid Disease.
Ann Surg Oncol, 23(8):2564-70.
A. Rios, J. M. Rodriguez, D. Navas, A. Cepero, N. M. Torregrosa, M. D. Balsalobre and P. Parrilla. 2016.
INTRODUCTION: Blood relatives of patients with familial papillary thyroid carcinoma (FPTC) have a higher rate of thyroid disease. This study analyzed the utility of a screening protocol for thyroid disease on blood relatives of patients with FPTC. METHODS: STUDY POPULATION: Members of families diagnosed with FPTC. INCLUSION CRITERIA: (1) first- and second-degree relatives; and (2) older than age 11 years. Screening: This includes the subject's clinical history, a physical examination, blood tests, and an ultrasound examination. CONTROL GROUP: A nonrelated healthy population paired by age and sex with the study group. RESULTS: Sixty-eight percent of blood relatives (128/189) accepted having the screening. The results showed 44.5 % (n = 57) of the relatives did not have disease, 44 % (n = 56) had benign thyroid disease, and 11.5 % (n = 15) had a disease suggestive of malignancy. After the screening, surgery was indicated in 26 patients, and the final results of the study were: (1) 44.5 % (n = 57) were healthy subjects; (2) 50 % (n = 64) had benign thyroid disease (26 cases with a functional disease, and/or 56 with an organic disease); and (3) 5.5 % (n = 7) had malignant thyroid disease. The first-degree relatives had a higher tendency to have the disease than second degree ones (64 vs. 46 %; p = 0.0482). In the control group, the incidence of thyroid cancer was 1.3 % compared with 5.5 % in the study group (p = 0.0182). CONCLUSIONS: Screening allows for the early detection of papillary carcinoma and benign thyroid disease and for this reason we recommend that it is performed periodically. However, more studies, with larger sample sizes, are needed to determine the benefit of screening.
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http://dx.doi.org/10.1245/s10434-016-5149-8

Dynamic Risk Stratification in Patients with Differentiated Thyroid Cancer Treated Without Radioactive Iodine.
J Clin Endocrinol Metab, 101(7):2692-700.
D. P. Momesso, F. Vaisman, S. P. Yang, D. A. Bulzico, R. Corbo, M. Vaisman and R. M. Tuttle. 2016.
CONTEXT: Although response to therapy assessment is a validated tool for dynamic risk stratification in patients with differentiated thyroid cancer (DTC) treated with total thyroidectomy (TT) and radioactive iodine therapy (RAI), it has not been well studied in patients treated with lobectomy or TT without RAI. Because these responses 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. OBJECTIVE: This study aimed to validate the response to therapy assessment in patients with DTC treated with lobectomy or TT without RAI. DESIGN AND SETTING: This was a retrospective study, which took place at a referral center. PATIENTS: A total of 507 adults with DTC were treated with lobectomy (n = 187) or TT (n = 320) without RAI. They had a median age of 43.7 y, 88% were female, 85.4% had low risk, and 14.6% intermediate risk. MAIN OUTCOME MEASURE: Main outcome measured was recurrent/persistent structural evidence of disease (SED) during a median followup period of 100.5 months (24-510). RESULTS: Recurrent/persistent SED was observed in 0% of the patients with excellent response to therapy (nonstimulated Tg for TT < 0.2 ng/mL and for lobectomy < 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 nonspecific imaging findings; n = 2/152); 31.6% of the patients with biochemical incomplete response (nonstimulated Tg for TT > 5 ng/mL and for lobectomy > 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 < .0001). Initial American Thyroid Association risk estimates were significantly modified based on response to therapy assessment. CONCLUSIONS: Our data validate the newly proposed response to therapy assessment in patients with DTC treated with lobectomy or TT without RAI as an effective tool to modify initial risk estimates of recurrent/persistent SED and better tailor followup 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, 23(8):2571-6.
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.
PubMed-ID: 27026437
http://dx.doi.org/10.1245/s10434-016-5199-y

Subclinical hyperthyroidism: first do no harm.
Clin Endocrinol (Oxf), 85(1):15-6.
A. L. Mitchell and S. H. Pearce. 2016.
PubMed-ID: 27028121
http://dx.doi.org/10.1111/cen.13070

Preserving Parathyroid Gland Vasculature to Reduce Post-thyroidectomy Hypocalcemia.
World J Surg, 40(6):1382-9.
I. Park, J. Rhu, J. W. Woo, J. H. Choi, J. S. Kim and J. H. Kim. 2016.
BACKGROUND: The failure to preserve parathyroid function in patients who have undergone total thyroidectomy is of major concern, because hypocalcemia is difficult to prevent and remains a common postoperative complication. Here, we describe procedures designed to preserve the vasculature supplying the parathyroid glands and examine both recent outcomes and retrospective reports of results obtained prior to the application of these preservation techniques. METHODS: Our technique for preserving parathyroid function during thyroidectomy was adopted in 2009 and involves separating a relatively long segment of a vessel distally from the thyroid gland. We reviewed the medical records of 1,411 patients who underwent total thyroidectomy, with or without lateral neck dissection, at the Samsung Medical Center from January 2006 through June 2014 to determine outcomes. Patients were divided into three groups according to the time period during which the surgery took place: Group A, 2006-2008 (before the vasculature-preserving technique was applied); Group B, 2009-2011 (the time when the technique was first adopted); and Group C, 2012-2014 (more recent results of the technique). We analyzed the incidence of hypoparathyroidism in the three groups, as well as risk factors that influenced its development. RESULTS: The rates of transient and permanent hypoparathyroidism in Group A were 25.4 and 4.3 %, respectively. However, the incidence of hypoparathyroidism decreased significantly over time after the vasculature-preserving procedure was adopted. Transient hypoparathyroidism developed in 4.8 % of Group C patients, and only four (0.7 %) of the 565 patients in this group required calcium supplementation, despite the fact that a greater number of patients were included who underwent total thyroidectomy combined with lateral neck dissection. Although female sex and lateral neck dissection tended to increase the rate of transient hypoparathyroidism, multivariate analysis showed that the vasculature-preserving procedure was the only significant risk factor related to postoperative hypoparathyroidism. CONCLUSION: The blood flow of the final branch to the parathyroid gland is mostly in the lateral-to-medial direction; therefore, mobilization and preservation of the vessels lateral to the gland is essential to prevent devascularization of the parathyroid gland.
PubMed-ID: 27028753
http://dx.doi.org/10.1007/s00268-016-3423-3

Hyperthyroidism.
Lancet, 388(10047):906-18.
S. De Leo, S. Y. Lee and L. E. Braverman. 2016.
Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source. The most common cause of hyperthyroidism is Graves' disease, followed by toxic nodular goitre. Other important causes of thyrotoxicosis include thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and factitious ingestion of excess thyroid hormones. Treatment options for Graves' disease include antithyroid drugs, radioactive iodine therapy, and surgery, whereas antithyroid drugs are not generally used long term in toxic nodular goitre, because of the high relapse rate of thyrotoxicosis after discontinuation. beta blockers are used in

symptomatic thyrotoxicosis, and might be the only treatment needed for thyrotoxicosis not caused by excessive production and release of the thyroid hormones. Thyroid storm and hyperthyroidism in pregnancy and during the post-partum period are special circumstances that need careful assessment and treatment.
PubMed-ID: 27038492
http://dx.doi.org/10.1016/S0140-6736(16)00278-6

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.
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http://dx.doi.org/10.1210/jc.2016-1315

Tumor-Infiltrating T Cells and the PD-1 Checkpoint Pathway in Advanced Differentiated and Anaplastic Thyroid Cancer.
J Clin Endocrinol Metab, 101(7):2863-73.
J. J. Bastman, H. S. Serracino, Y. Zhu, M. R. Koenig, V. Mateescu, S. B. Sams, K. D. Davies, C. D. Raeburn, R. C. McIntyre, Jr., B. R. Haugen and J. D. French. 2016.
CONTEXT: Five to 10% of patients with differentiated thyroid cancers (DTC) develop invasive and/or distant metastatic disease that is marginally improved with standard therapies. Prognosis is poor for patients with anaplastic thyroid cancer, with a median survival of 3-5 months. We suggest that a paradigm shift is necessary in the treatment of advanced cases. OBJECTIVE: We hypothesized that a T-cell response is generated in advanced thyroid cancer and may be a viable therapeutic target. DESIGN: Primary DTCs were analyzed by quantitative RT-PCR (n = 92) for expression of CD3, CD8, forkhead box (Fox)-P3, programmed death (PD)-1, PD-1 ligand-1, and PD-1 ligand-2 and biopsied for cellular analysis by flow cytometry (n = 11). Advanced pT4 cases (n = 22) and metastases (n = 5) were analyzed by immunohistochemistry. SETTING: The study was conducted at the University of Colorado Hospital. PATIENTS: Thyroid cancer patients undergoing thyroidectomy or completion surgery for advanced disease between 2002 and 2013 participated in the study. INTERVENTION: There were no interventions. MAIN OUTCOME MEASURE: Immune markers were analyzed for association with disease severity. RESULTS: Immune markers were commonly expressed at the RNA level. PD-L1 was higher ($P = .0443$) in patients with nodal metastases. FoxP3(+) ($P < .0001$), PD-1(+)CD8(+) ($P = .0058$), and PD-1(+)CD4(+) ($P = .0104$) T cells were enriched in DTC biopsies. CD8(+) and FoxP3(+) T cells were detected by immunohistochemistry in all pT4 tumors and a subset of metastases. PD-1(+) lymphocytes were found in 50% of DTCs. PD-L1 was expressed by tumor and associated leukocytes in 13 of 22 cases, and expression was more diffuse in anaplastic thyroid cancer ($P = .0373$). BRAF(V600E) mutation was associated with higher frequencies of tumor-associated lymphocytes ($P = .0095$) but not PD-L1 expression. CONCLUSIONS: PD-1 checkpoint blockades may have therapeutic efficacy in patients with aggressive forms of thyroid cancer.
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http://dx.doi.org/10.1210/jc.2015-4227

Dissection of Levels II Through V Is Required for Optimal Outcomes in Patients with Lateral Neck Lymph Node Metastasis from Papillary Thyroid Carcinoma.
J Am Coll Surg, 222(6):1066-73.
M. Javid, E. Graham, J. Malinowski, C. E. Quinn, T. Carling, R. Udelsman and G. G. Callender. 2016.
BACKGROUND: Completeness of surgical resection is an important determinant of outcomes in patients with papillary thyroid carcinoma and regional lymph node metastasis. The extent of therapeutic lateral neck dissection remains controversial. This study aims to assess the impact of modified radical neck dissection of levels II to V in a large patient series. STUDY DESIGN: Retrospective analysis of consecutive patients with papillary thyroid carcinoma who underwent lateral neck dissection at a single institution from June 1, 2006 to December 31, 2014 was performed. RESULTS: A total of 241 lateral neck dissections were performed in 191 patients (118 [62%] women; median age 46 years [range 6 to 87 years]; median follow-up 14.3 months [range 0.1 to 107 months]). Overall, 202 initial neck dissections (195 modified radical neck dissections and 7 less extensive dissections) were performed. Among these initial dissections, 137 (68.8%), 132 (65.7%), 105 (52.0%), and 33 (16.9%) had positive lymph nodes in levels II, III, IV, and V, respectively. Ipsilateral lymph node persistence or recurrence occurred after 22 (10.9%) initial dissections, at level II in 10 (45.5%), level III in 8 (36.4%), level IV in 7 (31.8%), and level V in 3 (13.6%). Thirty-nine reoperative lateral neck dissection were performed, including 18 cases of persistence and recurrence after our initial dissections. In reoperative dissections, positive lymph nodes were confirmed in levels II, III, IV, and V in 18 (46.2%), 10 (25.6%), 13 (33.3%), and 5 (12.8%) dissections, respectively. Temporary nerve injury occurred in 6 (3.0%) initial and 4 (10.3%) reoperative dissections, respectively. There were no permanent nerve injuries. CONCLUSIONS: Omitting levels II and V during lateral neck dissection for papillary thyroid carcinoma potentially misses level II disease in two-thirds of patients and level V disease in one-fifth of patients. Formal modified radical neck dissection is necessary to avoid the morbidity of reoperative surgery.
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http://dx.doi.org/10.1016/j.jamcollsurg.2016.02.006

Risk Factors for Graves' Orbitopathy; the Australian Thyroid-Associated Orbitopathy Research (ATOR) Study.
J Clin Endocrinol Metab, 101(7):2711-20.
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 group consisting of tertiary endocrinology and ophthalmology outpatients and related private practices. PATIENTS OR OTHER PARTICIPANTS: A total of 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, confidence interval (CI): 1.06-1.29; P = .002) and by 7% for each year increase in the duration of GH (OR 1.07, CI: 1.05-1.10; P < .001). Smoking increased the odds for GO by 2.22 for current smoker and 2.07 for exsmoker (P < .001), compared with never smoking. The odds of GO are 86% less in Graves' patients using antithyroid medication than those not (OR 0.14, CI: 0.06-0.34; P < .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 antithyroid 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

Frequency of High-Risk Characteristics Requiring Total Thyroidectomy for 1-4 cm Well-Differentiated Thyroid Cancer.
Thyroid, 26(6):820-4.
W. P. Kluijfhout, J. D. Pasternak, J. Lim, J. S. Kwon, M. R. Vriens, O. H. Clark, W. T. Shen, J. E. Gosnell, I. Suh and Q. Y. Duh. 2016.
BACKGROUND: The extent of thyroidectomy for low-risk well-differentiated thyroid cancer (WDTC) remains controversial. Historically, total thyroidectomy (TT) has been recommended for WDTC >/=1 cm in size. However, recent National Comprehensive Cancer Network and American Thyroid Association guidelines recognize

unilateral thyroid lobectomy as a viable alternative for 1-4 cm cancers due to their otherwise favorable prognosis, with TT remaining the preferred option for tumors with unfavorable pathological characteristics. This study sought to determine how often a completion TT would be recommended based on these guidelines if lobectomy was initially performed in patients with 1-4 cm WDTC without preoperatively known risk factors. METHODS: Patients who underwent thyroidectomy for 1-4 cm WDTC (January 2000 to January 2010) were retrospectively reviewed. Patients with preoperatively known high-risk characteristics, including gross extrathyroidal extension (ETE) on preoperative imaging, clinically apparent lymph node metastases, distant metastases, history of radiation, and positive family history, were excluded. The pathology specimens from the cancer-containing lobe were evaluated for features that would lead to a recommendation for TT based on current guidelines, including aggressive histology, vascular invasion, microscopic ETE, positive margins, and any positive lymph nodes within the specimen. RESULTS: Of 1000 consecutive patients operated for WDTC, 287 would have been eligible for lobectomy as the initial operation. The mean age in this cohort was 45 years, and 80% were women. Aggressive tall-cell variant histology was found in one patient (0.5%), angio-invasion in 34 (12%), ETE in 48 (17%), positive margins in 51 (18%), and positive lymph nodes in 49 (18%) patients. Completion TT would have been recommended in 122/287 (43%) patients. Even in those with 1-2 cm cancers, completion TT would have been recommended in 52/143 (36%) patients. CONCLUSIONS: Nearly half of the patients with 1-4 cm WDTC who are eligible for lobectomy under current guidelines would require completion TT based on pathological characteristics of the initial lobe. Surgeons, endocrinologists, and patients need to balance the relative benefits, risks, and costs of initial TT versus the possible need for reoperative completion TT.
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http://dx.doi.org/10.1089/thy.2015.0495

Inter-Observer Variation in the Pathologic Identification of Extranodal Extension in Nodal Metastasis from Papillary Thyroid Carcinoma.
Thyroid, 26(6):816-9.
E. Du, B. M. Wenig, H. K. Su, M. E. Rowe, G. C. Haser, S. L. Asa, Z. Baloch, W. C. Faquin, G. Fellegara, T. Giordano, R. Ghossein, V. A. LiVolsi, R. Lloyd, O. Mete, U. Ozbek, J. Rosai, S. Suster, L. D. Thompson, A. T. Turk and M. L. Urken. 2016.
BACKGROUND: Extranodal extension (ENE) in lymph node metastases has been shown to worsen the prognosis of papillary thyroid cancer (PTC). Despite the clinical significance of ENE, there are no stringent criteria for its microscopic diagnosis, and its identification is subject to inter-observer variability. The objective of this study was to determine the level of agreement among expert pathologists in the identification of ENE in PTC cases. METHODS: Eleven expert pathologists from the United States, Italy, and Canada were asked to review 61 scanned slides of representative permanent sections of PTC specimens from Mount Sinai Beth Israel Medical Center in New York. Each slide was evaluated for the presence of ENE. The pathologists were also asked to report the criteria they use to identify ENE. RESULTS: The overall strength of agreement in identifying ENE was only fair (kappa = 0.35), and the proportion of observed agreement was 0.68. The proportions of observed agreement for the identification of perinodal structures (fat, nerve, skeletal, and thick-walled vessel involvement) ranged from 0.61 to 0.997. CONCLUSIONS: Overall agreement for the identification of ENE is poor. The lack of agreement results from both variation in pathologists' identification of features and disagreement on the histologic criteria for ENE. This lack of concordance may help explain some of the discordant information regarding prognosis in clinical studies when this feature is identified.
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http://dx.doi.org/10.1089/thy.2015.0551

The Rate and Clinical Significance of Incidental Thyroid Uptake as Detected by Gallium-68 DOTATATE Positron Emission Tomography/Computed Tomography.
Thyroid, 26(6):831-5.
P. Nockel, C. Millo, X. Keutgen, J. Klubo-Gwiezdzinska, J. Shell, D. Patel, N. Nilubol, P. Herscovitch, S. M. Sadowski and E. Kebebew. 2016.
BACKGROUND: Gallium-68 (Ga-68) DOTATATE is a radiolabeled peptide-imaging modality that targets the somatostatin receptor (SSTR), especially subtype 2 (SSTR2). Benign and malignant thyroid tumors have been observed to express SSTR. The aim of this study was to evaluate the frequency and clinical significance of incidental atypical thyroid uptake as detected by Ga-68 DOTATATE positron emission tomography/computed tomography (PET/CT). METHODS: A retrospective analysis was conducted of a prospective study in which 237 patients underwent Ga-68 DOTATATE PET/CT as part of a work-up for metastatic and unknown primary neuroendocrine tumors. The types of uptake in the thyroid gland (focal/diffuse) and maximum standardized uptake value (SUVmax) levels were evaluated and compared with the background uptake in the liver and salivary glands. RESULTS: Of 237 patients, 26 (11%) had atypical thyroid uptake as detected by Ga-68

DOTATATE PET/CT. There were no significant clinical or biochemical variables associated with atypical thyroid uptake. Fourteen (54%) patients had positive focal uptake, and 12 (46%) patients had diffuse uptake. Of the 14 patients with atypical focal uptake, 10 (71%) had thyroid nodules on the corresponding side, as detected by anatomic imaging. Three of 10 patients (21%) were found to have papillary thyroid cancer, and seven (70%) had adenomatoid nodules. Of the 12 patients with diffuse increased uptake, six (50%) had a history of hypothyroidism, five (42%) had chronic lymphocytic thyroiditis, and one (8%) had nontoxic multinodular goiter. CONCLUSIONS: Patients with an incidental focal abnormal thyroid uptake on Ga-68 DOTATATE PET/CT scan should have further clinical evaluation to exclude a diagnosis of thyroid cancer.
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http://dx.doi.org/10.1089/thy.2016.0174

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

Risk factors for recurrence in patients with papillary thyroid carcinoma undergoing modified radical neck dissection.
Br J Surg, 103(8):1020-5.
Y. M. Lee, T. Y. Sung, W. B. Kim, K. W. Chung, J. H. Yoon and S. J. Hong. 2016.
BACKGROUND: This study evaluated the impact of lymph node-related factors on the risk of and site of recurrence in patients who had papillary thyroid carcinoma with lymph node metastasis in the lateral compartment (classified as pN1b). METHODS: Patients underwent total thyroidectomy with unilateral modified radical neck dissection for classical papillary thyroid carcinoma. Risk factors for recurrence were evaluated according to the pattern of recurrence. RESULTS: A total of 324 patients were included in the study. The median follow-up was 63 (range 14-181) months. Recurrence was detected in 47 patients (14.5 per cent). In the multivariable analysis, a maximum diameter of metastatic lymph nodes larger than 2.0 cm (hazard ratio (HR) 1.15, 95 per cent c.i. 1.06 to 1.25; P = 0.033) and a central compartment metastatic lymph node ratio of more than 0.42 (HR 3.35, 1.65 to 6.79; P < 0.001) were identified as independent risk factors for locoregional recurrence. Age 45 years or older (HR 5.69, 1.24 to 26.12; P = 0.025) and extranodal extension of metastasis (HR 12.71, 1.64 to 98.25; P = 0.015) were risk factors for distant metastasis. In subgroup analysis of locoregional recurrence, several lymph node-related factors affected the risk of recurrence according to the specific site of metastasis. CONCLUSION: Lymph node-related factors are of importance for the risk of recurrence in patients with classical papillary thyroid carcinoma classified as pN1b.
PubMed-ID: 27121346
http://dx.doi.org/10.1002/bjs.10144

Continuous intraoperative monitoring of vagus and recurrent laryngeal nerve function in patients with advanced atrioventricular block.
Langenbecks Arch Surg, 401(4):551-6.
R. Schneider, A. Machens, M. Bucher, C. Raspe, K. Heinroth and H. Dralle. 2016.

PURPOSE: Intraoperative neuromonitoring of recurrent laryngeal nerve function after stimulation of the vagus nerve has been embraced as a risk minimization tool in thyroid surgery to prevent recurrent laryngeal nerve injury. Because this technology is increasingly used in an elderly and sicker population, the present study was conducted to determine the safety of this method in patients with second- or third-degree atrioventricular block. METHODS: This study aimed at evaluating the feasibility and safety of continuous intraoperative neuromonitoring (CIONM) in patients with second- or third-degree atrioventricular block. RESULTS: A total of six patients (12 nerves at risk), accounting for 0.3 % of all 1800 patients (3049 nerves at risk) who underwent thyroid surgery during the study period, were found to have second- or third-degree atrioventricular block. All these patients maintained normal systolic and diastolic blood pressures; heart rate; and peripheral arterial oxygen saturation before, during, and after CIONM. No clinically relevant changes in heart rate or blood pressure, cardiac arrhythmia, or other hemodynamically important events were noted despite careful monitoring of these patients. There was no interference between the biphasic waveform of the vocal muscle electromyogram and the spikes generated by the implanted cardiac pacemakers. Outcomes were uneventful with normal vocal fold and parathyroid gland function. CONCLUSIONS: Within the limitations of this series and considering experimental, animal, and human data, continuous IONM of the vagus nerve at </=2 Hz seems to be reasonably safe. Additional research is warranted to confirm these results in larger groups of patients with advanced atrioventricular block.
PubMed-ID: 27138019
http://dx.doi.org/10.1007/s00423-016-1433-0

Antiplatelet and Anticoagulant Medications Significantly Increase the Risk of Postoperative Hematoma: Review of over 4500 Thyroid and Parathyroid Procedures.
Ann Surg Oncol, 23(9):2874-82.
S. C. Oltmann, A. Y. Alhefdhi, M. H. Rajaei, D. F. Schneider, R. S. Sippel and H. Chen. 2016.
PURPOSE: Antiplatelet and/or anticoagulant medication use is common. Abstinence a week before surgery may still result in altered hemostasis. The study aim was to report on perioperative antiplatelet and anticoagulant use in thyroidectomy and parathyroidectomy patients, and to determine the association with postoperative hematoma (POH) rates. METHODS: Retrospective review of a prospective endocrine surgery database was performed. Procedure extent was defined as unilateral, bilateral, or extensive. Antiplatelets were categorized as none, 325 mg aspirin (ASA), <325 mg ASA, clopidogrel, or other. Anticoagulants were categorized as none, oral, or injectable. RESULTS: A total of 4514 patients were identified. POH developed in 22 patients (0.5 %). Rates were similar between age, gender, and reoperative status. POH were seven times more common after thyroidectomy (0.8 vs. 0.1 %, $p < 0.01$). Unilateral procedures had lower POH rates than bilateral or extensive (0.1 vs. 0.9 vs. 0.8 %, $p < 0.01$). POH rates in patients receiving 325 mg ASA (0.8 %) or clopidogrel (2.2 %) were much higher than patients not receiving antiplatelets (0.5 %) or receiving <325 mg ASA (0.1 %, $p = 0.04$). Oral anticoagulants (2.2 %) and injectable anticoagulants (10.7 %) had much higher POH rates than patients not receiving anticoagulants (0.4 %, $p < 0.01$). Target organ, patient gender, procedure extent, antiplatelet use, and anticoagulant use were included on logistic regression to determine association with POH. Bilateral procedures, thyroidectomy, clopidogrel, oral, and injectable anticoagulants were all independently associated with POH. CONCLUSIONS: POH occur more frequently after thyroidectomy and during bilateral procedures. Patients requiring clopidogrel or any anticoagulant coverage are at much higher risk for POH. These higher-risk patients should be considered for observation to ensure prompt POH recognition and intervention.
PubMed-ID: 27138383
http://dx.doi.org/10.1245/s10434-016-5241-0

BRAF(V600E) Mutation is Associated with Decreased Disease-Free Survival in Papillary Thyroid Cancer.
World J Surg, 40(7):1618-24.
S. Fraser, C. Go, A. Aniss, S. Sidhu, L. Delbridge, D. Learoyd, R. Clifton-Bligh, L. Tacon, V. Tsang, B. Robinson, A. J. Gill and M. Sywak. 2016.
BACKGROUND: The BRAF (V600E) mutation is a recognised molecular marker in papillary thyroid cancer (PTC), reported incidence from 30 to 80 %. BRAF(V600E) aberrantly activates the MAPK pathway, a central regulator of cell growth and proliferation. Previous studies have reported conflicting data regarding the impact of BRAF(V600E) on clinicopathological features of PTC. The study aims to determine whether BRAF(V600E) is useful as a prognostic biomarker in PTC. METHODS: A cohort study of patients undergoing surgery for PTC was undertaken. The primary outcome measure was disease-free survival. Secondary outcome measures were tumour size, nodal positivity and radioactive iodine ablation rate. All cases were re-examined to confirm PTC. Immunohistochemistry for BRAF(V600E) was performed on tissue microarrays. A single endocrine pathologist, blinded to clinicopathological data, interpreted staining. RESULTS: 496 patients with PTC were included, and 309 (62 %) were BRAF(V600E) positive. Tumour size was similar for BRAF(V600E)-positive and -negative

tumours (21.3 vs. 23.2 mm, p = 0.23). BRAF(V600E)-positive patients were significantly older at first operation (mean age 45 versus 49 years, p = 0.003). BRAF(V600E)-positive PTCs had a higher rate of disease recurrence (12.9 vs. 5.6 %, p = 0.004), lymph node metastasis (44 vs. 29.4 %, p = 0.004) and extra-thyroidal extension (44 vs. 22 %, p < 0.001). Five-year disease-free survival was 89.6 % for BRAF(V600E) positive and 96.3 % for negative tumours, p < 0.001. There was no difference between groups for vascular invasion or multifocality. The mean follow-up was 57 months for both groups. CONCLUSION: BRAF(V600E) in PTC predicts an increased risk of lymph node metastasis, extra-thyroidal extension and reduced disease-free survival. It is an additional useful prognostic biomarker.
PubMed-ID: 27138882
http://dx.doi.org/10.1007/s00268-016-3534-x

[Anatomy and neuromonitoring of the bifascicular N. recurrens].
Chirurg, 87(5):441.
H. Dralle. 2016.
PubMed-ID: 27142409
http://dx.doi.org/10.1007/s00104-016-0194-1

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

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

reported cost-utility data and provide valuable insights for informed decision-making by patients, physicians and payers.
PubMed-ID: 27155136
http://dx.doi.org/10.1111/cen.13096

Graves' disease in children: long-term outcomes of medical therapy.
Clin Endocrinol (Oxf), 85(4):632-5.
S. Rabon, A. M. Burton and P. C. White. 2016.
BACKGROUND AND OBJECTIVES: Management options are limited for the treatment of Graves' disease, and there is controversy regarding optimal treatment. We describe the demographic and biochemical characteristics of children with Graves' disease and the outcomes of its management. METHODS: This is a retrospective study reviewing medical records from 2001 to 2011 at a tertiary-care paediatric hospital. Diagnostic criteria included elevated free T4 and total T3, suppressed TSH, and either positive thyroid-stimulating immunoglobulin or thyroid receptor antibodies or clinical signs suggestive of Graves' disease, for example exophthalmos. Patients were treated with antithyroid drugs (ATD), radioactive iodine, or thyroidectomy. The main outcome measures were remission after medical therapy for at least 6 months and subsequent relapse. RESULTS: A total of 291 children met diagnostic criteria. A total of 62 were male (21%); 117 (40%) were Hispanic, 90 (31%) Caucasian, and 59 (20%) African American. Mean age (+/-standard deviation) at diagnosis was 12.3 +/- 3.8 (range 3-18.5) years. At diagnosis, 268 patients were started on an antithyroid drug and 23 underwent thyroid ablation or thyroidectomy. Fifty-seven (21%) children achieved remission and 16 (28%) of these patients relapsed, almost all within 16 months. Gender and ethnicity did not affect rates of remission or relapse. Of 251 patients treated with methimazole, 53 (21%) had an adverse reaction, including rash, arthralgias, elevated transaminases, or neutropenia. CONCLUSIONS: Most children with Graves' disease treated with ATD do not experience remission, but most remissions do not end in relapse. Adverse reactions to methimazole are common but generally mild.
PubMed-ID: 27169644
http://dx.doi.org/10.1111/cen.13099

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

Changing the Cancer Diagnosis: The Case of Follicular Variant of Papillary Thyroid Cancer-Primum Non Nocere and NIFTP.
Thyroid, 26(7):869-71.
S. Hodak, R. M. Tuttle, G. Maytal, Y. E. Nikiforov and G. Randolph. 2016.
PubMed-ID: 27184034
http://dx.doi.org/10.1089/thy.2016.0205

New drugs for medullary thyroid cancer: new promises?
Endocr Relat Cancer, 23(6):R287-97.
C. Spitzweg, J. C. Morris and K. C. Bible. 2016.
Medullary thyroid cancer (MTC) is a rare tumor arising from the calcitonin-producing parafollicular C cells of the thyroid gland, occurring either sporadically or alternatively in a hereditary form based on germline RET mutations in approximately one-third of cases. Historically, patients with advanced, metastasized MTC have had a poor prognosis, partly due to limited response to conventional chemotherapy and radiation therapy. In the past decade, however, considerable progress has been made in identifying key genetic alterations and dysregulated signaling pathways paving the way for the evaluation of a series of multitargeted kinase inhibitors that have started to meaningfully impact clinical practice. Two drugs, vandetanib and cabozantinib, are now approved in the US and EU for use in advanced, progressive MTC, with additional targeted agents also showing promise or awaiting results from clinical trials. However, the potential for toxicities with significant reduction in quality of life and lack of curative outcomes has to be carefully weighed against potential for benefit. Despite significant PFS prolongation observed in randomized clinical trials, most patients even with metastatic disease enjoy indolent courses with slow progression observed over years, wherein watchful waiting is still the preferred strategy. As advanced, progressive MTC is a rare and complex disease, a multidisciplinary approach centered in specialized centers providing interdisciplinary expertise in the individualization of available therapeutic options is preferred. In this review, we summarize current concepts of the molecular pathogenesis of advanced MTC and discuss results from clinical trials of targeted agents and also cytotoxic chemotherapy in the context of clinical implications and future perspectives.
PubMed-ID: 27185870
http://dx.doi.org/10.1530/ERC-16-0104

Risk Stratification of Neck Lesions Detected Sonographically During the Follow-Up of Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 101(8):3036-44.
L. Lamartina, G. Grani, M. Biffoni, L. Giacomelli, G. Costante, S. Lupo, M. Maranghi, K. Plasmati, M. Sponziello, F. Trulli, A. Verrienti, S. Filetti and C. Durante. 2016.
CONTEXT: The European Thyroid Association (ETA) has classified posttreatment cervical ultrasound findings in thyroid cancer patients based on their association with disease persistence/recurrence. OBJECTIVE: The objective of the study was to assess this classification's ability to predict the growth and persistence of such lesions during active posttreatment surveillance of patients with differentiated thyroid cancer (DTC). DESIGN: This was a retrospective, observational study. SETTING: The study was conducted at a thyroid cancer center in a large Italian teaching hospital. PATIENTS: Center referrals (2005-2014) were reviewed and patients selected with pathologically-confirmed DTC; total thyroidectomy, with or without neck dissection and/or radioiodine remnant ablation; abnormal findings on two or more consecutive posttreatment neck sonograms; and subsequent follow-up consisting of active surveillance. Baseline ultrasound abnormalities (thyroid bed masses, lymph nodes) were classified according to the ETA system. Patients were divided into group S (those with one or more lesions classified as suspicious) and group I (indeterminate lesions only). We recorded baseline and follow-up clinical data through June 30, 2015. MAIN OUTCOMES: The main outcomes were patients with growth (>3 mm, largest diameter) of one or more lesions during follow-up and patients with one or more persistent lesions at the final visit. RESULTS: The cohort included 58 of the 637 DTC cases screened (9%). A total of 113 lesions were followed up (18 thyroid bed masses, 95 lymph nodes). During surveillance (median 3.7 y), group I had significantly lower rates than group S of lesion growth (8% vs 36%, P = .01) and persistence (64% vs 97%, P = .014). The median time to scan normalization was 2.9 years. CONCLUSIONS: The ETA's evidence-based classification of sonographically detected neck abnormalities can help identify papillary thyroid cancer patients eligible for more relaxed follow-up.
PubMed-ID: 27186860
http://dx.doi.org/10.1210/jc.2016-1440

Incidence and Risk Factors for Occult Level 3 Lymph Node Metastases in Papillary Thyroid Cancer.
Ann Surg Oncol, 23(11):3587-92.
S. Fraser, N. Zaidi, O. Norlen, A. Glover, S. Kruijff, M. Sywak, L. Delbridge and S. B. Sidhu. 2016.
BACKGROUND: Papillary thyroid cancer (PTC) frequently disseminates into cervical lymph nodes. Lateral node involvement is described in up to 50 % patients undergoing prophylactic lateral neck dissection. This study aimed to assess this finding and identify which factors predict for occult lateral node disease. METHODS: Patients with fine needle aspiration-confirmed PTC (Bethesda V or VI), without evidence of cervical lymph node metastases, underwent a total thyroidectomy with prophylactic ipsilateral central and level 3 dissection. Level 3 nodes were removed by compartmental dissection or by sampling the sentinel nodes overlying the jugular vein,

according to surgeon preference. Data were collected prospectively from January 2011 to August 2014. Statistical analysis was performed by SPSS software. RESULTS: A total of 137 patients underwent total thyroidectomy with prophylactic ipsilateral central and level 3 dissection for PTC. The incidence of occult level 3 disease was 30 % (41/137 patients). A total of 48 % of patients (66/137) harbored occult central neck disease. A total of 80.5 % of patients with pN1b disease had macrometastases (>/=2 mm), and 15 % exhibited skip metastases with central compartment sparing. In patients with pN1b disease, a median of 6 level 3 nodes were retrieved, with an average involved nodal ratio of 0.29. Multivariate regression demonstrated risk factors for occult lateral neck metastasis include tumor size (odds ratio 1.1), upper pole tumors (odds ratio 6.6), and vascular invasion (odds ratio 3.2) ($p < 0.05$). CONCLUSIONS: PTC is associated with a significant incidence of occult central and lateral nodal metastases. In patients undergoing prophylactic central neck dissection, inclusion of level 3 dissection should be considered in patients with large upper lobe cancers.
PubMed-ID: 27188295
http://dx.doi.org/10.1245/s10434-016-5254-8

Noninvasive Follicular Variant of Papillary Thyroid Carcinoma and the Afirma Gene-Expression Classifier.
Thyroid, 26(7):911-5.
K. S. Wong, T. E. Angell, K. C. Strickland, E. K. Alexander, E. S. Cibas, J. F. Krane and J. A. Barletta. 2016.
BACKGROUND: It is now recognized that noninvasive follicular variant of papillary thyroid carcinoma (NFVPTC) is a distinct subset of FVPTC with an exceedingly indolent clinical course. The Afirma gene-expression classifier (GEC) helps guide clinicians in the management of thyroid nodules with indeterminate fine-needle aspiration (FNA) results. Thyroid surgery is recommended for nodules with a suspicious Afirma result, whereas observation is deemed reasonable for most nodules with a benign result. The aim of this study was to confirm that the Afirma test detects NFVPTCs and to determine how many carcinomas detected by the Afirma GEC represent NFVPTCs. METHODS: From a database of 249 FNAs sent for Afirma testing between January 2012 and October 2014, a search was conducted for cases with a preceding FNA diagnosis of atypia/follicular lesion of undetermined significance (AUS/FLUS) or suspicious for a follicular neoplasm (SFN), a suspicious Afirma result, and a corresponding resection specimen reviewed at Brigham and Women's Hospital. The diagnoses of the prior FNAs and subsequent resection specimens were recorded. Slides for all resection specimens with a diagnosis of FVPTC were reviewed to identify NFVPTCs. RESULTS: Sixty-three cases met the inclusion criteria. The preceding FNA diagnosis was AUS/FLUS in 34 (54%) cases and SFN in 29 (46%) cases. The surgical resection specimen demonstrated 16 (25%) FVPTCs, five (8%) follicular thyroid carcinomas, one (2%) classical type PTC, and 41 (65%) benign tumors/nodules. Of the 16 FVPTCs, 14 (88%) were NFVPTCs. Thus, NFVPTCs accounted for 64% of the carcinomas in the cohort. CONCLUSION: These results indicate that the Afirma GEC detects NFVPTCs and that many of the carcinomas detected by Afirma are NFVPTCs. While all care should be individualized and include clinical and sonographic assessment, these results suggest lobectomy as opposed to total thyroidectomy should be considered for nodules with a preceding AUS/FLUS or SFN on cytology and a suspicious Afirma result.
PubMed-ID: 27219469
http://dx.doi.org/10.1089/thy.2015.0644

Lobectomy is a more Cost-Effective Option than Total Thyroidectomy for 1 to 4 cm Papillary Thyroid Carcinoma that do not Possess Clinically Recognizable High-Risk Features.
Ann Surg Oncol, 23(11):3641-52.
B. H. Lang and C. K. Wong. 2016.
BACKGROUND: Although lobectomy is a viable alternative to total thyroidectomy (TT) in low-risk 1 to 4 cm papillary thyroid carcinoma (PTC), lobectomy is associated with higher locoregional recurrence risk and need for completion TT upon discovery of a previously unrecognized histologic high-risk feature (HRF). The present study evaluated long-term cost-effectiveness between lobectomy and TT. METHODS: Our base case was a hypothetical female cohort aged 40 years with a low-risk 2.5 cm PTC. A Markov decision tree model was constructed to compare cost-effectiveness between lobectomy and TT after 25 years. Patients with an unrecognized HRF (including aggressive histology, microscopic extrathyroidal extension, lymphovascular invasion, positive resection margin, nodal metastasis >5 mm, and multifocality) underwent completion TT after lobectomy. Outcome probabilities, utilities, and costs were estimated from the literature. The threshold for cost-effectiveness was set at US$50,000/quality-adjusted life-year (QALY). Sensitivity and threshold analyses were used to examine model uncertainty. RESULTS: After 25 years, each patient who underwent lobectomy instead of TT cost an extra US$772.08 but gained an additional 0.300 QALY. The incremental cost-effectiveness ratio was US$2577.65/QALY. In the sensitivity analysis, the lobectomy arm began to become cost-effective only after 3 years. Despite varying the reported prevalence of clinically unrecognized HRFs, complication from surgical

procedures, annualized recurrence rates, unit cost of surgical procedure or complication, and utility score, lobectomy remained more cost-effective than TT. CONCLUSIONS: Despite the higher locoregional recurrence risk and having almost half of the patients undergoing completion TT after lobectomy upon discovery of a previously unrecognized HRF, initial lobectomy was a more cost-effective long-term option than initial TT for 1 to 4 cm PTCs without clinically recognized HRFs.
PubMed-ID: 27221359
http://dx.doi.org/10.1245/s10434-016-5280-6

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

Molecular-Directed Treatment of Differentiated Thyroid Cancer: Advances in Diagnosis and Treatment.
JAMA Surg, 151(7):663-70.
L. Yip and J. A. Sosa. 2016.
IMPORTANCE: Thyroid cancer incidence is increasing, and when fine-needle aspiration biopsy results are cytologically indeterminate, the diagnosis is often still established only after thyroidectomy. Molecular marker testing may be helpful in guiding patient-oriented and tailored management of thyroid nodules and thyroid cancer. OBJECTIVE: To summarize available data on the use of molecular testing to improve the diagnosis and prognostication of thyroid cancer. EVIDENCE REVIEW: A MEDLINE review was conducted using the primary search terms molecular, thyroid cancer, thyroid nodule, and gene expression classifier in search strings. Articles were restricted to those published between January 1, 2010, and June 1, 2015, inclusive of adult humans, and reported in the English language only. FINDINGS: Of 867 titles screened, 67 articles were further identified for review of the full text. The 2 most studied molecular marker testing techniques for indeterminate thyroid nodules include gene expression classifier analysis and evaluation for somatic mutations or rearrangements that are commonly found in thyroid cancer (7-gene panel). Nodules with benign results on gene expression classifier analysis can be associated with less than a 5% risk of cancer and may be observed, while nodules with positive results on the 7-gene panel may have a higher risk of cancer (80%-100%) and definitive surgery can be recommended. However, cancer prevalence and geographic variations in histologic subtypes may affect accuracy and clinical applicability of both tests. Molecular marker tests such as ThyroSeq version 2.1 are more comprehensive, but they need further validation. Preoperative risk stratification using molecular markers also may be used to better define the optimal extent of thyroidectomy for patients with thyroid cancer. CONCLUSIONS AND RELEVANCE: Molecular markers potentially can augment the diagnostic specificity of fine-needle aspiration biopsy to better differentiate cytologically indeterminate nodules that can be safely observed from cytologically indeterminate nodules that may be associated with differentiated thyroid cancer. Long-term follow-up data are still needed; in the end, patient preference regarding the relative risks and benefits of molecular testing is at the crux of decision making.
PubMed-ID: 27223483
http://dx.doi.org/10.1001/jamasurg.2016.0825

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

Clinical Presentation and Diagnostic Challenges of Thyroid Lymphoma: A Cohort Study.
Thyroid, 26(8):1061-7.
A. Sharma, S. Jasim, C. C. Reading, K. M. Ristow, J. C. Villasboas Bisneto, T. M. Habermann, V. Fatourechi and M. Stan. 2016.
BACKGROUND: Thyroid lymphoma is a relatively rare disease often posing a diagnostic challenge. Reaching the final diagnosis can be delayed if insufficient biopsy material is obtained for immunohistochemistry analysis. The aim of this study was to evaluate the clinical, biochemical, and radiological features of thyroid lymphoma. METHODS: A retrospective analysis was conducted of all Mayo Clinic patients evaluated between 2000 and 2014 who had a tissue biopsy positive for thyroid lymphoma. RESULTS: Seventy-five subjects had biopsy-proven thyroid lymphoma, and 62.7% were primary thyroid lymphomas. The median age at diagnosis was 67 years (range 20-90 years). A total of 50.7% were male, and 54.7% had a history of Hashimoto's thyroiditis. Presenting symptoms included neck mass (88%), dysphagia (45.3%), and hoarseness (37.3%). The typical ultrasound appearance consisted of a solid, hypoechoic mass with increased vascularity and variable edge characteristics. Fine-needle aspiration (FNA) biopsies were abnormal in 70.7% of cases, and 42% indicated a specific lymphoma subtype. The diagnosis was confirmed in 53.3% by core biopsy, in 21.3% by thyroidectomy (partial or total), in 12% through incisional biopsy, and in 12% by lymph node biopsy. Core biopsy had a higher sensitivity compared with FNA (93% vs. 71%, p = 0.006). CONCLUSION: A rapidly enlarging neck mass in the setting of Hashimoto's thyroiditis should raise suspicion for thyroid lymphoma. Radiologically, this usually presents as a large, unilateral, thyroid-centered mass, hypoechoic by ultrasound, and expanding into adjacent soft tissues. Core-needle biopsy should be the first diagnostic test to expedite reaching the final diagnosis and decrease patient burden of additional tests and interventions.
PubMed-ID: 27256107
http://dx.doi.org/10.1089/thy.2016.0095

Patients with high-risk differentiated thyroid cancer have a lower I-131 ablation success rate than low-risk ones in spite of a high ablation activity.
Clin Endocrinol (Oxf),
J. Winter, M. Winter, T. Krohn, A. Heinzel, F. F. Behrendt, R. M. Tuttle, F. M. Mottaghy and F. A. Verburg. 2016.
OBJECTIVE: To examine success rates in strictly defined high-risk differentiated thyroid cancer (DTC) patients who received a high-activity (>/=5550 MBq) adjuvant postoperative I-131 therapy and compare these to the rates found in highest risk and low-risk patients. DESIGN: Retrospective database study. PATIENTS: We examined 377 patients with DTC who received I-131 ablation. Patients with distant metastases were classified as very high risk. Patients with primary tumours >4 cm, extensive extrathyroidal invasion (pT4a or pT4b in accordance with the 7th edition of the TNM system), and patients with >/=5 lymph node metastases or any lateral compartment lymph node metastases were considered high risk. All other patients were considered low risk. MEASUREMENTS: Ablation success rate at first TSH-stimulated follow-up. RESULTS: The ablation success rate was 72.6% in low-risk patients, 51.7% in high-risk patients and 13.8% in highest risk patients (all

differences P < 0.001). In none of the groups, a significant difference in the initial I-131 activity was found between patients with successful and unsuccessful ablation (low risk: P = 0.16, high risk: P = 0.91 and highest risk: P = 0.48). Furthermore, there was no difference in ablation success between patients who received <5550 MBq and those who received >/=5550 Mbq (low risk: P = 0.31, high risk: P = 0.69 and highest risk: P = 0.22). CONCLUSIONS: Patients with high-risk DTC have a significantly reduced I-131 ablation success rate compared to low-risk ones in spite of high initial I-131 activities. As successful ablation is prognostically important, efforts should be made to improve outcome in these patients.
PubMed-ID: 27256714
http://dx.doi.org/10.1111/cen.13123

Comparing a thyroid prognostic nomogram to the existing staging systems for prediction risk of death from thyroid cancers.
Eur J Surg Oncol, 42(10):1491-6.
K. A. Pathak, P. Lambert, R. W. Nason and T. Klonisch. 2016.
OBJECTIVE: Thyroid prognostic nomogram can be applied across different histological types for predicting the individualized risk of death from thyroid cancer. The objective of this study was to compare the strength of our recently published thyroid prognostic nomogram with 12 existing staging systems to predict the risk of death from thyroid cancer. METHOD: This study included 1900 thyroid cancer patients, from a population based cohort of 2296 patients, on whom adequate staging information was available. Competing risk sub-hazard models were used to compare 12 pre-existing prognostic models with the nomogram model. Their relative strengths for prediction of patients' individualized risks of death from thyroid cancer were compared using Akaike information criterion (AIC), delta AIC, and concordance index. R version 3.2.2 was used to analyze the data. RESULTS: Our cohort of 450 males and 1450 females included 1796 (93.4%) differentiated thyroid cancers. Amongst the compared models, thyroid prognostic nomogram model appeared to be better than other models for predicting the risk of death from all non-anaplastic thyroid cancer (concordance index = 94.4), differentiated thyroid cancer (concordance index = 94.1) and papillary thyroid cancer (concordance index = 94.7). The difference from next best staging systems was most pronounced in non-anaplastic thyroid cancer (delta AIC = 114.8), followed by differentiated thyroid cancer (delta AIC = 35.6) and papillary thyroid cancer (delta AIC = 8.4). CONCLUSIONS: Thyroid prognostic nomogram model was found to be better than the other models compared for predicting risk of death from thyroid cancer.
PubMed-ID: 27265038
http://dx.doi.org/10.1016/j.ejso.2016.05.016

(99m)Tc-Methoxy-Isobutyl-Isonitrile Scintigraphy Is a Useful Tool for Assessing the Risk of Malignancy in Thyroid Nodules with Indeterminate Fine-Needle Cytology.
Thyroid, 26(8):1101-9.
A. Campenni, L. Giovanella, M. Siracusa, A. Alibrandi, S. A. Pignata, S. Giovinazzo, F. Trimarchi, R. M. Ruggeri and S. Baldari. 2016.
BACKGROUND: Thyroid nodular disease is a very common clinical problem. The diagnostic algorithm includes laboratory tests, thyroid ultrasound (US), thyroid scintigraphy, and, if necessary, US-guided fine-needle aspiration cytology. However, cytology results are reported as indeterminate in a not negligible number of patients. This is a central problem in the workup of patients, since about 55-85% of those undergoing surgery do not have thyroid cancer at final histology diagnosis. The aim of this study was to evaluate prospectively the role of (99m)Tc-methoxy-isobutyl-isonitrile ((99m)Tc-MIBI) thyroid scintigraphy in differentiating malignant from benign thyroid nodules with indeterminate cytology using quantitative analysis. METHOD: One hundred five patients affected by nodular thyroid goiter and with a euthyroid or hypothyroid functional status were prospectively evaluated. All patients had a suspicious nodule >/=15 mm in maximal diameter on US. All nodules were "cold" on (99m)Tc-pertechnetate scintigraphy and had a cytological diagnosis of class III or IV according to the Bethesda system. Planar images of the thyroid were acquired 10 and 60 minutes after (99m)Tc-MIBI administration. All cold nodules were MIBI-positive. Using quantitative analysis, the MIBI washout index (WOind) was calculated as a percentage reduction value of mean MIBI nodular uptake between early (+10 minutes) and late (+60 minutes) scans. RESULTS: Subdividing the patients into positive and negative for malignancy (either including or excluding patients with Hurthle cell adenoma) and performing receiver operating characterist curve analysis, the optimal WOind cutoff in differentiating malignant from benign follicular lesions was set at -19%. The overall sensitivity and specificity of (99m)Tc-MIBI quantitative analysis in identifying patients with malignant lesions was 100% and 90.9%, respectively. However, after excluding patients with Hurthle cell adenomas from the negative patient group, the overall sensitivity and specificity both reached 100%. CONCLUSION: The use of MIBI scintigraphy using quantitative analysis in the workup of cold nodules with indeterminate cytology is suggested in order to stratify patient risk for a malignant lesion better, thus reducing the number of patients

referred to surgery. Surgical treatment should be planned in those patients with a WOind up to -19%.
PubMed-ID: 27266385
http://dx.doi.org/10.1089/thy.2016.0135

T1a Versus T1b Differentiated Thyroid Cancers: Do We Need to Make the Distinction?
Thyroid, 26(8):1046-52.
K. L. Anderson, Jr., L. M. Youngwirth, R. P. Scheri, M. T. Stang, S. A. Roman and J. A. Sosa. 2016.
BACKGROUND: The 7th edition of the American Joint Committee on Cancer (AJCC) staging system trialed a subdivision of T1 tumors into T1a (<1 cm) and T1b (1.0-2 cm). The 2009 American Thyroid Association (ATA) guidelines recommended total thyroidectomy for tumors >1 cm, and lobectomy for those </=1 cm. These AJCC staging parameters remain a focus of debate, and ATA guidelines are in transition. The aim of this study was to determine if the T1 staging subdivision is associated with different treatment strategies and patterns of patient survival. METHODS: All adult patients with AJCC pT1 differentiated thyroid cancer (DTC) from the National Cancer Data Base (NCDB; 1998-2012) and Surveillance, Epidemiology, and End Results (SEER) program (2004-2012) were divided into two groups based on tumor size: T1a versus T1b. Demographic, clinical, and pathologic features were evaluated. Multivariate regression analysis was used to determine factors associated with undergoing total thyroidectomy and radioactive iodine. Cox proportional hazards models were performed to determine factors associated with overall and disease-specific survival. RESULTS: Among 149,912 DTC patients, 98,111 (65.4%) were T1a and 51,801 (34.6%) T1b in the NCDB; in SEER, among 18,381 patients, 11,208 (61.0%) had T1a and 7173 (39.0%) T1b tumors. Patients with T1b cancers were younger (48 vs. 51 years T1a) and more likely to have private insurance (76.2% vs. 74.1%), no comorbidities (86.0% vs. 83.8%), and undergo treatment at academic medical centers (41.4% vs. 40.3%; all $p < 0.01$). They also were more likely to undergo total thyroidectomy (87.7% vs. 74.3%), and had more lymphovascular invasion (10.2% vs. 3.3%), positive surgical margins (7.9% vs. 3.8%), metastatic lymph nodes (35.8% vs. 23.8%), and distant metastases (0.4% vs. 0.3%; all $p < 0.01$). Factors associated with radioactive-iodine use included younger patient age, lower income, having insurance, positive surgical margins, and T1b stage ($p < 0.01$). After adjustment, overall ($p = 0.23$) and disease-specific survival ($p = 0.93$) were similar among patients with T1a versus T1b tumors. CONCLUSION: These results illustrate that patients with pT1a versus pT1b tumors undergo different treatment strategies. Based on the newly published 2015 ATA guidelines, whereby either lobectomy or total thyroidectomy can be performed for low-risk tumors, it might be anticipated that treatment differences will diminish over time. Therefore, division of AJCC T1 staging into T1a versus T1b subgroups might become obsolete over time.
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http://dx.doi.org/10.1089/thy.2016.0073

Can We Predict the Lateral Compartment Lymph Node Involvement in RET-Negative Patients with Medullary Thyroid Carcinoma?
Ann Surg Oncol, 23(11):3653-9.
M. M. Chandeze, S. Noullet, M. Faron, C. Tresallet, G. Godiris-Petit, F. Tissier, C. Buffet, L. Leenhardt, N. Chereau and F. Menegaux. 2016.
BACKGROUND: Lateral lymph node dissection (LND) in the absence of macroscopic nodal metastasis remains controversial in sporadic medullary thyroid carcinoma (MTC). OBJECTIVES: The aims of our study were to determine the risk of lateral lymph node (LN) metastases with a focus on lateral contralateral N1, and to define a risk-adapted surgical treatment for these patients. METHODS: All patients who underwent surgery from 1980 to 2012 for previously untreated RET-negative MTC were reviewed. We focused on the lateral compartments of LN metastases and identified three groups: no lateral LN metastases, ipsilateral lateral (ILL)-LN metastases with no contralateral LN involvement, and contralateral lateral (CLL)-LN metastases. RESULTS: Overall, 131 patients underwent surgery for RET-negative MTC. A total thyroidectomy with LND was performed in 112 patients (85 %), including 97 patients who had an ILL-LND and 92 patients who had a CLL-LND. Lateral LN metastases (N1) occurred in 40 patients (37 %): 31 patients (32 %) had ILL-LN metastases with no contralateral LN involvement, and 9 patients (10 %) had CLL-LN metastases. The preoperative cut-offs for LN metastases in the ILL compartment were very low, with a smallest tumor size of 5 mm, and lowest serum calcitonin level of 38 pg/ml. Disease-free survival rates decreased from 92 % for patients with no lateral LN metastases to 41 % for patients with ILL-LN metastases and 0 % for patients with CLL-LN metastases. CONCLUSIONS: ILL-LND should be performed in every patient and only a minority of MTC patients with small micro-MTC, and low serum calcitonin levels should not have a CLL-LND.
PubMed-ID: 27271930
http://dx.doi.org/10.1245/s10434-016-5292-2

Treatment of hyperthyroidism with antithyroid drugs corrects mild neutropenia in Graves' disease.
Clin Endocrinol (Oxf),
N. Aggarwal, S. A. Tee, W. Saqib, T. Fretwell, G. P. Summerfield and S. Razvi. 2016.
CONTEXT: Neutropenia secondary to antithyroid drug (ATD) therapy in Graves' disease (GD) is well recognized. However, the effect of hyperthyroidism, prior to and after ATD therapy, on neutrophil counts in patients with GD is unclear. OBJECTIVE: To study the prevalence of neutropenia in newly diagnosed untreated GD and the effect of ATD on the neutrophil count. DESIGN: Prospective study from August 2010 to December 2014. SETTING: Endocrinology outpatient clinic in a single centre. PATIENTS: Consecutive patients (n = 206) with newly diagnosed GD. INTERVENTION: ATD therapy. MAIN OUTCOME MEASURES: Prevalence and factors predicting neutropenia (<2 x 109 /l) and change in neutrophil counts following ATD. RESULTS: At diagnosis, 29 (14.1%) of GD individuals had neutropenia. Non-Caucasians [odds ratio (95% CI) of 4.06 (1.14-14.45), P = 0.03] and patients with higher serum thyroid hormone levels [OR 1.07 (1.02-1.13), P = 0.002 for serum FT3] were the only independent predictors of neutropenia. All patients with neutropenia had normalized blood neutrophil levels after achieving euthyroidism with ATD therapy. In patients in whom data were available posteuthyroidism (n = 149), change in neutrophil count after achieving euthyroidism was independently related to reduction in thyroid hormone levels (P < 0.01). CONCLUSIONS: GD is associated with neutropenia in one in seven patients at diagnosis, especially in non-Caucasians and those with higher serum thyroid hormone levels. Neutrophil counts increase with treatment with ATD and are related to reduction in thyroid hormone concentrations. It is therefore important to check neutrophil levels in newly diagnosed patients with GD prior to commencing ATD therapy as otherwise low levels may incorrectly be attributed to ATD therapy.
PubMed-ID: 27291145
http://dx.doi.org/10.1111/cen.13133

[Total thyroidectomy without radioiodine ablation for low-risk thyroid cancer].
Chirurg, 87(8):698.
H. Dralle. 2016.
PubMed-ID: 27299751
http://dx.doi.org/10.1007/s00104-016-0203-4

Incidence of Nonthyroidal Primary Malignancy and the Association with (131)I Treatment in Patients with Differentiated Thyroid Cancer.
Thyroid, 26(8):1110-6.
D. Hirsch, T. Shohat, A. Gorshtein, E. Robenshtok, I. Shimon and C. Benbassat. 2016.
BACKGROUND: The occurrence of nonthyroidal primary malignancy (NTPM) and the potential association of with radioiodine (RAI) treatment are important concerns in patients with differentiated thyroid cancer (DTC), but incidence data are conflicting. The aims of the present study were to investigate the incidence of NTPM and its association with RAI treatment in a cohort of DTC patients treated at a single tertiary medical center. METHODS: The data of 1943 patients with DTC recorded in the Rabin Medical Center Thyroid Cancer Registry were cross-matched with data from the Israeli National Cancer Registry to identify those diagnosed with an NTPM. Patient medical files were reviewed. Second primary malignancy (SPM) was defined as new malignancy diagnosed at least two years after DTC diagnosis. RESULTS: For 1434 of the 1943 patients (73.8%), the American Joint Committee on Cancer TNM stage was 1-2. The mean follow-up was 9.3 years. Of the 1943 patients, 1574 (81%) were treated with RAI, and 1467 were followed for at least 2 years, and of these, 1145 patients (78%) received a cumulative dose of </=200 mCi. A total of 409 NTPMs were diagnosed in 368/1943 patients with DTC (18.9%; 265 female, mean age 53.9 +/- 15 years), including 173 SPMs (42.3%) in 166/368 patients. The most common NTPM and SPM was breast cancer followed by hematologic malignancies. In patients followed for >/=2 years, SPMs were diagnosed in 9% of RAI-treated patients and 10.5% of non-RAI-treated patients. SPM rates were 10.2% and 7.8% for a cumulative RAI dose of </=100 mCi and >100 mCi respectively. Hazard ratios for SPM in patients that received/did not receive RAI treatment was 1.27 (95% confidence interval 0.88-1.82; p = 0.1). There was no correlation between first or cumulative RAI dose and diagnosis of SPM. CONCLUSIONS: NTPMs are not uncommon in patients with DTC and usually antecede the DTC. In a population of mostly low-risk DTC patients, in whom limited activities of RAI are usually administered, this treatment is apparently not associated with an overall increased risk of SPMs compared with subjects not receiving RAI treatment.
PubMed-ID: 27302111
http://dx.doi.org/10.1089/thy.2016.0037

Follicular and Diffuse Sclerosing Variant Papillary Thyroid Carcinomas as Independent Predictive Factors of Loco-Regional Recurrence: A Comparison Study Using Propensity Score Matching.
Thyroid, 26(8):1077-84.
S. K. Kim, I. Park, J. W. Woo, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2016.
BACKGROUND: Only about half of papillary thyroid carcinoma (PTC) cases are classified as conventional PTC (CV-PTC), whereas various histologic variants constitute the remaining cases. Since controversies about the clinical behavior and outcomes of PTC variants continue, the purpose of this study was to compare the outcomes of patients with PTC variants who were treated at a large tertiary referral center in Korea. METHODS: The medical records for 15,598 CV-PTCs, 435 follicular variants of PTC (FV-PTCs), and 66 diffuse sclerosing variants of PTC (DSV-PTCs) were retrospectively reviewed. Loco-regional recurrences (LRR) among PTC variants were compared using propensity score matching. RESULTS: Analysis I compared CV-PTC with FV-PTC. After rigorous matching, 367 pairs were established. Recurrence-free survival (RFS) rates in CV-PTC were 96.1% at 5 years, 92.2% at 10 years, and 92.2% at 15 years, while those for FV-PTC were 98.8% at 5 years, 98.8% at 10 years, and 98.8% at 15 years (p = 0.026). Analysis II compared CV-PTC with DSV-PTC. Rigorous matching yielded 56 pairs. RFS rates for CV-PTC were 87.4% at 5 years, 87.4% at 10 years, and 87.4% at 15 years, while those for DSV-PTC were 68.9% at 5 years, 57.5% at 10 years, and were not available at 15 years (p = 0.013). CONCLUSIONS: Compared with CV-PTC, FV-PTC showed less aggressive behaviors and more favorable outcomes. However, DSV-PTC showed more aggressive behaviors and a less favorable outcome than CV-PTC did. Therefore, the management strategy and follow-up plan for PTC should be differentiated according to the histologic variant.
PubMed-ID: 27324748
http://dx.doi.org/10.1089/thy.2016.0113

Follicular variant of papillary thyroid carcinoma: comparison of ultrasound-guided core needle biopsy and ultrasound-guided fine needle aspiration in a multicentre study.
Clin Endocrinol (Oxf),
S. Y. Hahn, J. H. Shin, H. K. Lim and S. L. Jung. 2016.
OBJECTIVE: Pre-operative diagnosis of the follicular variant of papillary thyroid carcinoma (FVPTC) by ultrasound-guided fine needle aspiration (US-FNA) remains a challenge. The goal of this study was to investigate whether ultrasound-guided core needle biopsy (US-CNB) is superior to US-FNA in refining the surgical indications for the treatment of FVPTC. DESIGN: This retrospective study enrolled 212 patients with 218 FVPTCs who were surgically confirmed at three university hospitals from January 2008 through December 2014. All patients underwent both or either US-FNA or US-CNB. FNA and CNB results were divided into identified surgical candidates or not based on the Bethesda system. Relevant clinical information and the rate of surgical candidates were compared between US-FNA and US-CNB groups. RESULTS: Among 218 thyroid nodules, US-FNA was performed for 200 nodules and US-CNB for 51 nodules. Thirty-three nodules underwent both US-FNA and US-CNB. The rates of surgical candidates identified by US-FNA and US-CNB were 61.5% and 86.3%, respectively (P = 0.001). The rates of surgical candidates identified by repeat US-FNA and initial US-FNA with subsequent US-CNB were 53.9% and 78.8%, respectively (P = 0.042). A precise diagnosis of FVPTC was made in 1% of the patients in the US-FNA group and in 29.4% of the patients in the US-CNB group. The predominant US findings of FVPTCs included solid tumours (89.4%), wider-than-tall shape (82.6%), no calcifications (51.3%), hypoechogenicity (46.3%) and indeterminate diagnosis on US (50.5%). CONCLUSIONS: In patients with FVPTC, US-CNB is a superior indicator for surgery compared to US-FNA. If a FVPTC is suspected but is initially indeterminate at FNA cytology, subsequent US-CNB should be considered instead of repeat US-FNA.
PubMed-ID: 27338864
http://dx.doi.org/10.1111/cen.13144

Activity and Safety of Sunitinib in Patients with Advanced Radioiodine Refractory Thyroid Carcinoma: A Retrospective Analysis of 57 Patients.
Thyroid, 26(8):1085-92.
V. Atallah, A. Hocquelet, C. Do Cao, S. Zerdoud, C. De La Fouchardiere, S. Bardet, A. Italiano, A. Dierick-Galet, N. Leduc, F. Bonichon, S. Leboulleux and Y. Godbert. 2016.
BACKGROUND: The aim of this study was to evaluate the effectiveness of sunitinib in patients with progressive radioiodine refractory (RAIR) thyroid cancer (TC). MATERIALS AND METHODS: A multicentric retrospective analysis was performed of patients treated in six TUmeurs THYroidiennes REFractaires participating centers. All patients with progressive RAIR TC who were treated with sunitinib outside a clinical trial between August 2007 and March 2015 were retrospectively and consecutively included. The primary endpoint was the overall response rate (ORR) and disease control rate >/=6 months based on RECIST criteria. Secondary endpoints included evaluation of overall survival (OS) and progression-free survival (PFS) from the first dose of sunitinib.

Primary and secondary endpoints were also evaluated according to treatment setting: first or second line of tyrosine kinase inhibitor (TKI). RESULTS: Fifty-seven patients (29 men; 50.8%), mean age 62.2 years (range 43-80 years) with progressive RAIR TC were included. Sunitinib was the first-line TKI treatment for 32 (56.1%) patients and the second-line TKI treatment for 25 (43.9%) patients. For all patients, according to RECIST criteria, ORR was 35.1% (20 patients) and disease control rate >/=6 months was 68.4% (39 patients). No complete response was observed. Six (10.5%) patients showed disease progression. When sunitinib was used as first-line TKI therapy, ORR was 46.9% (15/32 patients), and disease control rate >/=6 months was 75% (24/32 patients). When sunitinib was used as second-line TKI therapy, ORR was 20% (5/25 patients), and disease control rate >/=6 months was 60% (15/25 patients). The median OS and PFS were 21.0 (range 15-29) and 10.2 months (range 6-13), respectively, for all patients. With sunitinib as first-line TKI-therapy, median OS and PFS was 30.0 (range 19.0-53.0) and 15 (range 7.0-21.0) months, respectively. As second-line therapy, median OS and PFS were 13 (range 8.0-20.0) and 6 (range 5.0-11.0) months, respectively. Eleven (19.3%) patients experienced grade 3 toxicity, and four patients (7.0%) experienced grade 4 toxicity. CONCLUSION: The efficacy of sunitinib as first- and second-line TKI therapy in a large cohort of patients treated for progressive RAIR TC is herein reported. Further prospective studies are needed to evaluate the effectiveness of sunitinib in RAIR TC.
PubMed-ID: 27370404
http://dx.doi.org/10.1089/thy.2015.0648

Thyroid Disease and Surgery in CHEER: The Nation's Otolaryngology-Head and Neck Surgery Practice-Based Network.
Otolaryngol Head Neck Surg, 155(1):22-7.
K. Parham, N. Chapurin, K. Schulz, J. J. Shin, M. A. Pynnonen, D. L. Witsell, A. Langman, A. Nguyen-Huynh, S. E. Ryan, A. Vambutas, A. Wolfley, R. Roberts and W. T. Lee. 2016.
OBJECTIVES: (1) Describe thyroid-related diagnoses and procedures in Creating Healthcare Excellence through Education and Research (CHEER) across academic and community sites. (2) Compare management of malignant thyroid disease across these sites. (3) Provide practice-based data related to flexible laryngoscopy vocal fold assessment before and after thyroid surgery based on the American Academy of Otolaryngology-Head and Neck Surgery Foundation's clinical practice guidelines. STUDY DESIGN: Review of retrospective data collection (RDC) database of the CHEER network using ICD-9 and CPT codes related to thyroid conditions. SETTING: Multisite practice-based network. SUBJECTS AND METHODS: There were 3807 thyroid patients (1392 malignant, 2415 benign) with 10,160 unique visits identified from 1 year of patient data in the RDC. Analysis was performed for identified cohort of patients using demographics, site characteristics, and diagnostic and procedural distribution. RESULTS: Mean number of patients with thyroid disease per site was 238 (range, 23-715). In community practices, 19% of patients with thyroid disease had cancer versus 45% in the academic setting (P < .001). While academic sites manage more cancer patients, community sites are also surgically treating thyroid cancer and performed more procedures per cancer patient (4.2 vs 3.5, P < .001). Vocal fold function was assessed by flexible laryngoscopy in 34.0% of preoperative patients and in 3.7% postoperatively. CONCLUSION: This is the first overview of malignant and benign thyroid disease through CHEER. It shows how the RDC can be used alone and with national guidelines to inform of clinical practice patterns in academic and community sites. This demonstrates the potential for future thyroid-related studies utilizing the otolaryngology-head and neck surgery practice-based research network.
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http://dx.doi.org/10.1177/0194599815627641

Prophylactic "First-Step" Central Neck Dissection (Level 6) Does Not Increase Morbidity After (Total) Thyroidectomy.
Ann Surg Oncol, 23(12):4016-22.
A. Selberherr, P. Riss, C. Scheuba and B. Niederle. 2016.
BACKGROUND: In terms of morbidity, prophylactic central neck dissection (CND; level 6) in potentially malignant thyroid disease is discussed controversially. The rates of (transient and permanent) hypoparathyroidism and palsy of the recurrent laryngeal nerve (RLN) after "first-step" (FS-)CND are analyzed in this study. METHODS: Bilateral and unilateral FSCND, i.e., lymph node dissection along the RLN before (total) thyroidectomy, was performed bilaterally in 68 (group 1) and unilaterally in 44 patients (group 2), respectively. The rates of hypoparathyroidism and palsy of the RLN were documented prospectively and were compared to 237 patients of group 3 (controls) who underwent (total) thyroidectomy only. RESULTS: Fifteen of 68 patients (22 %) of group 1 developed transient and one patient had permanent hypoparathyroidism. Transient unilateral palsy of the RLN was observed in ten patients (15 %); none were permanent. Transient hypoparathyroidism was monitored in 10 of 44 patients (23 %) of group 2 and permanent hypoparathyroidism in 1 (2 %). Six patients (14 %) developed temporary palsy of the RLN; one remained permanent. Palsy was seen in 3 patients on the

contralateral side of unilateral FSCND. Transient and permanent hypoparathyroidism was observed in 50 (21 %) and 2 (1 %) of 237 controls. Transient palsy of the RLN was documented in 22 (9 %) of 237 controls and permanent palsy of the RLN in 4 (2 %). CONCLUSIONS: In this single-center series, the overall permanent morbidity was low (1 %). Therefore, FSCND may be recommended (even prophylactically) for experienced high-volume surgeons in patients with thyroid nodules suspicious for malignancy.
PubMed-ID: 27393573
http://dx.doi.org/10.1245/s10434-016-5338-5

Is postablation whole-body 131 I scintigraphy still necessary in intermediate-risk papillary thyroid cancer patients with pre-ablation stimulated thyroglobulin <1 ng/mL?
Clin Endocrinol (Oxf),
B. Liu, Y. Chen, L. Jiang, Y. He, R. Huang and A. Kuang. 2016.
OBJECTIVE: Postablation whole-body scintigraphy, which is performed 5-7 days after administration of ablation activity of radioactive iodine-131 (131 I) in patients with thyroid cancer, is considered a routine procedure for remnant ablation and a useful tool for disease staging. However, the relationship of pre-ablation stimulated thyroglobulin (s-Tg) levels with postablation scintigraphic findings has not been evaluated. The current study was designed to determine the diagnostic value of postablation 131 I scintigraphy during initial staging and risk stratification in intermediate-risk papillary thyroid cancer (PTC) patients with pre-ablation s-Tg < 1 ng/ml at the time of ablation. DESIGN: From January 2013 to July 2015, consecutive PTC patients at intermediate-risk of recurrence according to American Thyroid Association criteria were prospectively recruited. Patients had to have pre-ablation s-Tg < 1 ng/ml in the absence of anti-Tg antibody at the time of ablation. Systematic pre-ablation neck ultrasonography was performed for each patient. Postablation whole-body planar scintigraphy was obtained 5 days after administration of ablation activity of 131 I. Single photon emission computed tomography/low-dose computed tomography was added for patients whose planar findings were inconclusive. RESULTS: Among 756 patients ablated, 240 (31.7%) patients were eligible for the analysis. Pre-ablation neck ultrasonography revealed lymph node metastases in eight of the 240 patients. Postablation scintigraphy showed ectopic neck uptake corresponding to the lymph nodes seen by ultrasonography in four patients and revealed neck lymph node metastases in another two patients whose ultrasonography findings were negative. None of the 240 patients showed distant metastasis on postablation scintigraphy. Neither staging nor initial risk stratification was altered by postablation scintigraphy in the included patients with pre-ablation s-Tg < 1 ng/ml. CONCLUSIONS: As postablation whole-body scintigraphy played a minimal role in improving staging or initial risk stratification in intermediate-risk PTC patients with pre-ablation s-Tg < 1 ng/ml, we propose that postablation scintigraphy may be omitted in this group of patients. Multi-institutional larger studies are necessary to draw definitive conclusions.
PubMed-ID: 27434740
http://dx.doi.org/10.1111/cen.13158

Hysterectomy, Oophorectomy, and Risk of Thyroid Cancer.
J Clin Endocrinol Metab, 101(10):3812-9.
J. Luo, M. Hendryx, J. E. Manson, X. Liang and K. L. Margolis. 2016.
CONTEXT: Estrogen has been suggested as a risk factor for thyroid cancer. OBJECTIVE: The aim of this study is to examine the associations between hysterectomy, bilateral salpingo-oophorectomy (BSO), and incidence of thyroid cancer. DESIGN: This was a prospective cohort study. SETTING: The study was conducted at 40 clinical centers in the United States. PARTICIPANTS: A total of 127 566 women aged 50-79 were enrolled in the Women's Health Initiative during 1993-1998. MAIN OUTCOME MEASURES: Hysterectomy and BSO were self-reported. Incident thyroid cancer cases were confirmed by medical record review. RESULTS: Three hundred forty-four incident thyroid cancer cases were identified during an average of 14.4 years of follow-up. Compared with women without hysterectomy, women with hysterectomy, regardless of ovarian status, had a significantly higher risk of thyroid cancer (hazard ratio 1.46 [95% confidence interval 1.16-1.85]). Hysterectomy with BSO was not associated with a lower risk for thyroid cancer compared with hysterectomy alone. Among women with hysterectomy alone, hormone therapy use was associated with lower risk of thyroid cancer (hazard ratio 0.47 [95% confidence interval 0.28-0.78]). However, we did not observe significant associations between hormone therapy use and thyroid cancer in women without hysterectomy or women with hysterectomy plus BSO. CONCLUSION: Our large prospective study observed that hysterectomy, regardless of oophorectomy status, was associated with increased risk of thyroid cancer among postmenopausal women. In addition, our data did not support the hypotheses that exogenous estrogen is a risk factor or that estrogen deprivation is a protective factor for thyroid cancer. Further research is needed to clarify whether these apparent associations may be due to shared risk factors between indications for hysterectomy and thyroid cancer.

PubMed-ID: 27459531
http://dx.doi.org/10.1210/jc.2016-2011

The significance of unrecognized histological high-risk features on response to therapy in papillary thyroid carcinoma measuring 1-4 cm: implications for completion thyroidectomy following lobectomy.
Clin Endocrinol (Oxf),
B. H. Lang, T. W. Shek and K. Y. Wan. 2016.
BACKGROUND: Although lobectomy is an alternative to total thyroidectomy (TT) for 1-4 cm papillary thyroid carcinoma (PTC) without high-risk features (HRFs) such as aggressive histology, vascular invasion, lymphovascular invasion (LVI), microscopic extrathyroidal extension, positive margin, nodal metastasis >5 mm and multifocality, these HRFs are not recognized until after surgery. Therefore, the chance of completion TT being required following lobectomy might be high. We evaluated the frequency of unrecognized HRFs and how they affected the response to therapy following TT and radioiodine (RAI). METHODS: Altogether, 1513 patients were analysed. Only 1-4 cm PTCs without recognizable HRFs were included. For response-to-therapy evaluation, only patients who had TT and post-RAI-stimulated thyroglobulin were analysed. Patients without an excellent response were defined as having 'incomplete response'. A multivariate analysis for incomplete response was performed. RESULTS: Of the 600 patients eligible for lobectomy, 257 (42.8%) had >/=1 unrecognized histological HRF before surgery. The prevalence of unrecognized HRFs was similar between 1-2 cm and >2-4 cm PTCs (P = 0.393). Of the 330 patients eligible for response-to-therapy evaluation, 260 (78.8%) had an excellent response while 70 (21.2%) had an incomplete response. LVI was the only independent unrecognized HRF for incomplete response (P = 0.021). CONCLUSIONS: The prevalence of unrecognized histological HRFs under the current recommendations is relatively high among 1-4 cm PTCs. Among the unrecognized histological HRFs, LVI was the only one which independently associated with an incomplete response (i.e. posing an increased risk of persistent/recurrent disease after curative surgery). These findings may have implications for patients who undergo lobectomy for 1-4 cm PTCs with no clinically recognizable HRFs under the current recommendations.
PubMed-ID: 27467318
http://dx.doi.org/10.1111/cen.13165

Risk factors for lymph node metastasis in papillary thyroid microcarcinoma: Older patients with fewer lymph node metastases.
Eur J Surg Oncol, 42(10):1478-82.
L. Zhang, J. Yang, Q. Sun, Y. Liu, F. Liang, Z. Liu, G. Chen, S. Chen, Z. Shang, Y. Li and X. Li. 2016.
BACKGROUND: Lymph node metastasis (LNM) is an important consideration in treatment strategy selection for papillary thyroid microcarcinoma (PTMC). The aim of this study was to investigate the risk factors for LNM and high-volume LNM (hvLNM, >5 metastatic lymph nodes). METHODS: A consecutive series of 1226 PTMC (947 female, 279 male) patients was reviewed. All patients underwent at least central neck dissection. Clinical-pathological features were assessed. All patients were allocated into Group A (</=39 yrs), Group B (40-59 yrs), or Group C (>/=60 yrs) for risk factor analysis. RESULTS: Among all patients, 438 LNM and 73 hvLNM were detected. Older patients had significantly fewer LNM (A: 51.45% of 346, B: 30.15% of 786, and C: 24.47% of 94) and fewer hvLNM (A: 11.85%, B: 3.94%, and C: 1.06%). Male, multifocality, and tumor diameter >0.5 cm were also correlated with LNM and hvLNM. In multivariate analysis, older patients had lower risk of LNM (odds ratio [OR] 0.389 in B, 0.305 in C), and chronic thyroiditis was protective factor for LNM (OR 0.524). Male (OR 1.651), tumor diameter >0.5 cm (OR 1.850), and multifocality (OR 1.928) were risk factors for LNM. Similarly, older patients had lower risk of hvLNM (OR 0.313 in B, OR 0.085 in C). Male (OR 2.590), tumor diameter >0.5 cm (OR 2.180), and multifocality (OR 1.980) were also risk factors for hvLNM. CONCLUSION: Older PTMC patients may have fewer LNM and lower risk of hvLNM. For patients >/=60 years old, dynamic observation may be an option for clinical management.
PubMed-ID: 27475736
http://dx.doi.org/10.1016/j.ejso.2016.07.002

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

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

Sustained Response to Vemurafenib in a BRAFV600E-Mutated Anaplastic Thyroid Carcinoma Patient.
Thyroid, 26(10):1515-6.
G. W. Prager, O. Koperek, M. E. Mayerhoefer, L. Muellauer, F. Wrba, B. Niederle, C. C. Zielinski and M. Raderer. 2016.
PubMed-ID: 27532222
http://dx.doi.org/10.1089/thy.2015.0575

Risk Factors of 131I-Induced Salivary Gland Damage in Thyroid Cancer Patients.
J Clin Endocrinol Metab, 101(11):4085-93.
B. Hollingsworth, L. Senter, X. Zhang, G. N. Brock, W. Jarjour, R. Nagy, P. Brock, K. R. Coombes, R. T. Kloos, M. D. Ringel, J. Sipos, I. Lattimer, R. Carrau and S. M. Jhiang. 2016.
CONTEXT: Sialadenitis and xerostomia are major adverse effects of 131I therapy in thyroid cancer patients. The risk factors for these adverse effects, other than administered activity of 131I, have not been investigated. OBJECTIVE: The aim of this study is to identify risk factors for 131I-induced salivary gland damage among follicular cell-derived thyroid cancer patients. DESIGN: We enrolled 216 thyroid cancer patients who visited The Ohio State University Wexner Medical Center between April 2013 and April 2014. Symptoms of xerostomia and sialadenitis were identified via questionnaire and medical record search. To validate the findings in a large cohort, we retrospectively searched for ICD-9/10 codes for sialadenitis, xerostomia, and autoimmune disease associated with Sjogren's syndrome (AID-SS) in our existing database (n = 1507). Demographic and clinical information was extracted from medical records. Multivariate analyses were performed to identify independent predictors for salivary gland damage. RESULTS: 131I treatment associated with higher incidence of xerostomia and sialadenitis. Patients with xerostomia had 46 mCi higher mean cumulative 131I activity and 21 mCi higher mean first-administered 131I activity than patients without xerostomia. Increased age associated with higher incidence of xerostomia, and females had a higher incidence of sialadenitis. Patients who experienced sialadenitis before 131I therapy had higher sialadenitis incidence after 131I therapy. 131I-treated patients diagnosed with AID-SS, whether before or after 131I treatment, had a higher incidence of xerostomia and sialadenitis among 131I-treated patients. CONCLUSION: Risk factors for 131I-induced salivary gland damage include administered 131I activity, age, gender, history of sialadenitis before 131I treatment, and AID-SS diagnosis.
PubMed-ID: 27533304
http://dx.doi.org/10.1210/jc.2016-1605

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

A Randomized Study Comparing Parathyroidectomy with Cinacalcet for Treating Hypercalcemia in Kidney Allograft Recipients with Hyperparathyroidism.
J Am Soc Nephrol, 27(8):2487-94.
J. M. Cruzado, P. Moreno, J. V. Torregrosa, O. Taco, R. Mast, C. Gomez-Vaquero, C. Polo, I. Revuelta, J. Francos, J. Torras, A. Garcia-Barrasa, O. Bestard and J. M. Grinyo. 2016.
Tertiary hyperparathyroidism is a common cause of hypercalcemia after kidney transplant. We designed this 12-month, prospective, multicenter, open-label, randomized study to evaluate whether subtotal parathyroidectomy is more effective than cinacalcet for controlling hypercalcemia caused by persistent hyperparathyroidism after kidney transplant. Kidney allograft recipients with hypercalcemia and elevated intact parathyroid hormone (iPTH) concentration were eligible if they had received a transplant >/=6 months before the study and had an eGFR>30 ml/min per 1.73 m(2) The primary end point was the proportion of patients with normocalcemia at 12 months. Secondary end points were serum iPTH concentration, serum phosphate concentration, bone mineral density, vascular calcification, renal function, patient and graft survival, and economic cost. In total, 30 patients were randomized to receive cinacalcet (n=15) or subtotal parathyroidectomy (n=15). At 12 months, ten of 15 patients in the cinacalcet group and 15 of 15 patients in the parathyroidectomy group (P=0.04) achieved normocalcemia. Normalization of serum phosphate concentration occurred in almost all patients. Subtotal parathyroidectomy induced greater reduction of iPTH and associated with a significant increase in femoral neck bone mineral density; vascular calcification remained unchanged in both groups. The most frequent adverse events were digestive intolerance in the cinacalcet group and hypocalcemia in the parathyroidectomy group. Surgery would be more cost effective than cinacalcet if cinacalcet duration reached 14 months. All patients were alive with a functioning graft at the end of follow-up. In conclusion, subtotal parathyroidectomy was superior to cinacalcet in controlling hypercalcemia in these patients with kidney transplants and persistent hyperparathyroidism.
PubMed-ID: 26647424
http://dx.doi.org/10.1681/ASN.2015060622

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

[Optical coherence tomography for differentiation of parathyroid gland tissue].
Chirurg, 87(5):416-22.
R. Ladurner, K. Hallfeldt, N. Al Arabi, J. Gallwas, U. Mortensen and S. Sommerey. 2016.
BACKGROUND: Optical coherence tomography (OCT) is a high-resolution imaging technique that allows the identification of microarchitectural features in real-time. OBJECTIVE: Can OCT be used to differentiate parathyroid tissue from other cervical tissue entities? MATERIAL AND METHODS: All investigations were carried out during cervical operations. Initially, ex vivo images were analyzed to define morphological imaging criteria for each tissue entity. These criteria were used to evaluate a first series of ex vivo images. In a second phase the practicability of the technique was investigated in vivo and in the third phase backscattering intensity measurements were analyzed employing linear discriminant analysis (LDA). RESULTS: In the ex vivo series parathyroid tissue could be differentiated from other tissue entities with a sensitivity and specificity of 84 % and 94 %, respectively. Parathyroid tissue was correctly identified in the in vivo series in only 69.2 %. The analysis of backscattering intensity profiles employing LDA reliably distinguished between the different tissue types. CONCLUSION: The OCT images displayed typical characteristics for each tissue entity. Due to technical problems in handling the probe the in vivo OCT images were of much poorer quality. Backscattering intensity measurements illustrated that OCT images provide an individual profile for each tissue entity independent of the defined morphological assessment criteria. The results show that OCT is fundamentally suitable for intraoperative differentiation of tissues.
PubMed-ID: 26661948
http://dx.doi.org/10.1007/s00104-015-0120-y

Diphtheria Toxin- and GFP-Based Mouse Models of Acquired Hypoparathyroidism and Treatment With a Long-Acting Parathyroid Hormone Analog.
J Bone Miner Res, 31(5):975-84.
R. Bi, Y. Fan, K. Lauter, J. Hu, T. Watanabe, J. Cradock, Q. Yuan, T. Gardella and M. Mannstadt. 2016.
Hypoparathyroidism (HP) arises most commonly from parathyroid (PT) gland damage associated with neck surgery, and is typically treated with oral calcium and active vitamin D. Such treatment effectively increases levels of serum calcium (sCa), but also brings risk of hypercalciuria and renal damage. There is thus considerable interest in using PTH or PTH analogs to treat HP. To facilitate study of this disease and the assessment of new treatment options, we developed two mouse models of acquired HP, and used them to assess efficacy of PTH(1-34) as well as a long-acting PTH analog (LA-PTH) in regulating blood calcium levels. In one model, we used PTHcre-iDTR mice in which the diphtheria toxin (DT) receptor (DTR) is selectively expressed in PT glands, such that systemic DT administration selectively ablates parathyroid cells. For the second model, we generated GFP-PT mice in which green fluorescent protein (GFP) is selectively expressed in PT cells, such that parathyroidectomy (PTX) is facilitated by green fluorescence of the PT glands. In the PTHcre-iDTR mice, DT injection (2 x 5 mug/kg, i.p.) resulted in moderate yet consistent reductions in serum PTH and sCa levels. The more severe hypoparathyroid phenotype was observed in GFP-PT mice following GFP-guided PTX surgery. In each model, a single subcutaneous injection of LA-PTH increased sCa levels more effectively and for a longer duration (>24 hours) than did a 10-fold higher dose of PTH(1-34), without causing excessive urinary calcium excretion. These new mouse models thus faithfully replicate two degrees of acquired HP, moderate and severe, and may be useful for assessing potential new modes of therapy. (c) 2015 American Society for Bone and Mineral Research.
PubMed-ID: 26678919
http://dx.doi.org/10.1002/jbmr.2769

Parathyroid 4D CT and Scintigraphy: What Factors Contribute to Missed Parathyroid Lesions?
Otolaryngol Head Neck Surg, 154(5):847-53.
L. Galvin, J. D. Oldan, M. Bahl, J. D. Eastwood, J. A. Sosa and J. K. Hoang. 2016.

OBJECTIVE: To determine the prevalence of missed lesions for parathyroid 4-dimensional computed tomography (4D CT) and scintigraphy and to describe the factors leading to missed lesions for both modalities. STUDY DESIGN: Case series with chart review. SETTING: Single center, hospital based. SUBJECTS AND METHODS: Forty patients undergoing 4D CT and scintigraphy before parathyroidectomy between July 2009 and October 2013 were included. Radiology reports and imaging were reviewed and correlated with operative notes to identify cases with missed lesions and the reasons for those misses. All lesions were then classified according to the following factors: multigland disease, lesion size, patient body weight, and multinodular goiter. RESULTS: Of the 40 patients, 6 had multigland disease, resulting in 51 lesions; 12 and 29 lesions were missed on 4D CT and scintigraphy, respectively. The sensitivity for detection of all lesions was 76% for 4D CT and 43% for scintigraphy. Sensitivities for single-gland disease were 88% for 4D CT and 50% for scintigraphy. Sensitivities for multigland disease were 53% for 4D CT and 24% for scintigraphy. Rates of multigland disease in patients with missed lesions were 75% on 4D CT and 48% on scintigraphy, as compared with patients with detected lesions, 23% and 18%, respectively (P </= .04). Mean weight of lesions missed on 4D CT was 0.3 and 0.6 g in detected lesions (P = .15). Mean weight of lesions missed on scintigraphy was 0.4 and 0.8 g in detected lesions (P = .03). CONCLUSION: 4D CT has higher sensitivity than scintigraphy. Missed lesions are more likely to occur with multigland disease for both modalities and in smaller lesions for scintigraphy.
PubMed-ID: 26932954
http://dx.doi.org/10.1177/0194599816630711

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

Letter to Editor: Comment on"Incidence and Prevalence of Primary Hyperparathyroidism in a Racially Mixed Population" by Yeh M.W., Ituarte P.H., Zhou H.C., Nishimoto S., Liu I.L., Harari A., Haigh P.I., Adams A.L.
J Clin Endocrinol Metab, 101(4):L52-3.
D. T. Waugh. 2016.
PubMed-ID: 27032329
http://dx.doi.org/10.1210/jc.2016-1162

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 Relationship of Parathyroidectomy and Bisphosphonates With Fracture Risk in Primary Hyperparathyroidism: An Observational Study.
Ann Intern Med, 164(11):715-23.
M. W. Yeh, H. Zhou, A. L. Adams, P. H. Ituarte, N. Li, I. L. Liu and P. I. Haigh. 2016.
BACKGROUND: The comparative effectiveness of surgical and medical treatments on fracture risk in primary hyperparathyroidism (PHPT) is unknown. OBJECTIVE: To measure the relationship of parathyroidectomy and bisphosphonates with skeletal outcomes in patients with PHPT. DESIGN: Retrospective cohort study. SETTING: An integrated health care delivery system. PARTICIPANTS: All enrollees with biochemically confirmed PHPT from 1995 to 2010. MEASUREMENTS: Bone mineral density (BMD) changes and fracture rate. RESULTS: In 2013 patients with serial bone density examinations, total hip BMD increased transiently in women with parathyroidectomy (4.2% at <2 years) and bisphosphonates (3.6% at <2 years) and declined progressively in both women and men without these treatments (-6.6% and -7.6%, respectively, at >8 years). In 6272 patients followed for fracture, the absolute risk for hip fracture at 10 years was 20.4 events per 1000 patients who had parathyroidectomy and 85.5 events per 1000 patients treated with bisphosphonates compared with 55.9 events per 1000 patients without these treatments. The risk for any fracture at 10 years was 156.8 events per 1000 patients who had parathyroidectomy and 302.5 events per 1000 patients treated with bisphosphonates compared with 206.1 events per 1000 patients without these treatments. In analyses stratified by baseline BMD status, parathyroidectomy was associated with reduced fracture risk in both osteopenic and osteoporotic patients, whereas bisphosphonates were associated with increased fracture risk in these patients. Parathyroidectomy was associated with fracture risk reduction in patients regardless of whether they satisfied criteria from consensus guidelines for surgery. LIMITATION: Retrospective study design and nonrandom treatment assignment. CONCLUSION: Parathyroidectomy was associated with reduced fracture risk, and bisphosphonate treatment was not superior to observation. PRIMARY FUNDING SOURCE: National Institute on Aging.

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http://dx.doi.org/10.7326/M15-1232

A Possible Link Between Parathyroid Hormone Secretion and Local Regulation of GABA in Human Parathyroid Adenomas.
J Clin Endocrinol Metab, 101(6):2594-601.
A. R. Hong, Y. A. Kim, J. H. Bae, H. S. Min, J. H. Kim, C. S. Shin, S. Y. Kim and S. W. Kim. 2016.
CONTEXT: gamma-Aminobutyric acid-B receptor 1 (GABABR1) forms a heterodimeric complex with calcium-sensing receptor (CaSR) in human brain tissue. However, the expression and implication of GABABR1 in human parathyroid adenoma has not yet been examined. OBJECTIVE: The objective of the study was to examine a possible link between GABABR1 and PTH secretion in human parathyroid adenoma Design and Methods: Sixty-five patients who underwent parathyroidectomy for primary hyperparathyroidism (PHPT) and 29 control patients with normal parathyroid glands were retrospectively included. All patients diagnosed with PHPT had parathyroid adenomas. We evaluated the protein expression of GABABR1, glutamic acid decarboxylase 65/67 (GAD65/67), and various factors proposed as regulators of PTH secretion including CaSR, vitamin D receptor (VDR), CYP24A1, CYP27B1, fibroblast growth factor, and alpha-klotho in parathyroid tissues from patients with parathyroid adenomas using immunohistochemistry. RESULTS: Expressions of CaSR, GABABR1, and VDR were significantly lower in PHPT patients than in control subjects ($P < .001$ for CaSR and GABABR1; $P = .006$ for VDR). Protein expression of GAD65/67, which indicates local production and regulation of GABAergic pathway, was significantly increased in PHPT ($P < .001$). There were no significant differences in CYP24A1, CYP27B1, fibroblast growth factor, and alpha-klotho expression between the two groups. Expression of GAD65/67 was significantly correlated with VDR, CYP24A1, CYP27B1, and alpha-klotho in PHPT (all $P < .01$) but not in the control groups. CaSR expression was positively associated with serum phosphorus level ($r = 0.274$, $P = .029$) and GAD65/67 was negatively correlated with serum PTH level ($r = -0.342$, $P = .005$). CONCLUSIONS: Local production and action of GABA may be regulated in human parathyroid adenomas. This suggests a possible link between PTH secretion and local regulation of GABA in parathyroid adenomas.
PubMed-ID: 27070188
http://dx.doi.org/10.1210/jc.2015-4329

High-resolution magic angle spinning (1)H nuclear magnetic resonance spectroscopy metabolomics of hyperfunctioning parathyroid glands.
Surgery, 160(2):384-94.
S. Battini, A. Imperiale, D. Taieb, K. Elbayed, A. E. Cicek, F. Sebag, L. Brunaud and I. J. Namer. 2016.
BACKGROUND: Primary hyperparathyroidism (PHPT) may be related to a single gland disease or multiglandular disease, which requires specific treatments. At present, an operation is the only curative treatment for PHPT. Currently, there are no biomarkers available to identify these 2 entities (single vs. multiple gland disease). The aims of the present study were to compare (1) the tissue metabolomics profiles between PHPT and renal hyperparathyroidism (secondary and tertiary) and (2) single gland disease with multiglandular disease in PHPT using metabolomics analysis. METHODS: The method used was (1)H high-resolution magic angle spinning nuclear magnetic resonance spectroscopy. Forty-three samples from 32 patients suffering from hyperparathyroidism were included in this study. RESULTS: Significant differences in the metabolomics profile were assessed according to PHPT and renal hyperparathyroidism. A bicomponent orthogonal partial least square-discriminant analysis showed a clear distinction between PHPT and renal hyperparathyroidism ($R(2)Y = 0.85$, $Q(2) = 0.63$). Interestingly, the model also distinguished single gland disease from multiglandular disease ($R(2)Y = 0.96$, $Q(2) = 0.55$). A network analysis was also performed using the Algorithm to Determine Expected Metabolite Level Alterations Using Mutual Information (ADEMA). Single gland disease was accurately predicted by ADEMA and was associated with higher levels of phosphorylcholine, choline, glycerophosphocholine, fumarate, succinate, lactate, glucose, glutamine, and ascorbate compared with multiglandular disease. CONCLUSION: This study shows for the first time that (1)H high-resolution magic angle spinning nuclear magnetic resonance spectroscopy is a reliable and fast technique to distinguish single gland disease from multiglandular disease in patients with PHPT. The potential use of this method as an intraoperative tool requires specific further studies.
PubMed-ID: 27106795
http://dx.doi.org/10.1016/j.surg.2016.03.002

Differentiating Atypical Parathyroid Neoplasm from Parathyroid Cancer.
Ann Surg Oncol, 23(9):2889-97.
I. Christakis, N. Bussaidy, C. Clarke, L. J. Kwatampora, C. L. Warneke, A. M. Silva, M. D. Williams, E. G. Grubbs, J. E. Lee and N. D. Perrier. 2016.

INTRODUCTION: The differentiation of benign parathyroid gland atypia and true parathyroid carcinoma (PC) can be challenging. In some instances, patients are classified as having 'atypical parathyroid neoplasms' (APNs), explicitly acknowledging that the distinction between benign and malignant disease appears impossible to determine. This 'grey area' diagnosis makes rendering an accurate prognosis difficult, and clouds clinical management and treatment planning. METHODS: We performed a retrospective chart review of all patients undergoing operation for primary hyperparathyroidism in our institution (2000-2014). Patients with a histopathological diagnosis of PC or APN were included. Demographics, clinical characteristics, and survival rates were analyzed, and analysis was conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). RESULTS: Fifty-four patients were included in the study-31 (57.41 %) with PC and 23 (42.59 %) with APN. PC versus APN was associated with higher parathyroid hormone (PTH) (p = 0.005) and with males (p = 0.002). Five-year overall survival (OS) from diagnosis was 82.64 % [95 % confidence interval (CI) 59.82-93.17] for the PC group and 93.33 % (95 % CI 61.26-99.03) for the APN group, while the 5-year recurrence-free survival rate was 59.63 % (95 % CI 36.32-76.81) in the PC group and 90.91 % (95 % CI 50.81-98.67) in the APN group. CONCLUSION: PC and APN are distinct clinical entities with differences in tumor biology reflected in overall recurrence rates, disease-free survival, and OS. APNs present with a less accentuated biochemical profile and demonstrate an indolent clinical course compared with PCs. Efforts to improve categorization and staging of PC and APN are needed.
PubMed-ID: 27160525
http://dx.doi.org/10.1245/s10434-016-5248-6

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

Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway.
J Clin Endocrinol Metab, 101(8):3045-53.
M. C. Astor, K. Lovas, A. Debowska, E. F. Eriksen, J. A. Evang, C. Fossum, K. J. Fougner, S. E. Holte, K. Lima, R. B. Moe, A. G. Myhre, E. H. Kemp, B. G. Nedrebo, J. Svartberg and E. S. Husebye. 2016.
OBJECTIVE: The epidemiology of hypoparathyroidism (HP) is largely unknown. We aimed to determine prevalence, etiologies, health related quality of life (HRQOL) and treatment pattern of HP. METHODS: Patients with HP and 22q11 deletion syndrome (DiGeorge syndrome) were identified in electronic hospital registries. All identified patients were invited to participate in a survey. Among patients who responded, HRQOL was determined by Short Form 36 and Hospital Anxiety and Depression scale. Autoantibodies were measured and candidate genes (CaSR, AIRE, GATA3, and 22q11-deletion) were sequenced for classification of etiology. RESULTS: We identified 522 patients (511 alive) and estimated overall prevalence at 102 per million divided among postsurgical HP (64 per million), nonsurgical HP (30 per million), and pseudo-HP (8 per million). Nonsurgical HP comprised autosomal dominant hypocalcemia (21%), autoimmune polyendocrine syndrome type 1 (17%), DiGeorge/22q11 deletion syndrome (15%), idiopathic HP (44%), and others (4%). Among the 283

respondents (median age, 53 years [range, 9-89], 75% females), seven formerly classified as idiopathic were reclassified after genetic and immunological analyses, whereas 26 (37% of nonsurgical HP) remained idiopathic. Most were treated with vitamin D (94%) and calcium (70%), and 10 received PTH. HP patients scored significantly worse than the normative population on Short Form 36 and Hospital Anxiety and Depression scale; patients with postsurgical scored worse than those with nonsurgical HP and pseudo-HP, especially on physical health. CONCLUSIONS: We found higher prevalence of nonsurgical HP in Norway than reported elsewhere. Genetic testing and autoimmunity screening of idiopathic HP identified a specific cause in 21%. Further research is necessary to unravel the causes of idiopathic HP and to improve the reduced HRQOL reported by HP patients.
PubMed-ID: 27186861
http://dx.doi.org/10.1210/jc.2016-1477

Impact of parathyroidectomy for primary hyperparathyroidism on quality of life: A case-control study using Short Form Health Survey 36.
Head Neck, 38(8):1213-20.
R. Dulfer, W. Geilvoet, A. Morks, E. M. van Lieshout, C. P. Smit, E. J. Nieveen van Dijkum, K. In't Hof, F. van Dam, C. H. van Eijck, P. W. de Graaf and T. M. van Ginhoven. 2016.
BACKGROUND: Physical and mental complaints are common in patients with primary hyperparathyroidism (PHPT) and negatively impact quality of life (QOL). Subjective symptoms in current guidelines are not considered an indication for surgery. The purpose of this study was to assess the effect of parathyroidectomy on QOL in patients with PHPT. METHODS: This multicenter case-control study investigated preoperative and postoperative QOL scores in patients operated for PHPT, measured with the Short Form Health Survey-36 (SF-36) questionnaire. Results were compared with patients undergoing a hemithyroidectomy, the control group. RESULTS: Fifty-two patients and 49 controls were included. Patients with PHPT had significantly lower QOL scores preoperatively and improved significantly after successful surgical treatment. Postoperatively, no differences were observed between the 2 groups. CONCLUSION: QOL was significantly lower in patients with untreated PHPT. Surgical treatment was associated with a significant increase in QOL. Decreased QOL should also be considered as an indicator for surgical treatment in patients with PHPT. (c) 2016 Wiley Periodicals, Inc. Head Neck 38:1213-1220, 2016.
PubMed-ID: 27198205
http://dx.doi.org/10.1002/hed.24499

Endocrine neoplasms in familial syndromes of hyperparathyroidism.
Endocr Relat Cancer, 23(6):R229-47.
Y. Li and W. F. Simonds. 2016.
Familial syndromes of hyperparathyroidism, including multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), and the hyperparathyroidism-jaw tumor (HPT-JT), comprise 2-5% of primary hyperparathyroidism cases. Familial syndromes of hyperparathyroidism are also associated with a range of endocrine and nonendocrine tumors, including potential malignancies. Complications of the associated neoplasms are the major causes of morbidities and mortalities in these familial syndromes, e.g., parathyroid carcinoma in HPT-JT syndrome; thymic, bronchial, and enteropancreatic neuroendocrine tumors in MEN1; and medullary thyroid cancer and pheochromocytoma in MEN2A. Because of the different underlying mechanisms of neoplasia, these familial tumors may have different characteristics compared with their sporadic counterparts. Large-scale clinical trials are frequently lacking due to the rarity of these diseases. With technological advances and the development of new medications, the natural history, diagnosis, and management of these syndromes are also evolving. In this article, we summarize the recent knowledge on endocrine neoplasms in three familial hyperparathyroidism syndromes, with an emphasis on disease characteristics, molecular pathogenesis, recent developments in biochemical and radiological evaluation, and expert opinions on surgical and medical therapies. Because these familial hyperparathyroidism syndromes are associated with a wide variety of tumors in different organs, this review is focused on those endocrine neoplasms with malignant potential.
PubMed-ID: 27207564
http://dx.doi.org/10.1530/ERC-16-0059

Cutting Edge in Thyroid Surgery: Autofluorescence of Parathyroid Glands.
J Am Coll Surg, 223(2):374-80.
J. Falco, F. Dip, P. Quadri, M. de la Fuente and R. Rosenthal. 2016.
BACKGROUND: Identification of parathyroid glands may be challenging during thyroid and parathyroid surgery. Accidental resection of the glands may increase the morbidity of the surgery. The aim of this study was to evaluate accuracy in identification of autofluorescent parathyroid glands with the use of near infrared light in real

time. STUDY DESIGN: Patients undergoing thyroid and parathyroid surgery between June and August 2015 were included in the study. During the procedure, the surgical field was exposed to near infrared laser light in order to analyze the intensity of the fluorescence of different tissues (parathyroid glands, thyroid glands, and background). Surgical images were recorded and analyzed. RESULTS: Twenty-eight patients were included in the study. Nineteen patients were women and 9 were men. Seven patients had primary hyperparathyroidism, 4 had hyperthyroidism, 3 had goiters, and 11 had thyroid cancer. Three patients had mixed pathologies, including 2 patients with thyroid cancer and primary hyperparathyroidism and 1 patient with goiter and primary hyperparathyroidism. Identification of autofluorescent parathyroid glands was achieved in all patients with near infrared light. The mean fluorescent intensity of parathyroid glands was 40.6 (+/-26.5), thyroid glands 31.8 (+/-22.3), and background 16.6 (+/-15.4). Parathyroid glands demonstrated statistically higher fluorescence intensity compared with the thyroid gland and background ($p < 0.0014$). No postoperative hypocalcemia or other complications related to the surgery were registered. CONCLUSIONS: Visualization of autofluorescent parathyroid glands with the use of near infrared light allows high rates of parathyroid gland identification and could be a safe, feasible, and noninvasive method for intraoperative identification of parathyroid glands in real time. Further clinical studies must be performed to determine the cost-effectiveness and clinical application of this method.
PubMed-ID: 27212004
http://dx.doi.org/10.1016/j.jamcollsurg.2016.04.049

The Truth about Double Adenomas: Incidence, Localization, and Intraoperative Parathyroid Hormone.
J Am Coll Surg, 222(6):1044-52.
L. De Gregorio, C. C. Lubitz, R. A. Hodin, R. D. Gaz, S. Parangi, R. Phitayakorn and A. E. Stephen. 2016.
BACKGROUND: Double adenoma is reported in 3% to 12% of patients with primary hyperparathyroidism. The aim of this study was to determine the true incidence of double adenoma and analyze the use of localization studies and intraoperative parathyroid hormone (IOTPH) assay in these cases. STUDY DESIGN: We conducted a retrospective review of a series of consecutive parathyroid surgical operations from 2010 to 2013. According to the surgical findings, the series was divided into single-gland disease (SGD), double-gland disease (DGD), and multi-gland disease (MGD, more than 2 glands). The sensitivity of ultrasound, technetium 99m-sestamibi, and 4-dimensional CT to correctly lateralize each gland in the DGD group was calculated. Results of the IOPTH assay and how they impacted the extent of surgery were analyzed. RESULTS: Three hundred and forty-seven patients had SGD (69%), 68 patients had DGD (13.5%), and 86 had MGD (17%). In the DGD group, sensitivity of ultrasound, technetium 99m-sestamibi, and 4-dimensional CT to lateralize each adenoma was 42%, 34.5%, and 64%, respectively. Initially, 27 patients (40%) with DGD had been planned for a focal exploration. The conversion to bilateral neck exploration was due to the IOPTH assay in 18 cases (two-thirds of the initially planned focal explorations). At 6-month follow-up, all DGD patients were normocalcemic. CONCLUSIONS: Localization studies in DGD can be misleading by reporting SGD. Four-dimensional CT seems to have the highest sensitivity. In focal explorations, the excision of all hyperfunctioning parathyroid tissue should be verified by IOPTH measurement.
PubMed-ID: 27234627
http://dx.doi.org/10.1016/j.jamcollsurg.2015.12.048

Impact of the Introduction of Calcimimetics on Timing of Parathyroidectomy in Secondary and Tertiary Hyperparathyroidism.
Ann Surg Oncol,
W. Y. van der Plas, A. F. Engelsman, A. Ozyilmaz, A. N. van der Horst-Schrivers, K. Meijer, G. M. van Dam, R. A. Pol, M. H. de Borst and S. Kruijff. 2016.
BACKGROUND: Hyperparathyroidism (HPT), both secondary and tertiary, is common in patients with end-stage renal disease, and is associated with severe bone disorders, cardiovascular complications, and increased mortality. Since the introduction of calcimimetics in 2004, treatment of HPT has shifted from surgery to predominantly medical therapy. OBJECTIVE: The aim of this study was to evaluate the impact of this change of management on the HPT patient population before undergoing (sub-)total parathyroidectomy (PTx). METHODS: Overall, 119 patients with secondary or tertiary HPT undergoing PTx were included in a retrospective, single-center cohort. Group A, who underwent PTx before January 2005, was compared with group B, who underwent PTx after January 2005. Patient characteristics, time interval between HPT diagnosis and PTx, and postoperative complications were compared. RESULTS: Group A comprised 70 (58.8 %) patients and group B comprised 49 (41.2 %) patients. The median interval between HPT diagnosis and PTx was 27 (interquartile range [IQR] 12.5-48.0) and 49 (IQR 21.0-75.0) months for group A and B, respectively ($p = 0.007$). Baseline characteristics were similar among both groups. The median preoperative serum parathyroid hormone (PTH) level was 936 pg/mL (IQR 600-1273) for group A versus 1091 pg/mL (IQR 482-1373) for group B ($p = 0.38$). PTx

resulted in a dramatic PTH reduction (less than twofold the upper limit: A, 80.0 %; B, 85.4 %), and postoperative complication rates were low in both groups (A: 7.8 %; B: 10.2 %) [p = 0.66]. CONCLUSIONS: The introduction of calcimimetics in 2004 is associated with a significant 2-year delay of surgery with continuously elevated preoperative PTH levels, while parathyroid surgery, even in a fragile population, is considered a safe and effective procedure.
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http://dx.doi.org/10.1245/s10434-016-5450-6

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

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

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

Adrenals

Meta-Analyses

MANAGEMENT OF ENDOCRINE DISEASE: Recurrence or new tumors after complete resection of pheochromocytomas and paragangliomas: a systematic review and meta-analysis.
Eur J Endocrinol, 175(4):R135-45.
L. Amar, C. Lussey-Lepoutre, J. W. 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 pheochromocytoma or thoraco-abdomino-pelvic paraganglioma. DESIGN: A systematic review and meta-analysis of published literature was performed. METHODS: Pubmed and Embase from 1980 to 2012 were searched for studies published in English on patients with non-metastatic pheochromocytoma or thoraco-abdomino-pelvic paraganglioma, complete tumor resection, postoperative follow-up exceeding 1 month, and 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: In total, 38 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 pheochromocytoma may be lower than that previously estimated, corresponding to five events for 100 patients followed up for 5 years after complete resection. Risk stratification is required to tailor the follow-up protocol after complete resection of a pheochromocytoma or paraganglioma. Large multicenter studies are needed to this end.
PubMed-ID: 27080352
http://dx.doi.org/10.1530/EJE-16-0189

THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and Subclinical Cushing Syndrome: a systematic review and meta-analysis.
Eur J Endocrinol,
I. Bancos, F. Alahdab, R. K. Crowley, V. Chortis, D. Delivanis, D. Erickson, N. Natt, M. Terzolo, W. Arlt, W. Young and M. H. Murad. 2016.
OBJECTIVE: Beneficial effects of adrenalectomy on cardiovascular risk factors in patients with Subclinical Cushing Syndrome (SCS) are uncertain. We sought to conduct a systematic review and meta-analysis with the following objectives: 1) determine the effect of adrenalectomy compared to conservative management on cardiovascular risk factors in patients with SCS and 2) compare the effect of adrenalectomy on cardiovascular risk factors in patients with SCS versus those with a non-functioning (NF) adrenal tumor. METHODS: Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial were searched on November 17th, 2015. Reviewers extracted data and assessed methodological quality in duplicate. RESULTS: We included 26 studies reporting on 584 patients with SCS and 457 patients with NF adrenal tumors. Studies used different definitions of SCS. Patients with SCS undergoing adrenalectomy demonstrated an overall improvement in cardiovascular risk factors (61% for hypertension, 52% for diabetes mellitus, 45% for obesity and 24% for dyslipidemia). When compared to conservative management, patients with SCS undergoing adrenalectomy experienced improvement in hypertension (RR 11, 95% CI 4.3 - 27.8) and diabetes mellitus (RR 3.9, 95%CI 1.5- 9.9), but not dyslipidemia (RR 2.6, 95%CI 0.97 -7.2) or obesity (RR 3.4 (95%CI 0.95-12)). Patients with NF adrenal tumors experienced improvement in hypertension (21/54 patients), however, insufficient data exist for comparison to patients with SCS. CONCLUSIONS: Available low to moderate quality evidence from heterogeneous studies suggests a beneficial effect of adrenalectomy on cardiovascular risk factors in patients with SCS overall and as compared to conservative management.
PubMed-ID: 27450696
http://dx.doi.org/10.1530/EJE-16-0465

Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis.

J Clin Endocrinol Metab, 101(7):2826-35.
S. C. Kayser, T. Dekkers, H. J. Groenewoud, G. J. van der Wilt, J. Carel Bakx, M. C. van der Wel, A. R. Hermus, J. W. Lenders and J. Deinum. 2016.
CONTEXT: For health care planning and allocation of resources, realistic estimation of the prevalence of primary aldosteronism is necessary. Reported prevalences of primary aldosteronism are highly variable, possibly due to study heterogeneity. OBJECTIVE: Our objective was to identify and explain heterogeneity in studies that aimed to establish the prevalence of primary aldosteronism in hypertensive patients. DATA SOURCES: PubMed, EMBASE, Web of Science, Cochrane Library, and reference lists from January 1, 1990, to January 31, 2015, were used as data sources. STUDY SELECTION: Description of an adult hypertensive patient population with confirmed diagnosis of primary aldosteronism was included in this study. DATA EXTRACTION: Dual extraction and quality assessment were the forms of data extraction. DATA SYNTHESIS: Thirty-nine studies provided data on 42 510 patients (nine studies, 5896 patients from primary care). Prevalence estimates varied from 3.2% to 12.7% in primary care and from 1% to 29.8% in referral centers. Heterogeneity was too high to establish point estimates (I(2) = 57.6% in primary care; 97.1% in referral centers). Meta-regression analysis showed higher prevalences in studies 1) published after 2000, 2) from Australia, 3) aimed at assessing prevalence of secondary hypertension, 4) that were retrospective, 5) that selected consecutive patients, and 6) not using a screening test. All studies had minor or major flaws. CONCLUSIONS: This study demonstrates that it is pointless to claim low or high prevalence of primary aldosteronism based on published reports. Because of the significant impact of a diagnosis of primary aldosteronism on health care resources and the necessary facilities, our findings urge for a prevalence study whose design takes into account the factors identified in the meta-regression analysis.
PubMed-ID: 27172433
http://dx.doi.org/10.1210/jc.2016-1472

Molecular Imaging in the Management of Adrenocortical Cancer: A Systematic Review.
Clin Nucl Med, 41(8):e368-82.
K. K. Wong, B. S. Miller, B. L. Viglianti, B. A. Dwamena, P. G. Gauger, G. J. Cook, P. M. Colletti, D. Rubello and M. D. Gross. 2016.
Adrenocortical cancer (ACC) is an uncommon primary neoplasm of the adrenal cortex with dismal prognosis. It often presents with symptoms and signs of adrenal cortical hormone hypersecretion and abdominal mass effect or is incidentally detected as an adrenal mass on imaging performed for other indications. Endocrine evaluation, comprehensive staging, and meticulous resection are crucial to ensure the best possible outcome. Despite extensive initial surgical resection, local and distant metastases are not uncommon with disappointing 5-year survival, although progress is being made at high-volume centers. Accurate restaging of recurrent disease is important to guide further management. Mitotane, external beam radiation and chemotherapy, and newer anticancer systemic treatments are used as adjunctives for inoperable disease and distant metastases. Contrast-enhanced CT and MRI are first-line imaging modalities for evaluation of ACC to characterize adrenal masses and to determine tumor resectability. Emerging literature supports F-FDG PET/CT use to determine the malignant potential of adrenal masses. In patients with a diagnosis of ACC, FDG PET/CT is sensitive for detecting metastatic disease, and its tumor accumulation has been correlated to pathology, Weiss scores, and prognosis. Metomidate, labeled with C for PET or with I for SPECT/CT, allows characterization of an adrenal mass as being of adrenocortical origin with high specificity. Taking advantage of its adrenocortical avidity, metomidate has been labeled with I for radionuclide therapy in a subset of ACC. In this review, we describe how nuclear medicine imaging, and specifically PET, can assist surgical management of ACC.
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http://dx.doi.org/10.1097/RLU.0000000000001112

Randomized controlled trials

- None –

Consensus Statements/Guidelines

Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors.
Eur J Endocrinol, 175(2):G1-G34.
M. Fassnacht, W. Arlt, I. Bancos, H. Dralle, J. Newell-Price, A. Sahdev, A. Tabarin, M. Terzolo, S. Tsagarakis and O. M. Dekkers. 2016.
: By definition, an adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. In most cases, adrenal incidentalomas are nonfunctioning adrenocortical adenomas, but may also represent conditions requiring therapeutic intervention (e.g. adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma or metastasis). The purpose of this guideline is to provide clinicians with best possible evidence-based recommendations for clinical management of patients with adrenal incidentalomas based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. We predefined four main clinical questions crucial for the management of adrenal incidentaloma patients, addressing these four with systematic literature searches: (A) How to assess risk of malignancy?; (B) How to define and manage low-level autonomous cortisol secretion, formerly called 'subclinical' Cushing's syndrome?; (C) Who should have surgical treatment and how should it be performed?; (D) What follow-up is indicated if the adrenal incidentaloma is not surgically removed? SELECTED RECOMMENDATIONS: (i) At the time of initial detection of an adrenal mass establishing whether the mass is benign or malignant is an important aim to avoid cumbersome and expensive follow-up imaging in those with benign disease. (ii) To exclude cortisol excess, a 1mg overnight dexamethasone suppression test should be performed (applying a cut-off value of serum cortisol </=50nmol/L (1.8microg/dL)). (iii) For patients without clinical signs of overt Cushing's syndrome but serum cortisol levels post 1mg dexamethasone >138nmol/L (>5microg/dL), we propose the term 'autonomous cortisol secretion'. (iv) All patients with '(possible) autonomous cortisol' secretion should be screened for hypertension and type 2 diabetes mellitus, to ensure these are appropriately treated. (v) Surgical treatment should be considered in an individualized approach in patients with 'autonomous cortisol secretion' who also have comorbidities that are potentially related to cortisol excess. (vi) In principle, the appropriateness of surgical intervention should be guided by the likelihood of malignancy, the presence and degree of hormone excess, age, general health and patient preference. (vii) Surgery is not usually indicated in patients with an asymptomatic, nonfunctioning unilateral adrenal mass and obvious benign features on imaging studies. We provide guidance on which surgical approach should be considered for adrenal masses with radiological findings suspicious of malignancy. Furthermore, we offer recommendations for the follow-up of patients with adrenal incidentaloma who do not undergo adrenal surgery, for those with bilateral incidentalomas, for patients with extra-adrenal malignancy and adrenal masses and for young and elderly patients with adrenal incidentalomas.
PubMed-ID: 27390021
http://dx.doi.org/10.1530/EJE-16-0467

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

Factors affecting parathyroid hormone levels in different types of primary aldosteronism.
Clin Endocrinol (Oxf), 85(2):267-74.
Y. Jiang, C. Zhang, L. Ye, T. Su, W. Zhou, L. Jiang, Y. Zhang and W. Wang. 2016.
BACKGROUND: Recent studies have found that mild secondary hyperparathyroidism might be another clinical feature of patients with primary aldosteronims (PA), but whether serum parathyroid hormone level (PTH) is correlated with subtypes of PA and what contributes to the elevated PTH level remains unclear. OBJECTIVE: To illustrate the changes of PTH in PA and to partly explain the mechanism of how the effects of aldosterone regulating the secretion of PTH in PA. METHODS: We enrolled a total of 120 patients with primary hypertension (PH) and 242 patients with PA, which included 89 APAs (aldosterone-producing adenoma), 119 IHAs (idiopathic hyperaldosteronism) and 34 UAHs (unilateral adrenal hyperplasia). The plasma levels of aldosterone, renin activity, parathyroid hormone and markers associated with calcium metabolism were measured. RESULTS: We found serum PTH level was significantly elevated in patients with PA compared with primary hypertension [9.0 (6.6, 11.7) vs 5.7 (4.4, 7.0)] pmol/l, $P < 0.001$]. However, no difference was found between the three PA subtypes ($P > 0.05$). Stepwise multiple regression analysis showed that in patients with PA, serum levels of K(+) and Ca(2+) were independently associated with serum PTH level. More importantly, elevated PTH level could be corrected either by unilateral adrenalectomy [9.9 (7.5, 12.8) vs 5.2 (4.4, 7.0) pmol/l, $P < 0.001$] or mineralocorticoid receptor (MR) antagonists treatment [11.7 (9.1, 13.4) vs 6.3 (5.1, 7.8) pmol/l, $P < 0.001$]. CONCLUSIONS: PTH level is elevated in PA patients and irrelevant with subtypes of PA. Serum K(+) and serum Ca(2+) level are main factors influence the plasma PTH level in PA patients. After medical or surgical treatment, PTH levels return to normal.
PubMed-ID: 26589237
http://dx.doi.org/10.1111/cen.12981

Patterns of Use and Short-Term Outcomes of Minimally Invasive Surgery for Malignant Pheochromocytoma: A Population-Level Study.
World J Surg, 40(5):1279.
C. K. Jha and A. Mishra. 2016.
PubMed-ID: 26675927
http://dx.doi.org/10.1007/s00268-015-3381-1

Preoperative risk factors of hemodynamic instability during laparoscopic adrenalectomy for pheochromocytoma.
Surg Endosc, 30(7):2984-93.
S. Gaujoux, S. Bonnet, C. Lentschener, J. M. Thillois, D. Duboc, J. Bertherat, C. M. Samama and B. Dousset. 2016.
BACKGROUND: Adrenalectomy for pheochromocytoma is considered to be a challenging procedure because of the risk of hemodynamic instability (HI), which is poorly defined and unpredictable. The objective of this retrospective study from a prospectively maintained database was to determine the predictive factors for perioperative HI, which is defined as a morbidity-related variable, in patients undergoing unilateral laparoscopic adrenalectomy (LA) for pheochromocytoma. METHODS: A total of 149 patients with unilateral pheochromocytoma undergoing LA were included. First, HI was defined using independent hemodynamic variables associated with perioperative morbidity. Next, a multivariable logistic regression analysis was performed to determine the independent preoperative risk factors for HI. RESULTS: There was no postoperative mortality, and the overall morbidity rate was 10.7 %. The use of a cumulative dose of norepinephrine >5 mg was

the only independent hemodynamic predictive factor for postoperative complications; thus, this variable was used to define HI. A multivariate analysis revealed that a symptomatic high preoperative blood pressure ($p = 0.003$) and a ten-fold increase in urinary metanephrine and/or normetanephrine levels ($p < 0.0001$) were significant predictors of HI. When no predictive factors were present, the risk of HI and the postoperative morbidity were 1.5 and 4.3 %, respectively. However, when two predictive factors were present, the HI risk and the postoperative morbidity were 53.8 and 30.8 %, respectively. CONCLUSION: Perioperative HI, defined as the need for a cumulative dose of norepinephrine >5 mg, is significantly associated with postoperative morbidity and can be predicted by symptomatic preoperative high blood pressure and above a ten-fold increase in urinary metanephrine and/or normetanephrine levels.
PubMed-ID: 26684206
http://dx.doi.org/10.1007/s00464-015-4587-x

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

Outcomes after resection of cortisol-secreting adrenocortical carcinoma.
Am J Surg, 211(6):1106-13.
G. A. Margonis, Y. Kim, T. B. Tran, L. M. Postlewait, S. K. Maithel, T. S. Wang, J. A. 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, G. A. Poultsides and T. M. Pawlik. 2016.
BACKGROUND: We sought to define the impact of cortisol-secreting status on outcomes after surgical resection of adrenocortical carcinoma (ACC). METHODS: The U.S ACC group database was queried to identify patients who underwent ACC resection between 1993 and 2014. The short-term and long-term outcomes were assessed. RESULTS: The incidence of all functional and cortisol-secreting tumors was 40.6% and 22.6%, respectively. On multivariable analysis, cortisol secretion remained associated with an increased risk of postoperative complications (odds ratio = 2.25, 95 % confidence interval = 1.04 to 4.88; P = .04). At a median follow-up of 17.6 months, 118 patients (50.4%) had developed a recurrence. On multivariable analysis, after adjusting for patient and disease-related factors cortisol secretion independently predicted shorter recurrence-free survival (Hazard ratio = 2.05, 95% confidence interval = 1.16 to 3.60; P = .01). CONCLUSIONS: Cortisol secretion was associated with an increased risk of postoperative morbidity. Recurrence remains high among patients with ACC after surgery; cortisol secretion was independently associated with a shorter recurrence-free survival. Tailoring postoperative surveillance of ACC patients based on their cortisol secreting status may be important.
PubMed-ID: 26810939
http://dx.doi.org/10.1016/j.amjsurg.2015.09.020

Improving Minimally Invasive Adrenalectomy: Selection of Optimal Approach and Comparison of Outcomes.
World J Surg, 40(7):1625-31.
T. C. Lairmore, J. Folek, C. M. Govednik and S. K. Snyder. 2016.
INTRODUCTION: Minimally invasive adrenalectomy is commonly performed by either a transperitoneal laparoscopic (TLA) or posterior retroperitoneoscopic (PRA) approach. Our group described the technique for robot-assisted PRA (RAPRA) in 2010. Few studies are available that directly compare outcomes between the available operative approaches. We reviewed our results for minimally invasive adrenalectomy using the three different approaches over a 10-year period. METHODS: Between January 2005 and April 2015, 160 minimally invasive adrenalectomies were performed. Clinicopathologic data were prospectively collected and retrospectively analyzed. The primary endpoints evaluated were operative time, blood loss, length of stay (LOS), and morbidity. RESULTS: The study included 67 TLA, 76 PRA, and 17 RAPRA procedures. Tumor size for PRA/RAPRA was smaller than for patients undergoing TLA (2.38 vs 3.6 cm, p </= 0.0001). Procedure time was shorter for PRA versus TLA (133.3 vs 152.8 min, p = 0.0381), as was LOS (1.85 vs 2.82 days, p = 0.0145). Procedure time was longer in RAPRA versus TLA/PRA (177 vs 153/133 min, p = 0.008), but LOS was significantly decreased (1.53 vs 2.82/1.85 days, p = 0.004). CONCLUSIONS: Minimally invasive adrenalectomy is associated with expected excellent outcomes regardless of approach. In our series, the posterior approach is associated with decreased operative time and LOS. Robotic technology provides potential advantages for the surgeon at the expense of more complex setup requirements and costs. Further study is required to demonstrate clear benefit of one surgical approach. Utilization of the entire spectrum of available operative techniques can allow for selection of the optimal approach based on individual patient factors.
PubMed-ID: 26932878
http://dx.doi.org/10.1007/s00268-016-3471-8

Are patients with hormonally functional phaeochromocytoma and paraganglioma initially receiving a proper adrenoceptor blockade? A retrospective cohort study.
Clin Endocrinol (Oxf), 85(1):62-9.
H. V. Luiz, M. J. Tanchee, M. G. Pavlatou, R. Yu, J. Nambuba, K. Wolf, T. Prodanov, R. Wesley, K. Adams, T. Fojo and K. Pacak. 2016.
OBJECTIVE: Pharmacological treatment is mandatory in patients with hormonally functional phaeochromocytoma and paraganglioma (PHAEO/PGL). We evaluated if patients initially diagnosed with hormonally functional PHAEO/PGL by various medical subspecialties received proper adrenoceptor blockade, and analysed factors predicting the prescription of adequate treatment. METHODS: In a retrospective cohort study, we reviewed data from patients initially diagnosed with hormonally functional PHAEO/PGL outside the National Institutes of Health and Cedars-Sinai Medical Center, who were referred to these institutions between January 2001 and April 2015. Logistic regression was used to assess factors associated with proper adrenoceptor blockade. RESULTS: A total of 381 patients were included. Adequate pharmacological treatment was prescribed to 69.3%, of which 93.1% received alpha-adrenoceptor blockers. Regarding patients who were inappropriately treated, 53% did not receive any medication. Independent predictors of the prescription of a proper blockade were the diagnosis by endocrinologists [odds ratio (OR) 4.14; 95% confidence interval (CI), 2.51-6.85; P < 0.001], the presence of high blood pressure (OR 5.94; 95% CI, 3.11-11.33; P < 0.001) and the evidence of metastasis (OR 5.96; 95% CI, 1.93-18.46; P = 0.002). CONCLUSIONS: Although most patients received adequate pharmacological treatment, almost one-third were either not treated or received inappropriate medications. The diagnosis by endocrinologists, the presence of high blood pressure and the evidence of metastatic disease were identified as independent predictors of a proper blockade. These results highlight the need to educate physicians about the importance of starting adequate adrenoceptor blockade in all patients with hormonally functional PHAEO/PGL.
PubMed-ID: 26998836
http://dx.doi.org/10.1111/cen.13066

Familial Adrenocortical Carcinoma in Association With Lynch Syndrome.
J Clin Endocrinol Metab, 101(6):2269-72.
B. G. Challis, N. Kandasamy, A. S. Powlson, O. Koulouri, A. K. Annamalai, L. Happerfield, A. J. Marker, M. J. Arends, S. Nik-Zainal and M. Gurnell. 2016.
CONTEXT: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with a poor prognosis. Although the majority of childhood ACC arises in the context of inherited cancer susceptibility syndromes, it remains less clear whether a hereditary tumor predisposition exists for the development of ACC in adults. Here, we report the first occurrence of familial ACC in a kindred with Lynch syndrome resulting from a pathogenic germline MSH2 mutation. CASE: A 54-year-old female with a history of ovarian and colorectal malignancy was found to have an

ACC. A detailed family history revealed her mother had died of ACC and her sister had previously been diagnosed with endometrial and colorectal cancers. A unifying diagnosis of Lynch syndrome was considered, and immunohistochemical analyses demonstrated loss of MSH2 and MSH6 expression in both AACs (proband and her mother) and in the endometrial carcinoma of her sister. Subsequent genetic screening confirmed the presence of a germline MSH2 mutation (resulting in deletions of exons 1-3) in the proband and her sister. CONCLUSION: Our findings provide strong support for the recent proposal that ACC should be considered a Lynch syndrome-associated tumor and included in the Amsterdam II clinical diagnostic criteria. We also suggest that screening for ACC should be considered in cancer surveillance strategies directed at individuals with germline mutations in DNA mismatch repair genes.
PubMed-ID: 27144940
http://dx.doi.org/10.1210/jc.2016-1460

Double adrenocortical adenomas harboring independent KCNJ5 and PRKACA somatic mutations.
Eur J Endocrinol, 175(2):K1-6.
K. Nanba, K. Omata, S. A. Tomlins, T. J. Giordano, G. D. Hammer, W. E. Rainey and T. Else. 2016.
OBJECTIVE: Co-secretion of cortisol and aldosterone can be observed in adrenal adenomas. The aim of this study was to investigate the molecular characteristics of a co-existing aldosterone- and a cortisol-producing adenoma (CPA) in the same patient. DESIGN AND METHODS: Two different adenomas within the same adrenal gland from a 49-year-old female patient with primary aldosteronism (PA) and Cushing's syndrome (CS) were studied. Multiple formalin-fixed paraffin-embedded tumor blocks were used for the analysis. Immunohistochemistry (IHC) was performed using a specific antibody against aldosterone synthase (CYP11B2). DNA and RNA were isolated separately from CYP11B2-positive and -negative tumor regions based on CYP11B2 IHC results. RESULTS: CYP11B2 IHC clearly demonstrated that three pieces from one adenoma were positive for CYP11B2 and the remaining three from the other adenoma were negative for CYP11B2. In quantitative real-time RT-PCR, CYP11B2 mRNA was upregulated in CYP11B2-positive tumor specimens (219-fold vs CYP11B2-negative tumor specimens). Targeted next-generation sequencing (NGS) detected novel KCNJ5 gene mutations (p.T148I/T149S, present in the same reads) and a PRKACA gene hotspot mutation (p.L206R) in the CYP11B2-positive and -negative tumors, respectively. Sanger sequencing of DNA from each tumor specimen (CYP11B2-positive tumor, n=3; CYP11B2-negative tumor, n=3) showed concordant results with targeted NGS. CONCLUSION: Our findings illustrate the co-existence of two different adrenocortical adenomas causing the concurrent diagnosis of PA and CS in the same patient. Molecular analysis was able to demonstrate that the two diseases resulted from independent somatic mutations seen in double adrenocortical adenomas.
PubMed-ID: 27165862
http://dx.doi.org/10.1530/EJE-16-0262

Attention Deficit Hyperactivity Disorder in Pediatric Patients with Pheochromocytoma and Paraganglioma.
Horm Metab Res, 48(8):509-13.
M. Batsis, U. Dagalakis, C. A. Stratakis, T. Prodanov, G. Z. Papadakis, K. Adams, M. Lodish and K. Pacak. 2016.
The aim of the study is to evaluate if there is an association between attention deficit hyperactivity disorder (ADHD) and the diagnosis of pheochromocytoma/paraganglioma (PHEO/PGL) in pediatric patients. A case series study of 43 patients under the age of 18 with PHEO/PGL tumors who were evaluated at the National Institute of Health between January 2006 and May 2014 is reported. Prior diagnosis of ADHD and treatment course with stimulant medications was recorded. Patient symptoms, catecholamine and metanephrine levels, tumor characteristics, and genetic analyses for syndromes associated with PHEO/PGL were evaluated. A chi-squared test was used to assess the prevalence of ADHD in the PHEO/PGL patients compared to the general population. Nine out of 43 (21%) of patients diagnosed with PHEO/PGL had been diagnosed with ADHD prior to tumor identification. Four of the 9 patients had been treated with amphetamine, dextroamphetamine, and/or methylphenidate, potentially exacerbating an adrenergic crisis. In addition, 4 patients exhibited hypertension at the initial diagnosis of their PHEO/PGL. Three patients had resolution of their ADHD symptoms after successful surgical removal of PHEO/PGL. Our study found a prevalence of ADHD in 21% of our PHEO/PGL patients, significantly higher than 7.2% seen in the general pediatric population. Symptoms of anxiety and difficulty in concentration in these patients may have been related to their underlying PHEO/PGL and were not recognized as part of the constellation of symptoms in a child with PHEO/PGL. In pediatric patients with hypertension and ADHD symptomatology, an evaluation to rule out PHEO/PGL is warranted prior to treatment with stimulant medications.
PubMed-ID: 27171833
http://dx.doi.org/10.1055/s-0042-106725

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

Procedural and clinical outcomes of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy.
Clin Endocrinol (Oxf), 85(5):710-6.
D. A. Delivanis, D. Erickson, T. D. Atwell, N. Natt, S. Maraka, G. D. Schmit, P. W. Eiken, M. A. Nathan, W. F. Young, Jr. and I. Bancos. 2016.
OBJECTIVE: The role of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy has not been fully investigated. Our aim was to describe the clinical presentation leading to the adrenal biopsy and evaluate the diagnostic performance, complications and non diagnostic rate of adrenal biopsy. DESIGN: Single-centre, retrospective cohort study. PATIENTS AND MEASUREMENTS: Medical records of patients who underwent adrenal biopsy between 1994 and 2014 were reviewed. Adrenal biopsy outcome was compared to a predefined reference standard. RESULTS: Biopsy was performed in 418 patients [62% men, median age 69 years (range, 15-91)] on 419 adrenal lesions, median size 3.1 cm (range, 0.6-24). The main indication for adrenal mass biopsy was (349/419, 83%) suspected adrenal metastasis from a known or suspected extra-adrenal primary source. Only 116 of 419, 28% of cases had prebiopsy biochemical testing for pheochromocytoma. Biopsy-related complications occurred in 4% of the patients. Histology revealed a metastasis in 231 of 419 (55%), benign adrenal tissue in 137 of 419 (33%), adrenocortical carcinoma in eight of 419 (2%), other lesions in 23 of 419 (5%) including seven cases of pheochromocytoma and six cases of infectious process. Biopsy was nondiagnostic in 20 of 419 (5%). All adrenal masses with unenhanced radiodensity </=10 HU (42/137, 31%) proved to be benign adrenal adenomas. Adrenal biopsy diagnosed malignancy with a sensitivity of 88.5%, specificity of 91.5%, positive predictive value of 93.4% and negative predictive value of 85.5%. CONCLUSION: When used in the appropriate clinical setting, adrenal biopsy is a powerful tool in the diagnostic algorithm of the evaluation of adrenal masses with features suspicious for malignancy. Efforts to increase awareness to perform biochemical testing for pheochromocytoma prior to adrenal biopsy are needed.
PubMed-ID: 27248805
http://dx.doi.org/10.1111/cen.13117

Clinical characteristics of PRKACA mutations in Chinese patients with adrenal lesions: a single-centre study.
Clin Endocrinol (Oxf),
X. Li, B. Wang, L. Tang, B. Lang, Y. Zhang, F. Zhang, L. Chen, J. Ouyang and X. Zhang. 2016.
CONTEXT: Recent studies have identified that the somatic PRKACA L206R mutation can cause cortisol-producing adenomas (CPAs). This study investigated the prevalence and characteristics of PRKACA, GNAS and CTNNB1 mutations in adrenal lesions in patients from a single centre in China. DESIGN, PATIENTS AND

MEASUREMENTS: We sequenced PRKACA, GNAS and CTNNB1 genes in 108 patients, including 60 patients with CPAs (57 with unilateral and three with bilateral adenomas), 13 with nonfunctional adenomas, 12 with adrenocortical carcinomas (ACCs), 15 with primary bilateral macronodular hyperplasia (PBMAH) and eight with aldosterone and cortisol cosecreting adenomas. Mutations in PRKACA, GNAS and CTNNB1 were examined, and clinical characteristics were compared. RESULTS: Among the unilateral CPAs, we identified somatic mutations in PRKACA (L206R) in 23 cases (40.4%), GNAS (R201C and R201H) in six cases (10.5%), CTNNB1 (S45C, L46P and S45P) in six cases (10.5%) and CTNNB1 plus GNAS in two cases (3.5%). PRKACA and GNAS mutations were mutually exclusive. Among the patients with nonfunctional adenoma, two carried CTNNB1 mutations. Among the patients with ACC, two carried GNAS and CTNNB1 mutations but none carried PRKACA mutations. One patient showed bilateral CPA, and one PBMAH patient carried PRKACA mutations. No mutations in PRKACA, GNAS or CTNNB1 were identified in the eight patients with aldosterone and cortisol cosecreting adenomas. PRKACA-mutant adenomas were associated with young age, overt Cushing's syndrome and high cortisol levels compared with non-PRKACA-mutant or CTNNB1-mutant lesions. CONCLUSIONS: PRKACA mutations are present in CPAs and bilateral adrenal macronodular hyperplasia. PRKACA mutation is associated with more severe autonomous cortisol secretion.
PubMed-ID: 27296931
http://dx.doi.org/10.1111/cen.13134

Serum RARRES2 Is a Prognostic Marker in Patients With Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 101(9):3345-52.
Y. Liu-Chittenden, D. Patel, K. Gaskins, T. J. Giordano, G. Assie, J. Bertherat and E. Kebebew. 2016.
CONTEXT: Retinoic acid receptor responder protein 2 (RARRES2) is a small secreted protein involved in multiple cancers, including adrenocortical carcinoma (ACC). However, discordant tumor and serum RARRES2 levels have been reported in various cancers. The etiology of this discordance is unknown and has not been studied in pair-matched tumor and serum samples. OBJECTIVE: To determine tissue and serum RARRES2 levels in patients with adrenocortical neoplasm and to elucidate the prognostic implications of RARRES2 levels. DESIGN, SETTINGS, AND PATIENTS: Tissue and serum RARRES2 levels were analyzed. A pair-matched analysis was performed to examine tissue and serum RARRES2 from 51 patients with benign adrenocortical tumors and 18 patients with ACC. Overall survival was analyzed based on RARRES2 expression. A mouse xenograft model was used to determine the source of serum RARRES2. RESULTS: Patients with ACC had decreased tumor RARRES2 gene expression ($P < .0001$) and increased serum RARRES2 levels ($P < .005$) as compared with patients with benign adrenocortical tumors. Higher serum RARRES2 levels were associated with improved overall survival ($P = .0227$). A mouse xenograft model demonstrated that higher tissue RARRES2 expression was associated with higher RARRES2 secretion in the serum and that there was an intrinsic mechanism in maintaining serum RARRES2 homeostasis. CONCLUSIONS: Serum and tissue RARRES2 expression levels are paradoxical in patients with ACC. The elevated RARRES2 in patient serum is unlikely to be secreted from tumor cells. Serum RARRES2 may be used as a novel prognostic marker for ACC.
PubMed-ID: 27336360
http://dx.doi.org/10.1210/jc.2016-1781

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

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

How to Quantify Recovery After Laparoscopic Adrenalectomy: An Assessment of Patient-reported Health-related Quality of Life.
Surg Laparosc Endosc Percutan Tech, 26(4):290-4.
O. Dovirak, J. Mao, K. Taylor, P. Chang and A. A. Wagner. 2016.
INTRODUCTION AND OBJECTIVE: Minimally invasive approaches to adrenal surgery were adopted in an attempt to reduce surgical morbidity. Despite the widespread use, few studies objectively evaluate health-related quality of life (HRQOL) in patients undergoing laparoscopic adrenalectomy (LA). We assessed patients' health status and recovery after LA with the use of validated questionnaires. METHODS: Patients seen in urology clinic for evaluation of adrenal surgery were enlisted in our prospective, patient-reported, HRQOL study assessing postoperative recovery. HRQOL was measured using Convalescence And Recovery Evaluation (CARE) and Short Form-12 questionnaires administered before surgery and at 2, 4, 8, 12 weeks and annually after surgery. All operations were performed using a laparoscopic transperitoneal approach by a single fellowship-trained surgeon. RESULTS: A total of 30 patients who met study inclusion criteria from July 2009 to November 2014 were included in our evaluation. Mean patient age was 53 years. Tumor size ranged from 2.0 to 5.5 cm and consisted of benign lesions, adrenal metastasis, and 1 adrenocortical carcinoma. Mean operative time was 98 minutes and median estimated blood loss was 50 mL. Median length of hospital stay was 1 day. Quality of life reflected by the CARE survey was impacted at 2 weeks postoperative and returned to baseline after 4 weeks. Pain and activity domains of CARE showed a significant decrease from baseline status. Physical component summary of Short Form-12 questionnaire supported the finding of negative impact of surgery on activity level within first 4 weeks of recovery. CONCLUSIONS: Despite minimally invasive approach, patients undergoing LA may require about 4 weeks to return to baseline activity, gastrointestinal, and pain status.
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http://dx.doi.org/10.1097/SLE.0000000000000290

Pheochromocytoma and paraganglioma in patients with neurofibromatosis type 1.
Clin Endocrinol (Oxf),
L. M. Gruber, D. Erickson, D. Babovic-Vuksanovic, G. B. Thompson, W. F. Young, Jr. and I. Bancos. 2016.
OBJECTIVE: Individuals with neurofibromatosis type 1 (NF1) are at an increased risk of developing a pheochromocytoma or paraganglioma (PHEO/PGL). However, the best case detection strategy is unknown. Our objectives were to describe the prevalence, clinical presentation and outcomes of PHEO/PGL associated with NF1 and formulate case detection testing recommendations for PHEO/PGL. DESIGN: A retrospective cohort study from 1959 to 2015, Tertiary medical centre. PATIENTS AND MEASUREMENTS: We studied 41 patients with NF1 and PHEO/PGL who were identified using the PHEO/PGL and NF1 databases: 3289 and 1415 patients, respectively. Our main outcome measures were prevalence of PHEO/PGL in NF1 and occurrence of

bilateral, recurrent, or metastatic disease and method of PHEO/PGL detection (symptoms vs incidental vs biochemical case detection testing). RESULTS: The prevalence of PHEO/PGL in patients with NF1 was 2.9%. The 41 patients included 23 men (56%) and 18 women. The median age at diagnosis was 41.0 years (range 14-67). The median tumour size was 3.4 cm (range 0.8-9.5). Bilateral PHEO was identified in 17% (n = 7) of patients, all women. Metastatic or recurrent disease occurred in 7.3% (n = 3). In the last 25 years, PHEO/PGL was diagnosed after incidental finding on computed imaging in 31% of patients (n = 11). Only three patients (7.3%) had PHEO/PGL discovered because of biochemical case detection testing. CONCLUSION: We recommend patients with NF1 have biochemical case detection testing for PHEO/PGL every 3 years starting at age 10 to 14 years. Biochemical case detection testing should also be carried out prior to elective surgical procedures and conception.
PubMed-ID: 27460956
http://dx.doi.org/10.1111/cen.13163

A Probabilistic Model for Cushing's Syndrome Screening in At-Risk Populations: A Prospective Multicenter Study.
J Clin Endocrinol Metab, 101(10):3747-54.
A. Leon-Justel, A. Madrazo-Atutxa, A. I. Alvarez-Rios, R. Infantes-Fontan, J. A. Garcia-Arnes, J. A. Lillo-Munoz, A. Aulinas, E. Urgell-Rull, M. Boronat, A. Sanchez-de-Abajo, C. Fajardo-Montanana, M. Ortuno-Alonso, I. Salinas-Vert, M. L. Granada, D. A. Cano and A. Leal-Cerro. 2016.
CONTEXT: Cushing's syndrome (CS) is challenging to diagnose. Increased prevalence of CS in specific patient populations has been reported, but routine screening for CS remains questionable. To decrease the diagnostic delay and improve disease outcomes, simple new screening methods for CS in at-risk populations are needed. OBJECTIVE: To develop and validate a simple scoring system to predict CS based on clinical signs and an easy-to-use biochemical test. DESIGN: Observational, prospective, multicenter. SETTING: Referral hospital. PATIENTS: A cohort of 353 patients attending endocrinology units for outpatient visits. INTERVENTIONS: All patients were evaluated with late-night salivary cortisol (LNSC) and a low-dose dexamethasone suppression test for CS. MAIN OUTCOME MEASURES: Diagnosis or exclusion of CS. RESULTS: Twenty-six cases of CS were diagnosed in the cohort. A risk scoring system was developed by logistic regression analysis, and cutoff values were derived from a receiver operating characteristic curve. This risk score included clinical signs and symptoms (muscular atrophy, osteoporosis, and dorsocervical fat pad) and LNSC levels. The estimated area under the receiver operating characteristic curve was 0.93, with a sensitivity of 96.2% and specificity of 82.9%. CONCLUSIONS: We developed a risk score to predict CS in an at-risk population. This score may help to identify at-risk patients in non-endocrinological settings such as primary care, but external validation is warranted.
PubMed-ID: 27490917
http://dx.doi.org/10.1210/jc.2016-1673

NET

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Prognostic factors in 151 patients with surgically resected non-functioning pancreatic neuroendocrine tumours.
ANZ J Surg, 86(7-8):563-7.
K. B. Song, S. C. Kim, J. H. Kim, S. M. Hong, K. M. Park, D. W. Hwang, J. H. Lee and Y. J. Lee. 2016.
BACKGROUND: Recently, non-functioning pancreatic neuroendocrine tumors (NF-PNETs) are increasing. It is important to know about the prognostic factors and long-term survival rates in patients with NF-PNET for the management of these diseases. METHODS: We retrospectively analysed the records of 151 patients with NF-PNET who had pancreatic resection between January 1995 and December 2010. RESULT: The 10-year overall survival, disease-specific survival and disease-free survival rate of the patients who underwent surgery for NF-PNET were 72.6%, 85.1% and 57.2% respectively. The three staging systems (2004 World Health Organization classification, 2006 European Neuroendocrine Tumor Society stages and 2010 grading system) showed comparable prognostic relevance in disease-specific survival of patients with resected NF-PNETs. Lymph nodes metastasis, high Ki-67 index and mitotic rate were the independent poor prognostic factors for disease-specific survival in the patients with surgically resected NF-PNET on multivariate analysis. CONCLUSION: We suggested that the three staging systems accurately reflect the prognosis in disease-specific survival of patients with resected NF-PNETs. Presence of lymph nodes metastases and high Ki-67 index and mitotic rate were the independent poor prognostic factors after resection of NF-PNET.
PubMed-ID: 25040037
http://dx.doi.org/10.1111/ans.12738

Bronchopulmonary Neuroendocrine Neoplasms and Their Precursor Lesions in Multiple Endocrine Neoplasia Type 1.
Neuroendocrinology, 103(3-4):240-7.
D. K. Bartsch, M. B. Albers, C. L. Lopez, J. C. Apitzsch, E. M. Walthers, L. Fink, V. Fendrich, E. P. Slater, J. Waldmann and M. Anlauf. 2016.
OBJECTIVE: The prevalence and clinical behavior of bronchopulmonary neuroendocrine tumors (bNET) associated with multiple endocrine neoplasia type 1 (MEN1) are not well defined. This study aimed to determine the prevalence, potential precursor lesions and prognosis of bNET in patients with MEN1. METHODS: A database of 75 prospectively collected MEN1 cases was retrospectively analyzed for bNET. Patient characteristics, imaging and treatment were evaluated. Resection specimens of operated patients were reassessed by two specialized pathologists. Available CT scans of the whole cohort were reviewed to determine the prevalence of bronchopulmonary nodules. RESULTS: Five of the 75 MEN1 patients (6.6%; 2 male, 3 female) developed histologically confirmed bNET after a median follow-up of 134 months. The median age at diagnosis of bNET was 47 years (range 31-67), and all patients were asymptomatic. Four patients underwent anatomic lung resections with lymphadenectomy; the remaining patient with multiple lesions had only a wedge resection of the largest bNET. Tumor sizes ranged from 7 to 32 mm in diameter, and all bNET were well differentiated. Two

patients had lymph node metastases. Two of 4 reevaluated resection specimens revealed multifocal bNET, and 3 specimens showed tumorlets (up to 3) associated with multifocal areas of a neuroendocrine cell hyperplasia within the subsegmental bronchi. One bNET-related death (1.3%) occurred during long-term follow-up. Review of the available CT scans of the patients without proven bNET revealed small bronchopulmonary lesions (>/=3 mm) in 16 of 53 cases (30.2%). CONCLUSIONS: bNET in MEN1 might be more common than previously recognized. Their natural course seems to be rather benign. Multifocal tumorlets and multifocal neuroendocrine cell hyperplasia might represent their precursor lesions.
PubMed-ID: 26113081
http://dx.doi.org/10.1159/000435921

Grade Increases in Gastroenteropancreatic Neuroendocrine Tumor Metastases Compared to the Primary Tumor.
Neuroendocrinology, 103(5):452-9.
F. Grillo, M. Albertelli, M. P. Brisigotti, T. Borra, M. Boschetti, R. Fiocca, D. Ferone and L. Mastracci. 2016.
BACKGROUND/AIM: The neuroendocrine tumor (NET) proliferation-based grading system (ENETS/WHO) for gastroenteropancreatic (GEP) tumors has proved reliable for prognostic stratification. To date, concerns exist regarding Ki-67 heterogeneity within the tumor and little is known on whether grade varies between primary and secondary sites. As tumor heterogeneity may have a significant impact on clinical management, our aim was to retrospectively evaluate Ki-67 on a series of GEP NETs in order to establish whether there is variability in different samples of the same lesion or between primary and metastatic disease (local/distant, synchronous/metachronous). METHODS: Sixty patients with multiple samples of tumor were accrued from a total of 338 GEP NETs; 44 of them also had tissue from local/distant metastases and a further 5 had multiple metastatic foci from unknown primary tumors. Immunohistochemistry for Ki-67 was performed on all paraffin blocks from both primary and metastatic tumors. RESULTS: Intratumor Ki-67 heterogeneity sufficient to change grade at first diagnosis was seen in 3/60 cases (5%). Out of 49 patients with primary NETs and/or multiple metastases, discrepancy in grade between sites was identified in 19 (39%) cases and in particular in 11/47 (23%) and in 10/12 (83%) patients with synchronous and metachronous metastases, respectively (p = 0.0002). Change in grade was more frequent in distant compared to locoregional metastases (p = 0.024) and in particular in distant sites other than the liver (p = 0.006). CONCLUSIONS: NETs show frequent differences in grade between primary sites and their synchronous/metachronous metastases; assessment of Ki-67 at all sites may prove to be significant for patient management.
PubMed-ID: 26337010
http://dx.doi.org/10.1159/000439434

Appendiceal Goblet Cell Carcinoids: Management Considerations from a Reference Peritoneal Tumour Service Centre and ENETS Centre of Excellence.
Neuroendocrinology, 103(5):500-17.
A. Lamarca, D. Nonaka, C. Lopez Escola, R. A. Hubner, S. O'Dwyer, B. Chakrabarty, P. Fulford and J. W. Valle. 2016.
BACKGROUND: Appendix goblet cell carcinoids are known to share histological features of adenocarcinoma and neuroendocrine tumours. Due to their low incidence, quality evidence is lacking for the management of these patients. METHODS: We performed a single-centre retrospective study of patients with a confirmed diagnosis of appendiceal goblet cell carcinoid (GCC; 1996-2014). Patients were divided into curative intent (CI) and palliative intent (PI) cohorts. Our primary end point was overall survival (OS). RESULTS: Seventy-four patients were eligible; 76% were treated with CI [surgery only (36%), cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC; 36%), adjuvant chemotherapy (20%) and a combination of CRS and HIPEC followed by adjuvant chemotherapy (9%)], and 23% had advanced-stage disease amenable to palliative treatment (chemotherapy or supportive care) only. Completion right hemicolectomy, performed in 64% of the CI cohort, did not impact on the relapse rate or disease-free survival. FOLFOX chemotherapy was used in both the adjuvant and palliative settings; safety was as expected, and we observed a high rate (60%) of disease control in the palliative cohort. The estimated median OS (all patients), disease-free survival (CI patients) and progression-free survival (PI patients) were 52.1 (95% CI 29.4-90.3), 75.9 (26.6-not reached) and 5.3 (0.6-5.7) months, respectively. Age and stage were independent factors associated with OS in the multivariable analysis. Tang classification showed a trend for impact on OS. No benefit from specific adjuvant approach was identified; however, selection bias for treatment approach was observed. CONCLUSION: Prospective trials are needed to define optimal approaches in GCC. All GCC patients should be managed by specialized centres due to their esoteric behaviour; we provide management considerations based on our experience and conclusions.
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http://dx.doi.org/10.1159/000440725

Risk and Protective Factors for Small Intestine Neuroendocrine Tumors: A Prospective Case-Control Study.
Neuroendocrinology, 103(5):531-7.
M. Rinzivillo, G. Capurso, D. Campana, N. Fazio, F. Panzuto, F. Spada, N. Cicchese, S. Partelli, P. Tomassetti, M. Falconi and G. Delle Fave. 2016.
BACKGROUND: The incidence of small intestine neuroendocrine tumors (SI-NETs) is increasing, but few studies have investigated risk factors for their occurrence, suggesting that family history (FH) of any cancer, smoking and previous cholecystectomy are associated with an increased risk. Such studies investigated small series or examined cancer registries without direct interviews. AIM: We therefore aimed at clarifying risk and protective factors for the occurrence of sporadic SI-NETs. SUBJECTS AND METHODS: We performed a multicenter case-control study. Patients with a histologic diagnosis of SI-NETs were prospectively evaluated, excluding familial syndromes. Controls with non-neoplastic/non-chronic disorders seen at gastrointestinal outpatients clinics were matched for sex and age (4:1). All subjects were directly interviewed by means of a specific questionnaire on potential risk and protective factors. Cases and controls were compared by Fisher's test or Student's t test for categorical or continuous variables. Explanatory variables were analyzed by simple logistic regression analysis. A multiple logistic regression analysis was performed with an Enter model; $p < 0.05$ was considered significant. RESULTS: 215 SI-NET patients and 860 controls were enrolled. FH of colorectal cancer (CRC) (8.8 vs. 5.0%) and breast cancer (10.2 vs. 4.8%), heavy smoking (24.7 vs. 14.8%) and drinking >21 alcohol units per week (7.4 vs. 3.8%) were all significantly more frequent in SI-NET patients than in controls. Multivariate analysis showed that FH of CRC (OR 2.23, 95% CI 1.29-3.84, $p = 0.003$), FH of breast cancer (OR 2.05, 95% CI 1.13-3.69, $p = 0.01$) and smoking (OR 1.47, 95% CI 1.07-2.03, $p = 0.01$) and in particular heavy smoking (OR 1.94, 95% CI 1.29-3.84, $p = 0.0008$) were associated with an increased risk for carcinoid occurrence, while use of aspirin can be considered a protective factor (OR 0.20, 95% CI 0.06-0.65, $p = 0.008$). CONCLUSION: FH of colorectal and breast cancer as well as smoking seem to be risk factors for the development of SI-NETs, while use of aspirin might be a protective factor. These factors partially overlap with those associated with CRC, but are different from those previously associated with pancreatic neuroendocrine tumors. These findings may suggest that the mechanisms of carcinogenesis for endocrine cells in different sites can be specific and similar to those of their exocrine counterparts.
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http://dx.doi.org/10.1159/000440884

Toward a Preoperative Classification of Lymph Node Metastases in Patients with Small Intestinal Neuroendocrine Tumors in the Era of Intestinal-Sparing Surgery.
Neuroendocrinology, 103(5):552-9.
S. Lardiere-Deguelte, L. de Mestier, F. Appere, M. P. Vullierme, M. Zappa, C. Hoeffel, M. Noaves, H. Brixi, O. Hentic, P. Ruszniewski, G. Cadiot, Y. Panis and R. Kianmanesh. 2016.
INTRODUCTION: In patients with small intestinal neuroendocrine tumors (siNETs), surgical resection of the primary tumor and associated mesenteric lymph nodes (LNs) is recommended, but is not well standardized and can be risky in patients with superior mesenteric vessel involvement. OBJECTIVE: We aimed to evaluate the correlation between the length of resected small bowel and the number of removed LNs, and to propose a preoperative morphological classification of siNET-associated LNs. METHODS: The records of patients operated on for siNETs at two expert centers between August 2005 and November 2013 were analyzed. Two specialist radiologists reviewed the preoperative imaging and classified mesenteric LNs into five stages according to their proximity to the trunk and/or branches of the superior mesenteric artery. RESULTS: 72 patients were included. The mean number of removed LNs was 12 +/- 15 and the length of removed small intestine was 53 +/- 43 cm. No correlation existed between the length of small bowel resection and the number of removed LNs. Overall, 9 (12%), 13 (18%), 36 (50%), 14 (19%) and 0 patients were classified into LN stages 0, I, II, III and IV. The correlation rate between the two observers was 0.98. Patients with LN stage III (hardly resectable) had more removed LNs than those with LN stages 0, I or II (easily removable). CONCLUSION: Optimal lymphadenectomy is not always associated with extended small bowel resection. In the era of small bowel-sparing surgery, the preoperative classification of mesenteric LNs could help to standardize the surgical management of patients with siNETs.
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http://dx.doi.org/10.1159/000441423

Surgical Treatment as a Principle for Patients with High-Grade Pancreatic Neuroendocrine Carcinoma: A Nordic Multicenter Comparative Study.
Ann Surg Oncol, 23(5):1721-8.

S. P. Haugvik, E. T. Janson, P. Osterlund, S. W. Langer, R. S. Falk, K. J. Labori, L. W. Vestermark, H. Gronbaek, I. P. Gladhaug and H. Sorbye. 2016.
BACKGROUND: This study aimed to evaluate the role of surgery for patients with high-grade pancreatic neuroendocrine carcinoma (hgPNEC) in a large Nordic multicenter cohort study. Prior studies evaluating the role of surgery for patients with hgPNEC are limited, and the benefit of the surgery is uncertain. METHODS: Data from patients with a diagnosis of hgPNEC determined between 1998 and 2012 were retrospectively registered at 10 Nordic university hospitals. Kaplan-Meier curves were used to compare the overall survival of different treatment groups, and Cox-regression analysis was used to evaluate factors potentially influencing survival. RESULTS: The study registered 119 patients. The median survival period from the time of metastasis was 23 months for patients undergoing initial resection of localized nonmetastatic disease and chemotherapy at the time of recurrence (n = 14), 29 months for patients undergoing resection of the primary tumor and resection/radiofrequency ablation of synchronous metastatic liver disease (n = 12), and 13 months for patients with synchronous metastatic disease given systemic chemotherapy alone (n = 78). The 3-year survival rate after surgery of the primary tumor and metastatic disease was 69 %. Resection of the primary tumor was an independent factor for improved survival after occurrence of metastatic disease. CONCLUSIONS: Patients with resected localized nonmetastatic hgPNEC and later metastatic disease seemed to benefit from initial resection of the primary tumor. Patients selected for resection of the primary tumor and synchronous liver metastases had a high 3-year survival rate. Selected patients with both localized hgPNEC and metastatic hgPNEC should be considered for radical surgical treatment.
PubMed-ID: 26678407
http://dx.doi.org/10.1245/s10434-015-5013-2

Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors.
J Nucl Med, 57(5):708-14.
S. A. Deppen, E. Liu, J. D. Blume, J. Clanton, C. Shi, L. B. Jones-Jackson, V. Lakhani, R. P. Baum, J. Berlin, G. T. Smith, M. Graham, M. P. Sandler, D. Delbeke and R. C. Walker. 2016.
Our purpose was to evaluate the safety and efficacy of (68)Ga-DOTATATE PET/CT compared with (111)In-pentetreotide imaging for diagnosis, staging, and restaging of pulmonary and gastroenteropancreatic neuroendocrine tumors. METHODS: (68)Ga-DOTATATE PET/CT and (111)In-pentetreotide scans were obtained for 78 of 97 consecutively enrolled patients with known or suspected pulmonary or gastroenteropancreatic neuroendocrine tumors. Safety and toxicity were measured by comparing vital signs, serum chemistry values, or acquisition-related medical complications before and after (68)Ga-DOTATATE injection. Added value was determined by changes in treatment plan when (68)Ga-DOTATATE PET/CT results were added to all prior imaging, including (111)In-pentetreotide. Interobserver reproducibility of (68)Ga-DOTATATE PET/CT scan interpretation was measured between blinded and nonblinded interpreters. RESULTS: (68)Ga-DOTATATE PET/CT and (111)In-pentetreotide scans were significantly different in impact on treatment ($P < 0.001$). (68)Ga-DOTATATE PET/CT combined with CT or liver MRI changed care in 28 of 78 (36%) patients. Interobserver agreement between blinded and nonblinded interpreters was high. No participant had a trial-related event requiring treatment. Mild, transient events were tachycardia in 1, alanine transaminase elevation in 1, and hyperglycemia in 2 participants. No clinically significant arrhythmias occurred. (68)Ga-DOTATATE PET/CT correctly identified 3 patients for peptide-receptor radiotherapy incorrectly classified by (111)In-pentetreotide. CONCLUSION: (68)Ga-DOTATATE PET/CT was equivalent or superior to (111)In-pentetreotide imaging in all 78 patients. No adverse events requiring treatment were observed. (68)Ga-DOTATATE PET/CT changed treatment in 36% of participants. Given the lack of significant toxicity, lower radiation exposure, and improved accuracy compared with (111)In-pentetreotide, (68)Ga-DOTATATE imaging should be used instead of (111)In-pentetreotide imaging where available.
PubMed-ID: 26769865
http://dx.doi.org/10.2967/jnumed.115.163865

Significance of preoperative radiographic pancreatic density in predicting pancreatic fistula after surgery for pancreatic neuroendocrine tumors.
Am J Surg, 212(1):40-6.
Y. Assadipour, S. C. Azoury, N. N. Schaub, Y. Hong, R. Eil, S. M. Inchauste, S. M. Steinberg, A. M. Venkatesan, S. K. Libutti and M. S. Hughes. 2016.
BACKGROUND: Postoperative pancreatic fistula remains the most severe and worrisome complication after surgery. Predictive preoperative assessment remains challenging. The authors examine the role of pancreatic computed tomography density in predicting postoperative pancreatic fistula after surgery for pancreatic neuroendocrine tumors. METHODS: A single institutional retrospective review of pancreatic surgery for

neuroendocrine tumors between 1998 and 2010 was conducted. Preoperative contrast-enhanced computed tomography scans were reviewed, with mean region of interest measurements of pancreatic parenchymal density obtained from 10-mm thick axial computed tomography images. RESULTS: A total of 119 patients were identified: 59 with enucleations and 60 with resections. Decreased preoperative pancreatic density was significantly associated with an increased grade of postoperative pancreatic fistula (P < .01). Subgroup analyses revealed that decreased gland density was associated with increased grade of postoperative pancreatic fistula in the resection (P < .01) but not in the enucleation group (P = .34). CONCLUSIONS: A significant association between postoperative pancreatic fistula grade and preoperative pancreatic computed tomography density is observed in patients undergoing resection for pancreatic neuroendocrine tumors.
PubMed-ID: 26782807
http://dx.doi.org/10.1016/j.amjsurg.2015.07.031

Potential value of EUS in pancreatic surveillance of VHL patients.
Eur J Endocrinol, 174(5):611-20.
S. J. van Asselt, A. H. Brouwers, H. M. van Dullemen, E. J. van der Jagt, A. H. Bongaerts, K. P. Koopmans, I. P. Kema, B. A. Zonnenberg, H. J. Timmers, W. W. de Herder, W. J. Sluiter, E. G. de Vries and T. P. Links. 2016.
BACKGROUND: Patients with von Hippel-Lindau (VHL) disease are prone to develop pancreatic neuroendocrine tumors (pNETs). However, the best imaging technique for early detection of pNETs in VHL is currently unknown. In a head-to-head comparison, we evaluated endoscopic ultrasound (EUS) and (11)C-5-hydroxytryptophan positron emission tomography ((11)C-5-HTP PET) compared with conventional screening techniques for early detection of pancreatic solid lesions in VHL patients. METHODS: We conducted a cross-sectional, prospective study in 22 patients at a tertiary care university medical center. Patients with VHL mutation or with one VHL manifestation and a mutation carrier as first-degree family member, with recent screening by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SRS), were eligible. Patients underwent EUS by linear Pentax echoendoscope and Hitachi EUB-525, and (11)C-5-HTP PET. Patient-based and lesion-based positivity for pancreatic solid lesions were calculated for all imaging techniques with a composite reference standard. RESULTS: In 10 of the 22 patients, 20 pancreatic solid lesions were detected: 17 with EUS (P < 0.05 vs CT/MRI+ SRS), 3 with (11)C-5-HTP PET, 3 with SRS, 9 with CT/MRI, and 9 with CT/MRI + SRS. EUS evaluations showed solid lesions with a median size of 9.7 mm (range 2.9-55 mm) and most of them were homogeneous, hypoechoic, isoelastic, and hypervascular. Moreover, EUS detected multiple pancreatic cysts in 18 patients with a median of 4 cysts (range 1-30). CONCLUSIONS: EUS is superior to CT/MRI + SRS for detecting pancreatic solid lesions in VHL disease.(11)C-5-HTP PET has no value as a screening method in this setting. EUS performs well in early detection of pNETs, but its role in VHL surveillance is unclear.
PubMed-ID: 26884551
http://dx.doi.org/10.1530/EJE-15-1012

Laparoscopic Insulinoma Enucleation from the Retro-Pancreatic Neck: A Stepwise Approach.
Ann Surg Oncol, 23(6):2001.
C. Conrad, G. Passot, M. H. Katz, J. B. Fleming, M. Kim, Y. S. Chun, T. A. Aloia, J. N. Vauthey and J. E. Lee. 2016.
BACKGROUND: Enucleation is the preferred surgical management of small, likely benign, insulinomas. Sparing pancreatic parenchyma and minimizing morbidity are of greater importance in these patients due to their anticipated long survival time. Although a laparoscopic approach is ideal, it can be particularly challenging when the insulinoma is retropancreatic or adjacent to critical vascular structures [i.e., superior mesenteric vein-portal vein confluence (SMV-PV)]. PATIENT: A 35-year-old woman with neuroglycopenic symptoms and hypoglycemia was diagnosed with hyperinsulinemia. Preoperative CT and EUS-FNA confirmed a 6- x 9-mm neuroendocrine tumor in the parenchyma of the posterior pancreatic neck along the left lateral aspect of the SMV-PV. TECHNIQUE: With the patient in stirrups and arms tucked (French Position), the lesser sac was opened to expose the pancreatic body. A retropancreatic tunnel was created anterior to the SMV-PV and the pancreatic neck encircled with umbilical tape to allow for retraction while minimizing pancreatic manipulation. The insulinoma was definitively identified using intraoperative ultrasound (IOUS). IOUS-guided clip placement facilitated direct identification and permitted safe image-guided enucleation. The enucleation was performed at the parenchymal interface, minimizing the risk of main pancreatic duct injury. CONCLUSIONS: Complete pancreatic neck mobilization and view through the laparoscope along the axis of the PV can facilitate exposure at the challenging location of the retropancreatic neck. Transpancreatic IOUS guidance is crucial to identify and safely enucleate small insulinomas in this location. This totally minimally invasive approach can reduce the morbidity of pancreatic surgery for these patients and permit organ-sparing despite the challenging anatomic location.

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http://dx.doi.org/10.1245/s10434-016-5106-6

Mixed Adeno-neuroendocrine Carcinoma: An Aggressive Clinical Entity.
Ann Surg Oncol, 23(7):2281-6.
S. Brathwaite, J. Rock, M. M. Yearsley, T. Bekaii-Saab, L. Wei, W. L. Frankel, J. Hays, C. Wu and S. Abdel-Misih. 2016.
BACKGROUND: Mixed adeno-neuroendocrine carcinoma (MANEC) is a rare pathologic diagnosis recently defined by the World Health Organization in 2010. Due to poor understanding of MANEC as a clinical entity, there is significant variation in the management of these patients. The purpose of our study was to characterize MANEC to develop evidence-based treatment strategies. METHODS: The Ohio State University patient database was queried for the diagnosis of MANEC and 46 patients were identified. For comparison, the database also was queried for goblet cell carcinoid (GCC) of the appendix, signet ring cell carcinoma, and carcinoid/neuroendocrine tumor of the appendix. Charts were then retrospectively reviewed for clinicopathologic characteristics, patient treatment, and survival data. RESULTS: The mean age of diagnosis of MANEC was 54 years. Eighty-seven percent of MANEC arose from the appendix, with 28 % of patients undergoing appendectomy and 35 % undergoing right hemicolectomy as their index operation. Immunohistochemical staining was positive for chromogranin (82 %), synaptophysin (97 %), and CD56 (67 %). Sixty-seven percent of patients presented with stage IV disease and 41 % had nodal metastases. Overall survival was 4.1 years, which was statistically significantly different (p </= 0.05) compared with carcinoid tumors (13.4 years), GCC (15.4 years), and signet ring carcinoma (2.2 years). CONCLUSIONS: MANEC is a more aggressive clinical entity than both GCC of the appendix and carcinoid/neuroendocrine tumors of the appendix. Based on these findings, we recommend patients with MANEC tumors undergo aggressive multidisciplinary cancer management and close surveillance.
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http://dx.doi.org/10.1245/s10434-016-5179-2

Surgical management of rectal carcinoids: trends and outcomes from the Surveillance, Epidemiology, and End Results database (1988 to 2012).
Am J Surg, 211(5):877-85.
Y. J. McConnell. 2016.
BACKGROUND: Local excision of small (<10 mm) rectal carcinoids is a standard treatment. Actual patterns of care and outcomes are understudied because of the rarity of this tumor. METHODS: Surveillance, Epidemiology, and End Results database (1988 to 2012) was interrogated for rectal carcinoid patients. Chi-square testing and Kaplan-Meier survival analysis were used to compare survival outcomes. RESULTS: Of all, 11,329 patients were identified-9,605 with only localized disease. The majority (77%) underwent local excision only. Full rectal resection was performed more frequently for tumors greater than 10 mm (11.7% to 12.2%) than for tumors less than 10 mm (4.5% to 4.9%, P < .001), and for higher T stage (T1: 4.0%, T2: 11.4%, T3/4:30.4%, P < .001). Nonoperative management was more common after year 2000 (11.2% to 13.7%) than prior (7.4% to 8.5%, P < .001). Cancer-specific survival improved across time periods but did not differ between nonoperative, local excision, or surgical resection. CONCLUSIONS: Nonexcisional management of small, localized rectal carcinoids is becoming more common and may offer equivalent survival to excision or resection.
PubMed-ID: 27048945
http://dx.doi.org/10.1016/j.amjsurg.2016.01.008

Symptomatic presentation as a predictor of recurrence in gastroenteropancreatic neuroendocrine tumors: A single institution experience over 15 years.
J Surg Oncol, 114(2):163-9.
G. G. Baptiste, L. M. Postlewait, C. G. Ethun, N. Le, M. R. McInnis, M. C. Russell, J. H. Winer, D. A. Kooby, C. A. Staley, S. K. Maithel and K. Cardona. 2016.
BACKGROUND AND OBJECTIVES: The prognostic implication of symptomatic presentation of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) remains unclear. METHODS: Patients who underwent resection of nonfunctional GEP-NETs (2000-2014) were analyzed. Primary outcomes were overall survival (OS) and distant recurrence-free survival (RFS). RESULTS: Symptomatic presentation was seen in 208 (61%) of 339 patients and was associated with younger age (55 vs. 59 yrs, P = 0.001), higher tumor grade (38% vs. 21%, P = 0.027), presence of lymphovascular invasion (58% vs. 33%, P < 0.001), presence of perineural invasion (54% vs. 29%, P = 0.002), and advanced disease (T3/T4/N1/M1 [63% vs. 44%, P = 0.002]), but not tumor size (2.6 vs. 2.5 cm, P = 0.74). Symptomatic presentation was associated with decreased 3-yr distant-RFS (80% vs. 89%, P = 0.012), but not OS. When accounting for adverse features, symptomatic presentation

remained independently associated with reduced distant-RFS (HR 3.51, P = 0.007). On subgroup-analysis of advanced disease patients, symptomatology was associated with reduced 3-yr distant-RFS (67% vs. 79%, P = 0.012) and persisted as an independent risk-factor for decreased distant-RFS (HR 3.01, P = 0.027). CONCLUSIONS: Symptomatic presentation of GEP-NETs is associated with aggressive features and worse distant-RFS. Trials assessing adjuvant therapy for advanced GEP-NETs are needed, and symptomatic presentation may be considered as one inclusion criterion. Following resection, symptomatic presentation should be taken into account when planning surveillance. J. Surg. Oncol. 2016;114:163-169. (c) 2016 Wiley Periodicals, Inc.
PubMed-ID: 27157897
http://dx.doi.org/10.1002/jso.24279

Hepatic Resection for Metastatic Neuroendocrine Cancer in Patients with Bone Metastases.
Ann Surg Oncol, 23(11):3693-8.
K. P. Croome, J. M. Burns, G. Q. F and D. M. Nagorney. 2016.
BACKGROUND: Hepatic resection (HR) of metastatic neuroendocrine cancer has been associated with prolonged survival and durable symptom control for selected patients with metastatic neuroendocrine tumor (NET). The present study investigates the outcomes of this operative approach in selected patients with known bone metastases. METHODS: All patients undergoing HR at Mayo Clinic Rochester and Mayo Clinic Florida for metastatic NET between January 1989 and August 2015 were identified, and were divided into two groups: those undergoing HR with a known diagnosis of bone metastases (HRmNET/LB) and those who had metastatic disease confined to the liver (HRmNET/L). RESULTS: A total of 25 patients in the HRmNET/LB group were propensity matched with 100 patients in the HRmNET/L group. Major liver resection was performed in 60 % of patients in the HRmNET/LB group and 55 % of patients in the HRmNET/L group (p = 0.42). Median survival for the HRmNET/LB group was 54.0 months, compared with 97.7 months for the HRmNET/L group (p = 0.03). In the HRmNET/LB group, median survival was 73.3 months for patients with gastrointestinal NET(GNET), compared with 42.7 months for patients with pancreatic NET (PNET). The median number of bone metastases was 2 (range 1-10), and the sites of bone metastases were the spine (68 %), pelvis (24 %), and ribs (12 %). Bone metastases were treated with radiotherapy in ten (40 %) patients, by radiofrequency ablation in two (8 %) patients, and by resection in one (4 %) patient. CONCLUSIONS: The present study is the first report to describe HR for patients with metastatic NET and known bone metastases. We demonstrated that in properly selected cases, excellent survival can be achieved with liver debulking in these patients.
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http://dx.doi.org/10.1245/s10434-016-5274-4

Neuroendocrine tumors of the pancreas: Degree of cystic component predicts prognosis.
Surgery, 160(3):708-13.
J. M. Cloyd, K. E. Kopecky, J. A. Norton, P. L. Kunz, G. A. Fisher, B. C. Visser, M. M. Dua, W. G. Park and G. A. Poultsides. 2016.
BACKGROUND: Although most pancreatic neuroendocrine tumors are solid, approximately 10% are cystic. Some studies have suggested that cystic pancreatic neuroendocrine tumors are associated with a more favorable prognosis. METHODS: A retrospective review of all patients with pancreatic neuroendocrine tumors who underwent operative resection between 1999 and 2014 at a single academic medical center was performed. Based on cross-sectional imaging performed before operation, pancreatic neuroendocrine tumors were classified according to the size of the cystic component relative to the total tumor size: purely cystic (100%), mostly cystic (>/=50%), mostly solid (<50%), and purely solid (0%). Clinicopathologic characteristics and recurrence-free survival were assessed between groups. RESULTS: In the study, 214 patients met inclusion criteria: 8 with purely cystic tumors, 7 with mostly cystic tumors, 15 with mostly solid tumors, and 184 with purely solid tumors. The groups differed in terms of tumor size (1.5 +/- 0.5, 3.0 +/- 1.7, 3.7 +/- 2.6, and 4.0 +/- 3.5 cm), lymph node positivity (0%, 0%, 26.7%, and 34.2%), intermediate or high grade (0%, 16.7%, 20.0%, and 31.0%), synchronous liver metastases (0%, 14.3%, 20.0%, and 26.6%) and need for pancreaticoduodenectomy (0%, 0%, 6.7%, and 25.0%), respectively. No cases of purely cystic pancreatic neuroendocrine tumors were associated with synchronous liver or lymph node metastasis, intermediate/high grade, recurrence, or death due to disease. Among patients presenting without metastatic disease, 10-year recurrence-free survival was 100% in patients with purely and mostly cystic tumors versus 53.0% in patients with purely and mostly solid tumors; however, this difference did not reach statistical significance. CONCLUSION: Pancreatic neuroendocrine tumors demonstrate a spectrum of biologic behavior with an increasing cystic component being associated with more favorable clinicopathologic features and prognosis. Purely cystic pancreatic neuroendocrine tumors may represent 1 subset that can be safely observed without immediate resection.

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http://dx.doi.org/10.1016/j.surg.2016.04.005

Ki-67 index and response to chemotherapy in patients with neuroendocrine tumours.
Endocr Relat Cancer, 23(7):563-70.
A. Childs, A. Kirkwood, J. Edeline, T. V. Luong, J. Watkins, A. Lamarca, D. Alrifai, P. Nsiah-Sarbeng, R. Gillmore, A. Mayer, C. Thirlwell, D. Sarker, J. W. Valle and T. Meyer. 2016.
Chemotherapy (CT) is widely used for neuroendocrine tumours (NETs), but there are no validated biomarkers to predict response. The Ki-67 proliferation index has been proposed as a means of selecting patients for CT, but robust data are lacking. The aim of this study was to investigate the relationship between response to chemotherapy and Ki-67 in NET. We reviewed data from 222 NET patients treated with CT. Tumours were graded according to Ki-67 index: G1 </=2%, G2 3-20% and G3 >20%. Response was assessed according to RECIST and survival calculated from start of chemotherapy to death. To explore Ki-67 as a marker of response, we calculated the likelihood ratio and performed receiver operating characteristic analysis. Overall, 193 patients had a documented Ki-67 index, of which 173 were also evaluable for radiological response: 10% were G1, 46% G2 and 43% G3; 46% were pancreatic NET (PNET). Median overall survival was 22.1 months. Overall response rate was 30% (39% in PNET vs 22% in non-PNET) and 43% of patients had stable disease. Response rate increased with grade: 6% in G1 tumours, 24% in G2 and 43% in G3. However, maximum likelihood ratio was 2.3 at Ki-67=35%, and the area under the ROC curve was 0.60. As reported previously, a high Ki-67 was an adverse prognostic factor for overall survival. In conclusion, response to CT increases with Ki-67 index, but Ki-67 alone is an unreliable means to select patients for CT. Improved methods to stratify patients for systemic therapy are required.
PubMed-ID: 27412968
http://dx.doi.org/10.1530/ERC-16-0099

Everolimus in ileum neuroendocrine tumours.
Lancet, 388(10041):236.
T. Walter and C. Lombard-Bohas. 2016.
PubMed-ID: 27479567
http://dx.doi.org/10.1016/S0140-6736(16)31039-X

Everolimus in ileum neuroendocrine tumours - Authors' reply.
Lancet, 388(10041):236-7.
J. C. Yao, M. Voi, N. Rouyrre and S. Singh. 2016.
PubMed-ID: 27479568
http://dx.doi.org/10.1016/S0140-6736(16)31045-5

Insulinoma Due to Multiple Pancreatic Microadenoma Localized by Multimodal Imaging.
J Clin Endocrinol Metab, 101(10):3559-63.
B. Babic, X. Keutgen, P. Nockel, M. Miettinen, C. Millo, P. Herscovitch, D. Patel, N. Nilubol, C. Cochran, P. Gorden and E. Kebebew. 2016.
CONTEXT: Insulinomas are usually due to a solitary tumor, but they can be challenging to localize. CASE DESCRIPTION: A 66-year-old woman presented with a 1-year history of episodic neuroglycopenic hypoglycemia and was suspected of having an insulinoma. On a supervised fast, she was found to be hypoglycemic at 39 mg/dL, with an insulin of 40 muU/mL 26 hours into the fast and a proinsulin of 35 pmol/L. Contrast-enhanced computed tomography and magnetic resonance imaging did not localize a pancreatic lesion. Intra-arterial calcium stimulation testing showed a step-up of venous insulin levels at injection of the superior mesenteric artery and proximal and mid-splenic artery, and a 68Ga-DOTATATE positron emission tomography/computed tomography showed focal uptake in the neck of the pancreas with a standardized uptake value of 12. Despite negative intraoperative pancreatic palpation and ultrasound, the patient underwent an extended distal pancreatectomy with normalization of biochemical levels and resolution of her symptoms. Pathology showed four subcentimeter neuroendocrine tumors that were positive for insulin, consistent with a diagnosis of multiple microadenomas. CONCLUSIONS: Multiple microadenomas are a rare cause of hyperinsulinemic hypoglycemia and localization, and resection of these tumors may be facilitated by multimodal imaging.
PubMed-ID: 27504852
http://dx.doi.org/10.1210/jc.2016-2717

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles