EUROPEAN SOCIETY OF ENDOCRINE SURGEONS

ESES Review of Recently Published Literature

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Contents

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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)

blue underline: Hyperlink to PubMed entry or web site of publisher. Clicking on hyperlink opens the corresponding web site in browser (in Vista: CTRL-click).

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Preliminary

Every time I promise that the ESES collection will be more in time, however it is getting later every time. So again my sincere apologizies and my only excuse (again) is my sickness. After a major overhaul of two of my key inner organs (with the associated hospitalization and recovery period) I hope I will be better off in the future and might be able to but the collection together in a more timely manner. Due to the back log created during 2018 the ESES collectors decided to jump the Collection 2018-2 and 2018-3. So the next collection will be 2019-1.

Yours

Ulrich Beutner

ESES Collection Coordinator

Journals covered

Journal	IF2016	Journal	IF2016
Acta Cytol	1.562†	J Bone Miner Res	6.284
Am J Kidney Dis	7.623	J Clin Endocrinol Metab	5.455
Am J Nephrol	2.542	J Clin Oncol	24.008
Am J Surg	2.612	J Endocrinol	4.706
Am Surgeon	0.700	J Endocrinol Invest	--
Ann Surg	8.980	J Nephrol	2.153
Ann Surg Oncol	4.041	J Nucl Med	6.646
ANZ J Surg	1.513	J Surg Oncol	2.993
Br J Surg	5.899	Lancet	47.831
Cancer	5.997	Langenbecks Arch Surg	2.203
Chirurg	0.646	Laryngoscope	2.471
Clin Endocrinol Oxf	3.327	N Engl J Med	72.406
Clin Nucl Med	3.640	Nat Rev Endocrinol (*prev:* Nat Clin Pract Endocrinol Metab)	18.318
Curr Opin Oncol	3.414	Nat Rev Clin Oncol (*prev*: Nat Clin Pract Oncol)	20.693
Endocr Relat Cancer	5.267	Nephrol Dial Transplant	4.470
Endocr Rev	15.745	Nephron Clin Pract	2.138
Eur Arch Otorhinolaryngol	1.660	Neuroendocrinology	3.608
Eur J Endocrinol	4.101	Oncologist	4.962
Eur J Surg Oncol	3.522	Otolaryngol Head Neck Surg	2.276
Gland Surg	---	Surg Clin North Am	2.206
Head Neck	3.376	Surg Endosc	3.747
Horm Metab Res	2.268	Surg Laparosc Endosc Percutan Tech	0.938
JAMA Otolaryngol Head Neck Surg (*prev:* Arch Oto …..)	2.951	Surg Oncol	3.304
JAMA Surg (*prev:* Arch Surg)	7.956	Surg Oncol Clin N Am	2.281
Int J Cancer	6.513	Surgery	3.904
J Am Coll Surg	4.307	Thyroid	5.515
J Am Soc Nephrol	8.966	Updates In Surgery	---
J Bone Miner Metab	2.423	World J Surg	2.673

Journal names are links to the journal's homepage!, IF2017: Impact factor 2014, †IF 2015, no IF for 2017

Thyroid

Meta-Analyses

Prognostic markers in well differentiated papillary and follicular thyroid cancer (WDTC).
Eur J Surg Oncol, 44(3):286-96.
S. L. Gillanders and J. P. O'Neill. 2018.
OBJECTIVES: WDTC (papillary and follicular thyroid cancer) make up around 90% of all thyroid tumours. Overall, the prognosis in patients with WDTC is excellent. However, there are small cohorts of patients who experience a more aggressive form of disease which is often associated with certain poor prognostic factors. Identifying these patients at an early stage is imperative for guiding treatment decisions. With recent developments in this area we plan to discuss the current evidence surrounding prognostic markers. METHODS: The literature regarding prognostic factors in WDTC was reviewed using an electronic database Medline - Pubmed. Using the MeSH search engine specific prognostic factors including age, size, grade, lymph node involvement, distant metastasis, extension/invasion, ethnic background, radioactive iodine avidity, and thyroglobulin level and their association with WDTC were evaluated. A broader search of prognostic markers in thyroid cancer was also carried out to avoid missing other pertinent markers. RESULTS: Multiple clinical and pathologic variables have been shown to be poor prognostic factors in WDTC with statistical significance. Extensive extrathyroidal extension and age may be the most important factors when predicting clinical outcomes in WDTC, although the age threshold may be increased from 45 to 55 years in due course. CONCLUSIONS: Management of WDTC has changed considerably over the last two years as reflected in evolving British and American Thyroid Guidelines. In all cases a combined multi-disciplinary approach, with consideration of the available guidelines and stratification systems should be utilised when planning an individualised treatment program to offer the best contemporary care to WDTC patients.
PubMed-ID: 28801060
http://dx.doi.org/10.1016/j.ejso.2017.07.013

Outpatient versus inpatient thyroidectomy: A systematic review and meta-analysis.
Head Neck, 40(1):192-202.
D. J. Lee, C. J. Chin, C. J. Hong, S. Perera and I. J. Witterick. 2018.
BACKGROUND: Outpatient thyroidectomy has gained popularity due to improved resource utilization. METHODS: We conducted a systematic review and meta-analysis using MEDLINE, EMBASE, CINAHL, Web of Science, and the Cochrane library. We included all studies examining the outcomes of outpatient thyroidectomy as compared with those of inpatient thyroidectomy. Risk of bias was assessed using the Newcastle-Ottawa scale. Postoperative complications (hematoma, hypocalcemia, and recurrent laryngeal nerve injury) and readmission/reintervention rates were compared. RESULTS: After screening 1665 records, 10 nonrandomized observational studies were included. There were fewer complication rates in the outpatient group than the inpatient group (relative risk [RR] 0.56; 95% confidence interval [CI] 0.37-0.83). There was no difference in readmission/reintervention rates (RR 0.60; 95% CI 0.33-1.09). CONCLUSION: The results suggest outpatient thyroidectomy may be as safe as inpatient thyroidectomy in appropriately selected patients. The results are limited by high risk of bias. Well-designed prospective studies are necessary to further assess the safety of outpatient thyroidectomy.
PubMed-ID: 29120517
http://dx.doi.org/10.1002/hed.24934

Inferior thyroid artery ligation increases hypocalcemia after thyroidectomy: A meta-analysis.
Laryngoscope, 128(2):534-41.
A. Sanabria, L. P. Kowalski and F. Tartaglia. 2018.
OBJECTIVE: To assess the effect of truncal ligation of the inferior thyroid artery in comparison with ligation of secondary branches as a risk factor for postoperative hypocalcemia. DATA SOURCES: A search was conducted using the Medical Subject Headings and free-text terms "thyroid*" and "truncal ligation*" in PubMed Central, PubMed, Embase, and Latin American and Caribbean Health Sciences Literature databases for trials published between January 1985 and October 2016. A Google search with the same terms, and a "snowball" approach was designed to retrieve the largest number of articles. REVIEW METHODS: Controlled trials (randomized or not) of adults who underwent total/bilateral subtotal thyroidectomy were searched, and truncal ligation versus nontruncal ligation of the inferior thyroid artery was compared. Data were acquired following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Methodological quality of randomized controlled

trials was assessed in accordance with Cochrane Collaboration guidelines, and for nonrandomized controlled trials, the Newcastle-Ottawa quality assessment scale for cohort studies was used. Pooled results are presented as risk differences with a random effects model. The main outcome was postoperative temporary and definitive hypocalcemia. RESULTS: We found 11 nonrandomized controlled trials and nine randomized controlled trials with 1940 patients: 977 patients in the trunk ligation group and 963 patients in the nontruncal ligation group. The risk difference for biochemical hypocalcemia was 6% (95% confidence interval [CI]: 2% to 11%), for symptomatic hypocalcemia 6% (95% CI: 1% to 10%), and definitive hypocalcemia 0% (95% CI: -1% to 1%) in the whole group. CONCLUSIONS: Truncal ligation of the inferior thyroid artery increases the risk of temporary and symptomatic hypocalcemia but not the risk of definitive hypocalcemia. Laryngoscope, 128:534-541, 2018.
PubMed-ID: 28561328
http://dx.doi.org/10.1002/lary.26681

Clinicopathologic and Prognostic Significance of Programmed Cell Death Ligand 1 Expression in Patients with Non-Medullary Thyroid Cancer: A Systematic Review and Meta-Analysis.
Thyroid, 28(3):349-61.
M. Aghajani, S. Graham, C. McCafferty, C. A. Shaheed, T. Roberts, P. DeSouza, T. Yang and N. Niles. 2018.
BACKGROUND: Evidence has shown that programmed cell death ligand 1 (PD-L1) overexpression is associated with poor prognosis and resistance to immune therapies in several human cancers. However, data on the prognostic significance of PD-L1 expression in thyroid cancer are limited and remain controversial. This systematic review and meta-analysis aimed to evaluate comprehensively the clinicopathologic significance and prognostic value of PD-L1 expression in non-medullary thyroid cancers. METHODS: Electronic databases, including Medline/PubMed, EMBASE, and the Cochrane Library, were searched up until July 5, 2017. In total, seven comparisons (from six articles) comprising 1421 patients were included in the pooled analysis. RESULTS: There was moderate quality evidence from four studies (n = 721) that shows positive PD-L1 expression was significantly associated with poor survival among thyroid cancer patients (pooled hazard ratio = 3.73 [confidence interval (CI) 2.75-5.06]). Increased PD-L1 expression was also found to be significantly associated with disease recurrence (odds ratio = 1.95 [CI 1.15-3.32]) and concurrent thyroiditis (odds ratio = 1.65 [CI 1.09-2.51]). CONCLUSIONS: The results confirm the prognostic significance of PD-L1 expression in thyroid cancer patients. PD-L1 expression has the potential to be implemented as a prognostic biomarker used to guide clinicians in identifying patients with more aggressive cancers, and for the selection of individuals that would derive durable clinical benefit from anti-PD-1/PD-L1 immunotherapy. Prospective clinical trials will be useful to support these findings.
PubMed-ID: 29455638
http://dx.doi.org/10.1089/thy.2017.0441

Clinicopathological Risk Factors for Distant Metastasis in Differentiated Thyroid Carcinoma: A Meta-analysis.
World J Surg, 42(4):1005-17.
H. G. Vuong, U. N. P. Duong, T. Q. Pham, H. M. Tran, N. Oishi, K. Mochizuki, T. Nakazawa, L. Hassell, R. Katoh and T. Kondo. 2018.
INTRODUCTION: Distant metastasis (DM) is not a frequent event in differentiated thyroid carcinoma (DTC) but has an adverse impact on mortality of patients with DTC. In the current study, we aimed to conduct a comprehensive systematic review and meta-analysis to investigate the risk factors for DM in DTCs and for each histological subtype. METHODS: Five electronic databases were searched from inception to December 2016 for relevant articles. Pooled odd ratios and 95% confidence interval were calculated using random-effect model. RESULTS: Thirty-four articles with 73,219 patients were included for meta-analyses. In DTCs, male gender, age >/=45 years, tumor size >/=4 cm, multifocality, vascular invasion (VI), extrathyroidal extension (ETE), lymph node metastasis (LNM), and lateral LNM were demonstrated to be associated with significant risks for DM. In addition, several clinicopathological factors such as age >/=45 years, VI, ETE, and LNM were shown to be significant risk factors for DM in both PTC and FTC subgroups. CONCLUSION: Our study demonstrated the promising value of several clinicopathological factors such as male gender, older age, VI, ETE, and LNM in predicting DM in PTCs and FTCs. Our study affirms the value of the selected clinicopathological factors for tumor risk stratification and assessment of patients' prognosis.
PubMed-ID: 28913696
http://dx.doi.org/10.1007/s00268-017-4206-1

Cancer Risk Associated with Nuclear Atypia in Cytologically Indeterminate Thyroid Nodules: A Systematic Review and Meta-Analysis.
Thyroid, 28(2):210-9.
P. Valderrabano, L. Khazai, Z. J. Thompson, S. C. Sharpe, V. D. Tarasova, K. J. Otto, J. E. Hallanger-Johnson, J. T. Wadsworth, B. M. Wenig, C. H. Chung, B. A. Centeno and B. McIver. 2018.
BACKGROUND: Indeterminate categories of thyroid cytopathology (categories B-III and B-IV of the Bethesda system) are integrated by a heterogeneous spectrum of cytological scenarios that are generally clustered for analysis and management recommendations. It has been suggested that aspirates exhibiting nuclear atypia have a higher risk of malignancy. This study aimed to assess whether cytologically indeterminate thyroid nodules with nuclear atypia have a significantly higher cancer risk than those without nuclear atypia. METHODS: On June 30, 2016, PubMed and EMBASE were searched for articles in English or Spanish using a search strategy developed by an endocrinologist and a librarian. Case reports were excluded, and no date limits were used. The references of all included studies were also screened for relevant missing studies. Studies were included if the prevalences of malignancy of cytologically indeterminate thyroid nodules with histological confirmation with and without nuclear atypia were reported. Studies were excluded if they had: (i) nodules suspicious for malignancy; (ii) nodules with non-indeterminate (B-III or B-IV) cytology on repeated biopsy, if performed; (iii) nodules not consecutively evaluated; or (iv) cohorts overlapping with another larger series. Two investigators independently assessed the eligibility and risk of bias of the studies. PRISMA and MOOSE guidelines were followed. Summary data were extracted from published reports by one investigator and independently reviewed by another. Data were pooled using a random-effects model. Heterogeneity was explored using subgroup analysis and mixed-effect model meta-regression. The odds ratio for malignancy of cytologically indeterminate thyroid nodules with nuclear atypia over cytologically indeterminate thyroid nodules without nuclear atypia was calculated. RESULTS: Of 2571 retrieved studies, 20 were eligible. The meta-analysis was conducted on summary data of 3532 cytologically indeterminate thyroid nodules: 1162 with and 2370 without nuclear atypia. The odds ratio for malignancy in cytologically indeterminate thyroid nodules with nuclear atypia was 3.63 [confidence interval 3.06-4.35]. There was no evidence of publication bias, and heterogeneity was insignificant ($I(2) < 0.01\%$, $p = 0.40$). CONCLUSIONS: Nuclear atypia is a significant indicator of malignancy in cytologically indeterminate thyroid nodules and needs to be standardized and implemented into clinical practice.
PubMed-ID: 29160163
http://dx.doi.org/10.1089/thy.2017.0419

Impact of Minimal Extra-Thyroid Extension in Differentiated Thyroid Cancer: Systematic Review and Meta-analysis.
J Clin Endocrinol Metab,
T. Diker-Cohen, D. Hirsch, I. Shimon, G. Bachar, A. Akirov, H. Duskin-Bitan and E. Robenshtok. 2018.
Background: Minimal extra-thyroid extension (mETE) in differentiated thyroid cancer (DTC) patients was defined as an intermediate risk feature in the 2015 American Thyroid Association guidelines. However, controversy persists as several studies suggested mETE has little effect on disease outcome. Objective: To assess the impact of mETE on DTC patients' outcome. Methods: Meta-analysis of controlled trials comparing DTC patients with and without mETE. Data Extraction and Synthesis: Thirteen retrospective studies including 23,816 patients were included, with a median follow-up of 86 months. mETE in patients without lymph node involvement (N0 disease) was associated with increased risk of recurrence (7 studies, OR 1.73, 95%CI 1.03-2.92). The absolute risk of recurrence was 2.2% in patients without extension and 3.5% in patients with mETE (p=0.04). In studies including patients with and without lymph-node involvement (N1/N0 disease), mETE resulted in a significantly higher risk of recurrence (8 studies, OR 1.82, 95%CI 1.14-2.91). The absolute risk of recurrence was 6.2% in patients without extension and 7% in patients with mETE (p=0.01). In patients with micro-papillary carcinoma (<1cm) the impact of mETE was non-significant (OR 2.40, 95%CI 0.95-6.03). Minimal ETE had no impact on disease-related mortality (8 studies, OR 0.5, 95%CI 0.11-2.21). Conclusion: mETE increases risk of recurrence in DTC patients. However, the absolute increase in risk is small, and in patients with N0 disease the risk is within the low-risk of recurrence category at 3.5%. Minimal ETE has no impact on disease-related mortality, and should not change tumor stage.
PubMed-ID: 29506045
http://dx.doi.org/10.1210/jc.2018-00081

A comprehensive review on MEN2B.
Endocr Relat Cancer, 25(2):T29-T39.
F. Castinetti, J. Moley, L. Mulligan and S. G. Waguespack. 2018.
MEN2B is a very rare autosomal dominant hereditary tumor syndrome associated with medullary thyroid carcinoma (MTC) in 100% cases, pheochromocytoma in 50% cases and multiple extra-endocrine features, many

of which can be quite disabling. Only few data are available in the literature. The aim of this review is to try to give further insights into the natural history of the disease and to point out the missing evidence that would help clinicians optimize the management of such patients. MEN2B is mainly characterized by the early occurrence of MTC, which led the American Thyroid Association to recommend preventive thyroidectomy before the age of 1 year. However, as the majority of mutations are de novo, improved knowledge of the nonendocrine signs would help to lower the age of diagnosis and improve long-term outcomes. Future large-scale studies will be aimed at characterizing more in detail the main characteristics and outcomes of MEN2B.
PubMed-ID: 28698189
http://dx.doi.org/10.1530/ERC-17-0209

Randomized controlled trials

Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery.
Br J Surg, 105(4):350-7.
J. Vidal Fortuny, S. M. Sadowski, V. Belfontali, S. Guigard, A. Poncet, F. Ris, W. Karenovics and F. Triponez. 2018.
BACKGROUND: Hypoparathyroidism, the most common complication after thyroid surgery, leads to hypocalcaemia and significant medical problems. An RCT was undertaken to determine whether intraoperative parathyroid gland angiography with indocyanine green (ICG) could predict postoperative hypoparathyroidism, and obviate the need for systematic blood tests and oral calcium supplementation. METHODS: Between September 2014 and February 2016, patients who had at least one well perfused parathyroid gland on ICG angiography were randomized to receive standard follow-up (measurement of calcium and parathyroid hormone (PTH) on postoperative day (POD) 1 and systematic supplementation with calcium and vitamin D; control group) or no supplementation and no blood test on POD 1 (intervention group). In all patients, calcium and PTH levels were measured 10-15 days after thyroidectomy. The primary endpoint was hypocalcaemia on POD 10-15. RESULTS: A total of 196 patients underwent ICG angiography during thyroid surgery, of whom 146 had at least one well perfused parathyroid gland on ICG angiography and were randomized. None of these patients presented with hypoparathyroidism, including those who did not receive calcium supplementation. The intervention group was statistically non-inferior to the control group (exact 95 per cent c.i. of the difference in proportion of patients with hypocalcaemia -0.053 to 0.053; P = 0.012). Eleven of the 50 excluded patients, in whom no well perfused parathyroid gland could be identified by angiography, presented with hypoparathyroidism on POD 1, and six on POD 10-15, which was significantly different from the findings in randomized patients (P = 0.007). CONCLUSION: ICG angiography reliably predicts the vascularization of the parathyroid glands and obviates the need for postoperative measurement of calcium and PTH, and supplementation with calcium in patients with at least one well perfused parathyroid gland. Registration number: NCT02249780 (http://www.clinicaltrials.gov).
PubMed-ID: 29405252
http://dx.doi.org/10.1002/bjs.10783

Ten-Year Follow-Up of a Randomized Clinical Trial of Total Thyroidectomy Versus Dunhill Operation Versus Bilateral Subtotal Thyroidectomy for Multinodular Non-toxic Goiter.
World J Surg, 42(2):384-92.
M. Barczynski, A. Konturek, A. Hubalewska-Dydejczyk, F. Golkowski and W. Nowak. 2018.
BACKGROUND: The aim of this study was to validate in a 10-year follow-up the initial outcomes of various thyroid resection methods for multinodular non-toxic goiter (MNG) reported in World J Surg 2010;34:1203-13. MATERIALS AND METHODS: Six hundred consenting patients with MNG were randomized to three groups of 200 patients each: total thyroidectomy (TT), Dunhill operation (DO), bilateral subtotal thyroidectomy (BST). Obligatory follow-up period of 60 months was extended up to 120 months for all the consenting patients. The primary outcome measure was the prevalence of recurrent goiter and need for revision thyroid surgery. The secondary outcome measure was the cumulative postoperative and post-revision morbidity rate. RESULTS: The primary outcomes were twice as inferior at 10 years when compared to 5-year results for DO and BST, but not for TT. Recurrent goiter was found at 10 years in 1 (0.6%) TT versus 15 (8.6%) DO versus 39 (22.4%) BST ($p < 0.001$), and revision thyroidectomy was necessary in 1 (0.6%) TT versus 5 (2.8%) DO versus 14 (8.0%) BST patients ($p < 0.001$). Any permanent morbidity at 10 years was present in 5 (2.8%) TT patients following initial surgery versus 7 (4.0%) DO and 10 (5.7%) BST patients following initial and revision thyroidectomy

(nonsignificant differences). At 10 years, 23 (11.5%) TT versus 25 (12.5%) DO versus 26 (13.0%) BST patients were lost to follow-up. CONCLUSIONS: Total thyroidectomy can be considered the preferred surgical approach for patients with MNG, as it abolishes the risk of goiter recurrence and need for future revision thyroidectomy when compared to more limited thyroid resections, whereas the prevalence of permanent morbidity is not increased at experienced hands. REGISTRATION NUMBER: NCT00946894 (http://www.clinicaltrials.gov).
PubMed-ID: 28942461
http://dx.doi.org/10.1007/s00268-017-4230-1

Consensus Statements/Guidelines

Thyroid cancer surgery guidelines in an era of de-escalation.
Eur J Surg Oncol, 44(3):297-306.
K. J. Kovatch, C. W. Hoban and A. G. Shuman. 2018.
Well-differentiated thyroid carcinoma has seen a tremendous rise in global incidence over the past three decades, largely owing to widespread screening and identification of small, incidentally detected tumors. With this increased incidence has emerged a movement questioning whether all cases of thyroid cancer merit a treatment approach focused on oncologic completeness. Such trends towards thoughtful, evidence-based treatment de-escalation paradigms reflect better risk stratification of thyroid cancers, and recognition that not all detected disease poses a threat to health or survival. Thus, national and professional guidelines are evolving to incorporate higher thresholds for surgery, acceptance of less than total thyroidectomy in specific circumstances, higher thresholds for adjuvant therapy, and introduction of the role of active surveillance for selected cases of low risk disease. Despite these common themes, there are significant differences among guidelines. This lack of consensus in guidelines persists due to variation in clinical practice patterns, differences in consideration and interpretation of existing evidence, cultural and geographical considerations, and resources available for both diagnosis and treatment.
PubMed-ID: 28385370
http://dx.doi.org/10.1016/j.ejso.2017.03.005

Surgical management of the recurrent laryngeal nerve in thyroidectomy: American Head and Neck Society Consensus Statement.
Head Neck, 40(4):663-75.
C. E. Fundakowski, N. W. Hales, N. Agrawal, M. Barczynski, P. M. Camacho, D. M. Hartl, E. Kandil, W. E. Liddy, T. J. McKenzie, J. C. Morris, J. A. Ridge, R. Schneider, J. Serpell, C. F. Sinclair, S. K. Snyder, D. J. Terris, R. M. Tuttle, C. W. Wu, R. J. Wong, M. Zafereo and G. W. Randolph. 2018.
"I have noticed in operations of this kind, which I have seen performed by others upon the living, and in a number of excisions, which I have myself performed on the dead body, that most of the difficulty in the separation of the tumor has occurred in the region of these ligaments.... This difficulty, I believe, to be a very frequent source of that accident, which so commonly occurs in removal of goiter, I mean division of the recurrent laryngeal nerve." Sir James Berry (1887).
PubMed-ID: 29461666
http://dx.doi.org/10.1002/hed.24928

Other Articles

Computer-aided system for diagnosing thyroid nodules on ultrasound: A comparison with radiologist-based clinical assessments.
Head Neck, 40(4):778-83.
L. Gao, R. Liu, Y. Jiang, W. Song, Y. Wang, J. Liu, J. Wang, D. Wu, S. Li, A. Hao and B. Zhang. 2018.
BACKGROUND: The purpose of this study was to compare the diagnostic efficiency of a thyroid ultrasound computer-aided diagnosis (CAD) system with that of 1 radiologist. METHODS: This study retrospectively reviewed 342 surgically resected thyroid nodules from July 2013 to December 2013 at our center. The nodules were assessed on typical ultrasound images using the CAD system and reviewed by 1 experienced radiologist. The radiologist stratified the risk of malignancy using the Thyroid Imaging Reporting and Data Systems (TIRADS) and the American Thyroid Association (ATA) guidelines. RESULTS: The radiologist, using TI-RADS

and ATA guidelines, performed better than the CAD system (P < .01). The sensitivity of the CAD system was similar to that of an experienced radiologist (P > .05; P < .01; and P > .05). However, we found that the CAD system had lower specificity (P < .01). CONCLUSION: The sensitivity of a thyroid ultrasound CAD system in differentiating nodules was similar to that of an experienced radiologist. However, the CAD system had lower specificity.
PubMed-ID: 29286180
http://dx.doi.org/10.1002/hed.25049

An Evolving Understanding of the Clinical Implications of NIFTP.
World J Surg, 42(2):327-8.
L. Yip and S. E. Carty. 2018.
PubMed-ID: 29127466
http://dx.doi.org/10.1007/s00268-017-4329-4

Effect of Age on Response to Therapy and Mortality in Patients With Thyroid Cancer at High Risk of Recurrence.
J Clin Endocrinol Metab, 103(2):689-97.
S. Shah and L. Boucai. 2018.
Context: Age at diagnosis has been identified as a major determinant of thyroid cancer-specific survival, with older patients being at higher risk for mortality, but the association of age with risk of recurrence has not been studied to date. Objective: To examine the effect of a patient's age on response to therapy and disease-specific mortality in a cohort of thyroid cancer patients at high risk of recurrence, as defined by the American Thyroid Association (ATA) risk stratification system. Design: Retrospective cohort study of 320 patients, median age 49.3 years, with follicular cell-derived thyroid carcinoma classified at ATA high risk and followed for a median of 7 years. Main Outcome Measures: Association of age with response to therapy, overall mortality, disease-specific mortality, and timing of metastases. Results: Age was a major determinant of response to therapy. There was a significantly larger percentage of excellent responders among young patients (age <55) than among old patients (age >/=55), 40.3% vs 27.5%, P = 0.002, respectively, whereas the proportion of structural incomplete responders was higher in the old group compared with the young group, 53% vs 33%, P = 0.002, respectively. ATA high-risk young patients with a structural incomplete response to therapy had a significantly better disease-specific survival than old patients (74% vs 12%, P < 0.001, respectively). Conclusions: Age was a key predictor of response to therapy and disease-specific survival in ATA high-risk thyroid cancer patients. Its incorporation as a variable in the ATA risk stratification system would improve its power to predict response to therapy as well as mortality.
PubMed-ID: 29220531
http://dx.doi.org/10.1210/jc.2017-02255

Yonsei Experience of 5000 Gasless Transaxillary Robotic Thyroidectomies.
World J Surg, 42(2):393-401.
M. J. Kim, K. H. Nam, S. G. Lee, J. B. Choi, T. H. Kim, C. R. Lee, J. Lee, S. W. Kang, J. J. Jeong and W. Y. Chung. 2018.
BACKGROUND: Since the use of robot systems in thyroid surgery was introduced in 2007, we have advanced a novel method of robotic thyroidectomy (RT) using a gasless transaxillary approach (TAA). We report our experience with this technique and detail the surgical outcome of 5000 robotic thyroidectomies. METHODS: From October 2007 to May 2016, we successfully performed 5000 robotic thyroidectomies using a gasless TAA at the Department of Surgery, Yonsei University Health System. The medical records of the patients are reviewed retrospectively, and the details of clinicopathologic characteristics, operation times, perioperative complications, and oncologic outcomes are analyzed. RESULTS: The 5000 patients with thyroid tumor (4804 with cancer and 196 with benign tumor) underwent RT using a gasless TAA. Mean operation time was 134.5 +/- 122.0 min. The most common histologic subtype of thyroid cancer was papillary (98%), and the mean tumor size was 8.0 +/- 6.0 mm. Stage I was found in 85.4% patients regarding tumor nodes metastasis staging. The 196 benign tumors consisted of 104 adenomatous hyperplasias (53.0%), 43 follicular adenomas (21.9%), 30 Graves' diseases (15.3%), and 19 others (9.7%). Postoperative complication occurred in 24.1% without any serious one, and overall morbidity tended to decrease over time. No disease-specific mortality was observed during the follow-up period. Locoregional recurrence was developed in 26 patients (0.5%). CONCLUSION: The authors have tried to improve RT technique using gasless TAA and achieved acceptable surgical outcomes. The rapid evolution of surgical robot technology and our constant effort to advance RT technique using gasless TAA would make it possible to reduce the perioperative morbidity and gain the best possible operative and oncologic outcomes.

PubMed-ID: 28879559
http://dx.doi.org/10.1007/s00268-017-4209-y

Differentiated thyroid cancer: millions spent with no tangible gain?
Endocr Relat Cancer, 25(1):51-7.
L. Furuya-Kanamori, A. Sedrakyan, A. A. Onitilo, N. Bagheri, P. Glasziou and S. A. R. Doi. 2018.
The incidence of differentiated thyroid cancer (DTC) has rapidly increased worldwide over the last decades. It is unknown if the increase in diagnosis has been mirrored by an increase in thyroidectomy rates with the concomitant economic impact that this would have on the health care system. DTC and thyroidectomy incidence as well as DTC-specific mortality were modeled using Poisson regression in New South Wales (NSW), Australia per year and by sex. The incidence of 2002 was the point from which the increase in rates was assessed cumulatively over the subsequent decade. The economic burden of potentially avoidable thyroidectomies due to the increase in diagnosis was estimated as the product of the additional thyroidectomy procedures during a decade attributable to rates beyond those reported for 2002 and the national average hospital cost of an uncomplicated thyroidectomy in Australia. The following results were obtained. The incidence of both DTC and thyroidectomy doubled in NSW between 2003 and 2012, while the DTC-specific mortality rate remained unchanged over the same period. Based on the 2002 incidence, the projected increase over 10 years (2003-2012) in thyroidectomy procedures was 2196. This translates to an extra cost burden of over AUD$ 18,600,000 in surgery-related health care expenditure over one decade in NSW. Our findings suggest that, if this rise is solely attributable to overdetection, then the rising expenditure serves no additional purpose. Reducing unnecessary detection and a conservative approach to managing DTC are sensible and would lead to millions of dollars in savings and reduced harms to patients.
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http://dx.doi.org/10.1530/ERC-17-0397

Less is More: The Impact of Multidisciplinary Thyroid Conference on the Treatment of Well-Differentiated Thyroid Carcinoma.
World J Surg, 42(2):343-9.
M. D. Moore, E. Postma, K. D. Gray, T. M. Ullmann, J. R. Hurley, S. Goldsmith, V. R. Sobel, A. Schulman, T. Scognamiglio, P. J. Christos, E. Hassett, J. Luick, D. Whitehall, R. Zarnegar and T. J. Fahey, 3rd. 2018.
BACKGROUND: In 2006, a multidisciplinary thyroid conference (MDTC) was implemented to better plan management of thyroid cancer patients at our institution. This study assessed the clinical impact of a MDTC on radioactive iodine (RAI) treatment patterns. METHODS: A prospective database (2003-2014) collected patient and tumor characteristics, RAI doses, and tumor recurrences. Patients treated with total thyroidectomy for differentiated thyroid carcinoma >/=1 cm were stratified based on American Thyroid Association (ATA) risk classification. RAI regimens were compared before initiation of MDTC (2003-2005, n = 88), after establishment of MDTC (2007-2009, n = 95), and after the release of 2009 ATA guidelines (2011-2014, n = 181). RAI doses were defined as low (</=75 mCi), intermediate (76-150 mCi), and high (>150 mCi). RESULTS: There was a significant decrease in the number of patients who received high-dose RAI after implementation of MDTC compared to before initiation of MDTC in the intermediate and high-risk patient groups ($p = 0.04$ and $p < 0.01$) without an associated increase in tumor recurrence (11 vs. 7%, $p = 0.74$). On multivariable analysis, presentation of a patient at MDTC was a negative predictor for receiving high-dose RAI ($p = 0.002$). As might be expected, there was also a significant decrease in use of RAI after the 2009 ATA guidelines were issued compared to after implementation of MDTC ($p < 0.01$). CONCLUSION: In conjunction with implementation of a thyroid malignancy multidisciplinary conference, we observed significantly decreased postoperative dosing of RAI without increased tumor recurrence. The 2009 ATA guidelines were associated with a further decrease in RAI administration. Treatment for patients with thyroid carcinoma is optimized by a multidisciplinary approach.
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http://dx.doi.org/10.1007/s00268-017-4308-9

DNA Mismatch Repair Deficiency Promotes Genomic Instability in a Subset of Papillary Thyroid Cancers.
World J Surg, 42(2):358-66.
M. Javid, T. Sasanakietkul, N. G. Nicolson, C. E. Gibson, G. G. Callender, R. Korah and T. Carling. 2018.
BACKGROUND: Efficient DNA damage repair by MutL-homolog DNA mismatch repair (MMR) enzymes, MLH1, MLH3, PMS1 and PMS2, are required to maintain thyrocyte genomic integrity. We hypothesized that persistent oxidative stress and consequent transcriptional dysregulation observed in thyroid follicles will lead to MMR deficiency and potentiate papillary thyroid tumorigenesis. METHODS: MMR gene expression was analyzed by targeted microarray in 18 papillary thyroid cancer (PTC), 9 paracarcinoma normal thyroid (PCNT) and 10 normal thyroid (NT) samples. The findings were validated by qRT-PCR, and in follicular thyroid cancers (FTC) and

follicular thyroid adenomas (FTA) for comparison. FOXO transcription factor expression was also analyzed. Protein expression was assessed by immunohistochemistry. Genomic integrity was evaluated by whole-exome sequencing-derived read-depth analysis and Mann-Whitney U test. Clinical correlations were assessed using Fisher's exact and t tests. RESULTS: Microarray and qRT-PCR revealed reduced expression of all four MMR genes in PTC compared with PCNT and of PMS2 compared with NT. FTC and FTA showed upregulation in MLH1, MLH3 and PMS2. PMS2 protein expression correlated with the mRNA expression pattern. FOXO1 showed lower expression in PMS2-deficient PTCs (log2-fold change -1.72 vs. -0.55, U = 11, p < 0.05 two-tailed). Rate of LOH, a measure of genomic instability, was higher in PMS2-deficient PTCs (median 3 and 1, respectively; U = 26, p < 0.05 two-tailed). No correlation was noted between MMR deficiency and clinical characteristics. CONCLUSIONS: MMR deficiency, potentially promoted by FOXO1 suppression, may explain the etiology for PTC development in some patients. FTC and FTA retain MMR activity and are likely caused by a different tumorigenic pathway.
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http://dx.doi.org/10.1007/s00268-017-4299-6

Overall Survival of Papillary Thyroid Carcinoma Patients: A Single-Institution Long-Term Follow-Up of 5897 Patients.
World J Surg, 42(3):615-22.
Y. Ito, A. Miyauchi, M. Kihara, M. Fukushima, T. Higashiyama and A. Miya. 2018.
INTRODUCTION: Papillary thyroid carcinoma (PTC) generally shows an excellent prognosis except in cases with aggressive backgrounds or clinicopathological features. Although the cause-specific survival (CSS) of PTC patients has been extensively investigated, the overall survival (OS) of these patients is unclear. We herein investigated both the OS and CSS of a large PTC patient series. MATERIALS AND METHODS: We enrolled 5897 PTC patients who underwent initial surgery between 1987 and 2005 (658 males and 5339 females; median age 51 years). Their median postoperative follow-up period was 177 months. Univariate and multivariate analyses for OS and CSS assessed the effects of gender, older age (>/=55 years), distant metastasis at diagnosis (M1), significant extrathyroid extension, tumor size (cutoffs 2 and 4 cm), large node metastasis (N >/= 3 cm), and extranodal tumor extension. RESULTS: To date, 387 patients (7%) in this series have died from various causes, including 117 (2%) due to PTC. The 10-, 15-, and 20-year OS rates are 97, 95, and 90%, respectively. Older age and M1 were important prognostic factors for OS and CSS. Older age was a more significant factor than M1 for OS and vice versa for CSS. In the older patients, M1 was a prominent prognostic factor for both OS and CSS. In the young patients, M1 had less prognostic impact than in the older patients, and the prognostic values of M1 and N >/= 3 cm for OS and CSS were identical and similar, respectively. CONCLUSIONS: The most important prognostic value for OS was patient age, indicating that PTC is generally indolent. However, the control of distant metastasis in older patients remains a future challenge in order to further improve their OS and CSS. PTC of >/=3 cm in young patients should be carefully followed, even in the absence of metastases, and these patients should undergo aggressive therapies for recurrent lesions and metastases.
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http://dx.doi.org/10.1007/s00268-018-4479-z

Risk Factors for Central Neck Lymph Node Metastases in Micro- Versus Macro- Clinically Node Negative Papillary Thyroid Carcinoma.
World J Surg, 42(3):623-9.
L. Sessa, C. P. Lombardi, C. De Crea, S. E. Tempera, R. Bellantone and M. Raffaelli. 2018.
BACKGROUND: Tumor size has been advocated as possible risk factors for occult central lymph node metastases (CNM) in papillary thyroid carcinoma (PTC) patients. This prospective study evaluated factors that could identify patients at higher risk of occult CNM, especially comparing micro-PTC and macro-PTC. METHODS: One hundred and eighty-six patients were recruited. All the patients had cN0 clinically unifocal PTC and underwent total thyroidectomy and bilateral prophylactic central neck dissection. Risk factors for occult CNM in micro- and macro-PTC patients were evaluated. RESULTS: Eighty-two patients showed CNM. The rate of CNM did not differ among different sizes cut off (</=20 mm, </=10 mm, </=5 mm P = NS). Significantly more pN1a than pN0 patients had pT3 tumors (35/82 vs. 26/104) (P < 0.05), extracapsular invasion (35/82 vs. 22/104) (P < 0.01) and microscopic multifocal disease (50/82 vs. 47/104) (P < 0.05). Independent risk factors for CNM were extracapsular invasion and multifocality at multivariate analysis. Risk factors for CNM in 77 micro-PTC were extracapsular invasion (16/31 pN1 vs. 10/46 pN0, P < 0.05) and multifocality (21/31 pN1 vs. 16/46 pN0, P < 0.01). Among 109 macro-PTC, risk factors for CNM were angioinvasion (15/51 pN1 vs. 7/58 pN0, P < 0.05) and classic PTC at the final histology (PTC vs. tall cell variant vs. follicular variant PTC) (P < 0.05). CONCLUSIONS: Risk factors for CNM can differ between micro- and macro-PTC, but no preoperatively known

clinical parameter is predictor of CNM in cN0 clinically unifocal PTC.
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http://dx.doi.org/10.1007/s00268-017-4390-z

Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign?
World J Surg, 42(2):321-6.
D. N. Parente, W. P. Kluijfhout, P. J. Bongers, R. Verzijl, K. M. Devon, L. E. Rotstein, D. P. Goldstein, S. L. Asa, O. Mete and J. D. Pasternak. 2018.
BACKGROUND: Renaming encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was recently suggested to prevent the overtreatment, cost and stigma associated with this low-risk entity. The purpose of this study is to document the incidence and further assess the clinical outcomes of reclassifying EFVPTC to NIFTP. METHODS: We searched synoptic pathologic reports from a high-volume academic endocrine surgery hospital from 2004 to 2013. The standard of surgical pathology practice was based on complete submission of malignant thyroid nodules along with the nontumorous thyroid parenchyma. Rigid morphological criteria were used for the diagnosis of noninvasive EFVPTC, currently known as NIFTP. A retrospective chart review was conducted looking for evidence of malignant behavior. RESULTS: One hundred and two patients met the strict inclusion criteria of NIFTP. The incidence of NIFTP in our cohort was 2.1% of papillary thyroid cancer cases during the studied time period. Mean follow-up was 5.7 years (range 0-11). Five patients were identified with nodal metastasis and one patient with distant metastasis. Overall, six patients showed evidence of malignant behavior representing 6% of patients with NIFTP. CONCLUSION: Our study demonstrates that the incidence of NIFTP is significantly lower than previously thought. Furthermore, evidence of malignant behavior was seen in a significant number of NIFTP patients. Although the authors fully support the de-escalation of aggressive treatment for low-risk thyroid cancers, NIFTP behaves as a low-risk thyroid cancer rather than a benign entity and ongoing surveillance is warranted.
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http://dx.doi.org/10.1007/s00268-017-4182-5

An Analysis of The American Joint Committee on Cancer 8th Edition T Staging System for Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 103(6):2199-206.
B. Tran, D. Roshan, E. Abraham, L. Wang, N. Garibotto, J. Wykes, P. Campbell and A. Ebrahimi. 2018.
Background: The American Joint Committee on Cancer (AJCC) removed microscopic extrathyroidal extension (ETE) from the 8th edition T staging for papillary thyroid cancer (PTC) based on increasing evidence that it is not an independent prognostic factor. Objectives: We compared the prognostic performance of AJCC 7th (pT7) and 8th (pT8) edition T stage systems, particularly in patients >/=55 years old without macroscopic ETE or distant metastases in whom T classification affects AJCC Tumor Node Metastasis (TNM) stage. Method: A retrospective analysis of disease-free survival (DFS) in 577 patients with PTC comparing pT8 vs pT7 using the Akaike information criterion (AIC), Harrell's C-index, and Proportion of Variation Explained (PVE). Results: Of 105 patients with AJCC7 T3 disease, 74 were down-staged. Overall, the prognostic performance of pT7 and pT8 was similar. However, in patients >/=55 years old without macroscopic ETE or distant metastases, pT8 was inferior to pT7 on the basis of higher AIC, lower C-index (0.67 vs 0.76), and lower PVE (30% vs 45%). In this subset, microscopic ETE was associated with multiple other adverse prognostic features and reduced DFS (hazard ratio, 2.8; 95% confidence interval, 1.5 to 5.2; P = 0.002), irrespective of tumor size. Discussion: In our cohort, pT8 was inferior to pT7 in patients >/=55 years old without macroscopic ETE or distant metastases in whom T classification affects TNM stage. Microscopic ETE was strongly associated with other adverse prognostic factors and reduced DFS in this patient subgroup and may be an effective surrogate for disease biology in PTC, irrespective of whether it is an independent prognostic factor.
PubMed-ID: 29672723
http://dx.doi.org/10.1210/jc.2017-02551

Long-term voice quality outcomes after total thyroidectomy: a prospective multicenter study.
Surgery, 163(4):796-800.
F. Borel, N. Christou, O. Marret, M. Mathonnet, C. Caillard, S. Bannani, D. Drui, F. Espitalier, C. Blanchard and E. Mirallie. 2018.
BACKGROUND: Postthyroidectomy voice disorders can occur without any recurrent laryngeal nerve injury, and probably are the most frequent complication after thyroidectomy. We report the long-term voice quality outcomes after total thyroidectomy without vocal cord palsy using a simple self-assessment tool: the voice handicap index

self-questionnaire. METHODS: This observational prospective multicenter study included 203 patients from the "ThyrQoL" study (ClinicalTrial NCT02167529), who underwent total thyroidectomy between October 2014 and August 2015 in 3 French Hospitals (Nantes, La Roche-sur-Yon, and Limoges). Exclusion criteria included confirmed malignant disease, age <18 years, and preoperative voice troubles with confirmed vocal cord palsy. Direct flexible laryngoscopy was performed after surgery. Nineteen patients with a postoperative vocal cord palsy were excluded from analysis. RESULTS: One hundred and seventy-six patients with no vocal cord palsy were analyzed. Voice handicap index scores were significantly altered on postoperative month 2 compared with preoperative values (7.02 +/- 11.56 vs 14.41 +/- 19.44; P<.0001). Voice handicap index scores were not significantly different on postoperative month 6 compared with preoperative values (7.02 +/- 11.56 vs 7.61 +/- 14.02; P=.381). Thirty-six patients (20.5%) described significant voice impairment 2 months after total thyroidectomy. Nine patients (5.7%) still experienced significant discomfort at 6 months. CONCLUSION: Twenty percent of patients had initial voice impairment at 2 months postthyroidectomy, with a progressive recovery to preoperative levels at 6 months with <6% with persistent voice complaints.
PubMed-ID: 29162343
http://dx.doi.org/10.1016/j.surg.2017.09.023

Robot-Assisted Transaxillary Thyroidectomy (RATT): A Series Appraisal of More than 250 Cases from Europe.
World J Surg, 42(4):1018-23.
G. Materazzi, L. Fregoli, P. Papini, S. Bakkar, M. C. Vasquez and P. Miccoli. 2018.
BACKGROUND: Robot-assisted transaxillary thyroidectomy (RATT) is widely accepted in Asian countries. However, concerns regarding the balance between its real advantages and safety and cost have been raised by North American authorities. In Europe, assessments have been limited by small numbers since now. The purpose here is to report a large European experience with RATT. METHODS: A retrospective analysis was conducted of 257 patients who underwent RATT for nodular disease between February 2012 and September 2016. Data collected included patient demographics, diagnosis, ultrasound-estimated mean thyroid volume and nodule size, type of resection, operative time, postoperative pain and morbidity, and the hospital length of stay. Pain was assessed by visual analog scale score 12 h postoperatively (on the first postoperative day, before discharge). Feasibility, effectiveness, and safety were the outcomes of interest. Follow-up of thyroid carcinoma patients was carried out measuring thyroglobulin levels and ultrasound examination (median follow-up 24 months (6-48 months)). First control after 12 months and successively once a year. RESULTS: There were 253 women and 4 men, with a mean age of 37.3 years. Indications included benign disease in 116, papillary carcinoma in 56, and indeterminate nodule in 85. Mean thyroid volume was 16.8 mL, and nodule size was 25.3 mm. A hemithyroidectomy was performed in 138 patients and total thyroidectomy in 118. The mean operative time was 77.5 min for the former and 99.7 min for the latter. One conversion was required. Complications included transient hypoparathyroidism in 7/118 (total thyroidectomy) patients (5.9%), transient vocal fold palsy in 3/257 (1.1%), 1 delayed tracheal injury (0.4%), and 3 postoperative hematoma (1.1%). Mean visual analog scale score was 1.79, and the mean length of stay was 1.6 days for hemithyroidectomy and 1.9 days for total thyroidectomy. CONCLUSION: RATT is safe and effective and could serve as a viable treatment modality in selected cases.
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http://dx.doi.org/10.1007/s00268-017-4213-2

Video-Assisted Thyroidectomy for Papillary Thyroid Carcinoma: Oncologic Outcome in Patients with Follow-Up >/= 10 Years.
World J Surg, 42(2):402-8.
R. Bellantone, M. Raffaelli, C. De Crea, L. Sessa, E. Traini, P. Princi and C. P. Lombardi. 2018.
BACKGROUND: Video-assisted thyroidectomy (VAT) arisen as a valid treatment for selected patients with papillary thyroid carcinoma (PTC), but no data concerning long-term oncologic outcome are available. The primary aim of the study was to evaluate the oncologic outcome of patients who underwent VAT for PTC with a follow-up >/= 10 years. METHODS: The medical charts of all the patients who successfully underwent VAT for PTC were reviewed. The patients with a minimum follow-up period of 120-months were included. Patients with unifocal PTC </= 1 cm, in the absence of lymph node metastases, without gross extracapsular invasion and age < 45 years were considered "low-risk" patients and followed with ultrasound and serum thyroglobulin (sTg) on levothyroxine (LT4); the remaining patients underwent nuclear medicine evaluation. RESULTS: Two hundred and fifty-seven patients, operated on between May 2000 and October 2006, were included. Postoperative complications included four transient recurrent palsies, 76 transient and 1 permanent hypocalcemia. One hundred and four low-risk patients were followed with ultrasound and sTg on LT4. At a mean follow-up of 136.6 months, mean sTg on LT4 was 0.1 +/- 0.1 ng/ml. None of them showed recurrence. The remaining 153 patients

underwent nuclear medicine evaluation. Among these 153, 62 did not undergo radioiodine ablation (RAI). At a mean follow-up of 150.8 months, mean sTg on LT4 was 0.1 +/- 0.1 ng/ml. None of them showed recurrence. The remaining 91 patients underwent RAI. Mean pre-RAI sTg off-LT4 was 8.3 +/- 5.8 ng/ml, mean radioiodine uptake was 2.8 +/- 4.4%. Among these 91, three pN1a patients developed a lateral neck node recurrence. No other recurrence was registered. At the latest follow-up mean sTg on LT4 in this subgroup of patients was 0.1 +/- 0.2 ng/ml. CONCLUSIONS: The long-term (>/= 10 years) oncologic outcome further demonstrates that VAT is a valid option for selected PTC patients.
PubMed-ID: 29238849
http://dx.doi.org/10.1007/s00268-017-4392-x

Importance of surgeon-performed ultrasound in the preoperative nodal assessment of patients with potential thyroid malignancy.
Surgery, 163(1):112-7.
R. Monteiro, A. Han, M. Etiwy, A. Swearingen, V. Krishnamurthy, J. Jin, J. J. Shin, E. Berber and A. E. Siperstein. 2018.
INTRODUCTION: A comprehensive cervical ultrasound evaluation is essential in the operative planning of patients with thyroid disease. Reliance on radiographic reports alone may result in incomplete operative management as pathologic lymph nodes are often not palpable and evaluation of the lateral neck is not routine. This study examined the role of surgeon-performed ultrasound in the evaluation of patients who underwent lateral neck dissection for thyroid cancer. METHODS: We conducted a retrospective review of a prospectively maintained database of patients who underwent therapeutic lymph node dissection for thyroid cancer between 2001 and 2016 at our tertiary referral center. All patients had surgeon-performed ultrasound preoperatively by 1 of 7 endocrine surgeons. These findings were compared with prereferral imaging studies to determine the value of surgeon-performed ultrasound to their overall treatment. RESULTS: Of 92 patients who underwent thyroidectomy with lateral neck dissection, 97% had prereferral imaging of the neck (ultrasonography, computed tomography, positron emission tomography). Of these patients, nodal disease was suggested by computed tomography scanning in 70.8% and by ultrasonography in 54%. Of all patients, 45% had positive lateral neck nodes detected only on surgeon-performed ultrasound despite prior neck imaging. Nodal disease was identified in 50% of patients with only 1 study and 50% of patients with greater than 1 study before surgeon-performed ultrasound. Of patients with nodes detected by surgeon-performed ultrasound, only 67% had a prereferral diagnosis of thyroid cancer. CONCLUSIONS: Our data demonstrate that reliance on standard preoperative imaging alone would have led to an incorrect initial operation in 45% of our patients. Awareness of the limitations of prereferral imaging is important for surgeons treating patients with thyroid and parathyroid disease. Surgeon-performed ultrasound is a useful tool in the diagnosis and accurate staging of patients.
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http://dx.doi.org/10.1016/j.surg.2017.10.005

Long-term outcome of prophylactic thyroidectomy in children carrying RET germline mutations.
Br J Surg, 105(2):e150-e7.
A. Machens, M. Elwerr, K. Lorenz, F. Weber and H. Dralle. 2018.
BACKGROUND: A comprehensive assessment has not been undertaken of long-term outcomes in children carrying germline RET mutations and undergoing prophylactic thyroidectomy with the aim of preventing medullary thyroid cancer (MTC). METHODS: A retrospective outcome study (1994-2017) of prophylactic thyroidectomy in children, with and without central node dissection, was performed at a tertiary surgical centre. RESULTS: Some 167 children underwent prophylactic thyroidectomy, 109 without and 58 with concomitant central node dissection. In the highest-risk mutational category, MTC was found in five of six children (83 per cent) aged 3 years or less. In the high-risk category, MTC was present in six of 20 children (30 per cent) aged 3 years or less, 16 of 36 (44 per cent) aged 4-6 years, and 11 of 16 (69 per cent) aged 7-12 years (P = 0.081). In the moderate-risk category, MTC was seen in one of nine children (11 per cent) aged 3 years or less, one of 26 (4 per cent) aged 4-6 years, three of 26 (12 per cent) aged 7-12 years, and seven of 16 (44 per cent) aged 13-18 years (P = 0.006). Postoperative hypoparathyroidism was more frequent in older children (32 per cent in the oldest age group versus 3 per cent in the youngest; P = 0.002), whether or not central node dissection was carried out. Three children developed recurrent laryngeal nerve palsy; all had undergone central node dissection (P = 0.040). All complications resolved within 6 months. Postoperative normalization of calcitonin serum levels was achieved in 114 (99.1 per cent) of 115 children with raised preoperative values. No residual structural disease or recurrence was observed. CONCLUSION: Early prophylactic thyroidectomy is a viable surgical concept in experienced hands, sparing older children the postoperative morbidity associated with delayed neck surgery.

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http://dx.doi.org/10.1002/bjs.10746

DICER1 Mutations Are Frequent in Adolescent-Onset Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 103(5):2009-15.
J. D. Wasserman, N. Sabbaghian, S. Fahiminiya, R. Chami, O. Mete, M. Acker, M. K. Wu, A. Shlien, L. de Kock and W. D. Foulkes. 2018.
Context: Papillary thyroid carcinoma (PTC) is a common malignancy in adolescence and is molecularly and clinically distinct from adult PTC. Mutations in the DICER1 gene are associated with thyroid abnormalities, including multinodular goiter and differentiated thyroid carcinoma. Objective: In this study, we sought to characterize the prevalence of DICER1 variants in pediatric PTC, specifically in tumors without conventional PTC oncogenic alterations. Patients: Patients (N = 40) who underwent partial or total thyroidectomy and who were <18 years of age at the time of surgery were selected. Design: The 40 consecutive thyroidectomy specimens (30 malignant, 10 benign) underwent genotyping for 17 PTC-associated variants, as well as full sequencing of the exons and exon-intron boundaries of DICER1. Results: Conventional alterations were found in 12 of 30 (40%) PTCs (five BRAFV600E, three RET/PTC1, four RET/PTC3). Pathogenic DICER1 variants were identified in 3 of 30 (10%) PTCs and in 2 of 10 (20%) benign nodules, all of which lacked conventional alterations and did not recur during follow-up. DICER1 alterations thus constituted 3 of 18 (16.7%) PTCs without conventional alterations. The three DICER1-mutated carcinomas each had two somatic DICER1 alterations, whereas two follicular-nodular lesions arose in those with germline DICER1 mutations and harbored characteristic second somatic RNase IIIb "hotspot" mutations. Conclusions: DICER1 is a driver of pediatric thyroid nodules, and DICER1-mutated PTC may represent a distinct class of low-risk malignancies. Given the prevalence of variants in children, we advocate for inclusion of DICER1 sequencing and gene dosage determination in molecular analysis of pediatric thyroid specimens.
PubMed-ID: 29474644
http://dx.doi.org/10.1210/jc.2017-02698

Weight gain after treatment of Graves' disease in children.
Clin Endocrinol (Oxf), 88(1):66-70.
G. T. Alonso, S. Rabon and P. C. White. 2018.
OBJECTIVE: The frequency of and risk factors for weight gain in children treated for Graves' disease have not been described. We evaluated change in BMI-Z score and predictors of weight gain in this population. DESIGN: Retrospective review of data from January 2000 to July 2011. PATIENTS: Two hundred and twenty two children and adolescents with Graves' disease (ages 2-18 years) evaluated following radioactive iodine administration (RAI); (n = 101), thyroidectomy (n = 9) and initiation of medical therapy (n = 112). MEASUREMENTS: Changes in body mass index Z score over 12 months (DeltaBMI-Z0-12). RESULTS: All treatment groups in each gender and race increased BMI-Z (median DeltaBMI-Z0-12 was positive). T3 levels following RAI (P = .04) and weight lost at the time of administration (P = .02) in the RAI group and free T4 levels in the medical therapy group (P = .03) were positively correlated with DeltaBMI-Z0-12 . Race was a significant predictor only in the medical therapy group (P = .01). Age negatively correlated with DeltaBMI-Z0-12 in both the RAI (P < .001) and medical therapy groups (P = .003). Gender, maximum TSH in the 12 months after RAI and initial dose of LT4 replacement did not correlate with DeltaBMI-Z0-12 . The prevalence of overweight and obesity in our cohort was similar to US children. CONCLUSIONS: Weight gain during treatment for Graves' disease is common in children, and many children become overweight or obese during treatment. Risk factors include greater degree of hyperthyroidism at presentation and time of RAI and younger age. Weight lost upon presentation may also predict greater weight gain. Control of subsequent hypothyroidism does not appear to affect weight gain.
PubMed-ID: 29023978
http://dx.doi.org/10.1111/cen.13493

Characteristics of Follicular Variant Papillary Thyroid Carcinoma in a Pediatric Cohort.
J Clin Endocrinol Metab, 103(4):1639-48.
S. L. Samuels, L. F. Surrey, C. P. Hawkes, M. Amberge, S. Mostoufi-Moab, J. E. Langer, N. S. Adzick, K. Kazahaya, T. Bhatti, Z. Baloch, V. A. LiVolsi and A. J. Bauer. 2018.
Context: In adults, noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) is considered a low risk for metastasis and persistent/recurrent disease. Objective: The goal of this study was to assess the clinical, sonographic, and histopathologic features of FVPTC in a pediatric cohort. Design: A retrospective review of subjects <19 years of age with papillary thyroid carcinoma (PTC) who underwent thyroidectomy between January 2010 and July 2015. Setting: Multidisciplinary academic referral center. Patients: Patients with FVPTC, defined as a tumor >/=1 cm in the largest dimension with predominant follicular growth, complete lack of well-

formed papillae, and nuclear features of PTC. Main Outcome Measures: Tumor size and location, presence of a tumor capsule, capsule and vascular invasion, lymph node invasion, and distant metastasis. Results: Eighteen patients with FVPTC were identified from a case cohort of 110 patients with PTC. On histopathology, 13 (72%) had unifocal nodules and 14 (78%) had completely encapsulated FVPTC. Capsule invasion was frequent (nine of 14; 64%), and vascular invasion was found in one-third of patients (six of 18; 33%). No lymph node metastases were found in the 13 patients (72%) who had a central neck lymph node dissection. One patient with vascular invasion had distant metastases. Conclusion: When strictly defined, FVPTC in pediatric patients has a low risk for bilateral disease and metastasis. Prospective studies are needed to confirm whether lobectomy with surveillance is sufficient to achieve remission in pediatric patients with low-risk FVPTC.
PubMed-ID: 29438531
http://dx.doi.org/10.1210/jc.2017-02454

Diagnostic Accuracy of Ultrasound With Color Flow Doppler in Children With Thyroid Nodules.
J Clin Endocrinol Metab, 103(5):1958-65.
A. W. Gannon, J. E. Langer, R. Bellah, S. Ratcliffe, J. Pizza, S. Mostoufi-Moab, A. R. Cappola and A. J. Bauer. 2018.
Context: Thyroid nodules are increasingly recognized in children and are associated with a greater risk for thyroid cancer compared with adults. Thyroid ultrasound is the favored tool for evaluation of thyroid nodules; however, there are limited data regarding the accuracy of thyroid ultrasound to confirm features associated with a low risk of thyroid cancer in children. Objectives: We examined whether thyroid ultrasound is capable of accurately identifying thyroid nodules at a low risk of malignancy in children. Design and Setting: Using a retrospective cohort study design, we identified children age </=18 years with thyroid nodules and adequate follow-up. Ultrasound images were reviewed independently by two blinded expert radiologists, and ultrasound characteristics were analyzed to determine optimal predictive value and reliability. Patients and Results: A total of 417 subjects were found to have thyroid nodules, and 152 subjects had adequate follow-up; 59 (38.8%) of these were diagnosed with thyroid cancer. We evaluated 236 individual nodules. Features most consistent with benign nodules included small size, isoechoic echogenicity, partially cystic structure, sharp or noninfiltrative margins, absent Doppler flow, and absent calcifications. Significant variability was found between expert interpretations of ultrasound features. Thyroid nodule composition appears to be the most sensitive and reliable feature for stratifying the risk of thyroid cancer. Ultrasound accurately identified benign thyroid nodules in 80.9% of subjects (95% confidence interval, 74-86.6). Conclusions: Ultrasonography is useful for the evaluation of thyroid nodules, but we found no combination of ultrasound features sufficient to exclude thyroid cancer without a biopsy.
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http://dx.doi.org/10.1210/jc.2017-02464

Long-Term Outcome After Surgery for Medullary Thyroid Carcinoma: A Single-Center Experience.
World J Surg, 42(2):367-75.
F. Torresan, E. Cavedon, C. Mian and M. Iacobone. 2018.
BACKGROUND: Medullary thyroid carcinoma (MTC) is a rare C cells-derived tumor, with a hardly predictable long-term prognosis. This study was aimed to evaluate the predictive factors of cure and survival after surgery for MTC in a monocentric series. METHODS: A retrospective analysis of the long-term outcomes was assessed in 255 MTC patients operated between 1980 and 2015 at Padua University hospital. RESULTS: Sporadic MTC occurred in 65.1% and hereditary MTC in 34.9% of patients. At a median follow-up of 93 months (range 7-430), the cure rate was 56.8%. The overall 10-year survival was 84.4%, and MTC-related death rate was 15.3%. Patients who died because of MTC had a median age of 61 years (range 21-84) and were at stages III-IV in all cases; deaths occurred in 18% of sporadic MTC, 6% of MEN2a and 66.7% of MEN2b patients. None of the patients at stages I-II died because of the disease, but 17.7% had persistent/recurrent disease. Based on univariate analysis, age, gender, genetic variant, extent and year of surgery, tumor size, lymph-nodal metastases and tumor stage significantly affected cure and survival rates. At multivariate analysis, only patient- and tumor-related features (age, lymph-nodal status and stage) remained significant independent prognostic factors. CONCLUSIONS: Radical surgery is the only chance of definitive cure in MTC, but it is possible only at early stage; in advanced stages, even extensive surgery could not grant cure and prolonged survival. Stage, nodal metastases and age remain the main predictive factors for cure and survival.
PubMed-ID: 29134313
http://dx.doi.org/10.1007/s00268-017-4321-z

Papillary Thyroid Carcinoma (PTC) in Children and Adults: Comparison of Initial Presentation and Long-Term Postoperative Outcome in 4432 Patients Consecutively Treated at the Mayo Clinic During Eight Decades (1936-2015).
World J Surg, 42(2):329-42.
I. D. Hay, T. R. Johnson, S. Kaggal, M. S. Reinalda, N. M. Iniguez-Ariza, C. S. Grant, S. T. Pittock and G. B. Thompson. 2018.
BACKGROUND: Contemporary guidelines for managing PTC advise an approach wherein primary tumor and regional metastases (RM) are completely resected at first surgery and radioiodine remnant ablation (RRA) is restricted to high-risk patients, policies our group has long endorsed. To assess our therapeutic efficacy, we studied 190 children and 4242 adults consecutively treated during 1936-2015. SUBJECTS AND METHODS: Mean follow-up durations for children and adults were 26.9 and 15.2 years, respectively. Bilateral lobar resection was performed in 86% of children and 88% of adults, followed by RRA in 30% of children and 29% of adults; neck nodes were excised in 86% of children and 66% of adults. Tumor recurrence (TR) and cause-specific mortality (CSM) details were taken from a computerized database. RESULTS: Children, when compared to adults, had larger primary tumors which more often were grossly invasive and incompletely resected. At presentation, children, as compared to adults, had more RM and distant metastases (DM). Thirty-year TR rates were no different in children than adults at any site. Thirty-year CSM rates were lower in children than adults (1.1 vs. 4.9%; p = 0.01). Comparing 1936-1975 (THEN) with 1976-2015 (NOW), 30-year CSM rates were similar in MACIS <6 children (p = 0.67) and adults (p = 0.08). However, MACIS <6 children and adults in 1976-2015 had significantly higher recurrence at local and regional, but not at distant, sites. MACIS 6+ adults, NOW, compared to THEN, had lower 30-year CSM rates (30 vs. 47%; p < 0.001), unassociated with decreased TR at any site. CONCLUSIONS: Children, despite presenting with more extensive PTC when compared to adults, have postoperative recurrences at similar frequency, typically coexist with DM and die of PTC less often. Since 1976, both children and adults with MACIS <6 PTC have a <1% chance at 30 years of CSM; adults with higher MACIS scores (6 or more) have a 30-year CSM rate of 30%.
PubMed-ID: 29030676
http://dx.doi.org/10.1007/s00268-017-4279-x

Risk profile analysis and complications after surgery for autoimmune thyroid disease.
Br J Surg, 105(6):677-85.
O. Thomusch, C. Sekulla, F. Billmann, G. Seifert, H. Dralle and K. Lorenz. 2018.
BACKGROUND: Surgical approaches to autoimmune thyroid disease are currently hampered by concerns over postoperative complications. Risk profiles and incidences of postoperative complications have not been investigated systematically, and studies with sufficient power to show valid data have not been performed. METHODS: A prospective multicentre European study was conducted between July 2010 and December 2012. Questionnaires were used to collect data prospectively on patients who had surgery for autoimmune thyroid disease and the findings were compared with those of patients undergoing surgery for multinodular goitre. Logistic regression analysis was used to evaluate risk factors for thyroid surgery-specific complications, transient and permanent recurrent laryngeal nerve (RLN) palsy and hypoparathyroidism. RESULTS: Data were available for 22 011 patients, of whom 18 955 were eligible for analysis (2488 who had surgery for autoimmune thyroid disease and 16 467 for multinodular goitre). Surgery for multinodular goitre and that for autoimmune thyroid disease did not differ significantly with regard to general complications. With regard to thyroid surgery-specific complications, the rate of temporary and permanent vocal cord palsy ranged from 2.7 to 6.7 per cent (P = 0.623) and from 0.0 to 1.4 per cent (P = 0.600) respectively, whereas the range for temporary and permanent hypoparathyroidism was 12.9 to 20.0 per cent (P < 0.001) and 0.0 to 7.0 per cent (P < 0.001) respectively. In logistic regression analysis of transient and permanent vocal cord palsy, autoimmune thyroid disease was not an independent risk factor. Autoimmune thyroid disease, extent of thyroid resection, number of identified parathyroid glands and no autotransplantation were identified as independent risk factors for both transient and permanent hypoparathyroidism. CONCLUSION: Surgery for autoimmune thyroid disease is safe in comparison with surgery for multinodular goitre in terms of general complications and RLN palsy. To avoid the increased risk of postoperative hypoparathyroidism, special attention needs to be paid to the parathyroid glands.
PubMed-ID: 29579336
http://dx.doi.org/10.1002/bjs.10770

Outpatient thyroidectomy is safe in the elderly and super-elderly.
Laryngoscope, 128(1):290-4.
J. S. Grubey, Y. Raji, W. S. Duke and D. J. Terris. 2018.
OBJECTIVES: 1) Determine the safety of outpatient thyroidectomy in the geriatric patient population. 2) Analyze the risk of postoperative complications from thyroid surgery in patients aged over 65 years (elderly) and aged

over 80 years (super-elderly) undergoing ambulatory thyroidectomy compared to patients aged 21 through 40 years. STUDY DESIGN: A retrospective analysis of consecutive patients undergoing thyroidectomy between January 2008 and July 2015 at a tertiary academic institution. METHOD: Patients were stratified by age, and three subsets within this population were considered and analyzed further: youthful/control (aged 21-40 years), elderly (aged 65-79 years), and super-elderly (>/= 80 years). Patient demographics, surgical and pathological data, admission status, complication, and readmission rates were recorded. RESULTS: A total of 1,429 thyroidectomies were accomplished; of these, 1,207 (84.5%) were outpatient operations. Among the outpatients, 85.2% were female, 14.1% were male, and the mean age was 50.3 +/- 15.2 years. The control (youthful) group was comprised of 328 patients with a mean age of 33.3 years; the elderly group of 201 patients had a mean age of 70.3 years; and 16 patients in the super-elderly group had a mean age 82.7 years. The complication rates (5.2%, 5.0%, and 6.3%, respectively; P = 0.98) and re-admission rates (1.5%, 1.5%, and 0.0%, respectively; P = 0.89) were not different among these groups. CONCLUSION: Outpatient thyroid surgery is as safe in appropriately selected elderly and super-elderly patients as it is in a control group of youthful patients. Therefore, age should not be a contraindication to conducting thyroidectomy on an ambulatory basis. LEVEL OF EVIDENCE: 4. Laryngoscope, 128:290-294, 2018.
PubMed-ID: 28573781
http://dx.doi.org/10.1002/lary.26707

Management of the lateral neck compartment in patients with sporadic medullary thyroid cancer.
Head Neck, 40(1):79-85.
I. Pena, G. L. Clayman, E. G. Grubbs, J. M. Bergeron, Jr., S. G. Waguespack, M. E. Cabanillas, R. Dadu, M. I. Hu, B. M. Fellman, Y. Li, N. D. Gross, S. Y. Lai, E. M. Sturgis and M. E. Zafereo. 2018.
BACKGROUND: The purpose of this retrospective analysis was to evaluate the benefits of an elective lateral neck dissection (ELND) in patients with medullary thyroid cancer (MTC) without radiographically apparent lateral neck metastases. METHODS: Patients with sporadic MTC without radiographic evidence of lateral neck metastasis who underwent definitive surgery were divided into 2 groups based on surgical approach: no ELND (the observation group) and ipsilateral or bilateral ELND (the ELND group). Primary outcomes were biochemical cure, locoregional recurrence, distant metastasis, and overall survival (OS). RESULTS: Sixty-six patients met inclusion criteria: 44 patients (67%) in the observation group and 22 patients (33%) in the ELND group. Two of 44 patients (5%) in the observation group developed subsequent (ipsilateral) lateral neck disease. At last follow-up, locoregional disease control rates among the observation and ELND groups were 98% and 100% (P > .999), respectively, whereas biochemical cure rates were 82% and 85% (P > .999), respectively, and 5-year OSs were 84% and 100% (P = .156), respectively. CONCLUSION: Patients with MTC without lateral neck metastasis have similar biochemical cure rates with observation or elective dissection of lateral neck compartments.
PubMed-ID: 29044788
http://dx.doi.org/10.1002/hed.24969

Natural History of Contralateral Nodules After Lobectomy in Patients With Papillary Thyroid Carcinoma.
J Clin Endocrinol Metab, 103(2):407-14.
A. Ritter, G. Bachar, D. Hirsch, C. Benbassat, O. Katz, N. Kochen, T. Diker-Cohen, A. Akirov, I. Shimon and E. Robenshtok. 2018.
Background: Bilateral thyroid nodularity is considered an indication for total thyroidectomy in papillary thyroid carcinoma (PTC). However, the natural history and outcome of contralateral nodules have never been studied. Objective: To investigate the natural history of nonsuspicious contralateral nodules after lobectomy for PTC. Methods: We included patients who had one or more solid nodules (>/=3 mm) in the contralateral lobe with benign cytology before surgery or small nonsuspicious nodules per ultrasonography. Results: One hundred and twelve patients were included. Median age was 57 years, and median size of the PTC (initial lobectomy) was 8 mm (range, 0.5 to 28 mm). On the contralateral side, the median size of nodules was 7 mm (range, 3 to 30 mm). Thirty-three nodules (29%) had fine-needle aspiration (FNA) before surgery, and all were benign. After a median follow-up of 6 years, median growth was zero (range, -20 to 19 mm). Twenty-six nodules (23%) increased >/=3 mm in size (median, 6 mm; range, 4 to 19 mm). Twenty patients (18%) developed new nodules. Twelve patients (11%) underwent completion thyroidectomy for growth (three), suspicious FNA (seven; Bethesda III to V), malignancy (one), or unknown reason (one). Overall, according to the completion thyroidectomy specimen, six patients (5%) were diagnosed with contralateral PTC (five micro-PTCs, one 20 mm), and all were without evidence of disease at the end of follow-up. There were no surgical difficulties or local complications during completion surgery. Conclusions: Lobectomy for low-risk patients with a small PTC and nonsuspicious contralateral thyroid nodule(s) is a reliable and safe initial treatment option. In the few patients who required completion thyroidectomy, treatment with surgery and radioiodine was effective.

PubMed-ID: 29240898
http://dx.doi.org/10.1210/jc.2017-01616

Use of methylene blue and near-infrared fluorescence in thyroid and parathyroid surgery.
Langenbecks Arch Surg, 403(1):111-8.
S. L. Hillary, S. Guillermet, N. J. Brown and S. P. Balasubramanian. 2018.
PURPOSE: Intraoperative localisation and preservation of parathyroid glands improves outcomes following thyroid and parathyroid surgery. This can be facilitated by fluorescent imaging and methylene blue; a fluorophore is thought to be taken up avidly by parathyroid glands. This preliminary study aims to identify the optimum dose of methylene blue (MB), fluorescent patterns of thyroid and parathyroid glands and develop a protocol for the use of intravenous MB emitted fluorescence to enable parathyroid identification. METHODS: This is a phase 1b, interventional study (NCT02089542) involving 41 patients undergoing thyroid and/or parathyroid surgery. After exposure of the thyroid and/or parathyroid gland(s), intravenous boluses of between 0.05 and 0.5 mg/kg of MB were injected. Fluobeam(R) (a hand held fluorescence real-time imager) was used to record fluorescence from the operating field prior and up to 10 min following administration. RESULTS: The optimum dose of MB to visualise thyroid and parathyroid glands was 0.4 mg/kg body weight. The median time to onset of fluorescence was 23 and 22 s and the median time to peak fluorescence was 41.5 and 40 s, respectively. The peak fluorescence for thyroid and parathyroid glands compared to muscle were 2.6 and 4.3, respectively. Parathyroid auto-fluorescence prior to methylene blue injection was commonly observed. CONCLUSIONS: A clinical protocol for detection of fluorescence from MB during thyroid and parathyroid surgery is presented. Parathyroids (especially enlarged glands) fluoresce more intensely than thyroid glands. Auto-fluorescence may aid parathyroid detection, but MB fluorescence is needed to demonstrate viability.
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http://dx.doi.org/10.1007/s00423-017-1641-2

Monitoring of the posterior cricoarytenoid muscle represents another option for neural monitoring during thyroid surgery: Normative vagal and recurrent laryngeal nerve posterior cricoarytenoid muscle electromyographic data.
Laryngoscope, 128(1):283-9.
W. Liddy, S. R. Barber, B. M. Lin, D. Kamani, N. Kyriazidis, B. Lawson and G. W. Randolph. 2018.
OBJECTIVE: Intraoperative neural monitoring (IONM) of laryngeal nerves using electromyography (EMG) is routinely performed using endotracheal tube surface electrodes adjacent to the vocalis muscles. Other laryngeal muscles such as the posterior cricoarytenoid muscle (PCA) are indirectly monitored. The PCA may be directly and reliably monitored through an electrode placed in the postcricoid region. Herein, we describe the method and normative data for IONM using PCA EMG. STUDY DESIGN: Retrospective review. METHODS: Data were reviewed retrospectively for thyroid and parathyroid surgery patients with IONM of laryngeal nerves from January to August 2016. Recordings of vocalis and PCA EMG amplitudes and latencies with stimulation of laryngeal nerves were obtained using endotracheal (ET) tube-based and postcricoid surface electrodes. RESULTS: Data comprised EMG responses in vocalis and PCA recording channels with stimulation of the vagus, recurrent laryngeal nerve (RLN), and external branch of the superior laryngeal nerve from 20 subjects (11 left, 9 right), as well as PCA EMG threshold data with RLN stimulation from 17 subjects. Mean EMG amplitude was 725.69 +/- 108.58 microvolts (microV) for the ipsilateral vocalis and 329.44 +/- 34.12 microV for the PCA with vagal stimulation, and 1,059.75 +/- 140.40 microV for the ipsilateral vocalis and 563.88 +/- 116.08 microV for the PCA with RLN stimulation. There were no statistically significant differences in mean latency. For threshold cutoffs of the PCA with RLN stimulation, mean minimum and maximum threshold intensities were 0.37 milliamperes (mA) and 0.84 mA, respectively. CONCLUSION: This study shows robust and reliable PCA EMG waveforms with direct nerve stimulation. Further studies will evaluate feasibility and application of the PCA electrode as a complementary quantitative tool in IONM. LEVEL OF EVIDENCE: 4. Laryngoscope, 128:283-289, 2018.
PubMed-ID: 28144954
http://dx.doi.org/10.1002/lary.26456

Surgeon volume and prognosis of patients with advanced papillary thyroid cancer and lateral nodal metastasis.
Br J Surg, 105(3):270-8.
H. I. Kim, T. H. Kim, J. H. Choe, J. H. Kim, J. S. Kim, Y. N. Kim, H. Kim, S. W. Kim and J. H. Chung. 2018.
BACKGROUND: Surgery is the most important treatment modality for papillary thyroid cancer (PTC). However, the relationship between surgeon volume and long-term oncological outcomes has not been explored. METHODS: Patients diagnosed with N1b PTC after initial thyroid surgery between 1 July 1994 and 31 December 2011 were eligible for inclusion in the study. Surgeons were categorized into high (at least 100

operations per year) and low (fewer than 100 operations per year) volume groups. Kaplan-Meier survival analysis according to surgeon volume was performed, and Cox proportional hazard modelling was used to estimate hazard ratios (HRs) with 95 per cent confidence intervals according to patient, tumour and surgeon factors. RESULTS: A total of 1103 patients with a median follow-up of 81 (i.q.r. 62-108) months were included in the study. During follow-up, 200 patients (18.1 per cent) developed structural recurrence. A high surgeon volume was associated with low structural recurrence (P = 0.006). After adjustment for age, sex and conventional risk factors for recurrence (histology, tumour size, gross extrathyroidal extension, margin status, more than 5 positive lymph nodes, radioactive iodine therapy), the adjusted HR for structural recurrence for low-volume surgeons was 1.46 (95 per cent c.i. 1.08 to 1.96), compared with high-volume surgeons. Distant metastasis (P = 0.242) and disease-specific mortality (P = 0.288) were not affected by surgeon volume. CONCLUSION: Surgeon volume is associated with structural recurrence, but not distant metastasis or cancer-specific death in patients with N1b PTC. Surgeon volume is important in initial surgery for advanced PTC with extensive nodal metastasis in order to ensure curative outcome and reduce treatment-related morbidity.
PubMed-ID: 29405275
http://dx.doi.org/10.1002/bjs.10655

Management of chyle leakage after thyroidectomy, cervical lymph node dissection, in patients with thyroid cancer.
Head Neck, 40(1):7-15.
I. Park, N. Her, J. H. Choe, J. S. Kim and J. H. Kim. 2018.
BACKGROUND: The purpose of this study was to evaluate the incidence and pattern of chyle leakage after thyroidectomy and/or cervical lymph node dissection and to establish management protocols for chyle leakage. METHODS: Patients who underwent surgical management for thyroid cancer were analyzed retrospectively. RESULTS: For this study, 131 patients with chyle leakage were identified; the overall incidence was 0.9%. Of them, 43.7% of patients underwent central neck dissection without lateral neck dissection, and chyle leakage was easily controlled with conservative management. Patients whose chyle drainage was reduced by >50% after dietary modification had a significantly shorter hospital stay (P < .001); NPO was the most effective dietary modification. CONCLUSION: The occurrence of chyle leakage after central compartment dissection even without lateral neck dissection was not rare, but was easily controlled with conservative management. Surgical management should be considered if the drainage amount does not decrease by >50% of the original amount of the day of detection after 2 days of NPO.
PubMed-ID: 29120521
http://dx.doi.org/10.1002/hed.24852

Relationship Between (18)F-fluorodeoxyglucose Accumulation and the BRAF (V600E) Mutation in Papillary Thyroid Cancer.
World J Surg, 42(1):114-22.
J. W. Chang, K. W. Park, J. H. Heo, S. N. Jung, L. Liu, S. M. Kim, I. S. Kwon and B. S. Koo. 2018.
BACKGROUND: To determine whether (18)F-fluoro-2-deoxyglucose ((18)F-FDG)-PET/CT is useful for predicting the BRAF (V600E) mutation status of a primary papillary thyroid carcinoma (PTC). METHODS: A retrospective analysis was performed in 108 patients who underwent (18)F-FDG positron emission tomography-computed tomography (PET/CT) for staging before thyroidectomy and BRAF analysis in biopsy-confirmed PTC. The maximum standardized uptake value (SUVmax) of the primary tumor was calculated according to FDG accumulation. Univariate and multivariate analyses were performed to assess the association between the SUVmax and clinicopathological variables. RESULTS: The BRAF (V600E) mutation was detected in 71 of 108 (65.7%) patients. In all subjects, the tumor size and BRAF (V600E) mutation were independently related to the SUVmax according to multivariate analyses (P = 0.002 and 0.007, respectively). The SUVmax was significantly higher in tumors with the BRAF (V600E) mutation than in tumors with wild-type BRAF (10.24 +/- 11.89 versus 4.02 +/- 3.86; P = 0.007). In the tumor size >1 cm subgroup, the BRAF (V600E) mutation was the only factor significantly associated with the SUVmax (P = 0.016). A SUVmax cutoff level of 4.9 was determined to be significant for predicting the BRAF (V600E) mutation status (sensitivity 77.4%, specificity 100.0%, area under the curve 0.929; P < 0.0001) according to ROC curve analysis. CONCLUSIONS: The BRAF (V600E) mutation is independently associated with high (18)F-FDG uptake in PTC, especially in those with a tumor size >1 cm.
PubMed-ID: 28808756
http://dx.doi.org/10.1007/s00268-017-4136-y

Predictive Value of Malignancy of Thyroid Nodule Ultrasound Classification Systems: A Prospective Study.
J Clin Endocrinol Metab, 103(4):1359-68.
A. Persichetti, E. Di Stasio, R. Guglielmi, G. Bizzarri, S. Taccogna, I. Misischi, F. Graziano, L. Petrucci, A. Bianchini and E. Papini. 2018.
Context: British Thyroid Association (BTA), American Thyroid Association (ATA), and American Association of Clinical Endocrinologists (AACE/ACE/AME) recommend for thyroid nodules an ultrasound (US)-based stratification of risk of malignancy. Aim of our study was to assess the diagnostic accuracy of US classification systems and their reliability for indication to fine-needle aspiration (FNA). Design: Prospective study on 987 thyroid nodules consecutively referred for FNA. US images were independently reviewed by four experts for assignment of malignancy risk. Cytologically benign nodules had confirmation with a second FNA, whereas Bethesda class IV, V, and VI nodules were operated upon. Class III nodules had surgery or follow-up on the basis of clinical, immunocytochemical, and US features. Results: BTA: Malignancy rate was 2.8% in benign, 10.0% in indeterminate, 51.3% in suspicion, and 80.9% in malignant US class. Sensitivity was 0.74, specificity was 0.92, and accuracy was 0.89. ATA: Malignancy rate was 0.0% in benign, 2.2% in very low suspicion, 3.0% in low suspicion, 5.8% in intermediate, and 55.0% in high suspicion US class. Sensitivity was 0.81, specificity was 0.87, and accuracy was 0.86. AACE/ACE/AME: Malignancy rate was 1.1% in low-risk, 4.4% in intermediate-risk, and 54.9% in high-risk US class. Sensitivity was 0.82, specificity was 0.87, and accuracy was 0.86. K correlation coefficient was 78.9%, 76.9%, and 82.0% for BTA, ATA, and AACE/ACE/AME classifications. Conclusions: Classification systems had elevated predictive value of malignancy in high-risk classes. ATA and AACE/ACE/AME systems were effective for ruling out indication to FNA in low-US-risk nodules. A similar diagnostic accuracy and a substantial interobserver agreement was provided by the three- and the five-category classifications.
PubMed-ID: 29408952
http://dx.doi.org/10.1210/jc.2017-01708

Evaluating the projected surgical impact of reclassifying noninvasive encapsulated follicular variant of papillary thyroid cancer as noninvasive follicular thyroid neoplasm with papillary-like nuclear features.
Surgery, 163(1):60-5.
R. Mainthia, H. Wachtel, Y. Chen, E. Mort, S. Parangi, P. M. Sadow and C. C. Lubitz. 2018.
BACKGROUND: The reclassification of noninvasive encapsulated follicular variant of papillary thyroid cancer to noninvasive follicular thyroid neoplasm with papillary-like nuclear features will reduce nonefficacious and potentially harmful care. Reclassification is estimated in 18.6% of patients with papillary thyroid carcinoma; we aimed to quantify the implications of this change. METHODS: Pathology reports from April 2006 to April 2016 were reviewed to isolate cases that would have been designated as neoplasm with papillary-like nuclear features. Of the 1,335 cases of papillary thyroid carcinomas, 194 cases (14.5%) met criteria. Cases in which neoplasm with papillary-like nuclear features was found in combination with other thyroid malignancies (n = 25) and cases of prior thyroid lobectomy (n = 5) were excluded. Demographic, pathologic, treatment, and follow-up data were assessed for the remaining 164 potential neoplasm with papillary-like nuclear features cases. Logistic regression analysis was performed to evaluate association between fine-needle aspiration result and index procedure. RESULTS: Of the 164 patients with tumors who met neoplasm with papillary-like nuclear features criteria, fine-needle aspiration results were nondiagnostic (2%), benign (18%), atypia/follicular lesion of undetermined significance (26%), follicular neoplasm or suspicious for follicular neoplasm (20%), suspicious for malignancy (19%), malignant (6%), and not obtained (9%). Eighty-five (52%) patients underwent total thyroidectomy. A "suspicious for malignancy" fine-needle aspiration result was associated with undergoing total thyroidectomy versus thyroid lobectomy (P = .006). Thyroid lobectomy was the index procedure for 79 patients (48%); of these patients, 54% (n = 43, 3.2% of all patients with papillary thyroid carcinomas) underwent subsequent total thyroidectomy, and 24% received postoperative radioactive iodine treatment. There were no recurrences among the 125 patients with >3 months of follow-up. CONCLUSION: The reclassification of noninvasive encapsulated follicular variant of papillary thyroid cancer as neoplasm with papillary-like nuclear features will decrease nonefficacious treatment and reduce costs. However, the impact of this change with regard to extent of surgery was limited to 3.2% of patients with papillary thyroid carcinomas compared with the projected potential impact on 18.6%.
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http://dx.doi.org/10.1016/j.surg.2017.04.037

Influence of coexistent Hashimoto's thyroiditis on the extent of cervical lymph node dissection and prognosis in papillary thyroid carcinoma.
Clin Endocrinol (Oxf), 88(1):123-8.
E. Song, M. J. Jeon, S. Park, M. Kim, H. S. Oh, D. E. Song, W. G. Kim, W. B. Kim, Y. K. Shong and T. Y. Kim. 2018.
OBJECTIVE: Previous studies did not focus on the differences in the extent of cervical lymph node (LN) dissection according to coexistent Hashimoto's thyroiditis (HT) in patients with papillary thyroid carcinoma (PTC) and its clinical impact. We aimed to determine whether extensive cervical LN dissection is responsible for favourable clinical outcomes in PTC patients with HT and whether the coexistence of HT itself has an independent protective effect regardless of LN status. DESIGN: Retrospective cohort study. PATIENTS: 1369 patients with PTC who underwent total thyroidectomy with central compartment neck dissection. MEASUREMENTS: Metastatic LN ratio, defined as number of metastatic LNs divided by number of removed LNs, was used to evaluate the extent of LN dissection as well as the status of LN metastasis. Disease-free survival and dynamic risk stratification were compared for clinical outcomes. RESULTS: Presence of HT did not lower the risk of cervical LN metastasis (61.6% in patients with HT vs 65.1% in patients without HT, P = .292). Patients with HT had significantly larger numbers of removed LNs than patients without HT (11 vs 8, respectively, P < .001). Accordingly, metastatic LN ratio was smaller in patients with HT (P = .002), which was independently associated with structural persistent/recurrent disease (hazard ratio [HR] 2.33, 95% confidence interval [CI] 1.30-4.16, P = .004). HT itself was negatively associated with structural persistent/recurrent disease after adjustment for other clinicopathological factors (HR 0.39, 95% CI 0.18-0.87, P = .020). CONCLUSIONS: Coexistence of HT itself is an independent factor associated with favourable outcome in PTC patients, regardless of the extent of LN dissection.
PubMed-ID: 28906015
http://dx.doi.org/10.1111/cen.13475

Prognostic implication of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with recurrent papillary thyroid cancer.
Head Neck, 40(1):94-102.
J. H. Kang, D. W. Jung, K. J. Pak, I. J. Kim, H. J. Kim, J. K. Cho, S. C. Shin, S. G. Wang and B. J. Lee. 2018.
BACKGROUND: Fluorine-18 fluorodeoxyglucose positron emission tomography/CT ((18) F-FDG PET/CT) has been widely accepted as an effective method for detecting recurrent papillary thyroid cancer (PTC) in patients with increased serum thyroglobulin (Tg) or Tg antibody (TgAb) levels and negative whole-body scintigraphy (WBS) results. The role of WBS as a diagnostic tool in detecting recurrence has relatively decreased recently. However, only a few studies have examined the usefulness of (18) F-FDG PET/CT for evaluating patients with recurrent PTC, regardless of the WBS results. The purpose of this analysis was to evaluate the diagnostic value and prognostic role of (18) F-FDG PET/CT for patients with recurrent PTC, irrespective of their WBS results. METHODS: Sixty-six patients with locoregional recurrent PTC who underwent (18) F-FDG PET/CT and neck CT within 6 months before surgical treatment were included in this retrospective analysis. Imaging findings were compared with postoperative histopathologic results. The diagnostic values of (18) F-FDG PET/CT and neck CT were compared according to the serum Tg and TgAb levels and cervical levels. Each patient's status at the last follow-up was also reviewed, and survival probabilities were estimated using the Kaplan-Meier plot. RESULTS: The sensitivity, specificity, and diagnostic accuracy of (18) F-FDG PET/CT for the entire patient group were 38.5%, 90.2%, and 58.3%, respectively. The corresponding neck CT values were 55.0%, 85.7%, and 66.7%, respectively. According to the serum Tg and TgAb levels, except for the specificity, most diagnostic values of (18) F-FDG PET/CT were worse than those of the neck CTs, with or without statistical significance. For the high maximum standardized uptake value (SUVmax) group (SUVmax >10) and the low SUVmax group, the median locoregional disease-free survival times were 33.3 months and 81.8 months, respectively (P < .001). CONCLUSION: The diagnostic value of (18) F-FDG PET/CT for localizing recurrent lesions was worse than that of the neck CT, irrespective of the WBS results. However, patients with a higher SUVmax showed a significantly worse prognosis than did those with a lower SUVmax. Therefore, we suggest that, in patients with recurrent PTC, (18) F-FDG PET/CT should be considered for prognostication rather than diagnosis.
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http://dx.doi.org/10.1002/hed.24967

Thyroid lobectomy is not sufficient for T2 papillary thyroid cancers.
Surgery, 163(5):1134-43.
S. R. Rajjoub, H. Yan, N. A. Calcatera, K. Kuchta, C. E. Wang, W. Lutfi, T. A. Moo-Young, D. J. Winchester and R. A. Prinz. 2018.
BACKGROUND: Histologic subtypes of papillary thyroid cancer affect prognosis. The objective of this study was

to examine whether survival is affected by extent of surgery for conventional versus follicular-variant papillary thyroid cancer when stratified by tumor size. METHODS: Using the National Cancer Data Base, we evaluated 33,816 adults undergoing surgery for papillary thyroid cancer from 2004 to 2008 for 1.0-3.9 cm tumors and clinically negative lymph nodes. Conventional and follicular-variant papillary thyroid cancers were divided into separate groups. Cox regression models stratified by tumor size were used to determine if extent of surgery affected overall survival. RESULTS: A total of 30,981 patients had total thyroidectomy and 2,835 had thyroid lobectomy; 22,899 patients had conventional papillary thyroid cancer and 10,918 had follicular-variant papillary thyroid cancer. On unadjusted KM analysis, total thyroidectomy was associated with improved survival for conventional (P = 0.02) but not for follicular-variant papillary thyroid cancer patients (P = 0.42). For conventional papillary thyroid cancer, adjusted analysis showed total thyroidectomy was associated with improved survival for 2.0-3.9 cm tumors (P = 0.03) but not for 1.0-1.9 cm tumors (P = 0.16). For follicular-variant, lobectomy and total thyroidectomy had equivalent survival for 1.0-1.9 cm (P = 0.45) and 2.0-3.9 cm (P = 0.88) tumors. CONCLUSION: Tumor size, histologic subtype, and surgical therapy are important factors in papillary thyroid cancer survival. Total thyroidectomy was associated with improved survival in patients with 2.0-3.9 cm conventional papillary thyroid cancer, and should be considered for 2.0-3.9 cm papillary thyroid cancers when preoperative molecular analysis is not used to distinguish conventional from follicular-variant.
PubMed-ID: 29426618
http://dx.doi.org/10.1016/j.surg.2017.12.026

All-cause and cardiovascular mortality risk after surgery versus radioiodine treatment for hyperthyroidism.
Br J Surg, 105(3):279-86.
P. Giesecke, V. Frykman, G. Wallin, S. Lonn, A. Discacciati, O. Torring and M. Rosenqvist. 2018.
BACKGROUND: Little is known about the long-term side-effects of different treatments for hyperthyroidism. The few studies previously published on the subject either included only women or focused mainly on cancer outcomes. This register study compared the impact of surgery versus radioiodine on all-cause and cause-specific mortality in a cohort of men and women. METHODS: Healthcare registers were used to find hyperthyroid patients over 35 years of age who were treated with radioiodine or surgery between 1976 and 2000. Comparisons between treatments were made to assess all-cause and cause-specific deaths to 2013. Three different statistical methods were applied: Cox regression, propensity score matching and inverse probability weighting. RESULTS: Of the 10 992 patients included, 10 250 had been treated with radioiodine (mean age 65.1 years; 8668 women, 84.6 per cent) and 742 had been treated surgically (mean age 44.1 years; 633 women, 85.3 per cent). Mean duration of follow-up varied between 16.3 and 22.3 years, depending on the statistical method used. All-cause mortality was significantly lower among surgically treated patients, with a hazard ratio of 0.82 in the regression analysis, 0.80 in propensity score matching and 0.85 in inverse probability weighting. This was due mainly to lower cardiovascular mortality in the surgical group. Men in particular seemed to benefit from surgery compared with radioiodine treatment. CONCLUSION: Compared with treatment with radioiodine, surgery for hyperthyroidism is associated with a lower risk of all-cause and cardiovascular mortality in the long term. This finding was more evident among men.
PubMed-ID: 29116656
http://dx.doi.org/10.1002/bjs.10665

Benign Thyroid Diseases and Risk of Thyroid Cancer: A Nationwide Cohort Study.
J Clin Endocrinol Metab, 103(6):2216-24.
C. M. Kitahara, K. R. F. D, J. O. L. Jorgensen, D. Cronin-Fenton and H. T. Sorensen. 2018.
Context: Thyroid nodules, adenomas, and goiter have consistently been associated with thyroid cancer risk. Few studies have assessed whether thyroid dysfunction and thyroid autoimmunity influence this risk. Objective: To examine thyroid cancer risk after diagnoses of a wide range of benign thyroid conditions. Design: Hospital and cancer registry linkage cohort study for the years 1978 to 2013. Setting: Nationwide (Denmark). Participants: Patients diagnosed with hyperthyroidism (n = 85,169), hypothyroidism (n = 63,143), thyroiditis (n = 12,532), nontoxic nodular goiter (n = 65,782), simple goiter (n = 11,582), other/unspecified goiter (n = 21,953), or adenoma (n = 6,481) among 8,258,807 residents of Denmark during the study period. Main Outcome Measures: We computed standardized incidence ratios (SIRs) for differentiated thyroid cancer, excluding the first 12 months of follow-up after benign thyroid disease diagnosis. Results: SIRs were significantly elevated for all benign thyroid diseases apart from hypothyroidism. SIRs were higher for men than women and in the earlier follow-up periods. Elevated SIRs were observed for localized and regional/distant thyroid cancer. After excluding the first 10 years of follow-up, hyperthyroidism [n = 27 thyroid cancer cases; SIR = 2.00; 95% confidence interval (CI): 1.32 to 2.92], nontoxic nodular goiter (n = 83; SIR = 4.91; 95% CI: 3.91 to 6.09), simple goiter (n = 8; SIR = 4.33; 95% CI: 1.87 to 8.53), other/unspecified goiter (n = 20; SIR = 3.94; 95% CI: 2.40 to 6.08), and adenoma (n = 9;

SIR = 6.02; 95% CI: 2.76 to 11.5) remained positively associated with thyroid cancer risk. Conclusions: We found an unexpected increased risk of differentiated thyroid cancer, including regional/distant disease, following diagnosis of hyperthyroidism and thyroiditis that could not be solely attributed to increased medical surveillance. Hypothyroidism was less clearly associated with thyroid cancer risk.
PubMed-ID: 29590402
http://dx.doi.org/10.1210/jc.2017-02599

Modification of the Surgical Strategy for the Dissection of the Recurrent Laryngeal Nerve Using Continuous Intraoperative Nerve Monitoring.
World J Surg, 42(2):444-50.
A. Marin Arteaga, G. Peloni, I. Leuchter, B. Bedat, W. Karenovics, F. Triponez and S. M. Sadowski. 2018.
BACKGROUND: The aim of this study was to describe first experiences and changes in management using continuous intraoperative neuromonitoring (C-IONM) in thyroid and parathyroid surgery. METHOD: Retrospective analysis of patients who underwent surgery with C-IONM since 2012. Surgical maneuvers were modified when electrophysiologic events occurred. Patients with persistent loss of signal (LOS) underwent postoperative laryngoscopy. RESULTS: One hundred and one patients (of 1586 neck surgeries) were included and 19 had events: In 13 these were temporary (resolved before end of surgery) and led to intraoperative modifications in surgical approach; in all cases traction was released, and in 8, recurrent laryngeal nerve (RLN) approach was changed [superior approach (2), inferior approach (2), both (4)]. Six patients had persistent LOS (5.9%, present at end of procedure), with RLN palsy (RLNP) on postoperative day 1: In three, LOS occurred at electrode placement on the vagus nerve, leading to distal placement of the electrode allowing ipsilateral dissection under continuous monitoring; all three had complete recovery at 6 months. In the three other patients, LOS occurred on the RLN: one probable thermal, one traction lesion and one accidental section of the anterior RLN branch. The RLN recovered within 6 months in two patients, and in the third, RLNP persisted after 6 months (1/101 = 1%). CONCLUSION: C-IONM provides real-time evaluation of the RLN function, allowing for adaptation of surgical maneuvers to prevent RLNP. It seems particularly useful in difficult cases like redo neck surgery, invasive thyroid cancer and intrathoracic or large goiter. Care should be given at electrode placement on the vagus nerve.
PubMed-ID: 28986621
http://dx.doi.org/10.1007/s00268-017-4277-z

High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance.
J Clin Endocrinol Metab, 103(2):446-51.
H. I. Kim, H. W. Jang, H. S. Ahn, S. Ahn, S. Y. Park, Y. L. Oh, S. Y. Hahn, J. H. Shin, J. H. Kim, J. S. Kim, J. H. Chung, T. H. Kim and S. W. Kim. 2018.
Objective: Thyroid-stimulating hormone (TSH) is a growth factor affecting initiation or progression of papillary thyroid cancer (PTC), which supports TSH suppressive therapy in patients with PTC. In patients with papillary thyroid microcarcinoma (PTMC) during active surveillance, however, the association between serum TSH level and growth of PTMC has not been demonstrated. Patients: We analyzed 127 PTMCs in 126 patients under active surveillance with serial serum TSH measurement and ultrasonography. Design: The patients were categorized into groups with the highest, middle, and lowest time-weighted average of TSH (TW-TSH). PTMC progression was defined as a volume increase of >/=50% compared with baseline. Kaplan-Meier survival analysis according to TW-TSH groups and Cox proportional hazard modeling was performed. We identified the cutoff point for TSH level by using maximally selected log-rank statistics. Results: During a median follow-up of 26 months, PTMC progression was detected in 28 (19.8%) patients. Compared with the lowest TW-TSH group, the adjusted hazard ratio (HR) for PTMC progression in the highest TW-TSH group was significantly higher [HR 3.55; 95% confidence interval (CI), 1.22 to 10.28; P = 0.020], but that in the middle TW-TSH group was not (HR 1.52; 95% CI, 0.46 to 5.08; P = 0.489). The cutoff point for the serum TSH level for PTMC progression was 2.50 mU/L. Conclusions: Sustained elevation of serum TSH levels during active surveillance is associated with PTMC progression. Maintaining a low-normal TSH range with levothyroxine treatment during active surveillance of PTMC might be considered in future studies.
PubMed-ID: 29211863
http://dx.doi.org/10.1210/jc.2017-01775

Postoperative IPTH compared with IPTH gradient as predictors of post-thyroidectomy hypocalcemia.
Laryngoscope, 128(3):769-74.
M. G. Al Khadem, E. M. Rettig, V. K. Dhillon, J. O. Russell and R. P. Tufano. 2018.
OBJECTIVES/HYPOTHESIS: Predicting patients' risk for hypocalcemia after thyroidectomy may allow for same-

day discharge. This study was designed to compare postoperative intact parathyroid hormone (IPTH) alone with percentage change in IPTH (IPTH gradient) in predicting post-thyroidectomy hypocalcemia. STUDY DESIGN: Retrospective cohort study. METHODS: Patients undergoing total thyroidectomy by the senior author from May 2015 to May 2016 were included. Serum IPTH was measured preoperatively and 1 hour postoperatively, and IPTH gradient was calculated. Postoperative hypocalcemia was mild (>/=8.0, <8.4) or severe (<8.0 and/or hypocalcemic symptoms). Postoperative IPTH and IPTH gradient were compared with hypocalcemia using logistic regression. Receiver operating characteristic analysis of IPTH measures as predictors of hypocalcemia was performed, and the area under the curve (AUC) was calculated. RESULTS: Overall, 119 patients were included. Forty-seven percent of the patients developed postoperative hypocalcemia, including 26 (22%) with mild and 30 (25%) with severe hypocalcemia. Thirteen patients had hypocalcemic symptoms. Median IPTH gradient and postoperative IPTH each differed significantly by category of hypocalcemia (P < .001). Higher IPTH gradient was significantly associated with odds of severe and symptomatic hypocalcemia (adjusted odds ratio [aOR]: 1.21, 95% confidence interval [CI]: 1.06-1.39 and aOR: 1.34, 95% CI: 1.05-1.71 per 10% increase), whereas lower postoperative IPTH was not (aOR: 1.27, 95% CI: 0.95-1.68 and aOR: 1.44, 95% CI: 0.90-2.31 per 10 pg/mL decrease). The AUC for predicting severe hypocalcemia was nonsignificantly higher for IPTH gradient than postoperative IPTH (AUC = 0.77 vs. 0.69, P = .10). The AUC for predicting symptomatic hypocalcemia was significantly higher for IPTH gradient (AUC = 0.75 vs. 0.72, P = .03). CONCLUSIONS: Our results suggest that the IPTH gradient may be more useful than postoperative IPTH alone in predicting risk of post-thyroidectomy hypocalcemia. LEVEL OF EVIDENCE: 4. Laryngoscope, 128:769-774, 2018.
PubMed-ID: 28842998
http://dx.doi.org/10.1002/lary.26805

Is hungry bone syndrome a cause of postoperative hypocalcemia after total thyroidectomy in thyrotoxicosis? A prospective study with bone mineral density correlation.
Surgery, 163(2):367-72.
P. Karunakaran, C. Maharajan, S. Ramalingam and S. V. Rachmadugu. 2018.
BACKGROUND: Hungry bone syndrome is a well-established cause of postoperative hypocalcemia in thyrotoxicosis. To date, the incidence of hungry bone syndrome after total thyroidectomy is unclear. This prospective study examined the incidence of postthyroidectomy hungry bone syndrome and its correlation with preoperative bone mineral density. METHODS: Forty thyrotoxic subjects (Group A; age: mean +/- SD; 36.5 +/- 9.8 years) and 40 euthyroid controls with benign thyroid nodules (Group B) undergoing total thyroidectomy were evaluated for preoperative bone mineral density and serum calcium, magnesium, phosphorus, parathyroid hormone, alkaline phosphatase, and 25-Hydroxy Vitamin D serially. At least 3 parathyroid glands were preserved. RESULTS: Both groups were age and sex matched. Thyrotoxic subjects had higher postoperative hypocalcemia (82.5% vs controls 22.5%, 95% confidence interval 37.9 to 75.4), low preoperative bone mineral density and raised alkaline phosphatase (each, P = .001). Among thyrotoxic subjects experiencing hypocalcemia (n = 33), 39.4% (13/33) exhibited hungry bone syndrome (characterized by simultaneous fall in serum calcium, magnesium, and phosphorus), 18.1% (6/33) had hypoparathyroidism and 12% had hypomagnesemia. Hypocalcemic subjects exhibiting hungry bone syndrome displayed further decreased preoperative bone mineral density in the spine (0.875 +/- 0.138 vs 1.024 +/- 0.149 g/cm(2), P = .004) and low serum magnesium 72-hour postsurgery (0.57 +/- 0.23 vs 0.88 +/- 0.25 mmol/L, P = .013) than those not exhibiting hungry bone syndrome. Postoperative serum calcium correlated with preoperative bone mineral density in the spine (P = .013). In group B subjects experiencing hypocalcemia (n = 9), none exhibited hungry bone syndrome but 77.78% (7/9) had hypoparathyroidism. All but one was eucalcemic after 6 months. CONCLUSION: Hungry bone syndrome occurs exclusively in thyrotoxic subjects and constitutes the major cause of postoperative hypocalcemia after total thyroidectomy. Vertebral osteoporosis and hypomagnesemia within 72 hours after total thyroidectomy is associated with the risk of hungry bone syndrome.
PubMed-ID: 29146231
http://dx.doi.org/10.1016/j.surg.2017.09.008

Recovery of Voice After Reconstruction of the Recurrent Laryngeal Nerve and Adjuvant Nimodipine.
World J Surg, 42(3):632-8.
P. Mattsson, A. Frostell, G. Bjorck, J. K. E. Persson, R. Hakim, J. Zedenius and M. Svensson. 2018.
BACKGROUND: Transection injury to the recurrent laryngeal nerve (RLN) has been associated with permanent vocal fold palsy, and treatment has been limited to voice therapy or local treatment of vocal folds. Microsurgical repair has been reported to induce a better function. The calcium channel antagonist nimodipine improves functional recovery after experimental nerve injury and also after cranial nerve injury in patients. This study aims to present voice outcome in patients who underwent repair of the RLN and received nimodipine during regeneration. METHODS: From 2002-2016, 19 patients were admitted to our center with complete unilateral

injury to the RLN and underwent microsurgical repair of the RLN. After nerve repair, patients received nimodipine for 2-3 months. Laryngoscopy was performed repeatedly up to 14 months postoperatively. The Voice Handicap Index (VHI) was administered, and patients' maximum phonation time (MPT) was recorded during the follow-up. RESULTS: All patients recovered well after surgery, and nimodipine was well tolerated with no dropouts. None of the patients suffered from atrophy of the vocal fold, and some patients even showed a small ab/adduction of the vocal fold on the repaired side with laryngoscopy. During long-term follow-up (>3 years), VHI and MPT normalized, indicating a nearly complete recovery from unilateral RLN injury. CONCLUSIONS: In this cohort study, we report the results of the first 19 consecutive cases at our center subjected to reconstruction of the RLN and adjuvant nimodipine treatment. The outcome of the current strategy is encouraging and should be considered after iatrogenic RLN transection injuries.
PubMed-ID: 29282507
http://dx.doi.org/10.1007/s00268-017-4235-9

Does mutational analysis influence the management of differentiated thyroid cancers?
Laryngoscope, 128(1):1-2.
A. Asarkar, M. Shaha, A. Shaha and C. O. Nathan. 2018.
PubMed-ID: 28514497
http://dx.doi.org/10.1002/lary.26650

Measuring Decision-Making During Thyroidectomy: Validity Evidence for a Web-Based Assessment Tool.
World J Surg, 42(2):376-83.
A. Madani, J. Gornitsky, Y. Watanabe, C. Benay, M. S. Altieri, P. H. Pucher, R. Tabah and E. J. Mitmaker. 2018.
BACKGROUND: Errors in judgment during thyroidectomy can lead to recurrent laryngeal nerve injury and other complications. Despite the strong link between patient outcomes and intraoperative decision-making, methods to evaluate these complex skills are lacking. The purpose of this study was to develop objective metrics to evaluate advanced cognitive skills during thyroidectomy and to obtain validity evidence for them. METHODS: An interactive online learning platform was developed (www.thinklikeasurgeon.com). Trainees and surgeons from four institutions completed a 33-item assessment, developed based on a cognitive task analysis and expert Delphi consensus. Sixteen items required subjects to make annotations on still frames of thyroidectomy videos, and accuracy scores were calculated based on an algorithm derived from experts' responses ("visual concordance test," VCT). Seven items were short answer (SA), requiring users to type their answers, and scores were automatically calculated based on their similarity to a pre-populated repertoire of correct responses. Test-retest reliability, internal consistency, and correlation of scores with self-reported experience and training level (novice, intermediate, expert) were calculated. RESULTS: Twenty-eight subjects (10 endocrine surgeons and otolaryngologists, 18 trainees) participated. There was high test-retest reliability (intraclass correlation coefficient = 0.96; n = 10) and internal consistency (Cronbach's alpha = 0.93). The assessment demonstrated significant differences between novices, intermediates, and experts in total score ($p < 0.01$), VCT score ($p < 0.01$) and SA score ($p < 0.01$). There was high correlation between total case number and total score (rho = 0.95, $p < 0.01$), between total case number and VCT score (rho = 0.93, $p < 0.01$), and between total case number and SA score (rho = 0.83, $p < 0.01$). CONCLUSION: This study describes the development of novel metrics and provides validity evidence for an interactive Web-based platform to objectively assess decision-making during thyroidectomy.
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http://dx.doi.org/10.1007/s00268-017-4322-y

Cost-effectiveness of lobectomy versus genetic testing (Afirma(R)) for indeterminate thyroid nodules: Considering the costs of surveillance.
Surgery, 163(1):88-96.
C. J. Balentine, D. J. Vanness and D. F. Schneider. 2018.
BACKGROUND: We evaluated whether diagnostic thyroidectomy for indeterminate thyroid nodules would be more cost-effective than genetic testing after including the costs of long-term surveillance. METHODS: We used a Markov decision model to estimate the cost-effectiveness of thyroid lobectomy versus genetic testing (Afirma(R)) for evaluation of indeterminate (Bethesda 3-4) thyroid nodules. The base case was a 40-year-old woman with a 1-cm indeterminate nodule. Probabilities and estimates of utilities were obtained from the literature. Cost estimates were based on Medicare reimbursements with a 3% discount rate for costs and quality-adjusted life-years. RESULTS: During a 5-year period after the diagnosis of indeterminate thyroid nodules, lobectomy was less costly and more effective than Afirma(R) (lobectomy: $6,100; 4.50 quality-adjusted life-years vs Afirma(R): $9,400; 4.47 quality-adjusted life-years). Only in 253 of 10,000 simulations (2.5%) did

Afirma(R) show a net benefit at a cost-effectiveness threshold of $100,000 per quality- adjusted life-years. There was only a 0.3% probability of Afirma(R) being cost saving and a 14.9% probability of improving quality-adjusted life-years. CONCLUSIONS: Our base case estimate suggests that diagnostic lobectomy dominates genetic testing as a strategy for ruling out malignancy of indeterminate thyroid nodules. These results, however, were highly sensitive to estimates of utilities after lobectomy and living under surveillance after Afirma(R).
PubMed-ID: 29128178
http://dx.doi.org/10.1016/j.surg.2017.10.004

Impact of potassium iodide on thyroidectomy for Graves' disease: Implications for safety and operative difficulty.
Surgery, 163(1):68-72.
R. W. Randle, M. F. Bates, K. L. Long, S. C. Pitt, D. F. Schneider and R. S. Sippel. 2018.
BACKGROUND: Potassium iodide often is prescribed prior to thyroidectomy for Graves' disease, but the effect of potassium iodide on the ease and safety of thyroidectomy for Graves' is largely unknown. METHODS: We conducted a prospective, cohort study of patients with Graves' disease undergoing thyroidectomy. For the first 8 months, no patients received potassium iodide; for the next 8 months, potassium iodide was added to the preoperative protocol for all patients. Outcomes included operative difficulty (based on the Thyroidectomy Difficulty Scale) and complications. RESULTS: We included a total of 31 patients in the no potassium iodide group and 28 in the potassium iodide group. According to the Thyroidectomy Difficulty Scale, gland vascularity decreased in the potassium iodide group (mean score 2.6 vs 3.3, P = .04), but there were no differences in friability, fibrosis, or size of the thyroid or in overall difficulty of operation (P = not significant for all). Despite similar operative difficulty, patients prescribed potassium iodide were less likely to experience transient hypoparathyroidism (7% vs 26%, P = .018) and transient hoarseness (0% vs 16%, P = .009) compared with the no potassium iodide group. CONCLUSION: Potassium iodide administration decreases gland vascularity, but does not change the overall difficulty of thyroidectomy. Preoperative use of potassium iodide solution was, however, associated with less transient hypoparathyroidism and transient hoarseness, suggesting that potassium iodide improves the safety of thyroidectomy for Graves' disease.
PubMed-ID: 29108701
http://dx.doi.org/10.1016/j.surg.2017.03.030

Tertiary Care Experience of Sorafenib in the Treatment of Progressive Radioiodine-Refractory Differentiated Thyroid Carcinoma: A Korean Multicenter Study.
Thyroid, 28(3):340-8.
M. Kim, T. H. Kim, D. Y. Shin, D. J. Lim, E. Y. Kim, W. B. Kim, J. H. Chung, Y. K. Shong, B. H. Kim and W. G. Kim. 2018.
BACKGROUND: Sorafenib, a multi-kinase inhibitor, is approved for the treatment of patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). This study evaluated the efficacy and safety of sorafenib in real-world clinical practice and compared the results to those of the DECISION trial. The clinical features associated with better clinical outcomes after sorafenib treatment were also evaluated. METHODS: This multicenter, retrospective cohort study evaluated 98 patients with progressive RAI-refractory DTC who were treated with sorafenib in six tertiary hospitals in Korea. The primary objective was the progression-free survival (PFS) according to Response Evaluation Criteria In Solid Tumors v1.1. Overall survival, response rate (defined as the best objective response according to Response Evaluation Criteria In Solid Tumors v1.1), and safety were also evaluated. RESULTS: The median PFS was 9.7 months; median overall survival was not reached during follow-up. Partial responses and stable disease were achieved in 25 (25%) and 64 (65%) patients, respectively. Stable disease of >6 months was achieved in 41 (42%) patients. Subgroup analyses identified several prognostic indicators of a better PFS: absence of disease-related symptoms (hazard ratio [HR] = 0.5; p = 0.041), lung-only metastasis (HR = 0.4; p = 0.048), a daily maintenance dose >/=600 mg (HR = 0.3; p = 0.005), and a thyroglobulin reduction >/=60% (HR = 0.4; p = 0.012). The mean daily dose of sorafenib was 666 +/- 114 mg, and drug withdrawals due to adverse events (AEs) occurred in 13% of patients. AEs and serious AEs were reported in 93 (95%) and 40 (41%) patients, respectively. The most frequent AE was hand-foot skin reaction (76%). CONCLUSIONS: The PFS of progressive RAI-refractory DTC patients treated with sorafenib was consistent with the findings of the DECISION trial. Disease-related symptoms, lung-only metastasis, a daily maintenance dose, and thyroglobulin reduction were significantly associated with PFS. These results suggest that sorafenib is an effective treatment option for patients with progressive RAI-refractory DTC.
PubMed-ID: 29350109
http://dx.doi.org/10.1089/thy.2017.0356

American Thyroid Association ultrasound system for the initial assessment of thyroid nodules: Use in stratifying the risk of malignancy of indeterminate lesions.
Head Neck, 40(4):722-7.
P. Trimboli, M. Deandrea, A. Mormile, L. Ceriani, F. Garino, P. P. Limone and L. Giovanella. 2018.
BACKGROUND: The ultrasound risk stratification system of the American Thyroid Association (ATA) is frequently adopted in clinical practice. Here, we evaluated its performance in a series of nodules with indeterminate fine-needle aspiration cytology (FNAC) report. METHODS: Indeterminate thyroid nodules diagnosed at 2 medical centers were retrospectively screened, ultrasound images were reevaluated, and lesions were classified according to the ATA. Single ultrasound parameters were also analyzed. RESULTS: One hundred seventy-three indeterminate lesions were included with 24.8% of malignancy. The high suspicion class showed a cancer rate (75%) significantly (P < .001) higher than that recorded in the other categories (16.8%). Between ultrasound parameters, halo and microcalcifications were the most sensitive and specific ones. The most accurate receiver operating characteristic (ROC)-derived cutoff of nodule's diameter was >4.1 cm. At multivariate analysis, only the ATA class of high suspicion and size >4.1 cm were significantly associated with cancer (odds ratios [ORs] 19.4 and 5.4, respectively). CONCLUSION: The ATA ultrasound system is reliable in the risk stratification of indeterminate thyroid lesions.
PubMed-ID: 29247582
http://dx.doi.org/10.1002/hed.25038

Anaplastic thyroid carcinoma: review of treatment protocols.
Endocr Relat Cancer, 25(3):R153-R61.
V. Tiedje, M. Stuschke, F. Weber, H. Dralle, L. Moss and D. Fuhrer. 2018.
Anaplastic thyroid carcinoma (ATC) is an orphan disease and in most patients fatal. So far no established treatment is available that prolongs survival. Several large retrospective studies have identified negative prognostic markers, analyzed efficacy of multimodal approaches such as radiotherapy with and without concurrent chemotherapy and chemotherapy protocols. Recently, single case reports have suggested some effectiveness of newer therapies targeting single somatic alterations in ATC. Overall, the conclusions that can be drawn from published retrospective studies and the scarce prospective approaches is that new treatment protocols should be developed including surgery, radiotherapy, chemotherapy and targeted therapy approaches and combinational therapy with immunotherapies. These protocols then need to be evaluated prospectively to improve ATC patients' outcome in routine care.
PubMed-ID: 29295821
http://dx.doi.org/10.1530/ERC-17-0435

Parathyroid, Thyroid and Recurrent Laryngeal Nerve Anatomy in an Indian Rhinoceros (Rhinoceros unicornis).
World J Surg, 42(2):514-20.
R. Udelsman, S. B. Citino, M. Prasad, P. I. Donovan and D. V. Fredholm. 2018.
INTRODUCTION: The parathyroid gland was first identified in the Indian rhinoceros in 1849 by Sir Richard Owen. We performed a necropsy in an Indian rhinoceros, recapitulating Owen's dissection and display what appear to be the initial identification of the recurrent laryngeal nerve in situ and the anatomy and histology of the largest rhinoceros parathyroid glands yet identified. MATERIALS AND METHODS: Patrick T. Rhino, a 41-year-old Indian rhinoceros was born in 1974. His early years were unremarkable. In 2006, he was donated to White Oak Conservation in Yulee, Florida, where he bred and sustained minor injuries. In his geriatric years, he developed a cataract and degenerative joint disease (DJD). At age 41, he developed progressive ataxia and lameness and was euthanized to minimize suffering when he was unable to stand. ROS, FH, SH and medication history were unremarkable. Physical exam was age and species appropriate. Pre-mortem serum demonstrated: creat 1.8 mg/dL (0.8-2.1), calcium 10.6 mg/dL (9.7-13.1), phos 3.8 mg/dL (2.5-6.7), alk phos 69 U/L (26-158) and intact PTH 44.1 pg/mL (rhinoceros reference range: unknown). Necropsy revealed intervertebral DJD with thoracic spondylosis, which combined with osteoporosis, resulted in thoracic myelopathy and ataxia. The neck block was sent in formalin to the Yale University School of Medicine. RESULTS: Detailed dissection was performed under loupe magnification. Presumed structures were photographed in situ and biopsied. The thyroid was identified deep to the strap muscles, received its blood supply from the inferior and superior thyroid arteries and was blue in color. The right recurrent laryngeal nerve, identified and photographed in situ for the first time in the rhinoceros, was deep to the inferior thyroid artery and was traced throughout its cervical course. Single parathyroid glands identified on the lateral thyroid lobes received their blood supply from the inferior thyroid arteries and were confirmed histologically. They appear to be the largest parathyroids yet identified in the rhinoceros with estimated weights of 6,280 and 11,000 mg, respectively. Although the etiology of the parathyroid gland enlargement is unknown, the specimen has been preserved recapitulating the dissection performed by Sir

Richard Owen. CONCLUSION: The parathyroids, thyroid and recurrent laryngeal nerve were identified in an Indian rhinoceros. This appears to be the first display of the rhinoceros recurrent laryngeal nerve in situ, and the parathyroid glands are the largest yet identified in the rhinoceros.
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Selective use of radioactive iodine (RAI) in thyroid cancer: No longer "one size fits all".
Eur J Surg Oncol, 44(3):348-56.
J. L. Marti, L. G. T. Morris and A. S. Ho. 2018.
A remarkable, evidence-based trend toward de-escalation has reformed the practice of radioactive iodine (RAI) administration for thyroid cancer patients. Updated guidelines have supported both decreased RAI doses for select populations, as well as expanded definitions of low-risk and intermediate-risk patients that may not require RAI. Correspondingly, there is now increased flexibility for hemithyroidectomy without need for RAI, and relaxed TSH suppression targets for low-risk thyroidectomy patients. Clinical judgment remains indispensable where multiple risk factors co-exist that individually are not indications for RAI. This is especially salient in intermediate-risk patients with a less than excellent response to therapy, determined through thyroglobulin and ultrasound surveillance. Such judgment, however, may lead to patterns of inappropriate RAI practices or overuse with little benefit to the patient and unnecessary harm. A multidisciplinary, risk-adapted approach is ever more important and obliges the surgeon to understand the likelihood that their patients will receive RAI. The risks and benefits of RAI, its evolved role in contemporary guidelines, and current patterns of use among endocrinologists are reviewed, as well as the practical implications for thyroid surgeons.
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http://dx.doi.org/10.1016/j.ejso.2017.04.002

Post-treatment surveillance of thyroid cancer.
Eur J Surg Oncol, 44(3):357-66.
L. Y. Wang and I. Ganly. 2018.
An increased incidence of differentiated thyroid cancer (DTC) has resulted in an increased population of thyroid cancer survivors requiring ongoing disease surveillance. Our institution's risk-adapted surveillance strategy is based on a contemporary understanding of disease biology, guided by analysis of prognostic factors and balanced application of available surveillance modalities. The goal of this strategy is to detect recurrent disease early, identify patients who would benefit from further treatment and reduce over investigation of low-risk patients. This article describes our center's risk-stratified approach to the postoperative surveillance of patients with differentiated thyroid cancer with reference to the recent 2015 American Thyroid Association management guidelines.
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http://dx.doi.org/10.1016/j.ejso.2017.07.004

Aggressive differentiated thyroid cancer.
Eur J Surg Oncol, 44(3):367-77.
N. Janjua and V. B. Wreesmann. 2018.
Differentiated thyroid cancer is characteristically associated with an innocuous clinical course, but a minority of cases may manifest surprisingly aggressive behaviour. Such aggressive DTC are directly responsible for the majority of thyroid cancer related deaths. Moreover, they contribute indirectly to increased DTC-related morbidity, because our inability to differentiate these tumours from innocuous DTC at an early stage fuels a significant degree of DTC overtreatment around the globe. In the present paper we describe how improved understanding of the clinicopathological thyroid tumour progression model and optimization of clinical staging systems continues to improve our ability to diagnose and treat aggressive DTC. Early recognition of aggressive DTC allows instillation of an aggressive management strategy which is based upon surgical-oncologic completeness, and minimization of treatment-related sequelae through continued development of reconstructive options and focussed delivery of adjuvant treatments.
PubMed-ID: 29169931
http://dx.doi.org/10.1016/j.ejso.2017.09.019

Management of the lateral neck in well differentiated thyroid cancer.
Eur J Surg Oncol, 44(3):332-7.
J. R. Cracchiolo and R. J. Wong. 2018.
Lateral neck lymph node metastases in well differentiated thyroid cancer are common, ranging from 30% to 60%, with the majority of these foci identifiable only as microscopic deposits. A skilled ultrasound evaluation of

the lymph nodes in the lateral neck is recommended for all patients presenting with newly diagnosed thyroid cancer undergoing surgical management. Ultrasound guided fine needle aspiration biopsy may be used to cytologically confirm suspected lateral neck nodal metastases prior to surgery. For patients with large volume nodal disease, extranodal extension, or multiple nodal metastases, computed tomography (CT) scan of the neck with contrast is an important additional imaging modality to accurately localize disease prior to surgery. Primary surgical management for lateral neck disease typically includes lateral neck dissection in conjunction with total thyroidectomy. Postoperative adjuvant radioactive iodine is typically recommended for patients with clinically evident nodal metastases, or for those with over 5 micrometastatic nodes. In the recurrent or persisting disease setting, complete surgical resection of local and regional disease remains the main treatment approach. However, sub-centimeter nodal disease may take an indolent course, and active surveillance may be a reasonable approach in selected clinical circumstances. Conversely, external beam radiation therapy (EBRT) may be considered for scenarios with unresectable disease, or microscopic residual disease following surgery in a clinically unfavorable setting. Two multi-kinase inhibitors (sorafenib and lenvatinib) are now FDA approved for treatment of RAI refractory thyroid cancer and now play an important role in the management of progressive, metastatic and surgically incurable disease.
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http://dx.doi.org/10.1016/j.ejso.2017.06.004

Management of the central compartment in differentiated thyroid carcinoma.
Eur J Surg Oncol, 44(3):327-31.
R. P. Goepfert and G. L. Clayman. 2018.
Management of differentiated thyroid carcinoma (DTC) is gradually evolving with considerations of de-escalation of treatment and/or active surveillance in a significant proportion of patients on the basis of an improved understanding of the long-term disease and functional outcomes from both surgical and non-surgical approaches. This is fueled by improved risk stratification using clinicopathologic prognostic factors as determined through high resolution ultrasound and fine needle aspiration cytology. This paper discusses general recommendations for preoperative decision-making in the management of the central compartment in DTC with particular reference to micropapillary thyroid carcinoma and encapsulated follicular variant papillary thyroid carcinoma. Given the multitude of specific factors that must be considered for each patient, therapeutic decisions should occur in a multidisciplinary setting weighing the risks of treatment morbidity against the risks of disease progression or recurrence. Recurrent/persistent disease merits special attention with regard to pre-operative planning and surgical risk, and should be managed by high-volume thyroid surgeons.
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http://dx.doi.org/10.1016/j.ejso.2017.09.004

Recombinant Parathyroid Hormone Versus Usual Care: Do the Outcomes Justify the Cost?
World J Surg, 42(2):431-6.
K. H. Chomsky-Higgins, H. M. Rochefort, C. D. Seib, J. E. Gosnell, W. T. Shen, Q. Y. Duh and I. Suh. 2018.
BACKGROUND: Hypoparathyroidism is a potential outcome of anterior neck surgery. Commonly it is managed by calcium and vitamin D supplementation in large doses, with attendant side effects. A recombinant human parathyroid hormone (rhPTH) is now available in the USA, offering a potentially more effective treatment. No cost-effectiveness model investigating this new medication versus standard care has yet been published. METHODS: We constructed a decision analytic model comparing usual care versus rhPTH treatment for postsurgical hypoparathyroidism. Threshold and sensitivity analyses on key parameters were conducted to assess robustness of the model. Costs and health outcomes were represented in US dollars and quality-adjusted life-years (QALYs). RESULTS: The rhPTH strategy was both more costly and more effective than the usual care (UC) strategy. In the base case, UC cost $37,196 and provided 7.54 QALYs. The rhPTH strategy cost $777,224 and provided 8.46 QALYs for an incremental cost-effectiveness ratio of $804,378/QALY. As this was above our willingness-to-pay of $100,000, treatment with rhPTH was not considered cost-effective. The model was robust to all other parameters. CONCLUSIONS: To our knowledge, this is the first formal cost-effectiveness analysis of rhPTH in comparison with UC. Our model suggests that although the new treatment is slightly more effective than UC, the modest gain in quality of life for patients who are reasonably well-managed by UC does not justify the cost. However, consideration must be given to rhPTH for patients who have failed UC, as the expenditure may be justified in that context.
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http://dx.doi.org/10.1007/s00268-017-4248-4

Trends in the Implementation of Active Surveillance for Low-Risk Papillary Thyroid Microcarcinomas at Kuma Hospital: Gradual Increase and Heterogeneity in the Acceptance of This New Management Option.
Thyroid, 28(4):488-95.
Y. Ito, A. Miyauchi, T. Kudo, H. Oda, M. Yamamoto, H. Sasai, H. Masuoka, M. Fukushima, T. Higashiyama, M. Kihara and A. Miya. 2018.
BACKGROUND: Active surveillance (AS) of low-risk papillary thyroid microcarcinoma (PMC) was adopted as a management modality in both the Japanese guidelines in 2011 and the American Thyroid Association guidelines in 2015. AS was initiated at Kuma Hospital in 1993 but was not immediately accepted by all physicians. This study investigated the history of acceptance of AS at Kuma Hospital over time. The results should assist in the implementation of AS at other hospitals in Japan and other countries. METHODS: This study included 4023 patients who were cytologically diagnosed with low-risk PMC at Kuma Hospital during the 24-year period between October 1993 and June 2016. The trend in the frequency of AS use over time was analyzed, dividing the 24-year study period into five parts based on the change in frequency of AS use: 1993-1997, 1998-2002, 2003-2006, 2007-2013, and 2014-2016. RESULTS: The frequency of AS use in the present cohort was 65%. The frequency gradually increased from 30% in 1993-1997 to 88% in 2014-2016, with a slight decrease from 51% in 1998-2002 to 42% in 2003-2006. Until 2007, patients were mostly seen by surgeons, and the frequency of AS use varied remarkably among individual surgeons. Since 2007, the number of patients whose therapeutic strategies are determined by endocrinologists has increased, and the frequency of AS use for low-risk PMC by endocrinologists has been higher than that by surgeons. CONCLUSIONS: At Kuma Hospital, acceptance of AS for low-risk PMC gradually increased over the 24-year study period, but AS was not equally accepted by all physicians. Such variations in the acceptance of AS among individual physicians are also expected to exist in other hospitals. However, due to increasing evidence of the safety and superiority of AS over immediate surgery for this indolent disease, it is expected that AS will gain faster acceptance in other hospitals in Japan and around the world.
PubMed-ID: 29608416
http://dx.doi.org/10.1089/thy.2017.0448

Distinctive Desmoplastic 3D Morphology Associated With BRAFV600E in Papillary Thyroid Cancers.
J Clin Endocrinol Metab, 103(3):1102-11.
M. Tarabichi, A. Antoniou, S. Le Pennec, D. Gacquer, N. de Saint Aubain, L. Craciun, T. Cielen, I. Laios, D. Larsimont, G. Andry, J. E. Dumont, C. Maenhaut and V. Detours. 2018.
Context: Although 60% of papillary thyroid carcinomas are BRAFV600E mutant (PTCV600E), the increased aggressiveness of these cancers is still debated. Objective: For PTCV600E we aimed to further characterize the extent of the stroma and its activation, the three-dimensional (3D) tumor-stroma interface, and the proliferation rates of tumor and stromal fibroblasts. Design: We analyzed exomes, transcriptomes, and images of 364 papillary thyroid carcinoma (PTCs) from The Cancer Genome Atlas (TCGA), including 211 PTCV600E; stained 22 independent PTCs for BRAFV600E and Ki67; sequenced the exomes and stained BRAFV600E in 5 primary tumor blocks and 4 nodal metastases from one patient with PTCV600E; and reconstructed the 3D volumes of one tumor and one metastatic block at histological resolution. Results: In TCGA, BRAFV600E was associated with higher expression of proliferation markers and lower expression of thyroid differentiation markers, independently of tumor purity. Moreover, PTCV600E, in line with their overall lower purity, also had higher expression of fibroblast- and T cell-associated genes and presented more fibrosis. Tumor cells that appeared disconnected on two-dimensional histological slices were revealed to be part of a unique tumor component in the 3D reconstructed microvolumes, and they formed a surprisingly complex connected space, infiltrating a proliferative stroma. Finally, in our PTC set, both stromal fibroblasts and tumor cells presented higher proliferation rates in PTCV600E. Conclusions: Our results support the increased aggressiveness associated with BRAFV600E in PTC and shed light on the important role of the stroma in tumor expansion. The greater and more active fibrotic component predicts better efficiency of combined targeted treatments, as previously proposed for melanomaV600E.
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Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials.
Eur J Surg Oncol, 44(3):307-15.
Y. Ito, A. Miyauchi and H. Oda. 2018.
Papillary microcarcinoma (PMC) of the thyroid is defined as papillary thyroid carcinoma (PTC) measuring </=1 cm. Many autopsy studies on subjects who died of non-thyroidal diseases reported latent small thyroid carcinoma in up to 5.2% of the subjects. A mass screening study for thyroid cancer in Japanese adult women detected small thyroid cancer in 3.5% of the examinees. This incidence was close to the incidence of latent

thyroid cancer and more than 1000 times the prevalence of clinical thyroid cancer in Japanese women reported at that time. The question of whether it was correct to treat such PMCs surgically then arose. In 1993, according to Dr. Miyauchi's proposal, Kuma Hospital initiated an active surveillance trial for low-risk PMC as defined in the text. In 1995, Cancer Institute Hospital in Tokyo, Japan, started a similar observation trial. The accumulated data from the trials at these two institutions strongly suggest that active surveillance (i.e., observation without immediate surgery) can be the first-line management for low-risk PMC. Although our data showed that young age and pregnancy might be risk factors of disease progression, we think that these patients can also be candidates for active surveillance, because all of the patients who showed progression signs were treated successfully with a rescue surgery, and none of them died of PTC. In this review, we summarize the data regarding the active surveillance of low-risk PMC as support for physicians and institutions that are considering adopting this strategy.
PubMed-ID: 28343733
http://dx.doi.org/10.1016/j.ejso.2017.03.004

Central Lymph Node Metastasis in Papillary Thyroid Carcinoma.
World J Surg, 42(3):630-1.
A. R. Shaha. 2018.
PubMed-ID: 29305712
http://dx.doi.org/10.1007/s00268-017-4459-8

Optimization of the risk-benefit ratio of differentiated thyroid cancer treatment.
Eur J Surg Oncol, 44(3):276-85.
H. O. Nasef, I. J. Nixon and V. B. Wreesmann. 2018.
The vast majority of differentiated thyroid cancers (DTC) are characterized by an innocuous nature, excellent patient survival, and limited treatment requirement. However, a significant proportion of affected patients is prone to receiving overtreatment, due to undertreatment concerns associated with the difficulty to differentiate them from a small minority affected by aggressive DTC. Identification of prognostic factors and development of staging systems has helped to reduce the proportion of overtreatment in DTC. However, the absolute number of overtreated patients continues to increase, as a result of an on-going incidence surge in early DTC associated with the increased application and sensitivity of modern diagnostic tools. In the present paper, we describe how DTC treatment can be optimized by thoughtful evidence-based balancing of oncologic safety against treatment associated morbidity.
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Surgical management of primary thyroid tumours.
Eur J Surg Oncol, 44(3):321-6.
P. Asimakopoulos and I. J. Nixon. 2018.
The majority of patients who present with well differentiated thyroid cancer will require surgery, but decisions on the appropriate primary procedure will depend on information relating to patient, tumour and surgical factors. As the incidence of thyroid cancer continues to rise, it is critical that clinicians involved in the management of these cases understand the factors which underpin surgical decision making for individual patients. Reporting outcomes in well differentiated thyroid cancer (WDTC) has always been challenging due to the low recurrence and mortality rate of the disease. Although early data supported total thyroidectomy for all patients with >1 cm WDTC, more recent evidence has supported lobectomy in selected, low risk patients. As a result we have seen a change in the approach of international guidelines from a blanket statement that total thyroidectomy should be the treatment for all patients towards a more selective approach to therapy. When selecting the most appropriate surgical approach to WDTC, the primary aim is to minimize the chance of death from disease or further recurrence. Additionally the impact of potential side effects of treatment (laryngeal nerve injury and hypocalcaemia) must also be weighed in the balance. In this review of surgical management of WDTC we aim to present a historical perspective on this subject and explore the arguments for and against total thyroidectomy and thyroid lobectomy in the low-risk patient group.
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http://dx.doi.org/10.1016/j.ejso.2016.12.015

Clinical guidance for radioiodine refractory differentiated thyroid cancer.
Clin Endocrinol (Oxf), 88(4):529-37.
M. L. Gild, D. J. Topliss, D. Learoyd, F. Parnis, J. Tie, B. Hughes, J. P. Walsh, D. S. A. McLeod, R. J. Clifton-Bligh and B. G. Robinson. 2018.
Prognosis from differentiated thyroid cancer is worse when the disease becomes refractory to radioiodine. Until recently, treatment options have been limited to local therapies such as surgery and radiotherapy, but the recent availability of systemic therapies now provides some potential for disease control. Multitargeted kinase inhibitors (TKIs) including lenvatinib and sorafenib have been shown to improve progression-free survival in phase III clinical trials, but are also associated with a spectrum of adverse effects. Other TKIs have been utilized as "redifferentiation" agents, increasing sodium iodide symporter expression in metastases and thus restoring radioiodine avidity. Some patients whose disease progresses on initial TKI therapy will still respond to a different TKI and clinical trials currently in progress will clarify the best options for such patients. As these drugs are not inexpensive, care needs to be taken to minimize not only biological but also financial toxicity. In this review, we examine the basic biology of radioiodine refractory disease and discuss optimal treatment approaches, with specific focus on choice and timing of TKI treatment. This clinical field remains fluid, and directions for future research include exploring biomarkers and considering adjuvant TKI use in certain patient groups.
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http://dx.doi.org/10.1111/cen.13508

Delayed initial radioiodine therapy related to incomplete response in low- to intermediate-risk differentiated thyroid cancer.
Clin Endocrinol (Oxf), 88(4):601-6.
H. Li, Y. Q. Zhang, C. Wang, X. Zhang, X. Li and Y. S. Lin. 2018.
OBJECTIVE: Whether the initiating time of radioiodine (RAI) therapy will affect the clinical outcome in differentiated thyroid cancer (DTC) remains controversial. The objective of this study was to evaluate the impact of RAI therapy initiating time on response to initial therapy in low- to intermediate-risk DTC. METHODS: A total of 235 consecutive patients with low- to intermediate-risk DTC were retrospectively reviewed. According to the time interval between thyroidectomy and RAI therapy, patients were divided into Group 1 (interval < 3 months, n = 187) and Group 2 (interval >/= 3 months, n = 48). Response to RAI therapy was evaluated as excellent, indeterminate, biochemical incomplete or structural incomplete response (ER, IDR, BIR or SIR) with a median follow-up of 780 days. The univariate and multivariate analyses were further conducted to identify factors associated with incomplete response (IR, including BIR and SIR). RESULTS: Response to initial therapy was significantly different between 2 groups (P < .05), after excluding the impact of other risk factors (age, gender, histological type, status of T and N, RAI dose, thyrotropin, stimulated thyroglobulin and follow-up time). A significantly higher IR rate (18.8% vs 4.3%, P = .001) and a lower ER proportion (62.5% vs 78.1%, P = .027) were observed in Group 2. By univariate analysis, both T status and N status, stimulated thyroglobulin and time interval were significant risk factors for IR (P < .05). Multivariate analysis demonstrated that the time interval was an independent risk factor for IR (P = .008). CONCLUSIONS: Delayed initial RAI therapy (>/=3 months after thyroidectomy) related to incomplete response in low- to intermediate-risk DTC.
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http://dx.doi.org/10.1111/cen.13551

Prognostic indicators of outcomes in patients with lung metastases from differentiated thyroid carcinoma during long-term follow-up.
Clin Endocrinol (Oxf), 88(2):318-26.
S. Y. Sohn, H. I. Kim, Y. N. Kim, T. H. Kim, S. W. Kim and J. H. Chung. 2018.
BACKGROUND: Distant metastases, although uncommon, represent maximum disease-related mortality in differentiated thyroid carcinoma (DTC). Lungs are the most frequent sites of metastases. We aimed to evaluate long-term outcomes and identify prognostic factors in metastatic DTC limited to the lungs. METHODS: This retrospective study included 89 patients with DTC and metastases limited to the lungs, who were treated between 1996 and 2012 at Samsung Medical Center. Progression-free survival (PFS) and cancer-specific survival (CSS) rates were evaluated according to clinicopathologic factors. Cox regression analysis was used to identify independent factors associated with structural progressive disease (PD) and cancer-specific death. RESULTS: With a median follow-up of 84 months, the 5- and 10-year CSS rates were 78% and 73%, respectively. Older age at diagnosis (>/=55 years), radioactive iodine (RAI) nonavidity, preoperative or late diagnosis of metastasis and macro-nodular metastasis (>/=1 cm) were predictive of decreased PFS and CSS. Multivariate analysis identified older age (P = .002), RAI nonavidity (P = .045) and preoperative (P = .030) or late diagnosis (P = .026) as independent predictors of structural PD. RAI avidity was also independent predictor of cancer-specific death (P = .025). CONCLUSION: Patients with DTC and metastatic disease limited to the lungs

had favourable long-term outcomes. Age, RAI avidity and timing of metastasis were found to be major factors for predicting prognosis.
PubMed-ID: 28972676
http://dx.doi.org/10.1111/cen.13489

Modification of the Surgical Strategy for the Dissection of the Recurrent Laryngeal Nerve Using Continuous Intraoperative Nerve Monitoring.
World J Surg, 42(2):451-2.
S. Sidhu. 2018.
PubMed-ID: 29204668
http://dx.doi.org/10.1007/s00268-017-4379-7

Advances in risk-oriented surgery for multiple endocrine neoplasia type 2.
Endocr Relat Cancer, 25(2):T41-T52.
A. Machens and H. Dralle. 2018.
Genetic association studies hinge on definite clinical case definitions of the disease of interest. This is why more penetrant mutations were overrepresented in early multiple endocrine neoplasia type 2 (MEN2) studies, whereas less penetrant mutations went underrepresented. Enrichment of genetic association studies with advanced disease may produce a flawed understanding of disease evolution, precipitating far-reaching surgical strategies like bilateral total adrenalectomy and 4-gland parathyroidectomy in MEN2. The insight into the natural course of the disease gleaned over the past 25 years caused a paradigm shift in MEN2: from the removal of target organs at the expense of greater operative morbidity to close biochemical surveillance and targeted resection of adrenal tumors and hyperplastic parathyroid glands. The lead time provided by early identification of asymptomatic MEN2 carriers under biochemical surveillance delimits a 'window of opportunity', within which (i) pre-emptive total thyroidectomy alone is adequate, circumventing morbidity attendant to central node dissection; (ii) subtotal 'tissue-sparing' adrenalectomy is sufficient, trading the risk of steroid dependency for the risk of a second pheochromocytoma in the adrenal remnant and (iii) parathyroidectomy is limited to enlarged glands, trading the risk of postoperative hypoparathyroidism for the risk of leaving behind hyperactive parathyroid glands. Future research should delineate further the mutation-specific, age-dependent penetrance of pheochromocytoma and primary hyperparathyroidism to refine the risk-oriented approach to MEN2. The sweeping changes in the management of MEN2 since the new millenium hold the hope that death and major morbidity from this uncommon disease can be eliminated in our lifetime.
PubMed-ID: 28883084
http://dx.doi.org/10.1530/ERC-17-0202

Reasons Associated with Total Thyroidectomy as Initial Surgical Management of an Indeterminate Thyroid Nodule.
Ann Surg Oncol, 25(5):1410-7.
T. E. Angell, C. M. Vyas, J. A. Barletta, E. S. Cibas, N. L. Cho, G. M. Doherty, A. A. Gawande, B. E. Howitt, J. F. Krane, E. Marqusee, K. C. Strickland, E. K. Alexander, F. D. Moore, Jr. and M. A. Nehs. 2018.
BACKGROUND: Diagnostic hemithyroidectomy (HT) is the most widely recommended surgical procedure for a nodule with indeterminate cytology; however, additional details may make initial total thyroidectomy (TT) preferable. We sought to identify patient-specific factors (PSFs) associated with initial TT in patients with indeterminate thyroid nodules. METHODS: Retrospective analysis of all patients with a thyroid nodule >/= 1 cm and initial cytology of atypia of undetermined significance or suspicious for follicular neoplasm between 2012 and 2015 who underwent thyroidectomy. Medical records were reviewed for patient demographics, neck symptoms, nodule size, cytology, molecular test results, final histopathology, and additional PSFs influencing surgical management. Variables were analyzed to determine associations with the use of initial TT. Logistic regression analyses were performed to identify independent associations. RESULTS: Of 325 included patients, 182/325 (56.0%) had HT and 143/325 (44.0%) had TT. While patient age and sex, nodule size, and cytology result were not associated with initial treatment, five PSFs were associated with initial TT ($p < 0.0001$). These included contralateral nodules, hypothyroidism, fluorodeoxyglucose avidity on positron emission tomography scan, family history of thyroid cancer, and increased surgical risk. At least one PSF was present in 126/143 (88.1%) TT patients versus 47/182 (25.8%) HT patients ($p < 0.0001$). Multivariate logistic regression analysis demonstrated that these variables were the strongest independent predictor of TT (odds ratio 45.93, 95% confidence interval 18.80-112.23, $p < 0.001$). CONCLUSIONS: When surgical management of an indeterminate cytology thyroid nodule was performed, several PSFs were associated with a preference by surgeons and patients for initial TT, which may be useful to consider in making decisions on initial operative extent.

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What Can Thyroidectomy-Specific Outcomes Teach Us About the American College of Surgeons' National Surgical Quality Improvement Program?
JAMA Surg, 153(1):e174594.
P. Angelos. 2018.
PubMed-ID: 29188275
http://dx.doi.org/10.1001/jamasurg.2017.4594

Safety and Outcomes of the Transoral Endoscopic Thyroidectomy Vestibular Approach.
JAMA Surg, 153(1):21-7.
A. Anuwong, K. Ketwong, P. Jitpratoom, T. Sasanakietkul and Q. Y. Duh. 2018.
Importance: Natural orifice transluminal endoscopic surgery thyroidectomy is a novel approach to avoid surgical scars. Objective: To compare the safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach (TOETVA) with those of open thyroidectomy (OT). Design, Setting, and Participants: This study retrospectively reviewed all TOETVA and OT operations performed from April 1, 2014, through August 31, 2016, at Police General Hospital, Bangkok, Thailand. All patients who underwent TOETVA and patients who underwent OT were included. Exclusion criteria were (1) previous neck surgery, (2) substernal goiter, (3) lymph node or distance metastasis, and (4) suspicious invasion to the adjacent organs. Propensity score matching was conducted to reduce selective bias. Main Outcomes and Measures: Operative time, blood loss, and complications related to thyroid surgery. Results: Of the 425 patients who underwent transoral endoscopic thyroidectomy (mean age, 35.3 [12.1] years; age range, 16-81 years; 389 [92.2%] female), 422 successfully were treated with the TOETVA; 3 patients were converted to a conventional operation because of bleeding. Twenty-five patients (5.9%) had transient recurrent laryngeal nerve palsy, and 46 (10.9%) had transient hypoparathyroidism. None had permanent recurrent laryngeal nerve palsy or permanent hypoparathyroidism. Three patients (0.7%) had transient mental nerve injury; all cases resolved by 4 months. One patient developed postoperative hematoma treated by OT. Twenty patients (4.7%) had seroma treated by simple aspiration. Operative time was longer for the TOETVA compared with the OT group (100.8 [39.7] vs 79.4 [32.1] minutes, P = 1.61 x 10-10). The mean (SD) visual analog scale score for pain was lower in the TOETVA group (1.1 [1.2] vs 2.8 [1.2], P = 2.52 x 10-38). Estimated mean (SD) blood loss (36.9 [32.4] vs 37.6 [23.1] mL, P = .43) and rate of complications (45 of 216 [20.8%] vs 38 of 216 [17.6%], P = .41) were not significantly different in the TOETVA vs OT group. Conclusions and Relevance: The TOETVA was performed as safely as OT, requires only conventional laparoscopic instruments, and avoids incisional scars; thus, the approach may be an option for select patients.
PubMed-ID: 28877292
http://dx.doi.org/10.1001/jamasurg.2017.3366

Medullary Thyroid Carcinoma-We Should Do Better.
JAMA Surg, 153(1):59.
J. E. Gosnell and Q. Y. Duh. 2018.
PubMed-ID: 28973093
http://dx.doi.org/10.1001/jamasurg.2017.3894

Transoral Endoscopic Thyroidectomy-An Emerging Remote Access Technique for Thyroid Excision.
JAMA Surg, 153(4):376-7.
W. B. Inabnet, 3rd, G. Fernandez-Ranvier and H. Suh. 2018.
PubMed-ID: 29490360
http://dx.doi.org/10.1001/jamasurg.2017.5306

Risk Factors Associated With Reoperation and Disease-Specific Mortality in Patients With Medullary Thyroid Carcinoma.
JAMA Surg, 153(1):52-9.
E. J. Kuo, S. Sho, N. Li, K. A. Zanocco, M. W. Yeh and M. J. Livhits. 2018.
Importance: The association of initial neck dissection with recurrence in medullary thyroid carcinoma (MTC) has not been evaluated on a population level to date. Objective: To elucidate risk factors associated with reoperation in MTC and disease-specific mortality. Design, Setting, and Participants: A retrospective analysis was performed of hospital data obtained from the California Cancer Registry and the Office of Statewide Health Planning and Development from January 1, 1999, through December 31, 2012. The dates of the analysis were January 1,

1999, to December 31, 2012. A population-based sample of 953 patients with MTC was identified. Patients who underwent thyroid surgery and had a minimum postoperative follow-up of 2 years (n = 609) were included in the analysis. Exposure: Initial neck dissection in MTC. Main Outcomes and Measures: Recurrent MTC leading to reoperation and disease-specific mortality. Results: Of the 609 patients with MTC who underwent thyroid surgery, the mean (SD) patient age at diagnosis was 52.6 (17.5) years, and 60.8% (n = 370) of the patients were female. The mean (SD) tumor size was 2.8 (2.0) cm. Although initial central neck dissection is recommended by published MTC guidelines, only 35.5% (216 of 609) of patients underwent central neck dissection at the time of the initial thyroidectomy. The rate of reoperation was 16.3% (99 of 609), and the median time to reoperation was 6.4 months. The presence of lymph node metastasis increased the risk of reoperation (hazard ratio [HR], 3.43; 95% CI, 2.00-5.90), while central and lateral neck dissection performed at the initial operation was protective (HR, 0.53; 95% CI, 0.30-0.93). In patients who underwent reoperation, 45.5% (45 of 99) were disease free at a median follow-up of 7.7 years. Five-year disease-specific mortality for the entire cohort was 13.5% (82 of 609). Independent risk factors for disease-specific mortality included older age (HR, 1.36 per decade; 95% CI, 1.17-1.59), tumor size greater than 2 cm (HR, 2.83; 95% CI, 1.08-7.44 for >2 to 4 cm and HR, 2.89; 95% CI, 1.09-7.71 for >4 cm), and regional (HR, 4.77; 95% CI, 2.29-9.94) and metastatic (HR, 21.08; 95% CI, 9.90-44.89) disease. Reoperation was not associated with increased mortality. Conclusions and Relevance: Lymph node dissection may decrease recurrence leading to reoperation for patients with MTC. Reoperation is a viable strategy to achieve long-term disease-free survival in appropriately selected patients. Central neck dissection remains underused.
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Risk Factors for Recurrence After Treatment of N1b Papillary Thyroid Carcinoma.
Ann Surg,
S. H. Lee, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim. 2018.
OBJECTIVES: To examine risk factors for posttreatment recurrence in papillary thyroid carcinoma (PTC) patients with initial presentation of lateral neck metastasis (N1b). SUMMARY OF BACKGROUND DATA: N1b PTC recurs after definitive treatment. METHODS: Study subjects were 437 consecutive PTC patients who underwent total thyroidectomy and therapeutic neck dissection of central and lateral compartments and postoperative radioactive iodine ablation therapy. The patients' demographics and pathological factors, including factors related to tumors and lymph nodes (LNs), and postoperative thyroglobulin levels were reviewed. Univariate and multivariate Cox proportional hazards regression analyses were used to identify factors associated with recurrence-free survival (RFS). RESULTS: During a median follow-up of 83 months (range, 32-135 months), recurrence occurred in 81 (18.1%) patients. Univariate analyses showed that male sex, tumor size, macroscopic extrathyroidal extension, perineural invasion, extranodal extension, LN involvement, LN ratio, MACIS score, and postoperative serum levels of thyroglobulin were significantly associated with RFS ($P < 0.05$). Multivariate analyses revealed that LN ratio (> 0.25) in the lateral compartment (adjusted hazard ratio = 2.099, 95% confidence interval = 1.278-3.448; $P = 0.003$), and postoperative serum levels of stimulated (>5.0 ng/mL; 3.172, 1.661-6.056, $P < 0.001$) and unstimulated (>0.1 ng/mL; 3.200, 1.569-6.526, $P = 0.001$) thyroglobulin were independent predictors of any-site RFS. Clinical and tumor factors were not independent predictors of RFS outcomes ($P > 0.1$). CONCLUSIONS: Posttreatment recurrence is predicted by the LN ratio in the lateral compartment and postoperative serum levels of thyroglobulin in patients with metastatic PTC in the lateral neck.
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http://dx.doi.org/10.1097/SLA.0000000000002710

Variation of Thyroidectomy-Specific Outcomes Among Hospitals and Their Association With Risk Adjustment and Hospital Performance.
JAMA Surg, 153(1):e174593.
J. B. Liu, J. A. Sosa, R. H. Grogan, Y. Liu, M. E. Cohen, C. Y. Ko and B. L. Hall. 2018.
Importance: Current surgical quality metrics might be insufficient to fully judge the quality of certain operations because they are not procedure specific. Hypocalcemia, recurrent laryngeal nerve (RLN) injury, and hematoma are considered to be the most relevant outcomes to measure after thyroidectomy. Whether these outcomes can be used as hospital quality metrics is unknown. Objectives: To evaluate whether thyroidectomy-specific outcomes vary among hospitals, whether the addition of thyroidectomy-specific variables affects risk adjustment, and whether differences in hospital performance are associated with thyroidectomy-specific care processes. Design, Setting, and Participants: In this retrospective cohort study, patients undergoing thyroidectomies from January 1, 2013, through December 31, 2015, at hospitals participating in the American College of Surgeons' National Surgical Quality Improvement Program were studied. Exposure: Thyroidectomy-related care. Main Outcomes and Measures: Clinically severe hypocalcemia, RLN injury, and clinically significant hematoma within

30 days of thyroid surgery and hospital-level performance variation, change in risk adjustment, and association with processes. Results: Overall, 14540 patients (mean [SD] age, 52.1 [15.0] years; 11 499 [79.1%] female) underwent operations at 98 hospitals. Because operations missing thyroidectomy-specific outcomes were excluded, the numbers of operations and hospitals analyzed differed by outcome. Of 14 540 operations included, clinically severe hypocalcemia occurred in 450 patients (3.3% overall, 0.6% after partial, and 4.7% after subtotal or total thyroidectomy), RLN injury in 755 patients (5.7% overall, 4.2% after partial, and 6.6% after subtotal or total thyroidectomy), and hematoma in 175 patients (1.3%). Hospital performance varied for hypocalcemia and RLN injury but not for hematoma. Hospital performance rankings were largely unaffected by the inclusion of thyroidectomy-specific data in risk adjustment. With regard to processes, patients undergoing thyroidectomies at the best-performing vs worst-performing hospitals less frequently had their postoperative parathyroid hormone level measured (593 [19.9%] vs 457 [31.7%], P < .001) and more often were prescribed oral calcium, vitamin D, or both (2281 [76.6%] vs 962 [66.8%], P < .001). When profiled by RLN injury, use of energy devices (1517 [69.1%] vs 507 [55.2%], P < .001) and intraoperative nerve monitoring (1223 [55.7%] vs 346 [37.7%], P < .001) were more prevalent at the best- compared with the worst-performing hospitals. Conclusions and Relevance: Postoperative hypocalcemia and RLN injury, but not hematoma, potentially could be used as thyroidectomy-specific national hospital quality improvement metrics. Strategies aimed at reducing these complications after thyroidectomy may improve the care of these patients.
PubMed-ID: 29188293
http://dx.doi.org/10.1001/jamasurg.2017.4593

p.Val804Met, the Most Frequent Pathogenic Mutation in RET, Confers a Very Low Lifetime Risk of Medullary Thyroid Cancer.
J Clin Endocrinol Metab, 103(11):4275-82.
C. Loveday, K. Josephs, D. Chubb, A. Gunning, L. Izatt, M. Tischkowitz, S. Ellard and C. Turnbull. 2018.
Context: To date, penetrance figures for medullary thyroid cancer (MTC) for variants in rearranged during transfection (RET) have been estimated from families ascertained because of the presence of MTC. Objective: To gain estimates of penetrance, unbiased by ascertainment, we analyzed 61 RET mutations assigned as disease causing by the American Thyroid Association (ATA) in population whole-exome sequencing data. Design: For the 61 RET mutations, we used analyses of the observed allele frequencies in approximately 51,000 individuals from the Exome Aggregation Consortium (ExAC) database that were not contributed via The Cancer Genome Atlas (TCGA; non-TCGA ExAC), assuming lifetime penetrance for MTC of 90%, 50%, and unbounded. Setting: Population-based. Results: Ten of 61 ATA disease-causing RET mutations were present in the non-TCGA ExAC population with observed frequency consistent with penetrance for MTC of >90%. For p.Val804Met, the lifetime penetrance for MTC, estimated from the allele frequency observed, was 4% [95% confidence interval (CI), 0.9% to 8%]. Conclusions: Based on penetrance analysis in carrier relatives of p.Val804Met-positive cases of MTC, p.Val804Met is currently understood to have high-lifetime penetrance for MTC (87% by age 70), albeit of later onset of MTC than other RET mutations. Given our unbiased estimate of penetrance for RET p.Val804Met of 4% (95% CI, 0.9% to 8%), the current recommendation by the ATA of prophylactic thyroidectomy as standard for all RET mutation carriers is likely inappropriate.
PubMed-ID: 29590403
http://dx.doi.org/10.1210/jc.2017-02529

Patient Age-Associated Mortality Risk Is Differentiated by BRAF V600E Status in Papillary Thyroid Cancer.
J Clin Oncol, 36(5):438-45.
X. Shen, G. Zhu, R. Liu, D. Viola, R. Elisei, E. Puxeddu, L. Fugazzola, C. Colombo, B. Jarzab, A. Czarniecka, A. K. Lam, C. Mian, F. Vianello, L. Yip, G. Riesco-Eizaguirre, P. Santisteban, C. J. O'Neill, M. S. Sywak, R. Clifton-Bligh, B. Bendlova, V. Sykorova and M. Xing. 2018.
Purpose For the past 65 years, patient age at diagnosis has been widely used as a major mortality risk factor in the risk stratification of papillary thyroid cancer (PTC), but whether this is generally applicable, particularly in patients with different BRAF genetic backgrounds, is unclear. The current study was designed to test whether patient age at diagnosis is a major mortality risk factor. Patients and Methods We conducted a comparative study of the relationship between patient age at diagnosis and PTC-specific mortality with respect to BRAF status in 2,638 patients (623 men and 2,015 women) with a median age of 46 years (interquartile range, 35 to 58 years) at diagnosis and a median follow-up time of 58 months (interquartile range, 26 to 107 months). Eleven medical centers from six countries participated in this study. Results There was a linear association between patient age and mortality in patients with BRAF V600E mutation, but not in patients with wild-type BRAF, in whom the mortality rate remained low and flat with increasing age. Kaplan-Meier survival curves rapidly declined with increasing age in patients with BRAF V600E mutation but did not decline in patients with wild-type BRAF,

even beyond age 75 years. The association between mortality and age in patients with BRAF V600E was independent of clinicopathologic risk factors. Similar results were observed when only patients with the conventional variant of PTC were analyzed. Conclusion The long-observed age-associated mortality risk in PTC is dependent on BRAF status; age is a strong, continuous, and independent mortality risk factor in patients with BRAF V600E mutation but not in patients with wild-type BRAF. These results question the conventional general use of patient age as a high-risk factor in PTC and call for differentiation between patients with BRAF V600E and wild-type BRAF when applying age to risk stratification and management of PTC.
PubMed-ID: 29240540
http://dx.doi.org/10.1200/JCO.2017.74.5497

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.
J Clin Oncol, 36(1):7-13.
V. Subbiah, R. J. Kreitman, Z. A. Wainberg, J. Y. Cho, J. H. M. Schellens, J. C. Soria, P. Y. Wen, C. Zielinski, M. E. Cabanillas, G. Urbanowitz, B. Mookerjee, D. Wang, F. Rangwala and B. Keam. 2018.
Purpose We report the efficacy and safety of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) combination therapy in BRAF V600E-mutated anaplastic thyroid cancer, a rare, aggressive, and highly lethal malignancy with poor patient outcomes and no systemic therapies with clinical benefit. Methods In this phase II, open-label trial, patients with predefined BRAF V600E-mutated malignancies received dabrafenib 150 mg twice daily and trametinib 2 mg once daily until unacceptable toxicity, disease progression, or death. The primary end point was investigator-assessed overall response rate. Secondary end points included duration of response, progression-free survival, overall survival, and safety. Results Sixteen patients with BRAF V600E-mutated anaplastic thyroid cancer were evaluable (median follow-up, 47 weeks; range, 4 to 120 weeks). All patients had received prior radiation treatment and/or surgery, and six had received prior systemic therapy. The confirmed overall response rate was 69% (11 of 16; 95% CI, 41% to 89%), with seven ongoing responses. Median duration of response, progression-free survival, and overall survival were not reached as a result of a lack of events, with 12-month estimates of 90%, 79%, and 80%, respectively. The safety population was composed of 100 patients who were enrolled with seven rare tumor histologies. Common adverse events were fatigue (38%), pyrexia (37%), and nausea (35%). No new safety signals were detected. Conclusion Dabrafenib plus trametinib is the first regimen demonstrated to have robust clinical activity in BRAF V600E-mutated anaplastic thyroid cancer and was well tolerated. These findings represent a meaningful therapeutic advance for this orphan disease.
PubMed-ID: 29072975
http://dx.doi.org/10.1200/JCO.2017.73.6785

Thyroid cancer: Balancing benefit and risk in TSH management of DTC.
Nat Rev Endocrinol, 14(3):136-7.
F. A. Verburg and M. Luster. 2018.
PubMed-ID: 29348477
http://dx.doi.org/10.1038/nrendo.2018.1

Thyroid Surgery Through the Mouth Might Not Be as Crazy as It Sounds.
JAMA Surg, 153(1):28.
M. W. Yeh. 2018.
PubMed-ID: 28877304
http://dx.doi.org/10.1001/jamasurg.2017.3384

Tumour growth rate of follicular thyroid carcinoma is not different from that of follicular adenoma.
Clin Endocrinol (Oxf), 88(6):936-42.
M. Kim, M. Han, J. H. Lee, D. E. Song, K. Kim, J. H. Baek, Y. K. Shong and W. G. Kim. 2018.
OBJECTIVE: Distinguishing malignancy from benign thyroid nodule has always been challenging, especially in follicular lesions. Thyroid nodules with small size and indeterminate cytology do not lead to immediate surgery. We tried to evaluate whether tumour size and tumour growth rate can distinguish follicular thyroid carcinoma (FTC) from follicular adenoma (FA). DESIGN AND PATIENTS: This retrospective study included patients with pathologically proven FTCs (n = 50) and FAs (n = 110) who underwent preoperative serial neck ultrasonography (US) at least 3 times: it comprises 30% of all follicular tumours (32% FAs and 25% FTCs). The growth rates of follicular tumours on serial US were measured using at least 3 consecutive examinations during a median follow-up of 4.1 years (range, 0.7-13.3 years) by experienced radiologists. RESULTS: The FA and FTC groups showed no significant difference in clinicopathological characteristics, including age, proportion of large nodules (>4 cm) and preoperative cytology. The maximum diameter of thyroid nodule was gradually increased in both groups with

statistical significance (P < .001 and P < .001, respectively). No significant differences in change of maximum diameter of thyroid nodule (P = .132) and tumour volume (P = .208) were found between the FA and FTC groups during the follow-up. The median time to a significant tumour growth from baseline was not different between the FA and FTC groups (1.4 years and 1.7 years, respectively, P = .556). When we divided the patients into four groups (rapid, moderate, slow and no growth) according to the growth velocity of the thyroid tumours, no significant difference in growth velocity was found among the groups. CONCLUSIONS: The tumour size and growth rate of the thyroid nodule itself could not predict malignancy. Diagnostic approaches that use molecular markers would be more important than clinical features for the decision of diagnostic surgery for patients with follicular tumours.
PubMed-ID: 29509975
http://dx.doi.org/10.1111/cen.13591

Treatment of refractory thyroid cancer.
Endocr Relat Cancer, 25(4):R209-R23.
A. Berdelou, L. Lamartina, M. Klain, S. Leboulleux and M. Schlumberger. 2018.
Distant metastases from thyroid cancer of follicular origin are uncommon. Treatment includes levothyroxine administration, focal treatment modalities with surgery, external radiation therapy and thermal ablation, and radioiodine in patients with uptake of (131)I in their metastases. Two-thirds of distant metastases become refractory to radioiodine at some point, and when there is a significant tumor burden and documented progression on imaging, a treatment with a kinase inhibitor may provide benefits.
PubMed-ID: 29371330
http://dx.doi.org/10.1530/ERC-17-0542

Patient quality of life and prognosis in multiple endocrine neoplasia type 2.
Endocr Relat Cancer, 25(2):T69-T77.
J. Grey and K. Winter. 2018.
Multiple endocrine neoplasia type 2 (MEN2) refers to the autosomal-dominant neuroendocrine tumour syndromes, MEN type 2A (MEN2A) and MEN type 2B (MEN2B). They are typified by the development of medullary thyroid cancer (MTC), phaeochromocytoma and parathyroid hyperplasia in MEN2A and MTC, phaeochromocytomas, ganglioneuromatosis and skeletal abnormalities in MEN2B. The aggressiveness of MTC is variable according to genotype, and although it is still the major cause of mortality in both conditions, prognosis has improved dramatically in those diagnosed and treated at a young age thanks to predictive genetic testing. Nevertheless, metastatic MTC, ganglioneuromatosis and a variety of other negative clinical and psychosocial impacts on quality of life and/or prognosis in MEN2 persist. In the absence, at the time of writing, of any large-scale research into quality of life specifically in MEN2, this review includes data from patient surveys and anonymised patient anecdotes from the records of the Association for Multiple Endocrine Neoplasia Disorders (AMEND), for whom the authors work. We recommend that these patients are cared for only in centres of expertise able to provide expert diagnosis, treatment and continuity of care, including psychological and transition support. Only in this way can the clinical advances of the last two and half decades be built upon further to ensure that the care of these complex, lifelong patients can be considered truly holistic.
PubMed-ID: 29066504
http://dx.doi.org/10.1530/ERC-17-0335

Less than total thyroidectomy for goiter: when and how?
Gland Surg, 6(Suppl 1):S49-S58.
O. Makay. 2017.
Benign goiter is the most common endocrine disease that requires surgery, especially in endemic areas suffering from iodine-deficiency. Recent European and American guidelines recommended total thyroidectomy for the surgical treatment of multinodular goiter. Total thyroidectomy has now become the technique of choice and is widely considered the most reliable approach in preventing recurrence. Nevertheless, total thyroidectomy carries a substantial risk in terms of hypoparathyroidism and the morbidity associated with injury to the inferior laryngeal nerve. In this context, partial/less-than-total thyroidectomy is being considered once again as a viable alternative. This review will discuss the extent of thyroid surgery for benign disease and the impact of the surgical protocol on the patient- and surgeon-specific risk factors for specific complication rates.
PubMed-ID: 29322022
http://dx.doi.org/10.21037/gs.2017.10.02

The risk/benefit ratio of differentiated thyroid cancer treatment: Exploring treatment de-escalation.
Eur J Surg Oncol, 44(3):275.
V. B. Wreesmann. 2018.
PubMed-ID: 29398325
http://dx.doi.org/10.1016/j.ejso.2018.01.084

Compartment Pressure Monitoring After Thyroid Surgery: A Possible Method to Detect a Rebleeding.
World J Surg, 42(3):905.
S. Mayilvaganan and S. Bothra. 2018.
PubMed-ID: 28791456
http://dx.doi.org/10.1007/s00268-017-4184-3

Compartment Pressure Monitoring After Thyroid Surgery: A Possible Method to Detect a Rebleeding: Reply.
World J Surg, 42(3):906-7.
T. von Ahnen, M. von Ahnen, S. Militz, D. Preusser and U. Wirth. 2018.
PubMed-ID: 29038826
http://dx.doi.org/10.1007/s00268-017-4300-4

The role and timing of parathyroid hormone determination after total thyroidectomy.
Gland Surg, 6(Suppl 1):S38-S48.
I. G. Mazotas and T. S. Wang. 2017.
Postoperative hypocalcemia is a common complication of total thyroidectomy resulting from manipulation, resection, or devascularization of the parathyroid glands. Parathyroid hormone (PTH) levels assessed in the perioperative period have been used to predict development of hypocalcemia. Articles examining the role of PTH measurement in the perioperative period following total or completion thyroidectomy are reviewed. Focus is placed on the timing of PTH measurement and the ability to predict which patients will develop hypocalcemia requiring supplementation. Postoperative PTH determination is highly accurate in predicting the development of hypocalcemia. Studies have examined PTH levels drawn at differing time points, ranging from intraoperatively until postoperative day 1 (POD1) with similar accuracy. This data is used to guide postoperative selective calcium and calcitriol supplementation in patients at highest risk for hypocalcemia. When evaluated within the first 4 hours postoperatively, predictive accuracy is maintained but can allow for earlier discharge for those patients at lower risk. Alternatively, some authors argue for routine supplementation, which can reduce the rate of postoperative hypocalcemia but increases the rate of unnecessary supplementation and potential risks associated with hypercalcemia. PTH determination at four hours after total thyroidectomy is an accurate predictor of hypocalcemia and can guide selective calcium supplementation for those at high risk, as well as facilitate a safe earlier hospital discharge for those at low risk of developing postoperative hypocalcemia.
PubMed-ID: 29322021
http://dx.doi.org/10.21037/gs.2017.09.06

Growing incidence of thyroid carcinoma in recent years: Factors underlying overdiagnosis.
Head Neck, 40(4):855-66.
A. Sanabria, L. P. Kowalski, J. P. Shah, I. J. Nixon, P. Angelos, M. D. Williams, A. Rinaldo and A. Ferlito. 2018.
There is an increasing incidence of well-differentiated thyroid cancer worldwide. Much of the increase is secondary to increased detection of small, low-risk tumors, with questionable clinical significance. This review addresses the factors that contribute to the increasing incidence and considers environmental, and patient-based and clinician-led influences. Articles addressing the causes of the increased incidence were critically reviewed. A complex interplay of environmental, medical, and social pressures has resulted in increased awareness of the thyroid disease risk, increased screening of thyroid cancers, and increased diagnosis of thyroid cancers. Although there is evidence to suggest that the true disease incidence may be changing slightly, most of the increase is related to factors that promote early diagnosis of low-risk lesions, which is resulting in a significant phenomenon of overdiagnosis. An improved understanding of these pressures at a global level will enable healthcare policymakers to react appropriately to this challenge in the future.
PubMed-ID: 29206325
http://dx.doi.org/10.1002/hed.25029

Therapeutic lateral neck dissection in well-differentiated thyroid cancer: Analysis on factors predicting distribution of positive nodes and prognosis.
Head Neck, 40(2):242-50.
D. Lombardi, A. Paderno, D. Giordano, D. Barbieri, S. Taboni, C. Piazza, C. Cappelli, F. Bertagna, V. Barbieri, S. Piana, S. Bellafiore, G. Spriano, G. Mercante and P. Nicolai. 2018.
BACKGROUND: Neck dissection is considered the treatment of choice in patients with lateral neck metastases from well-differentiated thyroid cancer. METHODS: A multicenter, retrospective review of patients who underwent therapeutic lateral neck dissection for well-differentiated thyroid carcinoma was carried out. RESULTS: The study included a total of 405 lateral neck dissections performed in 352 patients; 197 women (56%) and 155 men (44%). When considering ipsilateral neck metastases, levels IIa, IIb, III, IV, Va, Vb, and V (not otherwise specified) were involved in 42%, 6%, 73%, 67%, 11%, 31%, and 35% of cases, respectively. Five-year and 10-year overall survival (OS) were 93% and 81%, respectively. Age >55 years, pathologic T (pT)4 category, tumor diameter >4 cm, aggressive variants of well-differentiated thyroid carcinoma, endovascular invasion, and number of positive nodes >5 turned out to be the most important prognostic factors. CONCLUSION: Neck dissection is a valid treatment option in the presence of neck metastasis from well-differentiated thyroid carcinoma. Levels IIa, III, IV, and Vb should always be removed.
PubMed-ID: 28963802
http://dx.doi.org/10.1002/hed.24936

Preoperative Localization of Recurrence in the Thyroidectomy Bed Using a Radioactive Iodine(125) Seed.
Otolaryngol Head Neck Surg, 159(2):394-7.
H. W. Garner, R. Paz-Fumagalli and G. D. Young. 2018.
Intraoperative localization of nonpalpable recurrent thyroid cancer has been reported using needle localization, intraoperative ultrasound (US), dye injection, and radio-guided surgery. We describe the alternative technique of radioactive seed localization (RSL) in 3 patients with residual or recurrent papillary thyroid cancer. This technique has been used for many years in the setting of nonpalpable breast cancer, where it has been shown to be safe and has been associated with greater surgeon satisfaction as well as improved patient tolerability, cosmesis, and outcomes compared to needle localization. In addition, RSL allows complete decoupling of the radiology and surgery schedules. RSL was successful in our 3 patients with regard to safety, patient tolerability, and scheduling.
PubMed-ID: 29685086
http://dx.doi.org/10.1177/0194599818772049

Advances in the management of MEN2: from improved surgical and medical treatment to novel kinase inhibitors.
Endocr Relat Cancer, 25(2):T1-T13.
S. A. Wells, Jr. 2018.
Medullary thyroid carcinoma (MTC), a tumor derived from the neural crest, occurs either sporadically or as the dominant component of the type 2 multiple endocrine neoplasia (MEN) syndromes, MEN2A and MEN2B. The discovery that mutations in the RET protooncogene cause hereditary MTC was of great importance, since it led to the development of novel methods of diagnosis and treatment. For example, the detection of a mutated RET allele in family members at risk for inheriting MEN2A or MEN2B signaled that they would develop MTC, and possibly other components of the syndromes. Furthermore, the detection of a mutated allele created the opportunity, especially in young children, to remove the thyroid before MTC developed, or while it was confined to the gland. The discovery also led to the development of molecular targeted therapeutics (MTTs), mainly tyrosine kinase inhibitors, which were effective in the treatment of patients with locally advanced or metastatic MTC. While responses to MTTs are often dramatic, they are highly variable, and almost always transient, because the tumor cells become resistant to the drugs. Clinical investigators and the pharmaceutical industry are focusing on the development of the next generation of MTTs, which have minimal toxicity and greater specificity for mutated RET.
PubMed-ID: 29142004
http://dx.doi.org/10.1530/ERC-17-0325

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): impact on the reclassification of thyroid nodules.
Endocr Relat Cancer, 25(4):R247-R58.
I. Amendoeira, T. Maia and M. Sobrinho-Simoes. 2018.
The 2017 edition of the WHO book on Classification of Tumours of Endocrine Organs includes a new section

entitled 'Other encapsulated follicular-patterned thyroid tumours', in which the newly created NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) is identified and described in detail. Despite deleting the word 'carcinoma' from its name, NIFTP is not a benign tumor either and is best regarded as a neoplasm with 'very low malignant potential'. The main goal of the introduction of NIFTP category is to prevent overdiagnosis and overtreatment. Sampling constraints, especially when dealing with heterogeneous and/or large nodules, and difficulties in the invasiveness evaluation, are the major weaknesses of the histological characterization of NIFTP. At the cytological level, NIFTP can be separated from classic papillary carcinoma (cPTC) but not from encapsulated, invasive follicular variant PTC. The impact of NIFTP individualization for cytopathology is the drop of rates of malignancy for each Bethesda category in general and for indeterminate categories in particular. The biggest impact will be seen in institutions with a high frequency of FVPTC. The introduction of NIFTP has changed the utility of predictive values of molecular tests because RAS mutations and PAX8-PPARg rearrangements are frequently detected in NIFTP. This turns less promising the application of mutation detection panels as indicators of malignancy and will probably contribute to switch to a rule-out approach of molecular testing. Selection for surgery will go on being determined by a combined detection of clinical, cytological and ultrasound suspicious features.
PubMed-ID: 29439059
http://dx.doi.org/10.1530/ERC-17-0513

Short and long-term impact of parathyroid autotransplantation on parathyroid function after total thyroidectomy.
Gland Surg, 6(Suppl 1):S75-S85.
G. Hicks, R. George and M. Sywak. 2017.
The most common complication of total thyroidectomy is parathyroid insufficiency. Acute, transient, post-operative hypoparathyroidism increases length of hospitalization, morbidity and cost associated with total thyroidectomy. While permanent hypoparathyroidism poses a significant medical burden with lifetime medication, regular follow up and considerable disease burden related to chronic renal failure and other sequelae. Parathyroid autotransplantation has been demonstrated to result in biochemically functional grafts, leading to the procedures' common use during total thyroidectomy. The clearest indications for parathyroid auto transplantation are inadvertently removed or devascularized parathyroid glands. Some centers utilize routine autotransplantation to reduce the risk of permanent hypoparathyroidism. Novel fluorescence techniques to aid in parathyroid detection during thyroid surgery are under evaluation. This review aims to define the role and impact of parathyroid autotransplantation undertaken during total thyroidectomy.
PubMed-ID: 29322025
http://dx.doi.org/10.21037/gs.2017.09.15

A reappraisal of vascular anatomy of the parathyroid gland based on fluorescence techniques.
Gland Surg, 6(Suppl 1):S30-S7.
S. M. Sadowski, J. Vidal Fortuny and F. Triponez. 2017.
Identification of the parathyroid glands (PGs) during thyroid surgery may prevent their inadvertent surgical removal and prevent postoperative hypoparathyroidism. However, identification of the PGs does not guarantee their function, and their vascular supply needs to be preserved as well. The recent introduction of intraoperative indocyanine green (ICG) fluorescent angiography of the PGs during thyroid surgery allows for the appraisal of the vascular anatomy and evaluation of PG function. The use of this tool could lead to a significant reduction in the rate of postoperative hypoparathyroidism, as it allows surgeons to adapt their surgical technique for the preservation of the PGs. ICG fluorescent angiography is currently the only available real-time tool to assess the vascular blood supply of each individual PG intraoperatively and can thus assist surgeons in their decision-making. Herein, we review the relevant literature.
PubMed-ID: 29322020
http://dx.doi.org/10.21037/gs.2017.07.10

Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism.
Gland Surg, 6(Suppl 1):S3-S10.
L. Lorente-Poch, J. J. Sancho, L. Carballo and A. Sitges-Serra. 2017.
Background: Parathyroid failure is the most common complication after total thyroidectomy but permanent impairment of the parathyroid function is unusual. Limited data is available assessing long-term follow-up, quality of life and complications occurring in patients with permanent hypoparathyroidism (PH). We aimed to assess the incidence of complications derived from PH status, their influence on the quality of life perceived by PH patients and its relation to standard medical treatment with calcium salts and active vitamin D analogues. Methods:

Cross-sectional observational study of consecutive patients undergoing total thyroidectomy who developed PH and were followed at least twice a year at a referral endocrine surgery unit. PH was defined as intact parathyroid hormone (iPTH) levels <13 pg/mL and the need for replacement therapy with calcium and/or vitamin D for at least 1 year after surgery. Quality of life was assessed using the SF-36 questionnaire. Data regarding doses and type of vitamin D analogues and calcium supplementation, serum calcium fluctuations, bone densitometry and renal ultrasound were recorded. Results: The cohort included 32 patients (3 male/29 female) with a mean age of 51.2+/-15.2 years. The mean follow-up was 78+/-68 months and the total follow-up length was 70,080 PH patient/days. Five (15.6%) patients showed a decreased renal function. At least one clinical adverse event was observed in 18 (56.3%) patients. There was a slight decrease of the punctuation in the SF-36 questionnaire for the perceived quality of life that was only significant for the emotional role. Conclusions: PH and its treatment carry a mild to moderate burden of illness if followed closely. During a mean follow-up of nearly 6 years, only half of the patients suffered a relevant clinical event with little impact on their quality of life.
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http://dx.doi.org/10.21037/gs.2017.11.10

Incidence, prevalence and risk factors for post-surgical hypocalcaemia and hypoparathyroidism.
Gland Surg, 6(Suppl 1):S59-S68.
O. Edafe and S. P. Balasubramanian. 2017.
Hypocalcaemia following thyroid surgery is common and is associated with significant short and long term morbidity. Damage to or devascularisation of parathyroid glands is the predominant underlying mechanism; although other factors such as hungry bone syndrome may occasionally contribute to it in the immediate post-operative period. The reported incidence of post-surgical hypocalcaemia and/or hypoparathyroidism (PoSH) varies significantly in the literature; the variation thought to be at least partly due to differences in the definitions used. Figures on the prevalence of chronic or long term post-surgical hypocalcaemia in the population are unclear. Risk factors for PoSH have been extensively studied in recent years and may be classified into patient, disease and surgery related factors. Some risk factors are modifiable; but both modifiable and non-modifiable factors help in generating a risk profile that may be used to select patients for preventative measures and/or changes in surgical strategy. This narrative review discusses recent literature on the incidence, prevalence and risk factors for PoSH.
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http://dx.doi.org/10.21037/gs.2017.09.03

The PGRIS and parathyroid splinting concepts for the analysis and prognosis of protracted hypoparathyroidism.
Gland Surg, 6(Suppl 1):S86-S93.
A. Sitges-Serra. 2017.
Most patients with hypocalcemia after total thyroidectomy will recover the parathyroid function in a few weeks, but some 20-30% of them will still be in the need for replacement therapy one month after surgery and about 5-10% of those will develop permanent hypoparathyroidism. Although postoperative hypocalcemia has been related to several demographic and metabolic causes, parathyroid hormone (PTH) decline, resulting from autotransplantation, inadvertent excision or devascularization of the parathyroid glands, is the common final pathway. The number of parathyroid glands remaining in situ (PGRIS) is a key variable to understand the pathogenesis of protracted hypoparathyroidism and the chances for restoration of the parathyroid function. Normal-high serum calcium concentration, probably achieved by a more intensive medical treatment at the time of hospital discharge, has been identified as an independent variable favoring recovery of the parathyroid function. This we refer to as parathyroid splinting, a hypothesis holding that putting the injured parathyroid parenchyma at rest after thyroidectomy may improve long-term outcome of protracted hypoparathyroidism.
PubMed-ID: 29322026
http://dx.doi.org/10.21037/gs.2017.07.16

Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry.
Gland Surg, 6(Suppl 1):S69-S74.
D. R. Chadwick. 2017.
The UK Registry of Endocrine and Thyroid Surgeons (UKRETS) has been operated by the British Association of Endocrine and Thyroid Surgeons (BAETS) and Dendrite Clinical Systems Ltd. in a web-based electronic format since 2004. Data on over 90,000 endocrine procedures have been collected to date. Analysis of those cases undergoing bilateral thyroid resections in the interval July 2010 to June 2015 demonstrates that hypocalcaemia remains the commonest complication of thyroid surgery. After first-time total thyroidectomy, 23.6% of patients

develop hypocalcaemia, defined as a serum calcium <2.10 mmol/L (or <1.20 mmol/L ionized calcium) on the first post-operative day. Most require treatment with calcium +/- vitamin D supplements, with around 38% of all patients being treated by the time of discharge from the index admission. By 6 months post-operative, 7.3% of patients remain on calcium/vitamin D supplements, reflecting persistent (though not necessarily permanent) hypoparathyroidism. Risk factors for persistent hypocalcaemia are principally concomitant level VI lymph node dissection [odds ratio (OR) =2.73]; re-operative surgery (OR =1.44); and inter-surgeon variation.
PubMed-ID: 29322024
http://dx.doi.org/10.21037/gs.2017.09.14

A nomogram to predict the likelihood of permanent hypoparathyroidism after total thyroidectomy based on delayed serum calcium and iPTH measurements.
Gland Surg, 6(Suppl 1):S11-S9.
A. Sitges-Serra, J. Gomez, M. Barczynski, L. Lorente-Poch, M. Iacobone and J. Sancho. 2017.
Background: Retrospective studies have shown that delayed high-normal serum calcium and detectable iPTH are independent variables positively influencing outcome of prolonged parathyroid failure after total thyroidectomy (TT). The aim of the present study was to examine prospectively the ability of these two variables to predict permanent hypoparathyroidism in patients under replacement therapy for postoperative hypocalcemia. Methods: Prospective observational multicenter study of patients undergoing TT followed by postoperative parathyroid failure (serum calcium <8 mg/dL within 24 h and PTH <15 pg/mL 4 h after surgery). Serum calcium, vitamin D and iPTH were determined before thyroidectomy, 24 h after surgery, at 1 month and then periodically until recovery of the parathyroid function or permanent hypoparathyroidism was diagnosed after at least 1 year follow-up. Results: Some 145 patients with postoperative hypocalcemia were investigated [s-Ca(24h) 7.5 (0.5) mg/dL]. Hypocalcemia recovered within 30 days in 91 (63%) patients and 54 (37%) developed protracted hypoparathyroidism {iPTH 5.8 [4] pg/mL at 1 month}, of whom 32 recovered within 1 year and 22 developed permanent hypoparathyroidism. Protracted hypoparathyroidism was related to few parathyroid glands remaining in situ (PGRIS). Serum calcium concentration (mg/dL) at 1 postoperative month correlated positively with the rate of recovery (percent) from protracted hypoparathyroidism: <8.5 (20%); 8.5-9 (29%); 9.1-9.5 (70%); 9.6-10 (89%); >10 (83%) (P=0.013). Serum iPTH at 1 month was also higher (7.3 vs. 3.7 pg/mL; P=0.002) in recovered protracted hypoparathyroidism. The combination of both variables predicts the likelihood of recovery of the parathyroid function with >90% accuracy. Conclusions: High-normal serum calcium and low but detectable iPTH concentrations at 1 month after TT were associated with better outcome of protracted hypoparathyroidism. A nomogram combining both variables may guide medical treatment and monitoring of post-thyroidectomy prolonged hypoparathyroidism.
PubMed-ID: 29322018
http://dx.doi.org/10.21037/gs.2017.10.04

The effects of the Union for International Cancer Control/American Joint Committee on Cancer Tumour, Node, Metastasis system version 8 on staging of differentiated thyroid cancer: a comparison to version 7.
Clin Endocrinol (Oxf), 88(6):950-6.
F. A. Verburg, U. Mader, M. Luster and C. Reiners. 2018.
OBJECTIVE: To assess the changes resulting from the changes from UICC/AJCC TNM version 7 to version 8 and to subsequently determine whether TNM version 8 is an improvement compared to previous iterations of the TNM system and other staging systems for differentiated thyroid cancer (DTC) with regard to prognostic power. DESIGN: Database study of DTC patients treated in our centre between 1978 up to and including 1 July 2014. Results were compared to our previous comparison of prognostic systems using the same data set. PATIENTS: 2257 DTC patients. MEASUREMENTS: Staging in accordance with TNM 7 and TNM 8. Thyroid cancer-specific mortality; comparison was based on p-values of univariate Cox regression analyses as well as analysis of the proportion of variance explained (PVE). RESULTS: There is a redistribution from stage 3 to lower stages affecting 206 (9.1%) patients. DTC-related mortality according to Kaplan-Meier for younger and older patients in TNM 7 had a slightly lower prognostic power than that in accordance with TNM 8 (P = 8.0 10(-16) and P = 1.5 10(-21) , respectively). Overall staging is lower in 627/2257 (27.8%) patients. PVE (TNM 7: 0.29; TNM 8: 0.28) and the P-value of Cox regressions (TNM 7: P = 7.1*10(-52) ; TNM 8: P = 3.9*10(-49)) for TNM version 8 are marginally lower than that for TNM version 7, but still better than for any other DTC staging system. CONCLUSION: TNM 8 results in a marked downstaging of patients compared to TNM 7. Although some changes, like the change in age boundary, appear to be associated with an improvement in prognostic power, the overall effect of the changes does not improve the predictive power compared to TNM 7.
PubMed-ID: 29573277
http://dx.doi.org/10.1111/cen.13597

To identify or not to identify parathyroid glands during total thyroidectomy.
Gland Surg, 6(Suppl 1):S20-S9.
Y. K. Chang and B. H. H. Lang. 2017.
Hypoparathyroidism is one of the most common complications after total thyroidectomy and may impose a significant burden to both the patient and clinician. The extent of thyroid resection, surgical techniques, concomitant central neck dissection, parathyroid gland (PG) autotransplantation and inadvertent parathyroidectomy have long been some of the risk factors for postoperative hypoparathyroidism. Although routine identification of PGs has traditionally been advocated by surgeons, recent evidence has suggested that perhaps identifying fewer number of in situ PGs during surgery (i.e., selective identification) may further lower the risk of hypoparathyroidism. One explanation is that visual identification may often lead to subtle damages to the nearby blood supply of the in situ PGs and that may increase the risk of hypoparathyroidism. However, it is worth highlighting the current literature supporting either approach (i.e., routine vs. selective) remains scarce and because of the significant differences in study design, inclusions, definitions and management protocol between studies, a pooled analysis on this important but controversial topic remains an impossible task. Furthermore, it is worth nothing that identification of PGs does not equal safe preservation, as some studies demonstrated that it is not the number of PGs identified, but the number of PG preserved in situ that matters. Therefore a non-invasive, objective and reliable way to localize PGs and assess their viability intra-operatively is warranted. In this aspect, modern technology such as the indocyanine green (ICG) as near-infrared fluorescent dye for real-time in situ PG perfusion monitoring may have a potential role in the future.
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http://dx.doi.org/10.21037/gs.2017.06.13

Parathyroids

Meta-Analyses

Association of Parathyroid Hormone Level With Postthyroidectomy Hypocalcemia: A Systematic Review.
JAMA Surg, 153(1):69-76.
A. Mathur, N. Nagarajan, S. Kahan, E. B. Schneider and M. A. Zeiger. 2018.
Importance: There has been an increased interest in measuring parathyroid hormone (PTH) levels as an early predictive marker for the development of hypocalcemia after total thyroidectomy. However, significant variation exists in the timing, type of assay, and thresholds of PTH in the literature. Objective: We performed a systematic review to examine the utility of PTH levels in predicting temporary postthyroidectomy hypocalcemia. Evidence Review: A systematic literature review of studies published prior to May 25, 2016 was performed within PubMed, EMBASE, SCOPUS, and Cochrane databases using the following terms and keywords: "thyroidectomy," "parathyroid hormone," and "hypocalcaemia," "calcium," or "calcitriol." Each candidate full-text publication was reviewed by 2 independent reviewers and selected for data extraction if the study examined the prognostic significance of PTH obtained within 24 hours after thyroidectomy to predict hypocalcaemia. Studies were excluded if calcium supplementation was used routinely or based on a PTH level. Study characteristics, PTH parameters used to predict hypocalcemia, and their respective accuracies were summarized. Findings: The initial search yielded 2417 abstracts. Sixty-nine studies, comprising 9163 patients, were included. Overall, for an absolute PTH threshold, the median accuracy, sensitivity, and specificity were 86%, 85%, and 86%, respectively. For a percentage change over time the median accuracy, sensitivity, and specificity were 89%, 88%, and 90%, respectively. Conclusions and Relevance: The existing literature regarding PTH levels to predict postthyroidectomy hypocalcemia is extremely heterogeneous. A single PTH threshold is not a reliable measure of hypocalcemia. Additional prospective studies controlled for timing of laboratory draws and a priori defined PTH thresholds need to be performed to ascertain the true prognostic significance of PTH in predicting postthyroidectomy hypocalcaemia.
PubMed-ID: 29167863
http://dx.doi.org/10.1001/jamasurg.2017.3398

Randomized controlled trials

Recombinant Human Parathyroid Hormone Effect on Health-Related Quality of Life in Adults With Chronic Hypoparathyroidism.
J Clin Endocrinol Metab, 103(2):722-31.
T. J. Vokes, M. Mannstadt, M. A. Levine, B. L. Clarke, P. Lakatos, K. Chen, R. Piccolo, A. Krasner, D. M. Shoback and J. P. Bilezikian. 2018.
Context: Reduced health-related quality of life (HRQoL) is common in patients with hypoparathyroidism treated conventionally with calcium and active vitamin D supplements. Objective: To examine the effects of recombinant human parathyroid hormone [rhPTH(1-84)] on HRQoL as measured by the 36-Item Short-Form Health Survey (SF-36) during a multinational, randomized, placebo-controlled study. Patients: Adults (N = 122) with chronic hypoparathyroidism. Intervention(s): After an optimization period when calcium and/or active vitamin D supplements were adjusted to reach target serum calcium levels (8.0 to 9.0 mg/dL; 2.0 to 2.2 mmol/L), patients were randomly assigned to receive placebo (n = 39) or rhPTH(1-84) (n = 83) (starting dose, 50 mug/d, could be titrated up to 100 mug/d); supplement doses were adjusted to maintain target serum calcium levels. Main Outcome Measure(s): Change from baseline (postoptimization, at randomization) to week 24 in HRQoL as assessed by the SF-36. Results: Overall, the between-group differences were not statistically significant. However, in the rhPTH(1-84) group, there were significant improvements in the physical component summary score ($P = 0.004$), and in body pain ($P < 0.05$), general health ($P < 0.05$), and vitality ($P < 0.001$) domains as compared with baseline values. In the placebo group, there were no significant changes for any domains. The magnitude of change between 0 and 24 weeks in SF-36 scores was negatively correlated with baseline scores, such that patients with lower HRQoL at baseline were more likely to experience improvement in response to treatment. Conclusion: Treatment with rhPTH(1-84) may improve HRQoL in adults with hypoparathyroidism.

PubMed-ID: 29099947
http://dx.doi.org/10.1210/jc.2017-01471

Consensus Statements/Guidelines

- None -

Other Articles

Undiagnosed Primary Hyperparathyroidism and Recurrent Miscarriage: The First Prospective Pilot Study.
World J Surg, 42(3):639-45.
A. DiMarco, I. Christakis, V. Constantinides, L. Regan and F. F. Palazzo. 2018.
BACKGROUND: Primary hyperparathyroidism (pHPT) in pregnancy is reported to be associated with significant maternal and foetal complications and an up to threefold increase in the risk of miscarriage. However, the true incidence of pHPT in pregnancy, complete and miscarried, is unknown and there are no data on the prevalence of undiagnosed pHPT in recurrent miscarriage (RM) (>/=3 consecutive miscarriages under 24-week gestation). This is the first prospective study aiming to establish the prevalence of undiagnosed pHPT in RM. METHODS: Following UK National ethics committee approval, women who had experienced 3 or more consecutive miscarriages were recruited from a nationwide RM clinic. Serum corrected calcium, phosphate, PTH and vitamin D were evaluated. Patients with raised serum calcium and/or PTH were recalled for confirmatory tests. Power calculations suggested that a minimum of 272 patients were required to demonstrate a clinically significant incidence of pHPT. RESULTS: Three hundred women were recruited, median age 35 years (range 19-42). Eleven patients had incomplete data, leaving 289 patients suitable for analysis; 50/289 patients (17%) with abnormal tests were recalled. The prevalence of vitamin D deficiency (<25 nmol/l) and insufficiency (25-75 nmol/l) was 8.7 and 67.8%, respectively. One patient was diagnosed with pHPT (0.34%) and underwent successful parathyroidectomy. CONCLUSIONS: The prevalence of undiagnosed pHPT (0.34%) in RM in this study appears to be many times greater than the 0.05% expected in this age group. The findings of this pilot study merit follow-up with a larger-scale study. Routine serum calcium estimation is not currently undertaken in RM and should be considered.
PubMed-ID: 29349485
http://dx.doi.org/10.1007/s00268-017-4395-7

Classic Primary Hyperparathyroidism Versus Normocalcemic and Normohormonal Variants: Do They Really Differ?
World J Surg, 42(4):992-7.
A. Kiriakopoulos, A. Petralias and D. Linos. 2018.
BACKGROUND: Normocalcemic (NCpHPT) and normohormonal (NHpHPT) variants have been recognized primary hyperparathyroidism entities that pose serious challenges. We sought to define the differences among them in a series of surgically treated patients. PATIENTS AND METHODS: Between 2011 and 2015, 149 patients were enrolled into three groups: CpHPT (Ca > 10.2 mg/dL, PTH > 65 pg/mL), NCpHPT (normal Ca, PTH > 65 pg/mL) and NHpHPT (Ca > 10.2 mg/dL, normal PTH). Descriptive statistics and inter-group differences were computed, whereas multiple logistic/linear regression tests were used for further analysis. RESULTS: Of these patients 125 were female and 24 male, mean age 56.3 years (range 8-83). A total of 115 (77.2%) patients presented with CpHPT, 23 (15.4%) with NCpHPT and 11 (7.4%) with NHpHPT. MGD was found in 25 (16.8%) patients and SGD in 124 (83.2%); multivariate analysis failed to reveal statistically significant association of MGD with any pHPT variant (CpHPT 16.5% vs NCpHPT 21.7% vs NHpHPT 9.1%, p = 0.726). Conversely, NCpHPT patients exhibited statistically significant smaller adenoma weight (p = 0.023). Moreover, U/S in these patients had smaller positive predictive value (p = 0.278), whereas concordance between U/S and MIBI was also lower (p = 0.669). The utility of MIBI and U/S differed significantly (p < 0.001); more frequent use of U/S was observed for all groups. However, their predictive values did not differ significantly (p = 0.832). CONCLUSIONS: NCpHPT is more similar than different to CpHPT. NCpHPT constitutes the most challenging entity: it is associated with smaller adenoma weight, whereas U/S exhibited lower positive predictive value and lower concordance rate with MIBI. A trend for higher MGD presence in this group of patients was observed, though without statistical significance.

PubMed-ID: 29392434
http://dx.doi.org/10.1007/s00268-018-4512-2

Identification of Differential Transcriptional Patterns in Primary and Secondary Hyperparathyroidism.
J Clin Endocrinol Metab, 103(6):2189-98.
S. M. Sadowski, M. Pusztaszeri, M. C. Brulhart-Meynet, V. Petrenko, C. De Vito, J. Sobel, C. Delucinge-Vivier, E. Kebebew, R. Regazzi, J. Philippe, F. Triponez and C. Dibner. 2018.
Context: Hyperparathyroidism is associated with hypercalcemia and the excess of parathyroid hormone secretion; however, the alterations in molecular pattern of functional genes during parathyroid tumorigenesis have not been unraveled. We aimed at establishing transcriptional patterns of normal and pathological parathyroid glands (PGs) in sporadic primary (HPT1) and secondary hyperparathyroidism (HPT2). Objective: To evaluate dynamic alterations in molecular patterns as a function of the type of PG pathology, a comparative transcript analysis was conducted in subgroups of healthy samples, sporadic HPT1 adenoma and hyperplasia, and HPT2. Design: Normal, adenomatous, HPT1, and HPT2 hyperplastic PG formalin-fixed paraffin-embedded samples were subjected to NanoString analysis. In silico microRNA (miRNA) analyses and messenger RNA-miRNA network in PG pathologies were conducted. Individual messenger RNA and miRNA levels were assessed in snap-frozen PG samples. Results: The expression levels of c-MET, MYC, TIMP1, and clock genes NFIL3 and PER1 were significantly altered in HPT1 adenoma compared with normal PG tissue when assessed by NanoString and quantitative reverse transcription polymerase chain reaction. RET was affected in HPT1 hyperplasia, whereas CaSR and VDR transcripts were downregulated in HPT2 hyperplastic PG tissue. CDH1, c-MET, MYC, and CaSR were altered in adenoma compared with hyperplasia. Correlation analyses suggest that c-MET, MYC, and NFIL3 exhibit collective expression level changes associated with HPT1 adenoma development. miRNAs, predicted in silico to target these genes, did not exhibit a clear tendency upon experimental validation. Conclusions: The presented gene expression analysis provides a differential molecular characterization of PG adenoma and hyperplasia pathologies, advancing our understanding of their etiology.
PubMed-ID: 29659895
http://dx.doi.org/10.1210/jc.2017-02506

Parathyroidectomy for the treatment of hyperparathyroidism: Thirty-day morbidity and mortality.
Laryngoscope, 128(2):528-33.
J. A. Tang, A. M. Salapatas, L. B. Bonzelaar and M. Friedman. 2018.
OBJECTIVES/HYPOTHESIS: Evaluate morbidity and mortality rates for patients with different levels of hyperparathyroidism (HPT) undergoing parathyroidectomy (PTX), specifically comparing primary hyperparathyroidism to secondary and tertiary hyperparathyroidism. Assess predictive factors of increased morbidity and mortality. STUDY DESIGN: Retrospective national database review. METHODS: Patients undergoing PTX, defined by Current Procedural Terminology codes 60500, 60502, 60505, for the treatment of HPT, were identified in the American College of Surgeons National Surgical Quality Improvement Program database between 2006 and 2014. Incidence of morbidity and mortality was calculated for primary, secondary, and tertiary HPT. A t test, analysis of variance, and chi(2) analyses were used to assess preoperative characteristics among the three groups. RESULTS: A total of 21,267 patients were included in the analysis. There was an overall 7.2% morbidity and mortality rate, including 45 (0.21%) deaths, a 1.8% readmission rate, and a 1.9% reoperation rate, but morbidity and mortality rates were widely divergent when comparing primary to secondary and tertiary HPT. PTX resulted in a 4.9% morbidity and mortality rate for primary HPT (n = 14,500), 26.8% morbidity and mortality rate for secondary HPT (n = 1661), and 21.8% morbidity and mortality rate for tertiary HPT (n = 588). The primary reason for readmission was hypocalcemia (18.3%). Hematoma (7.2%) and postoperative hemorrhage (3.3%) were the two most common causes of reoperation. Elevated preoperative serum creatinine, alkaline phosphatase, and hypertension resulted in a higher rate of complications after PTX ($P < .0001$). CONCLUSIONS: Although surgery for primary HPT is an extremely common and safe procedure with minimal morbidity and mortality rates, PTX for secondary and tertiary HPT has significantly higher rates of morbidity and mortality, requiring special attention in the postoperative period. Predictive factors of poor outcomes include hypertension, elevated creatinine, and elevated alkaline phosphatase. LEVEL OF EVIDENCE: 4. Laryngoscope, 128:528-533, 2018.
PubMed-ID: 28493416
http://dx.doi.org/10.1002/lary.26604

Familial isolated primary hyperparathyroidism associated with germline GCM2 mutations is more aggressive and has a lesser rate of biochemical cure.
Surgery, 163(1):31-4.
M. El Lakis, P. Nockel, B. Guan, S. Agarwal, J. Welch, W. F. Simonds, S. Marx, Y. Li, N. Nilubol, D. Patel, L. Yang, R. Merkel and E. Kebebew. 2018.
BACKGROUND: Hereditary primary hyperparathyroidism may be syndromic or nonsyndromic (familial isolated hyperparathyroidism). Recently, germline activating mutations in the GCM2 gene were identified in a subset of familial isolated hyperparathyroidism. This study examined the clinical and biochemical characteristics and the treatment outcomes of GCM2 mutation-positive familial isolated hyperparathyroidism as compared to sporadic primary hyperparathyroidism. METHODS: We performed a retrospective analysis of clinical features, parathyroid pathology, and operative outcomes in 18 patients with GCM2 germline mutations and 457 patients with sporadic primary hyperparathyroidism. RESULTS: Age at diagnosis, sex distribution, race/ethnicity, and preoperative serum calcium concentrations were similar between the 2 groups. The preoperative serum levels of intact parathyroid hormone was greater in patients with GCM2-associated primary hyperparathyroidism (239 +/- 394 vs 136 +/- 113, P = .005) as were rates of multigland disease and parathyroid carcinoma in the GCM2 group (78% vs 14.3%, P < .001 and 5% vs 0%, P = .04, respectively), but the biochemical cure rate was less in the GCM2 group (86% vs 99%, P < .001). CONCLUSION: GCM2-associated primary hyperparathyroidism patients have greater preoperative parathyroid hormone levels, a greater rate of multigland disease, a lesser rate of biochemical cure, and a substantial risk of parathyroid carcinoma. Knowledge of these clinical characteristics could optimize the surgical management of GCM2-associated familial isolated hyperparathyroidism.
PubMed-ID: 29108698
http://dx.doi.org/10.1016/j.surg.2017.04.027

Lithium-Associated Hypercalcemia: Pathophysiology, Prevalence, Management.
World J Surg, 42(2):415-24.
A. D. Meehan, R. Udumyan, M. Kardell, M. Landen, J. Jarhult and G. Wallin. 2018.
BACKGROUND: Lithium-associated hypercalcemia (LAH) is an ill-defined endocrinopathy. The aim of the present study was to determine the prevalence of hypercalcemia in a cohort of bipolar patients (BP) with and without concomitant lithium treatment and to study surgical outcomes for lithium-associated hyperparathyroidism. METHODS: Retrospective data, including laboratory results, surgical outcomes and medications, were collected from 313 BP treated with lithium from two psychiatric outpatient units in central Sweden. In addition, data were collected from 148 BP without lithium and a randomly selected control population of 102 individuals. Logistic regression was used to compare odds of hypercalcemia in these respective populations. RESULTS: The prevalence of lithium-associated hypercalcemia was 26%. Mild hypercalcemia was detected in 87 out of 563 study participants. The odds of hypercalcemia were significantly higher in BP with lithium treatment compared with BP unexposed to lithium (adjusted OR 13.45; 95% CI 3.09, 58.55; p = 0.001). No significant difference was detected between BP without lithium and control population (adjusted OR 2.40; 95% CI 0.38, 15.41; p = 0.355). Seven BP with lithium underwent surgery where an average of two parathyroid glands was removed. Parathyroid hyperplasia was present in four patients (57%) at the initial operation. One patient had persistent disease after the initial operation, and six patients had recurrent disease at follow-up time which was on average 10 years. CONCLUSION: The high prevalence of LAH justifies the regular monitoring of calcium homeostasis, particularly in high-risk groups. If surgery is necessary, bilateral neck exploration should be considered in patients on chronic lithium treatment. Prospective studies are needed.
PubMed-ID: 29260296
http://dx.doi.org/10.1007/s00268-017-4328-5

Retropharyngeal Parathyroid Glands: Important Differences.
World J Surg, 42(2):437-43.
J. W. Gallagher, M. L. Kelley, L. Yip, S. E. Carty and K. L. McCoy. 2018.
INTRODUCTION: In primary hyperparathyroidism (PHPT), parathyroid ectopia is seen in up to 22% leading to more difficult surgery. We aimed to determine the rate and characteristics of retropharyngeal (RP) parathyroid glands. METHODS: A prospective database was queried for patients with sporadic PHPT who had surgery from 1997 to 2016. The data of RP patients were compared to those who had surgery for sporadic PHPT over the same time period with hyperfunctioning parathyroids in anatomically normal positions (N). RESULTS: RP glands occurred in 47/3006 (1.6%) patients and were more common at reoperative than initial surgery (5.5 vs 1.4%, p < 0.01). RP patients had prior failed surgery more often than N patients (17 vs 3.1%, p < 0.01). Preoperative calcium levels (p = 0.06), PTH levels (p = 0.15), and mean gland weights (p = 0.07) were similar among groups. For RP glands, ultrasound imaging was negative in all but one patient, while 99mTc-sestamibi accurately indicated a posterior midline position in only 13/47 (28%) and was negative in 21%. All RP glands were

anatomically superior. RP patients more often required > 1 post-resection intraoperative PTH level (36 vs 21%, p = 0.02). Failure due to persistent PHPT was more likely in RP patients (4.7 vs 2.1%, p = 0.2). CONCLUSION: In PHPT, hyperfunctioning RP glands are seen in 1.6% of cases and often associated with initial failure (17%). At reoperation, RP ectopia is 4X more common. RP glands are associated with a high rate of negative imaging, but imaging results suggestive of a midline abnormality can guide exploration. The RP space should be evaluated prior to ending an otherwise unfruitful surgery.
PubMed-ID: 28963593
http://dx.doi.org/10.1007/s00268-017-4236-8

Surgery for Primary Hyperparathyroidism with Normal Non-suppressed Parathyroid Hormone can be Both Challenging and Successful.
World J Surg, 42(2):409-14.
L. E. Orr, T. J. McKenzie, G. B. Thompson, D. R. Farley, R. A. Wermers and M. L. Lyden. 2018.
BACKGROUND: Criteria for diagnosing primary hyperparathyroidism (PHPT) include hypercalcemia in the presence of parathyroid hormone (PTH) levels that are either elevated (classic PHPT) or normal but non-suppressed. However, there is no standard definition of what constitutes normal non-suppressed levels, and data are lacking regarding the potential for surgical cure in these patients. METHODS: A retrospective review of patients undergoing parathyroidectomy for sporadic PHPT between 2012 and 2014 was performed. Patients with normal PTH were compared to classic PHPT patients to assess demographics, imaging, operative findings, and outcomes. RESULTS: In total, 332 patients met study criteria, and 60 (18%) had normal PTH levels. Negative sestamibi scans were seen more often with normal PTH levels (18.3 vs. 4.8%, p < 0.001). Patients with normal PTH were more likely to have >/=2 glands removed (26.7 vs. 14.3%, p = 0.02), and the specimens were more likely to be classified as only mildly hypercellular or normocellular (20 vs. 2.9%, p < 0.001). Average follow-up was 24 months (range 6-55). Cure rate was 88% in the normal PTH group, compared to 96% in classic PHPT (p = 0.02). Among patients with normal PTH, those with PTH </= 55 pg/mL had an 83% cure rate, whereas those with PTH 56-65 had a 96% cure rate (p = 0.12). CONCLUSIONS: Parathyroidectomy can have a high cure rate in the context of normal PTH levels despite an increased likelihood of negative imaging and multigland resection. Operative success is equivalent to classic PHPT when PTH levels are > 55 pg/mL.
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http://dx.doi.org/10.1007/s00268-017-4323-x

PTH(1-34) for Surgical Hypoparathyroidism: A 2-Year Prospective, Open-Label Investigation of Efficacy and Quality of Life.
J Clin Endocrinol Metab, 103(1):271-80.
A. Palermo, A. Santonati, G. Tabacco, D. Bosco, A. Spada, C. Pedone, B. Raggiunti, T. Doris, D. Maggi, F. Grimaldi, S. Manfrini and F. Vescini. 2018.
Context: Daily parathyroid hormone (PTH) (1-34) administrations can reduce the required total daily dose of calcium and calcitriol and restore normocalcemia in refractory hypoparathyroidism. However, most PTH(1-34) trials have been conducted on small cohorts including subjects with hypoparathyroidism of various etiologies, and quality of life (QOL) was not investigated. Objective: To investigate the effects of 24-month PTH(1-34) treatment in a homogeneous cohort of adult subjects with postoperative hypoparathyroidism and to evaluate QOL changes. Design: Prospective open-label study. Setting: Italian multicenter study. Participants: 42 subjects. Intervention: Twice-daily PTH(1-34) 20 mug subcutaneous injection. Main Outcome Measures: Calcium and vitamin D supplementation requirements, serum calcium, phosphate, and urinary calcium excretion (3, 6, 12, 18, 24 months). At baseline and at 6 and 24 months, QOL was evaluated by the RAND 36-Item Short Form (SF-36) Health Survey, covering eight domains of physical and mental health. Results: Mean serum calcium concentration significantly increased from baseline to 3 months (7.6 +/- 0.6 vs 8.9 +/- 1.1 mg/dL, P < 0.001) and remained stable until the end of the study, despite reductions in calcium and vitamin D supplementation. Phosphate levels gradually decreased from baseline to 6 months (4.3 +/- 1.1 vs 3.9 +/- 0.6 mg/dL, P < 0.019), remaining stable until 24 months. Serum alkaline phosphatase and calcium excretion gradually increased from baseline to 24 months. Data from SF-36 showed a significant improvement in the mean scores of all eight domains (P < 0.001). Conclusion: This study demonstrates the efficacy and safety of PTH(1-34) to treat adult patients with postsurgical hypoparathyroidism. PTH(1-34) may improve their mental and physical health.
PubMed-ID: 29099939
http://dx.doi.org/10.1210/jc.2017-01555

Development of Severe Hyperparathyroidism Despite Short-Term Renal Replacement Therapy.
World J Surg, 42(2):425-30.
M. Okada, Y. Tominaga, T. Hiramitsu and T. Ichimori. 2018.
BACKGROUND: We occasionally experience cases of severe secondary hyperparathyroidism (SHPT) that require parathyroidectomy (PTX) despite undergoing short-term renal replacement therapy (RRT). Because the characteristics of such cases have never been discussed, we aimed to elucidate the pathophysiology of severe SHPT after short-term RRT by retrospectively analyzing clinical data. METHODS: A total of 1013 patients with severe SHPT underwent PTX between January 2007 and April 2016 at Nagoya Daini Red Cross Hospital. Of these patients, 570 underwent RRT for >/=10 years (long RRT group) and 23 for </=1 year (short RRT group). We retrospectively investigated and compared patient characteristics, preoperative data, subjective symptoms, and bone lesion incidence between the two groups. RESULTS: A higher proportion of subjects with congenital or hereditary diseases as primary disease for chronic kidney disease (CKD) (21.7% (5/23) vs. 6.3% (36/570); P = 0.016) and longer predialysis period (21.2 +/- 14.0 vs. 10.1 +/- 9.2 years; P < 0.001) were observed in the short RRT group than in the long RRT group. Furthermore, lower serum calcium and phosphate levels, heavier parathyroid glands, and severe bone lesions were observed in the short RRT group than in the long RRT group. CONCLUSION: Severe SHPT after short-term RRT appeared to occur because of long-term CKD before initiating RRT. Therefore, treating mineral and bone disorders during the early CKD stage might prevent severe SHPT development before initiating RRT.
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http://dx.doi.org/10.1007/s00268-017-4164-7

Impact of autofluorescence-based identification of parathyroids during total thyroidectomy on postoperative hypocalcemia: a before and after controlled study.
Surgery, 163(1):23-30.
F. Benmiloud, S. Rebaudet, A. Varoquaux, G. Penaranda, M. Bannier and A. Denizot. 2018.
BACKGROUND: The clinical impact of intraoperative autofluorescence-based identification of parathyroids using a near-infrared camera remains unknown. METHODS: In a before and after controlled study, we compared all patients who underwent total thyroidectomy by the same surgeon during Period 1 (January 2015 to January 2016) without near-infrared (near-infrared- group) and those operated on during Period 2 (February 2016 to September 2016) using a near-infrared camera (near-infrared+ group). In parallel, we also compared all patients who underwent surgery without near-infrared during those same periods by another surgeon in the same unit (control groups). Main outcomes included postoperative hypocalcemia, parathyroid identification, autotransplantation, and inadvertent resection. RESULTS: The near-infrared+ group displayed significantly lower postoperative hypocalcemia rates (5.2%) than the near-infrared- group (20.9%; P < .001). Compared with the near-infrared- patients, the near-infrared+ group exhibited an increased mean number of identified parathyroids and reduced parathyroid autotransplantation rates, although no difference was observed in inadvertent resection rates. Parathyroids were identified via near-infrared before they were visualized by the surgeon in 68% patients. In the control groups, parathyroid identification improved significantly from Period 1 to Period 2, although autotransplantation, inadvertent resection and postoperative hypocalcemia rates did not differ. CONCLUSION: Near-infrared use during total thyroidectomy significantly reduced postoperative hypocalcemia, improved parathyroid identification and reduced their autotransplantation rate.
PubMed-ID: 29122325
http://dx.doi.org/10.1016/j.surg.2017.06.022

Persistent hyperparathyroidism as a risk factor for long-term graft failure: the need to discuss indication for parathyroidectomy.
Surgery, 163(5):1144-50.
M. Araujo, J. A. M. Ramalho, R. M. Elias, V. Jorgetti, W. Nahas, M. Custodio, R. M. A. Moyses and E. David-Neto. 2018.
BACKGROUND: Although a successful kidney transplant (KTx) improves most of the mineral and bone disorders (MBD) produced by chronic kidney disease (CKD), hyperparathyroidism may persist (pHPT). Current guidelines recommend parathyroidectomy if serum parathormone is persistently elevated 1 year after KTx, because pHPT has been recently associated with poor graft outcomes. However, whether patients with pHPT and adequate renal function are at risk for long-term graft failure is unknown. METHODS: Longitudinal follow-up of 911 adults submitted to KTx between January 2005 and December 2014, with estimated glomerular filtration rate (eGFR) >/= 30 mL/min 1 year after surgery. Clinical and laboratory data were collected from electronic database. Graft failure was defined as return to dialysis. RESULTS: Overall, 62% of the patients were classified as having pHPT 1 year after KTx. After a mean follow-up time of 47 months, there were 59 graft failures (49 in pHPT and 10 in non-pHPT group, P = .003). At last follow-up, death-censored graft survival was lower in the

pHPT group (P = .009), even after adjustment for age at KTx, donor age, donor type, acute rejection, parathyroidectomy, and eGFR at 1 year after transplantation (odds ratio [OR] 1.99; 1.004-3.971; P = .049). A PTH of 150 pg/mL at 6 months was the best cutoff to predict pHPT at 1 year (specificity = 92.1%). CONCLUSION: Having pHPT after a successful KTx increases the long-term risk of death-censored graft failure. This result highlights the need for better recognition and management of CKD-MBD before and during the first year after KTx, and opens a discussion on the more appropriate timing to perform parathyroidectomy.
PubMed-ID: 29331397
http://dx.doi.org/10.1016/j.surg.2017.12.010

Primary hyperparathyroidism: Dynamic postoperative metabolic changes.
Clin Endocrinol (Oxf), 88(1):129-38.
R. M. Kaderli, P. Riss, A. Geroldinger, A. Selberherr, C. Scheuba and B. Niederle. 2018.
OBJECTIVE: Little is known about the natural changes in parathyroid function after successful parathyroid surgery for primary hyperparathyroidism. The association of intact parathyroid hormone (iPTH) and calcium (Ca) with "temporary hypoparathyroidism" and "hungry bone syndrome" (HBS) was evaluated. DESIGN: Potential risk factors for temporary hypoparathyroidism and HBS were evaluated by taking blood samples before surgery, intra-operatively, at postoperative day (POD) 1, at POD 5 to 7, in postoperative week (POW) 8 and in postoperative month (POM) 6. PATIENTS: Of 425 patients, 43 (10.1%) had temporary hypoparathyroidism and 36 (8.5%) had HBS. MEASUREMENTS: The discriminative ability of iPTH and Ca on POD 1 for temporary hypoparathyroidism and HBS. RESULTS: Intact parathyroid hormone (IPTH) on POD 1 showed the highest discriminative ability for temporary hypoparathyroidism (C-index = 0.952), but not for HBS. IPTH was helpful in diagnosing HBS between POD 5 and 7 (C-index = 0.708). Extending the model by including Ca resulted in little improvement of the discriminative ability for temporary hypoparathyroidism (C-index = 0.964) and a decreased discriminative ability for HBS (C-index = 0.705). Normal parathyroid metabolism was documented in 139 (32.7%) patients on POD 1 and in 423 (99.5%) 6 months postoperatively, while 2 (0.5%) patients had persistent hyperparathyroidism, one diagnosed between POD 5 and 7 and another at POW 8. No patients suffered from permanent hypoparathyroidism. CONCLUSIONS: The necessity for Ca and vitamin D3 substitution cannot be predicted with certainty before POD 5 to 7 without serial laboratory measurements. Based on the results, a routine 8-week course of Ca and vitamin D3 treatment seems reasonable and its necessity should be evaluated in a follow-up study.
PubMed-ID: 28906021
http://dx.doi.org/10.1111/cen.13476

Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism.
Br J Surg, 105(3):223-9.
S. Bannani, N. Christou, C. Guerin, A. Hamy, F. Sebag, M. Mathonnet, P. Guillot, C. Caillard, C. Blanchard and E. Mirallie. 2018.
BACKGROUND: Normocalcaemic primary hyperparathyroidism (NcPHPT) is a new clinical entity being diagnosed increasingly among patients with mild primary hyperparathyroidism (PHPT). The aim of this study was to evaluate quality of life and non-specific symptoms before and after parathyroidectomy in patients with NcPHPT compared with those with hypercalcaemic mild PHPT (Hc-m-PHPT). METHODS: This was a prospective multicentre study of patients with mild PHPT from four university hospitals. Patients were evaluated before operation, and 3, 6 and 12 months after surgery for quality of life using the SF-36-v2(R) questionnaire, as well as for 25 non-specific symptoms. RESULTS: Before operation, the only statistically significant difference between the NcPHPT and Hc-m-PHPT groups was in the mean(s.d.) blood calcium level (2.54 versus 2.73 mmol; P < 0.001). At 1 year after surgery, the blood calcium level had improved significantly in both groups, with no significant difference between them. Quality of life improved significantly in each group compared with its preoperative score, with regard to the physical component summary (P = 0.040 and P = 0.016 respectively), whereas the mental component summary improved significantly in the Hc-m-PHPT group only (P = 0.043). Only two non-specific symptoms improved significantly in the NcPHPT group compared with nine in the Hc-m-PHPT group. CONCLUSION: Parathyroidectomy mildly improves quality of life and some non-specific symptoms in patients with NcPHPT.
PubMed-ID: 29405278
http://dx.doi.org/10.1002/bjs.10739

The impact of vitamin D status on hungry bone syndrome after surgery for primary hyperparathyroidism.
Eur J Endocrinol, 178(1):1-9.
R. M. Kaderli, P. Riss, D. Dunkler, P. Pietschmann, A. Selberherr, C. Scheuba and B. Niederle. 2018.
OBJECTIVE: Prolonged hypocalcemia but normal intact parathyroid hormone (iPTH) levels after surgery for primary hyperparathyroidism (PHPT) are referred to as 'hungry bone syndrome' (HBS). The aim was to evaluate preoperative risk factors for HBS with a focus on the impact of 25-hydroxyvitamin D (25(OH)D) deficiency. DESIGN: Patients having undergone initial successful surgery for sporadic PHPT within 6 years were considered for retrospective analysis. METHODS: A total of 385 patients were evaluated, of whom 33 (8.6%) developed HBS influencing negatively the postoperative bone metabolism. All patients underwent biochemical evaluations two days before parathyroid surgery and were followed biochemically on a daily basis in the first postoperative week and thereafter at 8 weeks and 6 months. CONCLUSIONS: No relationship was established between preoperative 25(OH)D deficiency and HBS. The only significant risk factor for HBS in multivariable analysis was high levels of preoperative iPTH. As HBS therefore cannot be predicted preoperatively, we recommend a consistent postoperative calcium and vitamin D supplementation to improve the bone metabolism.
PubMed-ID: 28877925
http://dx.doi.org/10.1530/EJE-17-0416

Predictors of multiglandular disease in primary hyperparathyroidism.
Langenbecks Arch Surg, 403(1):103-9.
M. Thier, S. Daudi, A. Bergenfelz and M. Almquist. 2018.
BACKGROUND: Primary hyperparathyroidism (pHPT) is caused by single- or multiglandular disease (MGD). Patients with MGD have an increased risk of complications at surgery and for persistence and recurrence after surgery. The study evaluated whether preoperative clinical and biochemical characteristics could predict MGD in patients with pHPT. METHODS: We retrospectively evaluated patients operated 1989-2013 for first-time, non-hereditary pHPT. MGD was defined in patients with more than one pathological gland excised at surgery or with persistent hypercalcemia after the excision of a single pathological parathyroid gland, confirmed by histopathology. Clinical and biochemical variables were compared in patients with single- and multiglandular disease. Logistic regression was used to identify variables predicting MGD, yielding odds ratios (OR) with 95% confidence intervals (CI). RESULTS: There were 707 patients, of which 79 (11%) had MGD. Patients with MGD were more likely to have negative sestamibi scintigraphy than patients with single-gland disease, 15 of 49 (31%) vs. 70 of 402 (17%; $p = 0.03$), to suffer from diabetes (12 of 74, 16%) vs. 45 out of 626 patients (7.2%; $p < 0.01$) and had lower preoperative levels of urinary calcium (3.80 vs. 4.44 mmol/L; $p = 0.04$). Multivariable analysis identified negative scintigraphy (OR 2.42; 95% CI 1.18 to 4.79), diabetes (OR 2.75; 95% CI 1.31 to 4.97) and elevated levels of osteocalcin (OR 3.79, 95% CI: 1.75 to 8.21) as predictors of MGD. CONCLUSION: Negative sestamibi scintigraphy, diabetes and elevated osteocalcin levels were predictors of MGD.
PubMed-ID: 29294178
http://dx.doi.org/10.1007/s00423-017-1647-9

Serum parathyroid hormone and alkaline phosphatase as predictors of calcium requirements after total parathyroidectomy for hypocalcemia in secondary hyperparathyroidism.
Head Neck, 40(2):324-9.
P. Ge, S. Liu, X. Sheng, S. Li, M. Xu, J. Jiang and S. Chen. 2018.
BACKGROUND: To prevent hypocalcemia, this study examined the efficiency of a calcium supplement formula guided by predicted calcium requirement in patients with renal failure after parathyroidectomy with autotransplantation. METHODS: In the first phase, a protocol was followed whereby intravenous calcium gluconate was repeatedly titrated based on serum calcium levels in 22 patients with parathyroidectomy with autotransplantation. In the second phase, the first equation protocol was applied in 74 patients with parathyroidectomy with autotransplantation and revised. RESULTS: There is a significant correlation between the postoperative amount of calcium requirement and preoperative serum alkaline phosphatase level ($r = 0.442$; $P < .001$) and parathyroid hormone level (PTH; $r = 0.889$; $P < .001$). For prediction of insufficient calcium supplement, the cutoff point of PTH and alkaline phosphatase level values were calculated by receiver operating characteristic (ROC) curve analysis and modified equations were developed by regression analysis. CONCLUSION: The preoperative PTH and alkaline phosphatase levels can predict postoperative calcium requirements, such that equations of calcium supplement allow the management of hypocalcemia efficiently in patients on dialysis after parathyroidectomy with autotransplantation.
PubMed-ID: 28963816
http://dx.doi.org/10.1002/hed.24965

Parathyroid hormone: Data mining for age-related reference intervals in adults.
Clin Endocrinol (Oxf), 88(2):311-7.
C. L. Farrell, L. Nguyen and A. C. Carter. 2018.
OBJECTIVE: Age-related changes in parathyroid hormone (PTH) have been previously documented in adults. However, because of the limitations of traditional approaches to establishing reference intervals, age-related reference intervals have not been defined. We sought to use a data mining approach to derive age-related PTH reference intervals. DESIGN AND PARTICIPANTS: Results from patients undergoing PTH testing over a 4-year period were extracted from the database of a private pathology laboratory in New South Wales, Australia. Patients were included in the study if they were 18 years or older and had simultaneous determination of PTH, serum calcium, estimated glomerular filtration rate and 25-hydroxyvitamin D (25-OHD). Patients with abnormalities of serum calcium or renal function were excluded. MEASUREMENTS: Bhattacharya analysis of log-transformed data was used to derive age-related PTH reference intervals across adulthood. RESULTS: Results were available for 33 652 subjects. Among patients with optimal 25-OHD status, older age was associated with higher PTH concentrations. Age-related reference intervals were derived and showed a 63% increase in the upper and lower reference limits between the youngest (18-29 years of age) and the oldest (80 years of age or older) age partitions. The appropriateness of using a single reference interval for patients of all ages was evaluated against objective criteria and was found to be unsatisfactory. CONCLUSIONS: Data mining was demonstrated to be a useful tool for establishing age-related PTH reference intervals. The technique demonstrated that increasing age is associated with higher PTH concentrations and that age-related reference intervals are important for accurate result interpretation.
PubMed-ID: 28949026
http://dx.doi.org/10.1111/cen.13486

Stratifying the Risk of Developing Clinical Hypocalcemia after Thyroidectomy with Parathyroid Hormone.
Otolaryngol Head Neck Surg, 158(1):76-82.
A. Castro, L. Del Rio and J. Gavilan. 2018.
Objective To identify the risk of clinical hypocalcemia in the first hours after thyroidectomy. Study Design Prospective observational study. Setting Single-institution tertiary hospital in Madrid, Spain. Subjects and Methods A total of 123 patients who underwent total or completion thyroidectomy between June 2010 and March 2012 were included. Pre- and postoperative intact parathyroid hormone (iPTH) levels were obtained. Patients remain hospitalized a minimum of 48 hours until blood calcium stabilized. Calcium and/or vitamin D supplements were prescribed only when signs or symptoms of hypocalcemia developed. Receiver operating characteristic curve analysis was employed to evaluate the postoperative iPTH level and the pre- to postoperative decrease in iPTH levels. Two cutoff values were determined to stratify the risk of developing clinical hypocalcemia into 3 groups. Results The areas under the receiver operating characteristic curve were 0.991 for the postoperative iPTH and 0.998 for the decrease in iPTH. An iPTH decrease of 80% had 100% sensitivity to detect patients who developed clinical hypocalcemia, while a postoperative iPTH <3 pg/mL had 100% specificity. Thus, patients with an iPTH decrease </=80% are at a very low risk of clinical hypocalcemia, and patients with a postoperative iPTH <3 pg/mL are at a very high risk. Patients with an iPTH decrease >80% and a postoperative iPTH >/=3 pg/mL are at intermediate risk. No significant correlation was found between the time when the sample was obtained and iPTH values. Conclusion This study stablishes a very accurate test to stratify the risk of clinical postthyroidectomy hypocalcemia based on pre- and postoperative iPTH levels.
PubMed-ID: 28895449
http://dx.doi.org/10.1177/0194599817730334

Effect of general anesthesia and intubation on parathyroid levels in normal patients and those with hyperparathyroidism.
Head Neck, 40(3):555-60.
U. Cinamon, D. Gavish, S. Ovnat Tamir, A. Goldfarb and T. Ezri. 2018.
BACKGROUND: Induction of general anesthesia and endotracheal intubation may precipitate parathyroid hormone (PTH) elevation in patients with primary hyperparathyroidism (HPT). The purposes of this study were to revisit this observation and to study its impact in healthy patients. METHODS: Patients with primary HPT who underwent parathyroidectomy were retrospectively studied. The PTH was sampled and compared: before, immediately after general anesthesia and endotracheal intubation, and 15 minutes after parathyroidectomy. Healthy adults who underwent elective operations were prospectively studied. The PTH was sampled before general anesthesia and endotracheal intubation, immediately after, and 15 minutes later. RESULTS: Thirty-one patients, aged 28-89 years (mean 60.1 +/- 13 years), were retrospectively studied. The PTH was significantly elevated after general anesthesia and endotracheal intubation (P = .014). Fifty patients, aged 21-86 years (mean 54 +/- 15 years), were prospectively studied. The PTH elevation after general anesthesia and endotracheal

intubation was not significant. CONCLUSION: General anesthesia and endotracheal intubation causes an immediate, steep, and significant PTH elevation in patients with primary HPT but only a minor change in healthy adults. The difference may be attributed to an impaired adrenergic response in patients with primary HPT.
PubMed-ID: 29130559
http://dx.doi.org/10.1002/hed.25002

Optimal Use of Preoperative Imaging in Primary Hyperparathyroidism.
JAMA Surg, 153(4):393-4.
E. Collins, S. Vaidyanathan and A. Scarsbrook. 2018.
PubMed-ID: 29322170
http://dx.doi.org/10.1001/jamasurg.2017.5563

4D-CT is Superior to Ultrasound and Sestamibi for Localizing Recurrent Parathyroid Disease.
Ann Surg Oncol, 25(5):1403-9.
M. Hamidi, M. Sullivan, G. Hunter, L. Hamberg, N. L. Cho, A. A. Gawande, G. M. Doherty, F. D. Moore, Jr. and M. A. Nehs. 2018.
BACKGROUND: Recurrent primary hyperparathyroidism (PHPT) presents a diagnostic challenge in localizing a hyperfunctioning gland. Although several imaging modalities are available for preoperative localization, 4D-CT is increasingly utilized for its ability to locate both smaller and previously unlocalized lesions. Currently, there is a paucity of data evaluating the utility of 4D-CT in the reoperative setting compared with ultrasound (US) and sestamibi. We aimed to determine the sensitivity of 4D-CT in localizing parathyroid adenomas in recurrent or persistent PHPT. METHODS: We performed a retrospective review of prospectively collected data from a tertiary-care hospital, and identified 58 patients who received preoperative 4D-CT with US and/or sestamibi between May 2008 and March 2016. Data regarding the size, shape, and number of parathyroid lesions were collected for each patient. RESULTS: A total of 62 lesions were identified intraoperatively among the 58 patients (6 with multigland disease) included in this investigation. 4D-CT missed 13 lesions identified intraoperatively, compared with 32 and 22 lesions missed by US and sestamibi, respectively. Sensitivity for correct lateralization of culprit lesions was 77.4% for 4D-CT, 38.5% for US, and 46% for sestamibi. 4D-CT was superior in lateralizing adenomas (49/62) compared with US (20/52; $p < 0.001$) and sestamibi (18/47; $p < 0.001$). The overall cure rate (6-month postoperative calcium < 10.7 mg/dL) was 89.7%. All patients with lesions correctly lateralized by 4D-CT were cured at 6 months. CONCLUSION: 4D-CT localized parathyroid adenomas with higher sensitivity among patients with recurrent or persistent PHPT compared with sestamibi or US-based imaging.
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http://dx.doi.org/10.1245/s10434-018-6367-z

Detection of Parathyroid Autofluorescence Using Near-Infrared Imaging: A Multicenter Analysis of Concordance Between Different Surgeons.
Ann Surg Oncol, 25(4):957-62.
B. Kahramangil, F. Dip, F. Benmiloud, J. Falco, M. de La Fuente, S. Verna, R. Rosenthal and E. Berber. 2018.
BACKGROUND: Parathyroid glands (PGs) exhibit autofluorescence (AF) when excited by near-infrared laser. This multicenter study aims to analyze how this imaging could facilitate the detection of PGs during thyroidectomy and parathyroidectomy procedures. METHODS: This was a retrospective Institutional Review Board-approved analysis of prospectively collected data at three centers. Near-infrared fluorescence imaging (NIFI) was used to detect AF from PGs during thyroidectomy and parathyroidectomy procedures. Logistic regression analysis was performed to assess the utility of NIFI to identify PGs and concordance at these centers. RESULTS: Overall, 210 patients underwent total thyroidectomy (n = 95), thyroid lobectomy (n = 41), and parathyroidectomy (n = 74) (n = 70 per center). Using NIFI, AF was detected from 98% of visually identified PGs. Upon initial exploration, 46% of PGs were not visible to the naked eye due to coverage by soft tissue, but AF from these glands could be detected by NIFI without any further dissection. Overall, a median of one PG per patient was detected by NIFI in this fashion before being identified visually (p = nonsignificant between centers). On logistic regression, smaller PGs were more likely to be missed visually, but localized by AF on NIFI (odds ratio with increasing size, 0.91; p = 0.02). CONCLUSIONS: In our experience, NIFI facilitated PG identification by detecting their AF, before conventional recognition by the surgeon, in 37-67% of the time. Despite the variability in this rate across centers, there was a concordance in detecting AF from 97 to 99% of the PGs using NIFI. We suggest the incorporation of AF on NIFI alongside conventional visual cues to aid identification of PGs during neck operations.
PubMed-ID: 29411199
http://dx.doi.org/10.1245/s10434-018-6364-2

Four-Dimensional Computed Tomography: Clinical Impact for Patients with Primary Hyperparathyroidism.
Ann Surg Oncol, 25(1):17.
N. Perrier. 2018.
PubMed-ID: 29124484
http://dx.doi.org/10.1245/s10434-017-6117-7

Four-Dimensional Computed Tomography: Clinical Impact for Patients with Primary Hyperparathyroidism.
Ann Surg Oncol, 25(1):117-21.
Y. Tian, S. T. Tanny, P. Einsiedel, M. Lichtenstein, D. L. Stella, P. M. Phal and J. A. Miller. 2018.
BACKGROUND: In recent years, four-dimensional computed tomography (4DCT) has emerged as a new localization study for primary hyperparathyroidism (pHPT). OBJECTIVE: We aimed to assess the added value of 4DCT in our institution in the first 4 years of use. METHODS: A retrospective cohort study was conducted from February 2004 to June 2015. Since 2011, patients over 50 years of age without concordant sestamibi-SPECT (SeS) and ultrasound (US) findings underwent 4DCT. Imaging results, surgical findings, histopathology, and postoperative biochemistry were collected. RESULTS: A total of 536 parathyroid operations in 510 patients were performed during the study period. The overall cure rate was 99.2% after reoperation in some patients, and the overall sensitivity for SeS was 76.0%, and 74.8% for US. Since 2011, 100 patients without concordant SeS/US findings have undergone 4DCT, with a sensitivity of 72.9%. This is in comparison to the sensitivities for SeS (48.3%) and US (52.3%). 4DCT was more sensitive in patients with persistent/recurrent disease (60.0% compared with SeS 43.8% and US 36.4%) and patients with multigland disease (67.4% compared with SeS 40.9% and US 42.1%). Comparison between outcomes in the pre- versus post-CT era demonstrated no difference in the initial cure rate (95.4 vs. 95.9%, p = 0.85) or the rate of minimally invasive parathyroidectomies (74.5 vs. 79.9%, p = 0.22). CONCLUSION: Parathyroid 4DCT can aid surgical planning in cases without concordant SeS/US findings; however, the introduction of 4DCT as a second-line test did not change our overall cure rate or rate of minimally invasive parathyroidectomy. The role of 4DCT as the primary localization study for pHPT merits further investigation.
PubMed-ID: 29063298
http://dx.doi.org/10.1245/s10434-017-6115-9

Primary hyperparathyroidism.
Nat Rev Endocrinol, 14(2):115-25.
M. D. Walker and S. J. Silverberg. 2018.
In this Review, we describe the pathogenesis, diagnosis and management of primary hyperparathyroidism (PHPT), with a focus on recent advances in the field. PHPT is a common endocrine disorder that is characterized by hypercalcaemia and elevated or inappropriately normal serum levels of parathyroid hormone. Most often, the presentation of PHPT is asymptomatic in regions of the world where serum levels of calcium are routinely measured. In addition to mild hypercalcaemia, PHPT can manifest with osteoporosis and hypercalciuria as well as with vertebral fractures and nephrolithiasis, both of which can be asymptomatic. Other clinical forms of PHPT, such as classical disease and normocalcaemic PHPT, are less common. Parathyroidectomy, the only curative treatment for PHPT, is recommended in patients with symptoms and those with asymptomatic disease who are at risk of progression or have subclinical evidence of end-organ sequelae. Parathyroidectomy results in an increase in BMD and a reduction in nephrolithiasis. Various medical therapies can increase BMD or reduce serum levels of calcium, but no single drug can do both. More data are needed regarding the neuropsychological manifestations of PHPT and the pathogenetic mechanisms leading to sporadic PHPT, as well as on risk factors for complications of the disorder. Future work that advances our knowledge in these areas will improve the management of the disorder.
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http://dx.doi.org/10.1038/nrendo.2017.104

Novel method to save the parathyroid gland during thyroidectomy: Subcapsular saline injection.
Head Neck, 40(4):801-7.
J. Y. Choi, H. W. Yu, I. E. Bae, J. K. Kim, C. Y. Seong, J. W. Yi, Y. J. Chai, S. J. Kim and K. E. Lee. 2018.
BACKGROUND: Saving the parathyroid gland during thyroidectomy remains challenging. Subcapsular saline injection (SCASI) was developed in February 2015. Its ability to spare the parathyroid gland was assessed. METHODS: All consecutive patients who underwent total thyroidectomy with or without neck lymph node dissection in 2013-2015 were included in this retrospective cohort study. Patients were divided into the SCASI and non-SCASI groups. Serum parathyroid hormone (PTH) levels were measured on day 1 and 6 months after

surgery. Transient and permanent hypoparathyroidism were defined as day 1 and 6 month PTH < 10.0 and <15.0 pg/mL, respectively. RESULTS: The groups (both had 98 patients each) did not differ in demographics, tumor size, operation extent, pathology, thyroiditis rate, and incidental parathyroid gland excision rate. Compared with non-SCASI patients, patients who underwent the SCASI method exhibited transient hypoparathyroidism (35.7% vs 19.4%, P < .001) and permanent hypoparathyroidism (4.1% vs 0%, P = .043) significantly less frequently. CONCLUSION: The procedure of SCASI effectively spared the parathyroid gland during thyroidectomy.
PubMed-ID: 29356201
http://dx.doi.org/10.1002/hed.25068

Adrenals

Meta-Analyses

Quality of life in patients with adrenal disease: A systematic review.
Clin Endocrinol (Oxf),
W. Ho and M. Druce. 2018.
BACKGROUND: Evaluating the patient with adrenal disease is challenging due to the lack of precise clinical and biochemical parameters for disease control. Quality of life (QOL) evaluation aims to measure the patient's subjective experience. OBJECTIVE: To describe how QOL is defined and measured in adrenal disease, critically appraise the use of QOL tools in published literature, discuss the implications of these findings and provide direction for further research in this field. MATERIALS AND METHODS: We searched the Cochrane library, EMBASE, Google Scholar, PsycINFO, PubMed, Web of Science databases to identify only primary studies where self-reported QOL was measured as a parameter in adults with confirmed adrenal disease, and results presented in English. Key data were independently extracted from each study and adherence to reporting guidelines evaluated. RESULTS: A total of 117 studies involving 13 717 subjects were included. The vast majority of studies did not define QOL. The most common approach was to combine generic and domain-specific tools, although disease-specific tools are increasingly being used. Adherence to reporting guidelines was variable. A narrative synthesis of the findings was performed. CONCLUSION: We present the first systematic review of QOL in adrenal disease. Quality of life is reduced in patients with adrenal disease, irrespective of adrenal hyperfunction or hypofunction. Quality of life improved with therapy but was not completely reversed despite biochemical remission. Authors should adhere to consistent reporting practices which are interpretable by clinicians. Further research is required to explain the mechanisms driving impaired QOL and value of QOL evaluations in the clinical context.
PubMed-ID: 29672878
http://dx.doi.org/10.1111/cen.13719

Primary Adrenal Insufficiency: Managing Mineralocorticoid Replacement Therapy.
J Clin Endocrinol Metab, 103(2):376-87.
D. Esposito, D. Pasquali and G. Johannsson. 2018.
Context: Mineralocorticoid (MC) replacement therapy in patients with primary adrenal insufficiency (PAI) was introduced more than 60 years ago. Still, there are limited data on how MC substitution should be optimized, because MC dosing regimens have only been systematically investigated in a few studies. We review the management of current standard MC replacement therapy in PAI and its plausible impact on outcome. Design: Using PubMed, we conducted a systematic review of the literature from 1939 to 2017, with the following keywords: adrenal insufficiency, MC deficiency, aldosterone, cardiovascular disease, hypertension, and heart failure. Results: The current standard treatment consists of fludrocortisone (FC) given once daily in the morning, aiming at normotension, normokalemia, and plasma renin activity in the upper normal range. Available data suggest that patients with PAI may be underreplaced with FC as symptoms and signs indicating chronic MC underreplacement, such as salt craving and postural dizziness persist, in many treated patients with PAI. Data acquired from large registry-based studies show that glucocorticoid doses for replacement in PAI are higher than those estimated from endogenous production. Glucocorticoid overreplacement may reduce the need of MC replacement but may also be a consequence of inadequate MC replacement. Conclusions: The commonly used MC replacement in PAI may not be adequate in some patients. Insufficient MC substitution may be responsible for poor cardiometabolic outcome and the failure to restore well-being adequately in patients with PAI. Well-designed studies oriented at optimizing MC replacement therapy are urgently needed.
PubMed-ID: 29156052
http://dx.doi.org/10.1210/jc.2017-01928

Randomized controlled trials

Randomized trial of low versus high carbon dioxide insufflation pressures in posterior retroperitoneoscopic adrenalectomy.
Surgery, 163(5):1128-33.
S. Fraser, O. Norlen, K. Bender, J. Davidson, S. Bajenov, D. Fahey, S. Li, S. Sidhu and M. Sywak. 2018.
BACKGROUND: Posterior retroperitoneoscopic adrenalectomy has gained widespread acceptance for the removal of benign adrenal tumors. Higher insufflation pressures using carbon dioxide (CO2) are required, although the ideal starting pressure is unclear. This prospective, randomized, single-blinded, study aims to compare physiologic differences with 2 different CO2 insufflation pressures during posterior retroperitoneoscopic adrenalectomy. METHODS: Participants were randomly assigned to a starting insufflation pressure of 20 mm Hg (low pressure) or 25 mm Hg (high pressure). The primary outcome measure was partial pressure of arterial CO2 at 60 minutes. Secondary outcomes included end-tidal CO2, arterial pH, blood pressure, and peak airway pressure. Breaches of protocol to change insufflation pressure were permitted if required and were recorded. RESULTS: A prospective randomized trial including 31 patients (low pressure: n = 16; high pressure: n = 15) was undertaken. At 60 minutes, the high pressure group had greater mean partial pressure of arterial CO2 (64 vs 50 mm Hg, P = .003) and end-tidal CO2 (54 vs 45 mm Hg, P = .008) and a lesser pH (7.21 vs 7.29, P = .0005). There were no significant differences in base excess, peak airway pressure, operative time, or duration of hospital stay. Clinically indicated protocol breaches were more common in the low pressure than the high pressure group (8 vs 3, P = .03). CONCLUSION: In posterior retroperitoneoscopic adrenalectomy, greater insufflation pressures are associated with greater partial pressure of arterial CO2 and end-tidal CO2 and lesser pH at 60 minutes, be significant. Commencing with lesser CO2 insufflation pressures decreases intraoperative acidosis.
PubMed-ID: 29395236
http://dx.doi.org/10.1016/j.surg.2017.10.073

Quality of Life in Primary Aldosteronism: A Comparative Effectiveness Study of Adrenalectomy and Medical Treatment.
J Clin Endocrinol Metab, 103(1):16-24.
M. Velema, T. Dekkers, A. Hermus, H. Timmers, J. Lenders, H. Groenewoud, L. Schultze Kool, J. Langenhuijsen, A. Prejbisz, G. J. van der Wilt and J. Deinum. 2018.
Context: In primary aldosteronism (PA), two subtypes are distinguished: aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH). In general, these are treated by adrenalectomy (ADX) and mineralocorticoid receptor antagonists (MRA), respectively. Objective: To compare the effects of surgical treatment and medical treatment on quality of life (QoL). Design: Post hoc comparative effectiveness study within the Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial. Setting: Twelve Dutch hospitals and one Polish hospital. Participants: Patients with PA (n = 184). Interventions: ADX or MRAs. Main Outcome Measures: At baseline and 6-month and 1-year follow-up, we assessed QoL by two validated questionnaires: RAND 36-Item Health Survey 1.0 (RAND SF-36) and European Quality of Life-5 Dimensions (EQ-5D). Results: At baseline, seven of eight RAND SF-36 subscales and both summary scores, as well as three of five EQ-5D dimensions and the visual analog scale, were lower in patients with PA compared with the general population, especially in women. The beneficial effects of ADX were larger than for MRAs for seven RAND SF-36 subscales, both summary scores, and health change. For the EQ-5D, we detected a difference in favor of ADX in two dimensions and the visual analog scale. Most differences in QoL between both treatments exceeded the minimally clinically important difference. After 1 year, almost all QoL measures had normalized for adrenalectomized patients. For patients on medical treatment, most QoL measures had improved but not all to the level of the general population. Conclusion: Both treatments improve QoL in PA, underscoring the importance of identifying these patients. QoL improved more after ADX for suspected APA than after initiation of medical treatment for suspected BAH.
PubMed-ID: 29099925
http://dx.doi.org/10.1210/jc.2017-01442

Consensus Statements/Guidelines

- None -

Other Articles

Unenhanced CT imaging is highly sensitive to exclude pheochromocytoma: a multicenter study.
Eur J Endocrinol, 178(5):431-7.
E. Buitenwerf, T. Korteweg, A. Visser, C. Haag, R. A. Feelders, H. Timmers, L. Canu, H. R. Haak, P. Bisschop, E. M. W. Eekhoff, E. P. M. Corssmit, N. C. Krak, E. Rasenberg, J. van den Bergh, J. Stoker, M. J. W. Greuter, R. P. F. Dullaart, T. P. Links and M. N. Kerstens. 2018.
BACKGROUND: A substantial proportion of all pheochromocytomas is currently detected during the evaluation of an adrenal incidentaloma. Recently, it has been suggested that biochemical testing to rule out pheochromocytoma is unnecessary in case of an adrenal incidentaloma with an unenhanced attenuation value </=10 Hounsfield Units (HU) at computed tomography (CT). OBJECTIVES: We aimed to determine the sensitivity of the 10 HU threshold value to exclude a pheochromocytoma. METHODS: Retrospective multicenter study with systematic reassessment of preoperative unenhanced CT scans performed in patients in whom a histopathologically proven pheochromocytoma had been diagnosed. Unenhanced attenuation values were determined independently by two experienced radiologists. Sensitivity of the 10 HU threshold was calculated, and interobserver consistency was assessed using the intraclass correlation coefficient (ICC). RESULTS: 214 patients were identified harboring a total number of 222 pheochromocytomas. Maximum tumor diameter was 51 (39-74) mm. The mean attenuation value within the region of interest was 36 +/- 10 HU. Only one pheochromocytoma demonstrated an attenuation value </=10 HU, resulting in a sensitivity of 99.6% (95% CI: 97.5-99.9). ICC was 0.81 (95% CI: 0.75-0.86) with a standard error of measurement of 7.3 HU between observers. CONCLUSION: The likelihood of a pheochromocytoma with an unenhanced attenuation value </=10 HU on CT is very low. The interobserver consistency in attenuation measurement is excellent. Our study supports the recommendation that in patients with an adrenal incidentaloma biochemical testing for ruling out pheochromocytoma is only indicated in adrenal tumors with an unenhanced attenuation value >10 HU.
PubMed-ID: 29467230
http://dx.doi.org/10.1530/EJE-18-0006

Minimally Invasive Surgery (MIS) in Children and Adolescents with Pheochromocytomas and Retroperitoneal Paragangliomas: Experiences in 42 Patients.
World J Surg, 42(4):1024-30.
M. K. Walz, L. D. Iova, J. Deimel, H. P. H. Neumann, B. Bausch, S. Zschiedrich, H. Groeben and P. F. Alesina. 2018.
BACKGROUND: Pheochromocytomas (PH) and paragangliomas (PGL) are rare tumours in children accounting for about 1% of the paediatric hypertension. While minimally invasive surgical techniques are well established in adult patients with PH, the experience in children is extremely limited. To the best of our knowledge, we herewith present the largest series of young patients operated on chromaffin tumours by minimally invasive access. MATERIALS: In the setting of a prospective study (1/2001-12/2016), 42 consecutive children and adolescents (33 m, 9 f) were operated on. Thirty-seven patients (88%) suffered from inherited diseases. Twenty-six patients had PH, 11 presented retroperitoneal PGL, and five patients suffered from both. Altogether, 70 tumours (mean size 2.7 cm) were removed (45 PH, 25 PGL). All operations were performed by a minimally invasive access (retroperitoneoscopic, laparoscopic, extraperitoneal). Partial adrenalectomy was the preferred procedure for PH (31 out of 39 patients). Twenty patients received alpha-receptor blockade preoperatively. RESULTS: One patient died after induction of anaesthesia due to cardiac arrest. All other complications were minor. Conversion to open surgery was necessary in two cases with PGL. Median operating time for unilateral PH was 55 min, in bilateral cases 125, 143 min in PGs, and 180 min in combined cases. Median blood loss was 20 ml (range 0-1000). Blood transfusion was necessary in two cases. Intraoperative, systolic peak pressure was 170 +/- 39 mmHg with alpha-receptor blockade and 191 +/- 33 mmHg without alpha-receptor blockade (p = 0.41). The median post-operative hospital stay was 3 days. After a mean follow-up of 8.5 years, two patients presented ipsilateral recurrence (after partial adrenalectomy). All patients with bilateral PH (n = 13) are steroid independent post-operatively. CONCLUSIONS: PH and PGL in children and adolescents should preferably be removed by minimally invasive surgery. Partial adrenalectomy provides long-term steroid independence in bilateral PH and a low rate of (ipsilateral) recurrence. alpha-Receptor blockade may not be necessary in these patients.
PubMed-ID: 29392429
http://dx.doi.org/10.1007/s00268-018-4488-y

Hemodynamic instability during surgery for pheochromocytoma: comparing the transperitoneal and retroperitoneal approach in a multicenter analysis of 341 patients.
Surgery, 163(1):176-82.
W. Vorselaars, E. L. Postma, E. Mirallie, J. Thiery, M. Lustgarten, J. D. Pasternak, R. Bellantone, M. Raffaelli, T.

Fahey, 3rd, M. R. Vriens, L. Bresler, L. Brunaud and R. Zarnegar. 2018.
BACKGROUND: Intraoperative hemodynamic instability is a major challenge during adrenalectomy for pheochromocytoma. Typically, pheochromocytoma is performed laparoscopically either through the retroperitoneal or transperitoneal approach. We aimed to determine if the operative approach affects intraoperative hemodynamic instability during surgery for pheochromocytoma in a large multicenter multicenter cohort. METHODS: Retrospective, multicenter analysis of consecutive patients with pheochromocytoma who underwent total unilateral laparoscopic adrenalectomy without conversion were included. Statistical analysis was performed using established intraoperative criteria for intraoperative hemodynamic instability: 1) systolic blood pressure >160 mm Hg; 2) systolic blood pressure > 200 mm Hg; 3) mean arterial pressure <60 mm Hg; 4) systolic blood pressure >160 mm Hg + mean arterial pressure <60 mm Hg; and 5) systolic blood pressure >200 mm Hg + mean arterial pressure <60 mm Hg; and 6) intravenous vasopressor + vasodilator. RESULTS: In total, 341 patients met the inclusion criteria, 101 (29.6%) underwent retroperitoneal adrenalectomy and 240 (70.4%) transperitoneal adrenalectomy. Multivariate analysis showed that retroperitoneal adrenalectomy carries greater risk for mean arterial pressure <60 mm Hg (odds ratio 6.255, confidence interval 1.134-34.235, P = .035) compared with transperitoneal adrenalectomy. Overall and cardiovascular morbidity rates were comparable between the 2 approaches. The medical center was a significant independent influencing factor for all 6 intraoperative hemodynamic instability definitions. CONCLUSION: Variability in institutional management of pheochromocytoma intraoperatively has significant impact on all 6 intraoperative hemodynamic instability definitions. Standardization of anesthesia should be considered to reduce this variability.
PubMed-ID: 29122324
http://dx.doi.org/10.1016/j.surg.2017.05.029

Trends of genetic screening in patients with pheochromocytoma and paraganglioma: 15-year experience in a high-volume tertiary referral center.
J Surg Oncol, 117(6):1217-22.
A. Asban, W. P. Kluijfhout, F. T. Drake, T. Beninato, E. Wang, K. Chomsky-Higgins, W. T. Shen, J. E. Gosnell, I. Suh and Q. Y. Duh. 2018.
BACKGROUND AND OBJECTIVES: Genetic testing for pheochromocytoma and paraganglioma allows for early detection of hereditary syndromes and enables close follow-up of high-risk patient. We investigated the trends in genetic testing among patients at a high-volume referral center and evaluated the prevalence of pheochromocytomas and paragangliomas. METHODS: We reviewed the charts of 129 patients who underwent adrenalectomy for pheochromocytoma and paraganglioma between January 2000 and July 2015. To evaluate for trends in genetic testing, patients were divided by year of diagnosis: 2000-2005 (group 1, n = 35), 2006-2010 (group 2, n = 44), and 2011-2015 (group 3, n = 50). RESULTS: Among 129 patients the mean age was 47 years and 56% were women. Groups 2 and 3 were more frequently referred for genetic consultation than group 1, 73%, and 94% versus 26% (P < 0.001). A total of 67% followed up on the referral. The prevalence of genetic mutation was 50% (21/42 tested). The percentage with a genetic syndrome was 23%, 28%, and 22% respectively for groups 1, 2, and 3. CONCLUSIONS: Referral for genetic counseling significantly increased in the past 15 years. However, only two-thirds of patients followed up with genetic counselors and, therefore, clinicians can do more to improve the adherence rate for genetic counseling.
PubMed-ID: 29315604
http://dx.doi.org/10.1002/jso.24961

Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study.
J Clin Endocrinol Metab, 103(2):438-45.
K. van der Tuin, A. R. Mensenkamp, C. M. J. Tops, E. P. M. Corssmit, W. N. Dinjens, A. N. A. van de Horst-Schrivers, J. C. Jansen, M. M. de Jong, H. P. M. Kunst, B. Kusters, E. M. Leter, H. Morreau, B. M. P. van Nesselrooij, R. A. Oldenburg, L. Spruijt, F. J. Hes and H. Timmers. 2018.
Context: Paraganglioma (PGL) has the highest degree of heritability among human neoplasms. Current clinical understanding of germline SDHA mutation carriers is limited. Objective: To estimate the contribution of SDHA mutations in PGL and to assess clinical manifestations and age-related penetrance. Design: Nationwide retrospective cohort study. Setting: Tertiary referral centers in the Netherlands (multicenter). Patients: Germline SDHA analysis was performed in 393 patients with genetically unexplained PGL. Subsequently, 30 index SDHA mutation carriers and 56 nonindex carriers were studied. Main Outcome Measures: SDHA mutation detection yield, clinical manifestations, and SDHA-related disease penetrance. Results: Pathogenic germline SDHA variants were identified in 30 of the 393 referred patients with PGL (7.6%), who had head and neck PGL (21 of 174 [12%]), pheochromocytoma (4 of 191 [2%]), or sympathetic PGL (5 of 28 [18%]). The median age at diagnosis was 43 years (range, 17 to 81 years) in index SDHA mutation carriers compared with 52 years (range, 7 to 90 years) in nonmutation carriers (P = 0.002). The estimated penetrance of any SDHA-related manifestation

was 10% at age 70 years (95% confidence interval, 0% to 21%) in nonindex mutation carriers. Conclusion: Germline SDHA mutations are relatively common (7.6%) in patients with genetically unexplained PGL. Most index patients presented with apparently sporadic PGL. In this SDHA series, the largest assembled so far, we found the lowest penetrance of all major PGL predisposition genes. This suggests that recommendations for genetic counseling of at-risk relatives and stringency of surveillance for SDHA mutation carriers might need to be reassessed.
PubMed-ID: 29177515
http://dx.doi.org/10.1210/jc.2017-01762

Mitotane Monotherapy in Patients With Advanced Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 103(4):1686-95.
F. Megerle, W. Herrmann, W. Schloetelburg, C. L. Ronchi, A. Pulzer, M. Quinkler, F. Beuschlein, S. Hahner, M. Kroiss and M. Fassnacht. 2018.
Context: Although mitotane is the only approved drug for the treatment of adrenocortical carcinoma (ACC), data on monotherapy in advanced disease are still scarce. Objective: To assess the efficacy of mitotane in advanced ACC in a contemporary setting and to identify predictive factors. Design and Setting: Multicenter cohort study of three German referral centers. Patients: One hundred twenty-seven patients with advanced ACC treated with mitotane monotherapy. Outcome Measures: Response Evaluation Criteria in Solid Tumors evaluation, progression-free survival (PFS) and overall survival (OS) by Kaplan-Meier method, and predictive factors by Cox regression. Results: Twenty-six patients (20.5%) experienced objective response, including three with complete remission. Overall, median PFS was 4.1 months (range 1.0 to 73) and median OS 18.5 months (range 1.3 to 220). Multivariate analysis indicated two main predictive factors: low tumor burden (<10 tumoral lesions), hazard ratio (HR) for progression of 0.51 (P = 0.002) and for death of 0.59 (P = 0.017); and initiation of mitotane at delayed advanced recurrence, HR 0.35(P < 0.001) and 0.34 (P < 0.001), respectively. Accordingly, 67% of patients with low tumor burden and mitotane initiation >/=360 days after primary diagnosis experienced a clinical benefit (stable disease >180 days). Patients who achieved mitotane levels >14 mg/L had significantly longer OS (HR 0.42; P = 0.003). Conclusions: At 20.5% the objective response rate was slightly lower than previously reported. However, >20% of patients experienced long-term disease control at >1 year. In general, patients with late diagnosis of advanced disease and low tumor burden might especially benefit from mitotane monotherapy, whereas patients with early advanced disease and high tumor burden are probably better candidates for combined therapy of mitotane and cytotoxic drugs.
PubMed-ID: 29452402
http://dx.doi.org/10.1210/jc.2017-02591

Minimally Invasive Adrenalectomy for Adrenocortical Carcinoma: Five-Year Trends and Predictors of Conversion.
World J Surg, 42(2):473-81.
N. A. Calcatera, C. Hsiung-Wang, N. R. Suss, D. J. Winchester, T. A. Moo-Young and R. A. Prinz. 2018.
BACKGROUND: Adrenocortical carcinoma (ACC) is rare but often fatal. Surgery offers the only chance of cure. As minimally invasive (MI) procedures for cancer become common, their role for ACC is still debated. We reviewed usage of MI approaches for ACC over time and risk factors for conversion using a large national database. METHODS: ACC patients with localized disease were identified in the National Cancer Data Base from 2010 to 2014. A retrospective review examined trends in the surgical approach over time. Patient demographics, surgical approach, and tumor characteristics between MI, open, and converted procedures were compared. RESULTS: 588 patients underwent adrenalectomy for ACC, of which 200 were minimally invasive. From 2010 to 2014, MI operations increased from 26 to 44% with robotic procedures increasing from 5 to 16%. The use of MI operations compared to open was not different based on facility type (p = 0.40) or location (p = 0.63). MI tumors were more likely to be confined to the adrenal (p < 0.001) but final margin status was not different (p = 0.56). Conversion was performed in 38/200 (19%). Average tumor size was 10.2 cm in the converted group compared to 8.6 cm in the MI group (p = 0.09). There was no difference in extent of disease (p = 0.33), margin status (p = 0.12), or lymphovascular invasion (p = 0.59) between MI and converted procedures. Tumor size > 5 cm was the only significant predictor of conversion (p = 0.04). No patients with pathologic stage I disease required conversion (0/19). CONCLUSIONS: The frequency of MI approaches for ACC is increasing. In the final year of the study, 44% of adrenalectomies were MI. Size > 5 cm was the only significant predictor of conversion.
PubMed-ID: 29022106
http://dx.doi.org/10.1007/s00268-017-4290-2

Expression of Contactin 4 Is Associated With Malignant Behavior in Pheochromocytomas and Paragangliomas.
J Clin Endocrinol Metab, 103(1):46-55.
L. Evenepoel, F. H. van Nederveen, L. Oudijk, T. G. Papathomas, D. F. Restuccia, E. J. T. Belt, W. W. de Herder, R. A. Feelders, G. J. H. Franssen, M. Hamoir, D. Maiter, H. K. Ghayee, J. W. Shay, A. Perren, H. Timmers, S. van Eeden, L. Vroonen, S. Aydin, M. Robledo, M. Vikkula, R. R. de Krijger, W. N. M. Dinjens, A. Persu and E. Korpershoek. 2018.
Context: Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine, usually benign, tumors. Currently, the only reliable criterion of malignancy is the presence of metastases. Objective: The aim of this study was to identify genes associated with malignancy in PPGLs. Design: Transcriptomic profiling was performed on 40 benign and 11 malignant PPGLs. Genes showing a significantly different expression between benign and malignant PPGLs with a ratio >/=4 were confirmed and tested in an independent series by quantitative real-time polymerase chain reaction (qRT-PCR). Immunohistochemistry was performed for the validated genes on 109 benign and 32 malignant PPGLs. Functional assays were performed with hPheo1 cells. Setting: This study was conducted at the Department of Pathology of the Erasmus MC University Medical Center Rotterdam Human Molecular Genetics laboratory of the de Duve Institute, University of Louvain. Patients: PPGL samples from 179 patients, diagnosed between 1972 and 2015, were included. Main outcome measures: Associations between gene expression and malignancy were tested using supervised clustering approaches. Results: Ten differentially expressed genes were selected based on messenger RNA (mRNA) expression array data. Contactin 4 (CNTN4) was overexpressed in malignant vs benign tumors [4.62-fold; false discovery rate (FDR), 0.001]. Overexpression at the mRNA level was confirmed using qRT-PCR (2.90-fold, P = 0.02; validation set: 4.26-fold, P = 0.005). Consistent findings were obtained in The Cancer Genome Atlas cohort (2.7-fold; FDR, 0.02). CNTN4 protein was more frequently expressed in malignant than in benign PPGLs by immunohistochemistry (58% vs 17%; P = 0.002). Survival after 7 days of culture under starvation conditions was significantly enhanced in hPheo1 cells transfected with CNTN4 complementary DNA. Conclusion: CNTN4 expression is consistently associated with malignant behavior in PPGLs.
PubMed-ID: 28938490
http://dx.doi.org/10.1210/jc.2017-01314

Diagnostic performance of unenhanced computed tomography and (18) F-fluorodeoxyglucose positron emission tomography in indeterminate adrenal tumours.
Clin Endocrinol (Oxf), 88(1):30-6.
D. A. Delivanis, I. Bancos, T. D. Atwell, G. D. Schmit, P. W. Eiken, N. Natt, D. Erickson, S. Maraka, W. F. Young and M. A. Nathan. 2018.
OBJECTIVE: Evidence on the diagnostic performance of adrenal imaging is limited. We aimed to assess the diagnostic performance of unenhanced computed tomography (CT) and (18) F-fluorodeoxyglucose ((18) FDG) positron emission tomography (PET)/CT imaging in a high-risk population for adrenal malignancy using an optimal reference standard. DESIGN: Retrospective cohort study. METHODS: Imaging studies of patients with adrenal nodules who underwent adrenal biopsy and/or adrenalectomy between 1994 and 2014 were reviewed and compared to the reference standard of histology. Eighty % of patients presented with known or suspected extra-adrenal malignancy. RESULTS: Unenhanced abdominal CT was performed in 353 patients with adrenal lesions; median size was 3 (0.7-15) cm and median radiodensity was 33 (-21-78) Hounsfield units (HU). Radiodensity of >10 HU diagnosed malignancy with a sensitivity of 100%, specificity of 33%, positive predictive value (PPV) of 72% and negative predictive value (NPV) of 100%. (18) FDG-PET/CT was performed in 89 patients; median tumour size was 2.1 (0.7-9.2) cm. Maximum standardized uptake (SUV max) was higher in malignant lesions when compared to benign lesions (median=10 [2.3-29.4] vs 3.7 [1.4-24.5], respectively, P<.0001). Similarly, median SUV max lesion to SUV max liver ratio (ALR) in malignant lesions was higher than in benign lesions (median=3 [0.74-13.4] vs 1.2 [0.5-6.6], respectively, P<.0001). (18) FDG-PET/CT ALR >1.8 diagnosed malignancy with a sensitivity of 87%, specificity of 84%, PPV of 85% and NPV of 86%. CONCLUSION: Noncontract CT radiodensity of </=10 HU excludes malignancy even in a high-risk population. For indeterminate adrenal lesions, given a superior specificity, (18) FDG-PET/CT could be considered as a second stage imaging study.
PubMed-ID: 28815667
http://dx.doi.org/10.1111/cen.13448

Extent of surgery for phaeochromocytomas in the genomic era.
Br J Surg, 105(2):e84-e98.
H. M. Rossitti, P. Soderkvist and O. Gimm. 2018.
BACKGROUND: Germline mutations are present in 20-30 per cent of patients with phaeochromocytoma. For

patients who develop bilateral disease, complete removal of both adrenal glands (total adrenalectomy) will result in lifelong adrenal insufficiency with an increased risk of death from adrenal crisis. Unilateral/bilateral adrenal-sparing surgery (subtotal adrenalectomy) offers preservation of cortical function and independence from steroids, but leaves the adrenal medulla in situ and thus at risk of developing new and possibly malignant disease. Here, present knowledge about how tumour genotype relates to clinical behaviour is reviewed, and application of this knowledge when choosing the extent of adrenalectomy is discussed. METHODS: A literature review was undertaken of the penetrance of the different genotypes in phaeochromocytomas, the frequency of bilateral disease and malignancy, and the underlying pathophysiological mechanisms, with emphasis on explaining the clinical phenotypes of phaeochromocytomas and their associated syndromes. RESULTS: Patients with bilateral phaeochromocytomas most often have multiple endocrine neoplasia type 2 (MEN2) or von Hippel-Lindau disease (VHL) with high-penetrance mutations for benign disease, whereas patients with mutations in the genes encoding SDHB (succinate dehydrogenase subunit B) or MAX (myelocytomatosis viral proto-oncogene homologue-associated factor X) are at increased risk of malignancy. CONCLUSION: Adrenal-sparing surgery should be the standard approach for patients who have already been diagnosed with MEN2 or VHL when operating on the first side, whereas complete removal of the affected adrenal gland(s) is generally recommended for patients with SDHB or MAX germline mutations. Routine assessment of a patient's genotype, even after the first operation, can be crucial for adopting an appropriate strategy for follow-up and future surgery.
PubMed-ID: 29341163
http://dx.doi.org/10.1002/bjs.10744

A Multi-institutional Comparison of Adrenal Venous Sampling in Patients with Primary Aldosteronism: Caution Advised if Successful Bilateral Adrenal Vein Sampling is Not Achieved.
World J Surg, 42(2):466-72.
T. S. Wang, G. Kline, T. W. Yen, Z. Yin, Y. Liu, W. Rilling, B. So, J. W. Findling, D. B. Evans and J. L. Pasieka. 2018.
INTRODUCTION: In patients with primary aldosteronism (PA), adrenal venous sampling (AVS) is recommended to differentiate between unilateral (UNI) or bilateral (BIL) adrenal disease. A recent study suggested that lateralization could be predicted, based on the ratio of aldosterone/cortisol levels (A/C) between the left adrenal vein (LAV) and inferior vena cava (IVC), with a 100% positive predictive value (PPV). This study aimed to validate those findings utilizing a larger, multi-institutional cohort. METHODS: A retrospective review was performed of patients with PA who underwent AVS from 2 tertiary-care institutions. Laterality was predicted by an A/C ratio of >3:1 between the dominant and non-dominant adrenal. AVS results were compared to LAV/IVC ratios utilizing the published criteria (Lt >/= 5.5; Rt </= 0.5). RESULTS: Of 222 patients, 124 (57%) had UNI and 98 (43%) had BIL disease based on AVS. AVS and LAV/IVC findings were concordant for laterality in 141 (64%) patients (69 UNI, 72 BIL). Using only the LAV/IVC ratio, 54 (24%) patients with UNI disease on AVS who underwent successful surgery would have been assumed to have BAH unless AVS was repeated, and 24 (11%) patients with BIL disease on AVS may have been incorrectly offered surgery (PPV 70%). Based on median LAV/IVC ratios (left 5.26; right 0.31; BIL 2.84), no LAV/IVC ratio accurately predicted laterality. DISCUSSION: This multi-institutional study of patients with both UNI and BIL PA failed to validate the previously reported PPV of LAV/IVC ratio for lateralization. Caution should be used in interpreting incomplete AVS data to differentiate between UNI versus BIL disease and strong consideration given to repeat AVS prior to adrenalectomy.
PubMed-ID: 29124355
http://dx.doi.org/10.1007/s00268-017-4327-6

Refining the Definitions of Biochemical and Clinical Cure for Primary Aldosteronism Using the Primary Aldosteronism Surgical Outcome (PASO) Classification System.
World J Surg, 42(2):453-63.
B. S. Miller, A. F. Turcu, A. T. Nanba, D. T. Hughes, M. S. Cohen, P. G. Gauger and R. J. Auchus. 2018.
INTRODUCTION: Determination of outcomes after adrenalectomy for primary aldosteronism (PA) is limited by the lack of standardized definitions of cure. The Primary Aldosteronism Surgical Outcomes (PASO) group recently established new consensus definitions for biochemical and clinical cure of PA. We hypothesize that utilization of PASO definitions will better stratify patient outcomes after surgery compared to original and current criteria utilized to document cure. MATERIALS AND METHODS: Patients undergoing adrenalectomy for PA from 1996 to 2016 were studied. Clinical data were reviewed. Three different sets of criteria (original, current, and PASO) were evaluated for differences in documentation of cure. Demographic data were reported as median (range). Comparisons were made using the Mann-Whitney U test; $p < 0.05$ is significant. RESULTS: A total of 314 patients with PA were identified. Ninety patients (60 males) elected to proceed with surgery. In Group 1 (35 patients), 30 patients had clinical follow-up and 29 (97%) were cured using original criteria. In Group 2 (55 patients), cure was recorded in 98% when original criteria for cure were applied, 89% cured applying

current criteria, and 6% had complete biochemical and clinical cure by PASO criteria. Aldosterone rose 3.6 ng/dL (0.1-34.8) in five patients during extended follow-up, with two patients changing from complete to partial or missing biochemical success. CONCLUSION: Significant heterogeneity exists in outcomes criteria utilized to document cure or clinical improvement after adrenalectomy for primary aldosteronism. Aldosterone levels change over time after adrenalectomy. PASO definitions of cure appear to allow for improved stratification of short- and long-term outcomes.
PubMed-ID: 29134312
http://dx.doi.org/10.1007/s00268-017-4311-1

It's Complicated: How Often are Patients with Primary Aldosteronism Cured After Adrenalectomy?
World J Surg, 42(2):464-5.
Q. Y. Duh and I. Suh. 2018.
PubMed-ID: 29159604
http://dx.doi.org/10.1007/s00268-017-4380-1

Each procedure matters: threshold for surgeon volume to minimize complications and decrease cost associated with adrenalectomy.
Surgery, 163(1):157-64.
K. L. Anderson, Jr., S. M. Thomas, M. A. Adam, L. N. Pontius, M. T. Stang, R. P. Scheri, S. A. Roman and J. A. Sosa. 2018.
BACKGROUND: An association has been suggested between increasing surgeon volume and improved patient outcomes, but a threshold has not been defined for what constitutes a "high-volume" adrenal surgeon. METHODS: Adult patients who underwent adrenalectomy by an identifiable surgeon between 1998-2009 were selected from the Healthcare Cost and Utilization Project National Inpatient Sample. Logistic regression modeling with restricted cubic splines was utilized to estimate the association between annual surgeon volume and complication rates in order to identify a volume threshold. RESULTS: A total of 3,496 surgeons performed adrenalectomies on 6,712 patients; median annual surgeon volume was 1 case. After adjustment, the likelihood of experiencing a complication decreased with increasing annual surgeon volume up to 5.6 cases (95% confidence interval, 3.27-5.96). After adjustment, patients undergoing resection by low-volume surgeons (<6 cases/year) were more likely to experience complications (odds ratio 1.71, 95% confidence interval, 1.27-2.31, P = .005), have a greater hospital stay (relative risk 1.46, 95% confidence interval, 1.25-1.70, P = .003), and at increased cost (+26.2%, 95% confidence interval, 12.6-39.9, P = .02). CONCLUSION: This study suggests that an annual threshold of surgeon volume (>/=6 cases/year) that is associated with improved patient outcomes and decreased hospital cost. This volume threshold has implications for quality improvement, surgical referral and reimbursement, and surgical training.
PubMed-ID: 29122321
http://dx.doi.org/10.1016/j.surg.2017.04.028

Accuracy of adrenal computed tomography in predicting the unilateral subtype in young patients with hypokalaemia and elevation of aldosterone in primary aldosteronism.
Clin Endocrinol (Oxf), 88(5):645-51.
H. Umakoshi, T. Ogasawara, Y. Takeda, I. Kurihara, H. Itoh, T. Katabami, T. Ichijo, N. Wada, Y. Shibayama, T. Yoshimoto, Y. Ogawa, J. Kawashima, M. Sone, N. Inagaki, K. Takahashi, M. Watanabe, Y. Matsuda, H. Kobayashi, H. Shibata, K. Kamemura, M. Otsuki, Y. Fujii, K. Yamamto, A. Ogo, T. Yanase, S. Okamura, S. Miyauchi, T. Suzuki, M. Tsuiki and M. Naruse. 2018.
CONTEXT: The current Endocrine Society Guideline suggests that patients aged <35 years with marked primary aldosteronism (PA) and unilateral adrenal lesions on adrenal computed tomography (CT) scan may not need adrenal vein sampling (AVS) before proceeding to unilateral adrenalectomy. This suggestion is, however, based on the data from only one report in the literature. OBJECTIVE: We sought to determine the accuracy of CT findings in young PA patients who had unilateral adrenal disease on CT with hypokalaemia and elevation of aldosterone. DESIGN AND PATIENTS: We retrospectively studied 358 PA patients (n = 30, aged <35 years; n = 39, aged 35-40 years; n = 289, aged >/=40 years) with hypokalaemia and elevation of aldosterone and unilateral disease on CT who had successful AVS. MAIN OUTCOME MEASURE: Accuracy of CT findings is determined by AVS findings and/or surgical outcomes in patients aged <35 years. RESULTS: Concordance of the diagnosis between CT and AVS was 90% (27/30) in patients aged <35 years, 79% (31/39) in patients aged 35-40 years and 69% (198/289) in those aged >/=40 years (trend for P < .01). Surgical benefit was confirmed in three patients aged <35 years and in three patients aged 35-40 years with the available surgical data who had discordance between CT and AVS findings. Collectively, the diagnostic accuracy of CT findings was 100% (30/30) if aged <35 years and 87% (34/39) if aged 35-40 years. CONCLUSION: Primary aldosteronism patients

aged <35 years with hypokalaemia and elevation of aldosterone and unilateral disease on adrenal CT could be spared AVS.
PubMed-ID: 29464741
http://dx.doi.org/10.1111/cen.13582

Long-Term Outcomes of the ADRENAL Trial.
N Engl J Med, 378(18):1744-5.
B. Venkatesh, S. Finfer, J. Myburgh, J. Cohen and L. Billot. 2018.
PubMed-ID: 29694789
http://dx.doi.org/10.1056/NEJMc1803563

Preoperative risk factors for haemodynamic instability during pheochromocytoma surgery in Chinese patients.
Clin Endocrinol (Oxf), 88(3):498-505.
M. Jiang, H. Ding, Y. Liang, J. Tang, Y. Lin, K. Xiang, Y. Guo and S. Zhang. 2018.
OBJECTIVE: Pheochromocytoma surgery carries a high risk of haemodynamic instability (HI). However, there are few studies investigating the risk factors for HI for pheochromocytoma surgery in a Chinese population. Therefore, our objective was to identify preoperative risk factors for HI during surgery in a Chinese population with pheochromocytoma. PATIENTS AND METHODS: In this retrospective study, 134 patients undergoing surgery for pheochromocytoma at a single university-affiliated hospital between November 2002 and July 2017 were enrolled. Demographics, comorbidities, preoperative medical preparation, operation details and perioperative haemodynamics of these patients were retrospectively collected and analysed. Multivariable logistic regression analysis was performed to identify the preoperative risk factors for intraoperative HI. RESULTS: 32.8% (44/134) patients suffered from intraoperative HI. According to the result of multivariate analysis, tumour diameter >50 mm (odds ratio [OR] 2.526; 95% confidence interval [CI] 1.163-5.485; P = .019), diabetes/prediabetes (OR 2.251; 95% CI 1.039-4.876; P = .040) and preoperative systolic blood pressure fluctuation >50 mm Hg (OR 3.163; 95% CI 1.051-9.522, P = .041) were independent predictors for intraoperative HI. The observed incidence of HI was 8.9%, 42.6%, 47.8% and 60% when zero, one, two or three risk factors were present, respectively. CONCLUSIONS: HI is common among Chinese patients undergoing surgery for pheochromocytoma. Our study identified three predictive factors for intraoperative HI: a large tumour diameter, diabetes/prediabetes and a great preoperative systolic blood pressure fluctuation. Furthermore, patients are more likely to suffer from HI when they have more predictive risk factors. Identification of these risk factors can help to improve perioperative management.
PubMed-ID: 29292527
http://dx.doi.org/10.1111/cen.13544

International survey on high- and low-dose synacthen test and assessment of accuracy in preparing low-dose synacthen.
Clin Endocrinol (Oxf), 88(5):744-51.
A. S. Cross, E. Helen Kemp, A. White, L. Walker, S. Meredith, P. Sachdev, N. P. Krone, R. J. Ross, N. P. Wright and C. J. Elder. 2018.
OBJECTIVE: The short synacthen test (SST) is widely used to assess patients for adrenal insufficiency, but the frequency and protocols used across different centres for the low-dose test (LDT) are unknown. This study aimed to survey centres and test the accuracy of ten different synacthen preparation strategies used for the LDT. METHODS: Members of 6 international endocrine societies were surveyed regarding diagnostic tests used for adrenal insufficiency, and in particular the SST. Synacthen was diluted for the LDT and concentrations measured using a synacthen ELISA. RESULTS: Survey responses were received from 766 individuals across 60 countries (52% adult, 45% paediatric endocrinologists). The SST is used by 98% of centres: 92% using high-dose (250 mug), 43% low-dose and 37% both. Ten low-dose dilution methods were assessed and variation in synacthen concentration was demonstrated with intramethod coefficients of variation (CV) ranging from 2.1% to 109%. The method using 5% dextrose as a diluent was the least variable (CV of 2.1%). The variation in dilution methods means that the dose of synacthen administered in a LDT may vary between 0.16 and 0.81 mug. CONCLUSIONS: The high-dose SST is the most popular diagnostic test of adrenal insufficiency, but up to 72% of paediatric endocrinologists use a LDT. There is considerable variation observed both within and between low-dose synacthen dilution methods creating considerable risk of inaccurate dosing and thereby invalid results.
PubMed-ID: 29392744
http://dx.doi.org/10.1111/cen.13559

Preoperative 18F-FDG PET/CT in Pheochromocytomas and Paragangliomas Allows for Precision Surgery.
Ann Surg,
P. Nockel, M. El Lakis, A. Gaitanidis, R. Merkel, D. Patel, N. Nilubol, T. Prodanov, K. Pacak and E. Kebebew. 2018.
BACKGROUND: Fluorodeoxyglucose (F-FDG) positron emission tomography/computed tomography (PET/CT) imaging is recommended in patients with metastatic pheochromocytoma (PC) and paraganglioma (PGL). There are no data on whether routine preoperative F-FDG PET/CT in all patients with PC/PGL impacts surgical management. OBJECTIVE: The aim of this study was to determine whether routine preoperative F-FDG PET/CT imaging affects the surgical management of patients with PC/PGLs. METHODS: We analyzed clinical, biochemical, genetic, and anatomic imaging data in 93 consecutive patients with PC/PGL who collectively underwent a total of 100 operations and who had preoperative F-FDG PET/CT imaging. RESULTS: Of 100 operations, preoperative F-FDG PET/CT showed additional lesions compared to anatomic imaging in 15 cases. These patients were more likely to undergo an open surgical approach ($P < 0.05$). Presence of genetic mutation, redo operations, sex, age, or tumor size had no significant association with finding additional lesions on F-FDG PET/CT. CONCLUSIONS: Additional lesions detected on preoperative F-FDG-PET/CT imaging have an impact on the surgical approach in patients with PC/PGLs. Therefore, surgeons should routinely obtain F-FDG-PET/CT imaging in patients with PC/PGL to allow for a more precise surgical intervention.
PubMed-ID: 29334561
http://dx.doi.org/10.1097/SLA.0000000000002671

A Novel T-Stage Classification System for Adrenocortical Carcinoma: Proposal from the US Adrenocortical Carcinoma Study Group.
Ann Surg Oncol, 25(2):520-7.
C. E. Poorman, C. G. Ethun, L. M. Postlewait, T. B. Tran, J. D. Prescott, T. M. Pawlik, T. S. Wang, J. Glenn, I. Hatzaras, R. Shenoy, J. E. Phay, K. Keplinger, R. C. Fields, L. X. Jin, S. M. Weber, A. Salem, J. K. Sicklick, S. Gad, A. C. Yopp, J. C. Mansour, Q. Y. Duh, N. Seiser, C. C. Solorzano, C. M. Kiernan, K. I. Votanopoulos, E. A. Levine, C. A. Staley, G. A. Poultsides and S. K. Maithel. 2018.
BACKGROUND: The 7th AJCC T-stage system for adrenocortical carcinoma (ACC), based on size and extra-adrenal invasion, does not adequately stratify patients by survival. Lymphovascular invasion (LVI) is a known poor prognostic factor. We propose a novel T-stage system that incorporates LVI to better risk-stratify patients undergoing resection for ACC. METHOD: Patients undergoing curative-intent resections for ACC from 1993 to 2014 at 13 institutions comprising the US ACC Group were included. Primary outcome was disease-specific survival (DSS). RESULTS: Of the 265 patients with ACC, 149 were included for analysis. The current T-stage system failed to differentiate patients with T2 versus T3 disease ($p = 0.10$). Presence of LVI was associated with worse DSS versus no LVI (36 mo vs. 168 mo; $p = 0.001$). After accounting for the individual components of the current T-stage system (size, extra-adrenal invasion), LVI remained a poor prognostic factor on multivariable analysis (hazard ratio 2.14, 95% confidence interval 1.05-4.38, $p = 0.04$). LVI positivity further stratified patients with T2 and T3 disease (T2: 37 mo vs. median not reached; T3: 36 mo vs. 96 mo; $p = 0.03$) but did not influence survival in patients with T1 or T4 disease. By incorporating LVI, a new T-stage classification system was created: [T1: </= 5 cm, (-)local invasion, (+/-)LVI; T2: > 5 cm, (-)local invasion, (-)LVI OR any size, (+)local invasion, (-)LVI; T3: > 5 cm, (-)local invasion, (+)LVI OR any size, (+)local invasion, (+)LVI; T4: any size, (+)adjacent organ invasion, (+/-)LVI]. Each progressive new T-stage group was associated with worse median DSS (T1: 167 mo; T2: 96 mo; T3: 37 mo; T4: 15 mo; $p < 0.001$). CONCLUSIONS: Compared with the current T-stage system, the proposed T-stage system, which incorporates LVI, better differentiates T2 and T3 disease and accurately stratifies patients by disease-specific survival. If externally validated, this T-stage classification should be considered for future AJCC staging systems.
PubMed-ID: 29164414
http://dx.doi.org/10.1245/s10434-017-6236-1

Adrenal Metastasectomy in the Presence and Absence of Extraadrenal Metastatic Disease.
Ann Surg,
A. E. Russo, B. R. Untch, M. G. Kris, J. F. Chou, M. Capanu, D. G. Coit, J. E. Chaft, M. I. D'Angelica, M. F. Brennan and V. E. Strong. 2018.
OBJECTIVE: To determine if there are differences in overall survival (OS) or event-free survival (EFS) in patients with and without concomitant extra-adrenal metastases undergoing adrenal metastasectomy.
BACKGROUND: There is growing interest in the use of local therapies in patients with oligometastatic disease. Previously published series have indicated that long-term survival is possible with resection. Adrenalectomy has been used to treat adrenal metastases in select patients. METHODS: Patients who underwent adrenal

metastasectomy from 1994 to 2015 were identified from a prospectively maintained institutional database of adrenalectomy patients, excluding adrenalectomies due to tumor extension or for palliation. Sites of disease, treatment history, and survival data were extracted from chart review. RESULTS: One hundred seventy-four patients were included. Tumor histology included 68 nonsmall cell lung cancer, 34 renal cancer, 18 colorectal cancer, 11 melanoma cancer, 10 hepatocellular cancer, 8 sarcoma cancer, and 25 other cancers. The median follow-up among survivors was 5.2 (1-21) years. OS at 3 and 5 years was 50% and 40%, respectively. Patients with (n = 83) and without (n = 91) extra-adrenal metastases did not differ with respect to age, adrenal tumor size, or margin status. Median OS (3.3 years for patients with concomitant extra-adrenal metastases and 3.0 years for patients with isolated adrenal metastases; P = 0.816) and EFS (9.39 vs 9.59 months; P = 0.87) were similar. Factors negatively associated with OS included adrenal tumor size (P < 0.01), renal primary versus other (P < 0.01), and adrenal margin status (P < 0.01). CONCLUSIONS: In selected patients undergoing adrenal metastasectomy, there were no significant differences in OS or EFS between patients with and without concomitant extra-adrenal metastases.
PubMed-ID: 29578911
http://dx.doi.org/10.1097/SLA.0000000000002749

NET

Meta-Analyses

- None -

Randomized controlled trials

Radioembolization Versus Bland Embolization for Hepatic Metastases from Small Intestinal Neuroendocrine Tumors: Short-Term Results of a Randomized Clinical Trial.
World J Surg, 42(2):506-13.
A. K. Elf, M. Andersson, O. Henrikson, O. Jalnefjord, M. Ljungberg, J. Svensson, B. Wangberg and V. Johanson. 2018.
BACKGROUND: Radioembolization (RE) with intra-arterial administration of (90)Y microspheres is a promising technique for the treatment of liver metastases from small intestinal neuroendocrine tumors (SI-NET) not amenable to surgery or local ablation. However, studies comparing RE to other loco-regional therapies are lacking. The aim of this randomized study was to compare the therapeutic response and safety after RE and bland hepatic arterial embolization (HAE), and to investigate early therapy-induced changes with diffusion-weighted MRI (DWI-MRI). METHODS: Eleven patients were included in a prospective randomized controlled pilot study, six assigned to RE and five to HAE. Response according to RECIST 1.1 using MRI or CT at 3 and 6 months post-treatment was recorded as well as changes in DWI-MRI parameters after 1 month. Data on biochemical tumor response, toxicity, and side effects were also collected. RESULTS: Three months after treatment, all patients in the HAE group showed partial response according to RECIST while none in the RE group did (p = 0.0022). After 6 months, the response rates were 4/5 (80%) and 2/6 (33%) in the HAE and RE groups, respectively (NS). DWI-MRI metrics could not predict RECIST response, but lower pretreatment ADC(120-800) and larger ADC(0-800) increase at 1 month were related to larger decrease in tumor diameter when all tumors were counted. CONCLUSION: HAE resulted in significantly higher RECIST response after 3 months, but no difference compared to RE remained after 6 months. These preliminary findings indicate that HAE remains a safe option for the treatment of liver metastases from SI-NET, and further studies are needed to establish the role of RE and the predictive value of MR-DWI.
PubMed-ID: 29167951
http://dx.doi.org/10.1007/s00268-017-4324-9

Consensus Statements/Guidelines

- None -

Other Articles

The number of positive nodes accurately predicts recurrence after pancreaticoduodenectomy for nonfunctioning neuroendocrine neoplasms.
Eur J Surg Oncol, 44(6):778-83.
S. Partelli, A. A. Javed, V. Andreasi, J. He, F. Muffatti, M. J. Weiss, F. Sessa, S. La Rosa, C. Doglioni, G. Zamboni, C. L. Wolfgang and M. Falconi. 2018.
BACKGROUND: The most appropriate nodal staging for pancreatic neuroendocrine neoplasms (PanNENs) is unclear. Aim of the study was to evaluate the effect of the number of positive lymph nodes on prognosis after pancreaticoduodenectomy for PanNENs. METHODS: A retrospective analysis of pancreaticoduodenectomies for nonfunctioning PanNENs was performed. PanNENs with nodal metastases (N+) were classified into N1 (1 to 3 positive lymph nodes) and N2 (4 or more positive lymph nodes). Univariate and multivariate analyses of disease-free survival were performed. RESULTS: 157 patients were included. 99 patients (63%) had N0 PanNENs whereas 58 patients (37%) had nodal involvement (N+). Patients with N0 PanNENs had a 3-year disease-free

survival rate of 89% compared with 83% and 75% in patients with N1 and N2 PanNENs, respectively (P < 0.0001). Independent predictors of disease-free survival were the presence of necrosis, lymph node ratio and nodal status. Factors positively correlated with the number of positive lymph nodes were the Ki67 value, the T stage and the number of examined lymph nodes. Similar percentage of N0 and N+ PanNENs was demonstrated for a cut-off of 13 examined lymph nodes. CONCLUSIONS: The number of positive lymph nodes is accurate in predicting recurrence for PanNENs. Thirteen examined lymph nodes seems to be the minimum number of lymph nodes to be resected/examined in patients who undergo pancreaticoduodenectomy for PanNENs.
PubMed-ID: 29610023
http://dx.doi.org/10.1016/j.ejso.2018.03.005

Natural History of Localized and Locally Advanced Atypical Lung Carcinoids after Complete Resection: A Joined French-Italian Retrospective Multicenter Study.
Neuroendocrinology, 106(3):264-73.
F. Marciello, O. Mercier, P. Ferolla, J. Y. Scoazec, P. L. Filosso, A. Chapelier, G. Guggino, R. Monaco, F. Grimaldi, S. Pizzolitto, J. Guigay, B. R. de Latour, D. Giuffrida, E. Longchampt, V. T. de Montpreville, E. Fadel, A. Colao, D. Planchard, M. Papotti, A. Faggiano and E. Baudin. 2018.
BACKGROUND: The natural history and the best modality of follow-up of atypical lung carcinoids (AC) remain ill defined. The aim of this study was to analyze recurrence-free survival (RFS) after complete resection (R0) of stage I-III pulmonary AC. Secondary objectives were prognostic parameters, the location of recurrences, and the modality of follow-up. METHODS: A retrospective review of 540 charts of AC patients treated between 1998 and 2008 at 10 French and Italian centers with experience in lung neuroendocrine tumor management was undertaken. The exclusion criteria were MEN1-related tumor, history of another cancer, referral after tumor relapse, and being lost to follow-up. A central pathological review was performed in each country. RESULTS: Sixty-two patients were included. After a median follow-up time of 91 months (mean 85, range 6-165), 35% of the patients experienced recurrence: 16% were regional recurrences and 19% were distant metastases. Median RFS was not reached. The 1-, 3-, and 5-year RFS rate was 90, 79, and 68%, respectively. In univariate analysis, lymph node involvement (p = 0.0001), stage (p = 0.0001), mitotic count (p = 0.004), and type of surgery (p = 0.043) were significantly associated with RFS. In multivariate analysis, lymph node involvement was significantly associated with RFS (HR 95% CI: 0.000-0.151; p = 0.004). During follow-up, somatostatin receptor scintigraphy, fibroscopy, and abdominal examination results were available for 22, 12, and 25 patients, respectively. The median time interval for imaging follow-up was 10 months. CONCLUSIONS: After complete resection of AC, recurrences were observed mostly within the first 5 years of follow-up, within bronchi, mediastinal nodes, the liver, and bones. In R0 patients, lymph node involvement could help to stratify follow-up intervals. Suboptimal imaging is evidenced.
PubMed-ID: 28813709
http://dx.doi.org/10.1159/000480015

A Lymph Node Ratio-Based Staging Model Is Superior to the Current Staging System for Pancreatic Neuroendocrine Tumors.
J Clin Endocrinol Metab, 103(1):187-95.
A. Gaitanidis, D. Patel, N. Nilubol, A. Tirosh and E. Kebebew. 2018.
Context: The incidence of pancreatic neuroendocrine tumors (PNETs) is increasing. Current staging systems include nodal positivity, but the association of lymph node status and worse survival is controversial. Objective: The study aim was to determine the prognostic significance of lymph node ratio (LNR) and compare it with nodal positivity for PNET. Design, Setting, Participants, and Intervention: A retrospective analysis of the Surveillance, Epidemiology, and End Results database between 2004 and 2011 was performed in patients who underwent a pancreatectomy with lymphadenectomy. The primary outcome was disease-specific survival (DSS). Results: Of the 896 patients analyzed, T stage, N stage, distant metastasis, grade, extent of resection, sex, and age >/=57 years were significantly associated with worse DSS on univariate analysis. On multivariate analysis, age >/=57 [hazard ratio (HR) 1.75, 95% confidence interval (CI), 1.12 to 2.74, P = 0.015], male sex (HR 1.58; 95% CI, 1.01 to 2.48; P = 0.046), grade (poorly differentiated/undifferentiated: HR 7.59; 95% CI, 4.71 to 12.23; P < 0.001), distant metastases (HR 2.45; 95% CI, 1.58 to 3.79; P < 0.001), and partial pancreatectomy (HR 2.55; 95% CI, 1.2 to 5.4; P = 0.015) were associated with worse DSS. Comparison between staging models constructed based on LNR cutoffs and the American Joint Committee on Cancer (AJCC) eighth edition staging system revealed that a model based on LNR >/=0.5 was superior. Conclusions: LNR >/=0.5 is independently associated with worse DSS. A staging system with LNR >/=0.5 was superior to the current AJCC eighth edition staging system.
PubMed-ID: 29069375
http://dx.doi.org/10.1210/jc.2017-01791

Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More.
Neuroendocrinology, 106(3):242-51.
N. Pawa, A. K. Clift, H. Osmani, P. Drymousis, A. Cichocki, R. Flora, R. Goldin, D. Patsouras, A. Baird, A. Malczewska, J. Kinross, O. Faiz, A. Antoniou, H. Wasan, G. A. Kaltsas, A. Darzi, J. B. Cwikla and A. Frilling. 2018.
BACKGROUND: Appendiceal neuroendocrine neoplasms (ANEN) are mostly indolent tumours treated effectively with simple appendectomy. However, controversy exists regarding the necessity of oncologic right hemicolectomy (RH) in patients with histologic features suggestive of more aggressive disease. We assess the effects of current guidelines in selecting the surgical strategy (appendectomy or RH) for the management of ANEN. Methods/Aims: This is a retrospective review of all ANEN cases treated over a 14-year period at 3 referral centres and their management according to consensus guidelines of the European and the North American Neuroendocrine Tumor Societies (ENETS and NANETS, respectively). The operation performed, the tumour stage and grade, the extent of residual disease, and the follow-up outcomes were evaluated. RESULTS: Of 14,850 patients who had appendectomies, 215 (1.45%) had histologically confirmed ANEN. Four patients had synchronous non-ANEN malignancies. One hundred and ninety-three patients had index appendectomy. Seventeen patients (7.9%) had lymph node metastases within the mesoappendix. Forty-nine patients underwent RH after appendectomy. The percentages of 30-day morbidity and mortality after RH were 2 and 0%, respectively. Twelve patients (24.5%) receiving completion RH were found to have lymph node metastases. Two patients had liver metastases, both of them synchronous. The median follow-up was 38.5 months (range 1-143). No patient developed disease recurrence. Five- and 10-year overall survival for all patients with ANEN as the only malignancy was both 99.05%. CONCLUSIONS: The current guidelines appear effective in identifying ANEN patients at risk of harbouring nodal disease, but they question the oncological relevance of ANEN lymph node metastases. RH might present an overtreatment for a number of patients with ANEN.
PubMed-ID: 28641291
http://dx.doi.org/10.1159/000478742

Genotype-phenotype pancreatic neuroendocrine tumor relationship in multiple endocrine neoplasia type 1 patients: A 23-year experience at a single institution.
Surgery, 163(1):212-7.
I. Christakis, W. Qiu, S. M. Hyde, G. J. Cote, E. G. Grubbs, N. D. Perrier and J. E. Lee. 2018.
BACKGROUND: The aim of this study was to investigate the genotype-phenotype relationship of pancreatic neuroendocrine tumors in patients with multiple endocrine neoplasia type 1 treated at our institution. METHODS: We conducted a retrospective chart review of all patients with multiple endocrine neoplasia type 1 treated at our center from January 1993 to December 2015. Presence of a pancreatic neuroendocrine tumor was determined based on imaging performed at any time from presentation to conclusion of follow-up. RESULTS: We reviewed 188 patients. The most common site of multiple endocrine neoplasia type 1 mutation was in exon 2 (34/188; 18%). Of 188 patients, 125 had a pancreatic neuroendocrine tumor (61%). Among all patients, 30 of 34 (88%) with an exon 2 mutation had a pancreatic neuroendocrine tumor compared with 95 of 154 (62%) with a mutation in exons 3-10 (P = .002). In the age group of 20 to 40 years, 8 of 9 patients with an exon 2 mutation had a pancreatic neuroendocrine tumor, compared with 24 of 52 patients (46%) with a mutation in exons 3-10 (P = .028). Patients with an exon 2 mutation had a greater frequency of pancreatic neuroendocrine tumor distant metastasis (53% vs 23%, P = .049). CONCLUSION: Young patients with multiple endocrine neoplasia type 1 and an exon 2 mutation appear to have a 2-fold greater risk for developing a pancreatic neuroendocrine tumor, and patients with an exon 2 mutation may be at greater risk for developing distant metastasis. Consideration should be given to more intensive screening and more liberal application of primary operative intervention in this potentially high-risk group.
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http://dx.doi.org/10.1016/j.surg.2017.04.044

68Gallium DOTANOC-PET Imaging in Lung Carcinoids: Impact on Patients' Management.
Neuroendocrinology, 106(2):128-38.
A. Lamarca, D. M. Pritchard, T. Westwood, G. Papaxoinis, D. Nonaka, S. Vinjamuri, J. W. Valle, P. Manoharan and W. Mansoor. 2018.
BACKGROUND: 68Gallium DOTA-PET imaging is preferable to standard somatostatin receptor scintigraphy where available; however, its role in the management of lung carcinoid tumours (LC) remains unclear. METHODS: All consecutive patients with histologically confirmed LC from two ENETS Centres of Excellence were identified retrospectively. The primary objective was to assess the impact of 68Ga-DOTANOC-PET on clinical management in patients with LC. RESULTS: Of 166 patients screened, 46 were eligible: 52% female,

median age 57 years (range 21-86); type of LC: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (4%), typical (44%), atypical (35%), not reported (17%); stage: localised (63%), locally advanced (13%), and metastatic (17%) (7% unknown). A total of 47 68Ga-DOTANOCs were performed with the following rationale: LC diagnosis confirmation (4; 9%), primary tumour identification (2; 4%), post-surgical assessment (19; 40%), staging (patients with known LC present at time of 68Ga-DOTANOC) (19; 40%), and consideration of peptide receptor radionuclide therapy (3; 7%). Twenty-seven (57%) scans showed evidence of non-physiological uptake: median maximum standardised uptake value 7.2 (range 1.42-53). 68Ga-DOTANOC provided additional information in 37% (95% CI 22-51) of patients and impacted on management in 26% (95% CI 12-41); 9 patients (21%) were identified to have occult sites of metastases. Out of the 19 patients with post-surgical 68Ga-DOTANOC, 3 (16%) were identified to have distant metastases. There were no differences in the rate of practice changing 68Ga-DOTANOC results by type of LC (p value 0.5). CONCLUSIONS: Our results support the role of 68Ga-DOTANOC for optimising the management of patients with LC, including post-surgical re-staging due to the potential for identifying occult metastases.
PubMed-ID: 28399530
http://dx.doi.org/10.1159/000472717

Are Cystic Pancreatic Neuroendocrine Tumors an Indolent Entity Results from a Single-Center Surgical Series.
Neuroendocrinology, 106(3):234-41.
S. Paiella, G. Marchegiani, M. Miotto, A. Malpaga, H. Impellizzeri, G. Montagnini, T. Pollini, C. Nessi, G. Butturini, P. Capelli, I. Posenato, A. Scarpa, M. D'Onofrio, R. De Robertis, S. Cingarlini, L. Boninsegna, C. Bassi, R. Salvia and L. Landoni. 2018.
INTRODUCTION: Cystic pancreatic neuroendocrine tumors (CPanNETs) represent an uncommon variant of pancreatic neuroendocrine tumors (PanNETs). Due to their rarity, there is a lack of knowledge with regard to clinical features and postoperative outcome. METHODS: The prospectively maintained surgical database of a high-volume institution was queried, and 46 resected CPanNETs were detected from 1988 to 2015. Clinical, demographic, and pathological features and survival outcomes of CPanNETs were described and matched with a population of 92 solid PanNETs (SPanNETs) for comparison. RESULTS: CPanNETs accounted for 7.8% of the overall number of resected PanNETs (46/587). CPanNETs were mostly sporadic (n = 42, 91%) and nonfunctioning (39%). Two functioning CPanNETs were detected (4.3%), and they were 2 gastrinomas. The median tumor diameter was 30 mm (range 10-120). All tumors were well differentiated, with 38 (82.6%) G1 and 8 (17.4%) G2 tumors. Overall, no CPanNET showed a Ki-67 >5%. A correct preoperative diagnosis of a CPanNET was made in half of the cases. After a median follow-up of >70 months, the 5- and 10-year overall survival of resected CPanNETs was 93.8 and 62.5%, respectively, compared to 92.7 and 84.6% for SPanNETs ($p > 0.05$). The 5- and 10-year disease-free survival rates were 94.5 and 88.2% for CPanNETs and 81.8 and 78.9% for SPanNETs, respectively ($p > 0.05$). CONCLUSION: In the setting of a surgical cohort, CPanNETs are rare, nonfunctional, and well-differentiated neoplasms. After surgical resection, they share the excellent outcome of their well-differentiated solid counterparts for both survival and recurrence.
PubMed-ID: 28586782
http://dx.doi.org/10.1159/000477849

A Nationwide Population-Based Study on the Survival of Patients with Pancreatic Neuroendocrine Tumors in The Netherlands.
World J Surg, 42(2):490-7.
C. G. Genc, H. J. Klumpen, M. G. H. van Oijen, C. H. J. van Eijck and E. J. M. Nieveen van Dijkum. 2018.
BACKGROUND: Large population-based studies give insight into the prognosis and treatment outcomes of patients with pancreatic neuroendocrine tumors (pNETs). Therefore, we provide an overview of the treatment and related survival of pNET in the Netherlands. METHODS: Patients diagnosed with pNET between 2008 and 2013 from the Netherlands Cancer Registry were included. Patient, tumors and treatment characteristics were reported. Survival analyses with log-rank testing were performed to compare survival. RESULTS: In total, 611 patients were included. Median follow-up was 25.7 months, and all-cause mortality was 42%. Higher tumor grade and TNM stage were significantly associated with worse survival in both the overall and metastasized population. The effect of distant metastases on survival was more significant in lower tumor stages (T1-3 $p < 0.05$, T4 $p = 0.074$). Resection of the primary tumor was performed in 255 (42%) patients. Patients who underwent surgery had the highest 5-year survival (86%) compared to PRRT (33%), chemotherapy (21%), targeted therapy and somatostatin analogs (24%) (all $p < 0.001$). Patients with T1M0 tumors (n = 115) showed favorable survival after surgical resection (N = 95) compared to no therapy (N = 20, $p = 0.008$). Resection also improved survival significantly in patients with metastases compared to other treatments (all $p > 0.05$). Without surgery, PRRT showed the best survival curves in patients with distant metastases. Grade 3 tumors and surgical

resection were independently associated with survival (HR 7.23 and 0.12, respectively). CONCLUSION: Surgical resection shows favorable outcome for all pNET tumors, including indolent tumors and tumors with distant metastases. Prospective trials should be initiated to confirm these results.
PubMed-ID: 29018912
http://dx.doi.org/10.1007/s00268-017-4278-y

Frequent BRAF mutations suggest a novel oncogenic driver in colonic neuroendocrine carcinoma.
J Surg Oncol, 117(2):284-9.
K. Idrees, C. Padmanabhan, E. Liu, Y. Guo, R. S. Gonzalez, J. Berlin, K. B. Dahlman, R. D. Beauchamp and C. Shi. 2018.
BACKGROUND AND OBJECTIVES: The World Health Organization (WHO) 2010 has classified GI neuroendocrine neoplasms into neuroendocrine tumor (NET) and high-grade neuroendocrine carcinoma (NEC). The genetic underpinnings of NEC are poorly understood. The aim of the study was to perform genomic profiling of NEC to better characterize this aggressive disease. METHODS: We identified nine patients with colonic NEC between January 1, 2005 and June 30, 2013. Whole exome sequencing (WES) was performed on tumor DNA from two patients with >/=80% tumor cellularity and matched normal tissue available. Focused BRAF mutational analysis was performed on an additional seven patients via sanger sequencing of BRAF exons 11 and 15. RESULTS: We identified BRAF exon 15 mutations (c.A1781G: p.D594G and c.T1799A: p.V600E) by WES in two patients. Upon additional screening of seven colonic NECs for BRAF exon 11 and 15 mutations, we identified BRAF V600E mutations in two of seven specimens (29%). Overall, BRAF exon 15 mutations were present in four of nine colonic NECs. CONCLUSION: Colonic NEC is a rare but aggressive tumor with high frequency (44%) of BRAF mutations. Further investigation is warranted to ascertain the incidence of BRAF mutations in a larger population as BRAF inhibition may be a potential avenue of targeted treatment for these patients.
PubMed-ID: 28940307
http://dx.doi.org/10.1002/jso.24834

Histologically Proven Bronchial Neuroendocrine Tumors in MEN1: A GTE 51-Case Cohort Study.
World J Surg, 42(1):143-52.
P. Lecomte, C. Binquet, M. Le Bras, A. Tabarin, C. Cardot-Bauters, F. Borson-Chazot, C. Lombard-Bohas, E. Baudin, B. Delemer, M. Klein, B. Verges, T. Aparicio, E. Cosson, A. Beckers, P. Caron, O. Chabre, P. Chanson, H. Du Boullay, I. Guilhem, P. Niccoli, V. Rohmer, J. Guigay, C. Vulpoi, J. Y. Scoazec and P. Goudet. 2018.
OBJECTIVE: To evaluate the natural history of MEN1-related bronchial endocrine tumors (br-NETs) and to determine their histological characteristics, survival and causes of death. br-NETs frequency ranges from 3 to 13% and may reach 32% depending on the number of patients evaluated and on the criteria required for diagnosis. METHODS: The 1023-patient series of symptomatic MEN1 patients followed up in a median of 48.7 [35.5-59.6] years by the Groupe d'etude des Tumeurs Endocrines was analyzed using time-to-event techniques. RESULTS: br-NETs were found in 51 patients (4.8%, [95% CI 3.6-6.2%]) and were discovered by imaging in 86% of cases (CT scan, Octreoscan, Chest X-ray, MRI). Median age at diagnosis was 45 years [28-66]. Histological examination showed 27 (53%) typical carcinoids (TC), 16 (31%) atypical carcinoids (AC), 2 (4%) large cell neuroendocrine carcinomas (LCNEC), 3(6%) small cell neuroendocrine carcinomas (SCLC), 3(6%) TC associated with AC. Overall survival was not different from the rest of the cohort (HR 0.29, [95% CI 0.02-5.14]). AC tended to have a worse prognosis than TC (p = 0.08). Seven deaths were directly related to br-NETs (three AC, three SCLC and one LCNEC). Patients who underwent surgery survived longer (p = 10(-4)) and were metastasis free, while 8 of 14 non-operated patients were metastatic. There were no operative deaths. CONCLUSIONS: Around 5% of MEN1 patients develop br-NETs. br-NETs do not decrease overall survival in MEN1 patients, but poorly differentiated and aggressive br-NETs can cause death. br-NETs must be screened carefully. A biopsy is essential to operate on patients in time.
PubMed-ID: 28785839
http://dx.doi.org/10.1007/s00268-017-4135-z

Preoperative (68)Ga-DOTA-Somatostatin Analog-PET/CT Hybrid Imaging Increases Detection Rate of Intra-abdominal Small Intestinal Neuroendocrine Tumor Lesions.
World J Surg, 42(2):498-505.
O. Norlen, H. Montan, P. Hellman, P. Stalberg and A. Sundin. 2018.
BACKGROUND: Small intestinal neuroendocrine tumors (SI-NETs) are the most common form of neoplasm in the small bowel. Radiological identification of primary tumors (PT), which may be multiple, is difficult, and therefore palpation of the entire small bowel is routinely performed during laparotomy. The aim was to determine detection rates of PT and peritoneal carcinomatosis (PC) with (68)Ga-DOTATOC/TATE-PET/CT in comparison

with i.v. contrast-enhanced computed tomography (CE-CT) and thus to clarify whether modern functional imaging can mitigate the need for palpation of bowel during surgery enabling oncologically adequate laparoscopic resection. METHODS: A total of 28 patients with SI-NET who preoperatively underwent both (68)Ga-DOTATOC/TATE-PET/CT and CE-CT were included. The detection rates of PT and PC for PET/CT and CE-CT were compared to the findings in the surgical and histopathological reports. Appropriate statistical tests were used, and significance was set to $p < 0.05$. RESULTS: Out of 82 PT, 43 PT were not detected by any imaging modality. More PT lesions were detected with PET/CT (n = 39 [47.5%]) than with CE-CT (n = 10 [12.2%], $p < 0.001$). Also, PET/CT identified significantly more PC lesions than CE-CT (78 and 38%, $p = 0.004$, respectively). CONCLUSION: PET/CT detected more PT and PC lesions than CE-CT. Some PTs and PC lesions were only detected by one of the modalities, and CT performed in conjunction with PET/CT should therefore be performed as a fully diagnostic CE-CT for optimal results. Palpation of the small bowel remains crucial during surgery in these patients because several PTs escaped detection by both PET/CT and CE-CT.
PubMed-ID: 29159606
http://dx.doi.org/10.1007/s00268-017-4364-1

Early and Late Complications After Surgery for MEN1-related Nonfunctioning Pancreatic Neuroendocrine Tumors.
Ann Surg, 267(2):352-6.
S. Nell, I. H. M. Borel Rinkes, H. M. Verkooijen, B. A. Bonsing, C. H. van Eijck, H. van Goor, R. H. J. de Kleine, G. Kazemier, E. J. Nieveen van Dijkum, C. H. C. Dejong, G. D. Valk and M. R. Vriens. 2018.
OBJECTIVE: To estimate short and long-term morbidity after pancreatic surgery for multiple endocrine neoplasia type 1 (MEN1)-related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs). BACKGROUND: Fifty percent of the MEN1 patients harbor multiple NF-pNETs. The decision to proceed to NF-pNET surgery is a balance between the risk of disease progression versus the risk of surgery-related morbidity. Currently, there are insufficient data on the surgical complications after MEN1 NF-pNET surgery. METHODS: MEN1 patients diagnosed with a NF-pNET who underwent surgery were selected from the DutchMEN1 study group database, including >90% of the Dutch MEN1 population. Early postoperative complications, new-onset diabetes mellitus, and exocrine pancreatic insufficiency were captured. RESULTS: Sixty-one patients underwent NF-pNET surgery at 1 of the 8 Dutch academic centers. Patients were young (median age 41 years) with low American Society of Anesthesiologists scores. Median NF-pNET size on imaging was 22 mm (3-157). Thirty-three percent (19/58) of the patients developed major early-Clavien-Dindo grade III to IV-complications mainly consisting International Study Group of Pancreatic Surgery grade B/C pancreatic fistulas. Twenty-three percent of the patients (14/61) developed endocrine or exocrine pancreas insufficiency. The development of major early postoperative complications was independent of the NF-pNET tumor size. Twenty-one percent of the patients (12/58) developed multiple major early complications. CONCLUSIONS: MEN1 NF-pNET surgery is associated with high rates of major short and long-term complications. Current findings should be taken into account in the shared decision-making process when MEN1 NF-pNET surgery is considered.
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http://dx.doi.org/10.1097/SLA.0000000000002050

Accuracy of Pancreatic Neuroendocrine Tumour Grading by Endoscopic Ultrasound-Guided Fine Needle Aspiration: Analysis of a Large Cohort and Perspectives for Improvement.
Neuroendocrinology, 106(2):158-66.
L. Boutsen, A. Jouret-Mourin, I. Borbath, A. van Maanen and B. Weynand. 2018.
INTRODUCTION: Since the WHO Classification of Tumours of the Digestive System has been published in 2010, resected pancreatic neuroendocrine tumours (pNETs) are graded as grade 1 (G1), grade 2 (G2) or grade 3 (G3) using the Ki67 labelling index (Ki67-LI). Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is often used for diagnosis, but few studies have assessed its value for grading. AIMS: The aims of this study were to compare the Ki67-LI obtained by cytological grading (cG) with that obtained by histological grading (hG) and to assess (1) the influence of tumour size and the number of counted cells on FNA grading as well as (2) the overall survival (OS) and progression-free survival based on cG. MATERIALS AND METHODS: EUS-FNA was performed for 102 pNETs (57 resected). cG (200 cells counted) was done on all FNAs. For 29 FNAs, >2,000 cells were counted (14 resected). A comparison was made between hG and cG for the 57 resected patients. Patients were followed up until June 2016. RESULTS: cG was consistent with hG in 39 of 57 patients with a concordance rate of 72% using a Ki67-LI cut-off of 5% for G1/G2. For Ki67-LI absolute values, the correlation was $r = 0.443$ and increased to $r = 0.824$ ($p < 0.001$) when only FNAs with >2,000 cells were counted. Twenty-one of 22 pNETs <2 cm had the same grading on cG and hG, whereas grading was discordant for 15 of 16 pNETs >2 cm. Thirty-eight patients died after 70.5 months of follow-up. OS for the whole cohort was 235 months and differed between cG1 (235 months), cG2 (36.3 months) and cG3 (10.9 months). CONCLUSION: cG of

pNETs is more accurate when tumours measure <2 cm and more cells are counted on FNA. Discrepancies are seen between G2 tumours which are often considered G1 on FNA due to tumour heterogeneity. EUS-FNA is valuable to distinguish between patients with good (cG1) and poor (cG3) prognosis.
PubMed-ID: 28494461
http://dx.doi.org/10.1159/000477213

Mesenteric Fibrosis in Midgut Neuroendocrine Tumors: Functionality and Radiological Features.
Neuroendocrinology, 106(2):139-47.
V. Rodriguez Laval, M. Pavel, I. G. Steffen, A. D. Baur, L. M. Dilz, C. Fischer, K. Detjen, V. Prasad, A. Pascher, D. Geisel and T. Denecke. 2018.
BACKGROUND: Mesenteric fibrosis (MF) surrounding a lymph node metastasis is a known phenomenon in midgut neuroendocrine tumors (NETs) with characteristic radiological appearance. Its etiology is poorly understood as it affects some but not all midgut NET patients with lymphatic involvement. This study assessed a potential relationship of MF with carcinoid syndrome, urinary 5-hydroxyindoleacetic acid (5-HIAA), and carcinoid heart disease (CHD). METHODS: A cohort of 81 patients with pathologically proven NETs with the primary site in the midgut and mesenteric lymphatic metastases on imaging were retrospectively included. Imaging characteristics of lymphatic and hepatic metastases at diagnosis (size, number, burden, and morphologic features, including presence of MF), Ki67 grading, 5-HIAA, functionality, and development of CHD were analyzed. RESULTS: Overall, 54% of patients had MF. The presence of MF was more frequently associated with mesenteric vessel encasement (100 vs. 46% without MF; $p < 0.001$), presence of hepatic metastases (91 vs. 62%; $p = 0.002$), larger hepatic tumor burden (15 vs. 5%; $p = 0.001$), and functionality (86 vs. 43%; $p < 0.001$). Multivariate analysis revealed 5-HIAA >/=395 micromol/day ($p = 0.020$), age ($p = 0.013$), and largest lymphatic metastasis >/=24 mm ($p = 0.009$) as independent predictors of MF, while functionality ($p = 0.098$) and CHD ($p = 0.070$) showed a tendency towards significance. MF was associated with decreased time to development of CHD in functional midgut NETs ($p = 0.043$). CONCLUSIONS: We found a significant association of MF with metastatic patterns and with criteria of functionality. The association of MF with elevated 5-HIAA, and consecutively with carcinoid syndrome and potential development of CHD, suggests a linked pathophysiological mechanism, which might be similar to that of endocardial fibrosis.
PubMed-ID: 28384635
http://dx.doi.org/10.1159/000474941

18F-FDG Uptake in Well-Differentiated Neuroendocrine Tumors Correlates with Both Ki-67 and VHL Pathway Inactivation.
Neuroendocrinology, 106(3):274-82.
M. Bucau, A. Laurent-Bellue, N. Pote, O. Hentic, J. Cros, N. Mikail, V. Rebours, P. Ruszniewski, R. Lebtahi and A. Couvelard. 2018.
BACKGROUND: 18F-FDG-PET scan positivity correlates with poor prognosis in neuroendocrine neoplasms (NEN). Glucose transporter 1 (GLUT1) and carbonic anhydrase 9 (CA9) are markers of aggressiveness in tumors. Together with von Hippel-Lindau protein (pVHL), they are involved in tumor cell metabolism via the hypoxia-inducible factor signaling pathway. The aim of this study was to compare, in a series of well-differentiated neuroendocrine tumors (NET), the 18F-FDG uptake and expression of the proliferation markers Ki-67, GLUT1, CA9, and pVHL. PATIENTS AND METHODS: This retrospective study included 27 patients with well-differentiated NET. 18F-FDG-PET images were evaluated by the maximum standardized uptake value (SUVmax). GLUT1, CA9, and pVHL were analyzed by immunohistochemistry. RESULTS: The NET were of pancreatic (n = 19), midgut (n = 4), duodenal (n = 1), esophageal (n = 1), rectal (n = 1), and pulmonary (n = 1) origin. Eight, 11, and 8 tumors were grade 1, 2, and 3, respectively. The mean/median Ki-67 index was 15/10% (1-60). The mean/median SUVmax was 6.2/5.2 (1.4-18.7). SUVmax correlated with greater tumor size ($p = 0.03$), higher expression of Ki-67 ($p = 0.04$), and lower expression of pVHL ($p = 0.008$). In the group of 16 NET with a low proliferative index (Ki-67 index <10%), 5/6 (83%) of the tumors with a high SUVmax had decreased pVHL expression ($p = 0.0013$). CONCLUSION: This study confirms that 18F-FDG-PET uptake correlates with both tumor size and proliferation in well-differentiated NET, and it highlights a subset of low-grade but 18F-FDG-PET-positive NET related to sporadic inactivation of the VHL pathway.
PubMed-ID: 28803235
http://dx.doi.org/10.1159/000480239

From Initial Description by Wermer to Present-Day MEN1: What have We Learned?
World J Surg, 42(4):1031-5.
N. D. Perrier. 2018.
INTRODUCTION: Pancreas, parathyroid, and pituitary, are referred to as the "3 Ps" of MEN1. The time has

come to move beyond those Ps and begin to discuss (1) prediction, (2) pausing progression, and (3) prevention of MEN1. METHODS: In preparation for the International Association of Endocrine Surgeons State of the Art address, updates and uncertainties of MEN were reviewed. This included a detailed examination of the MEN1 gene and the library of implicated mutations, exon sequencing databases and cell cycle pathways. Therapeutic options including radiofrequency ablation, systemic therapy, peptide receptor radionuclide therapy, immune checkpoint inhibitor mechanisms and preimplantation genetic testing were described. RESULTS: Several key points included mutations in exon 2 are suspected of being associated with a higher rate of distant metastases, a higher rate of PNET development, and more aggressive disease. The suggestion that missense mutations involving loss of interaction with CHES1 (associated with DNA repair) correlates with more aggressive disease and is more closely associated with death related to PNET than to death from other causes was mentioned. For advanced NETs, optimism for agents under study include lanreotide, a long-acting somatostatin analog, and everolimus (Afinitor), a mammalian target of rapamycin (mTOR) inhibitor. The NETest shows the potential value of being a multidimensional tumor marker for response to therapy. Preimplantation genetic diagnosis (PGD) is applicable. CONCLUSION: Adjunct modalities and determination of the effect of therapy for MEN1 is needed. Prediction through early detection of aggressive disease is an idea worth spreading. We are called us to engage with our patients about prevention, the only true cure.
PubMed-ID: 29383428
http://dx.doi.org/10.1007/s00268-017-4435-3

Outcomes of Cytoreductive Surgery for Metastatic Low-Grade Neuroendocrine Tumors in the Setting of Extrahepatic Metastases.
Ann Surg Oncol, 25(6):1768-74.
D. L. Chan, M. Dixon, C. H. L. Law, S. Koujanian, K. A. Beyfuss, S. Singh, S. Myrehaug and J. Hallet. 2018.
BACKGROUND: Neuroendocrine tumors (NETs) have a uniquely indolent biology. Management focuses on tumor and hormonal burden reduction. Data on cytoreduction with extrahepatic disease remain limited. OBJECTIVE: We sought to define the outcomes of cytoreduction for metastatic NETs with extrahepatic metastases. METHODS: Patients undergoing cytoreductive surgery for grade 1 or 2 NETs with extrahepatic metastases (with or without intrahepatic disease) were identified from an institutional database (2003-2014). Primary outcomes included postoperative hormonal response (> 50% urinary 5HIAA decrease), progression-free survival (PFS) and overall survival (OS), while secondary outcomes were 30-day postoperative major morbidity (Clavien grade III-V), mortality, and length of stay. RESULTS: Fifty-five patients were identified (median age 59.3 years, 80% small bowel primaries, 56.4% grade 1); 87% of patients presented with combined intra- and extrahepatic metastases. Resection most commonly included the liver (87%), small bowel (22%), mesenteric (25%) and retroperitoneal (11%) lymph nodes, and peritoneum (7%). Thirty-day major morbidity (Clavien III-V) was 18%, with 3.6% mortality, and median length of stay was 7 days [interquartile range (IQR) 5-9]. Liver embolization was performed in 31% of patients after surgery, at a median of 23 months following surgery. Overall, postoperative hormonal response occurred in 70% of patients. At median follow-up of 37 months (IQR range 22-93), 42 (76%) patients were alive and 23 (41.8%) had progressed. Five-year OS was 77% and 5-year PFS was 51%. CONCLUSION: Patients undergoing cytoreduction of metastatic well-differentiated NET in the setting of extrahepatic metastatic disease experience good tumoral control with favorable PFS and OS. Cytoreductive surgery can be safely included in the therapeutic armamentarium for NET with extrahepatic metastases.
PubMed-ID: 29560571
http://dx.doi.org/10.1245/s10434-018-6433-6

Current and emerging therapies for PNETs in patients with or without MEN1.
Nat Rev Endocrinol, 14(4):216-27.
M. Frost, K. E. Lines and R. V. Thakker. 2018.
Pancreatic neuroendocrine tumours (PNETs) might occur as a non-familial isolated endocrinopathy or as part of a complex hereditary syndrome, such as multiple endocrine neoplasia type 1 (MEN1). MEN1 is an autosomal dominant disorder characterized by the combined occurrence of PNETs with tumours of the parathyroids and anterior pituitary. Treatments for primary PNETs include surgery. Treatments for non-resectable PNETs and metastases include biotherapy (for example, somatostatin analogues, inhibitors of receptors and monoclonal antibodies), chemotherapy and radiological therapy. All these treatments are effective for PNETs in patients without MEN1; however, there is a scarcity of clinical trials reporting the efficacy of the same treatments of PNETs in patients with MEN1. Treatment of PNETs in patients with MEN1 is challenging owing to the concomitant development of other tumours, which might have metastasized. In recent years, preclinical studies have identified potential new therapeutic targets for treating MEN1-associated neuroendocrine tumours (including PNETs), and these include epigenetic modification, the beta-catenin-wingless (WNT) pathway,

Hedgehog signalling, somatostatin receptors and MEN1 gene replacement therapy. This Review discusses these advances.
PubMed-ID: 29449689
http://dx.doi.org/10.1038/nrendo.2018.3

Markers of Systemic Inflammatory Response are Prognostic Factors in Patients with Pancreatic Neuroendocrine Tumors (PNETs): A Prospective Analysis.
Ann Surg Oncol, 25(1):122-30.
A. Gaitanidis, D. Patel, N. Nilubol, A. Tirosh, S. Sadowski and E. Kebebew. 2018.
BACKGROUND: The prognosis and behavior of pancreatic neuroendocrine tumors (PNETs) vary and may be divergent even at the same stage or tumor grade. Markers of systemic inflammatory response are readily available and are inexpensive, and have been shown to be prognostic factors in several cancers. OBJECTIVE: The aim of this study was to evaluate the prognostic utility of markers of systemic inflammatory response in patients with PNETs. METHODS: A prospective study of 97 patients with PNETs was performed (median follow-up of 15 months, range 12-73 months). Neutrophil-to-lymphocyte ratios (NLRs) and lymphocyte-to-monocyte ratios (LMRs) were calculated at baseline and preoperatively. The primary outcome measures were progression-free survival (PFS) and recurrence-free survival (RFS) after curative resection. RESULTS: Among all patients, an NLR > 2.3 [hazard ratio (HR) 2.53, 95% confidence interval (CI) 1.05-6.08, p = 0.038] and the presence of distant metastases (HR 2.8, 95% CI 1.26-6.21, p = 0.012) were independent predictors of disease progression. Among patients who did not undergo surgery during the study period, both platelet-to-lymphocyte ratio (PLR) > 160.9 (HR 5.86, 95% CI 1.27-27.08, p = 0.023) and mean platelet volume > 10.75 fL (HR 6.63, 95% CI 1.6-27.48, p = 0.009) were independently associated with worse PFS on multivariable analysis. Among patients who underwent complete resection, an LMR < 3.46 was associated with a worse RFS (HR 9.72, 95% CI 1.19-79.42, p = 0.034). CONCLUSIONS: PLR > 160.9 and an MPV > 10.75 fL at baseline are independent predictors of disease progression, while an LMR < 3.46 is an independent predictor of tumor recurrence after complete resection in patients with PNETs.
PubMed-ID: 29134377
http://dx.doi.org/10.1245/s10434-017-6241-4

Predicting Survival and Response to Treatment in Gastroesophageal Neuroendocrine Tumors: An Analysis of the National Cancer Database.
Ann Surg Oncol, 25(5):1418-24.
K. D. Gray, M. D. Moore, S. Panjwani, A. Elmously, C. Afaneh, T. J. Fahey, 3rd and R. Zarnegar. 2018.
BACKGROUND: Neuroendocrine tumors (NETs) of the esophagus and stomach are rare neoplasms with variable behavior. We aim to describe their epidemiology and response to treatment. METHODS: NETs of the stomach and the esophagus were selected from the National Cancer Database (2004-2013) and classified by location. Survival analyses were performed with respect to tumor characteristics and treatment variables. RESULTS: NETs of the stomach (n = 2700; 92.8%) and esophagus (n = 210, 7.2%) were identified. Gastric cardia NETs had demographics and behavior similar to esophageal tumors and were associated with worse overall survival than NETs of the noncardia stomach independent of grade (p < 0.001). Poorly differentiated histology [hazard ratio (HR) 4.14, 95% confidence interval (CI) 2.26-7.57; p < 0.001] and distant metastases (HR 3.28, 95% CI 1.94-5.56; p < 0.001) were the greatest independent predictors of survival. For patients with poorly differentiated NETs, surgery was the only treatment to have benefit on overall survival (HR 0.38, 95% CI 0.27-0.54; p < 0.001) regardless of extent of disease. There was no additional benefit to adjuvant chemotherapy or radiation in patients undergoing resection (p = 0.39), even for patients with lymph node metastases (surgery alone versus surgery plus adjuvant therapy, p = 0.46), distant metastases (p = 0.19), or positive margins (p = 0.33). CONCLUSIONS: Esophageal and gastric cardia NETs have worse survival than those of the noncardia stomach. Surgery offers the only survival benefit for poorly differentiated tumors, with no additional survival advantage to adjuvant chemotherapy or radiation.
PubMed-ID: 29476295
http://dx.doi.org/10.1245/s10434-018-6389-6

Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors.
J Nucl Med, 59(1):66-74.
T. A. Hope, E. K. Bergsland, M. F. Bozkurt, M. Graham, A. P. Heaney, K. Herrmann, J. R. Howe, M. H. Kulke, P. L. Kunz, J. Mailman, L. May, D. C. Metz, C. Millo, S. O'Dorisio, D. L. Reidy-Lagunes, M. C. Soulen and J. R. Strosberg. 2018.
PubMed-ID: 29025982
http://dx.doi.org/10.2967/jnumed.117.202275

Redefining the Ki-67 Index Stratification for Low-Grade Pancreatic Neuroendocrine Tumors: Improving Its Prognostic Value for Recurrence of Disease.
Ann Surg Oncol, 25(1):290-8.
A. G. Lopez-Aguiar, C. G. Ethun, L. M. Postlewait, K. Zhelnin, A. Krasinskas, B. F. El-Rayes, M. C. Russell, J. M. Sarmiento, D. A. Kooby, C. A. Staley, S. K. Maithel and K. Cardona. 2018.
BACKGROUND: The Ki-67 index is an established prognostic marker for recurrence after resection of pancreatic neuroendocrine tumors (PanNETs) that groups tumors into three categories: low grade (< 3%), intermediate grade (3-20%), and high grade (> 20%). Given that the majority of resected PanNETs have a Ki-67 less than 3%, this study aimed to stratify this group further to predict disease recurrence more accurately. METHODS: The Ki-67 index was pathologically re-reviewed and scored by a pathologist blinded to all other clinicopathologic variables using tissue microarray blocks made in triplicate. All patients who underwent curative-intent resection of non-metastatic PanNETs at a single institution from 2000 to 2013 were included in the study. The primary outcome was recurrence-free survival (RFS). RESULTS: Of 113 patients with well-differentiated PanNETs resected, 83 had tissue available for pathologic re-review. The Ki-67 index was lower than 3% for 72 tumors (87%) and between 3 and 20% for 11 tumors (13%). Considering only Ki-67 less than 3%, the tumors were further stratified by Ki-67 into three groups: group A (< 1%, n = 43), group B (1-1.99%, n = 23), and group C (2-2.99%, n = 6). Compared with group A, groups B and C more frequently had advanced T stage (T3: 44% and 67% vs 12%; p = 0.003) and lymphovascular invasion (50% and 83% vs 23%; p = 0.007). Groups B and C had similar 1- and 3-year RFS, both less than group A. After combining groups B and C, a Ki-67 of 1-2.99% was associated with decreased RFS compared with group A (< 1%). This persisted in the multivariable analysis (hazard ratio [HR] 8.6; 95% confidence interval [CI] 1.0-70.7; p = 0.045), with control used for tumor size, margin-positivity, lymph node involvement, and advanced T stage. CONCLUSIONS: PanNETs with a Ki-67 of 1-2.99% exhibit distinct biologic behavior and earlier disease recurrence than those with a Ki-67 lower than 1%. This new stratification scheme, if externally validated, should be incorporated into future grading systems to guide both surveillance protocols and treatment strategies.
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http://dx.doi.org/10.1245/s10434-017-6140-8

Comparison of Recurrence Between Pancreatic and Duodenal Neuroendocrine Neoplasms After Curative Resection: A Single-Institution Analysis.
Ann Surg Oncol, 25(2):528-34.
T. Masui, A. Sato, K. Nakano, Y. Uchida, A. Yogo, T. Anazawa, K. Nagai, Y. Kawaguchi, K. Takaori and S. Uemoto. 2018.
BACKGROUND: The primary site of a neuroendocrine neoplasms (NEN) around the head of the pancreas is sometimes difficult to assess before resection, and the characteristics of the primary site around this region have not been elucidated for recurrence after curative resection. In this study, the clinicopathologic characteristics of pancreatic NEN (PanNEN) and duodenal NEN (DuNEN) were evaluated, and the risk factors as well as the recurrence types after resection were investigated. METHODS: Consecutively diagnosed NEN patients at the authors' hospital from January 2000 to July 2016 were evaluated in this study. For 117 PanNEN patients and 31 non-ampullary DuNEN patients, R0 resection was achieved. The median follow-up period was 8.1 years. RESULTS: In this study, 27 PanNEN patients (23.1%) had recurrences, with a median disease-free survival (DFS) of 133 months, whereas 11 DuNEN patients (35.5%) had recurrences, with a median DFS of 156 months. The PanNEN patients tended to have primary recurrence in the liver (85.2%), followed by lymph nodes (11.1%). The independent risk factors for short DFS were lymph node metastasis at resection (p = 0.001) and microvascular invasion (p = 0.048). In contrast, the DuNEN patients were likely to have lymph node metastasis (81.8%). The independent risk factors for short DFS were lymph node metastasis at resection (p = 0.003) and large diameter (p = 0.013). CONCLUSIONS: Most initial recurrences of PanNEN occurred in the liver, whereas those of DuNEN appeared in lymph nodes, suggesting that proper diagnosis of the primary site and appropriate imaging methods for surveillance after resection are necessary.
PubMed-ID: 29164413
http://dx.doi.org/10.1245/s10434-017-6260-1

Challenges Staging Neuroendocrine Tumors of the Pancreas, Jejunum and Ileum, and Appendix.
Ann Surg Oncol, 25(3):591-3.
E. K. Nakakura. 2018.
PubMed-ID: 28779367
http://dx.doi.org/10.1245/s10434-017-6026-9

Incidence and Prognosis of Primary Gastrinomas in the Hepatobiliary Tract.
JAMA Surg, 153(3):e175083.
J. A. Norton, D. S. Foster, L. H. Blumgart, G. A. Poultsides, B. C. Visser, D. L. Fraker, H. R. Alexander and R. T. Jensen. 2018.
PubMed-ID: 29365025
http://dx.doi.org/10.1001/jamasurg.2017.5083

Prospective Evaluation of Results of Reoperation in Zollinger-Ellison Syndrome.
Ann Surg, 267(4):782-8.
J. A. Norton, G. W. Krampitz, G. A. Poultsides, B. C. Visser, D. L. Fraker, H. R. Alexander and R. T. Jensen. 2018.
OBJECTIVE: To determine the role of reoperation in patients with persistent or recurrent Zollinger-Ellison Syndrome (ZES). BACKGROUND: Approximately, 0% to 60% of ZES patients are disease-free (DF) after an initial operation, but the tumor may recur. METHODS: A prospective database was queried. RESULTS: A total of 223 patients had an initial operation for possible cure of ZES and then were subsequently evaluated serially with cross sectional imaging-computed tomography, magnetic resonance imaging, ultrasound, more recently octreoscan-and functional studies for ZES activity. The mean age at first surgery was 49 years and with an 11-year mean follow-up 52 patients (23%) underwent reoperation when ZES recurred with imageable disease. Results in this group are analyzed in the current report. Reoperation occurred on a mean of 6 years after the initial surgery with a mean number of reoperations of 1 (range 1-5). After reoperation 18/52 patients were initially DF (35%); and after a mean follow-up of 8 years, 13/52 remained DF (25%). During follow-up, 9/52 reoperated patients (17%) died, of whom 7 patients died a disease-related death (13%). The overall survival from first surgery was 84% at 20 years and 68% at 30 years. Multiple endocrine neoplasia type 1 status did not affect survival, but DF interval and liver metastases did. CONCLUSIONS: These results demonstrate that a significant proportion of patients with ZES will develop resectable persistent or recurrent disease after an initial operation. These patients generally have prolonged survival after reoperation and 25% can be cured with repeat surgery, suggesting all ZES patients postresection should have systematic imaging, and if tumor recurs, advise repeat operation.
PubMed-ID: 29517561
http://dx.doi.org/10.1097/SLA.0000000000002122

Current Management and Predictive Factors of Lymph Node Metastasis of Appendix Neuroendocrine Tumors: A National Study from the French Group of Endocrine Tumors (GTE).
Ann Surg,
B. Rault-Petit, C. Do Cao, S. Guyetant, R. Guimbaud, V. Rohmer, C. Julie, E. Baudin, B. Goichot, R. Coriat, A. Tabarin, J. Ramos, P. Goudet, V. Hervieu, J. Y. Scoazec and T. Walter. 2018.
OBJECTIVE: The primary endpoint was to analyze the predictive factors of lymph node involvement (LN+). BACKGROUND: Indications for additional right hemicolectomy (RHC) with lymph node (LN) resection after appendectomy for appendix neuroendocrine tumor (A-NET) remain controversial, especially for tumors between 1 and 2 cm in size. METHODS: National study including all patients with nonmetastatic A-NET diagnosed after January, 2010 in France. RESULTS: In all, 403 patients were included. A-NETs were: within tip (67%), body (24%) or base (9%) of the appendix; tumor size was < 1 cm (62%), 1 to 2 cm (30%), or >2 cm (8%); grade 1 (91%); mesoappendix involvement 3 mm (5%); lymphovascular (15%) or perineural (24%) invasion; and positive resection margin (8%). According to the European NeuroEndocrine Tumor Society (ENETS) recommendations, 85 patients (21%) should have undergone RHC. The agreement between ENETS guidelines and the multidisciplinary tumor board for complementary RHC was 89%. In all, 100 (25%) patients underwent RHC with LN resection, 26 of whom had LN+. Tumor size (best cut-off at 1.95 cm), lymphovascular and perineural invasion, and pT classifications were associated with LN+. Among the 44 patients who underwent RHC for a tumor of 1 to 2 cm in size, 8 (18%) had LN+. No predictive factor of LN+ (base, resection margins, grade, mesoappendix, lymphovascular, perineural involvement) was found in this subgroup of patients. CONCLUSIONS: In the largest study using the latest pathological criteria for completion RHC in A-NET, a quarter of patients had residual tumor. Further studies are warranted to demonstrate the survival impact of RHC in this setting.
PubMed-ID: 29557879
http://dx.doi.org/10.1097/SLA.0000000000002736

Changes in gene expression in small bowel neuroendocrine tumors associated with progression to metastases.
Surgery, 163(1):232-9.
K. J. Keck, P. Breheny, T. A. Braun, B. Darbro, G. Li, J. S. Dillon, A. M. Bellizzi, T. M. O'Dorisio and J. R. Howe. 2018.
BACKGROUND: Small bowel neuroendocrine tumors (SBNETs) present frequently with metastases, yet little is known about the molecular basis of this progression. This study sought to identify the serial differential expression of genes between normal small bowel, primary small bowel neuroendocrine tumors, and liver metastases. METHODS: RNA isolated from matched normal small bowel tissue, primary small bowel neuroendocrine tumors, and liver metastases in 12 patients was analyzed with whole transcriptome expression microarrays and RNA-Seq. Changes in gene expression between primary small bowel neuroendocrine tumors and normal small bowels, and liver metastases versus primary small bowel neuroendocrine tumors were calculated. Common genes that were differentially expressed serially (increasing or decreasing from normal small bowel to primary small bowel neuroendocrine tumors to liver metastases) were identified, and 10 were validated using qPCR. RESULTS: Use of 2 transcriptome platforms allowed for a robust discrimination of genes important in small bowel neuroendocrine tumors progression. Serial differential expression was validated in 7/10 genes, all of which had been described previously in abdominal cancers, and with several interacting with members of the AKT, MYC, or MAPK3 pathways. Liver metastases had consistent underexpression of PMP22, while high expression of SERPINA10 and SYT13 was characteristic of both pSBTs and liver metastases. CONCLUSION: Identification of the serial differential expression of genes from normal tissues to primary tumors to metastases lends insight into important pathways for SBNETs progression. Differential expression of various genes, including PMP22, SYT13 and SERPINA10, are associated with the progression of SBNETs and warrant further investigation.
PubMed-ID: 29154080
http://dx.doi.org/10.1016/j.surg.2017.07.031

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Long-Term Survivorship in Multiple Endocrine Neoplasia Type 2B Diagnosed Before and in the New Millennium.
J Clin Endocrinol Metab, 103(1):235-43.
F. Raue, H. Dralle, A. Machens, T. Bruckner and K. Frank-Raue. 2018.
Context: Recent long-term outcomes and survival data are lacking for patients with multiple endocrine neoplasia type 2B (MEN2B). Objectives: To analyze long-term MEN2B outcomes and define prognostic factors. Design, Setting, and Participants: Retrospective comparative study of 75 patients with MEN2B from two German tertiary referral centers. Patients diagnosed and treated before and after 2000 were compared for demographic, biochemical, surgical, and outcome parameters. Intervention: Surgery. Main Outcome measure: Long-term survival. Results: We identified seven familial and 68 de novo cases of MEN2B; 61 exhibited the RET M918T genotype (2 others exhibited A883F and E768D/L790T mutations). Surgery was performed at a mean age of 16.4 +/- 11.2 years. The tumor stages at diagnosis for 71 patients were stage I, 15%; stage II, 6%; stage III, 35%; and stage IV, 44%. The mean follow-up was 9.6 +/- 9.0 years. The outcomes were 15 (20%) cured, 9 (12%) with minimal residual disease, 19 (25%) with metastatic disease, and 10 (13%) unknown. Medullary thyroid cancer (MTC) caused 22 deaths (29%) 7.3 +/- 6.2 years after diagnosis (mean age, 22.9 +/- 10.7 years). The overall survival rates at 5, 10, and 20 years were 85%, 74%, and 58%, respectively. After 2000 (vs before 2000), significantly more patients had stage I and II (32% vs 11%) and more were cured (43% vs 20%), with a higher survival trend (P = 0.058). The only prognostic factor was tumor stage at diagnosis. Conclusions: Patients with MEN2B developed MTC at an early age with wide ranging aggressiveness, but the outcome was generally better after 2000 than before 2000.
PubMed-ID: 29077903
http://dx.doi.org/10.1210/jc.2017-01884

EPAS1 Mutations and Paragangliomas in Cyanotic Congenital Heart Disease.
N Engl J Med, 378(13):1259-61.
A. Vaidya, S. K. Flores, Z. M. Cheng, M. Nicolas, Y. Deng, A. R. Opotowsky, D. M. Lourenco, Jr., J. A. Barletta, H. Q. Rana, M. A. Pereira, R. A. Toledo and P. L. M. Dahia. 2018.
PubMed-ID: 29601261
http://dx.doi.org/10.1056/NEJMc1716652

Voice and Swallowing Outcomes of Unilateral Vocal Fold Paralysis: Comparing Younger Adult and Geriatric Patients.
Otolaryngol Head Neck Surg, 158(5):904-11.
J. Bonilla-Velez, M. Small, F. J. Bonilla-Escobar, M. Sharum and O. E. Tulunay-Ugur. 2018.
Objective To compare voice and swallowing outcomes after treatment in younger adult (<65 years) and geriatric (>/=65 years) patients with unilateral vocal fold paralysis (UVFP). Study Design Case series with chart review.

Setting Tertiary care center. Subjects and Methods The cases of patients presenting to a tertiary voice clinic with UVFP between June 2005 and February 2015 were reviewed. Clinical characteristics and outcomes in a geriatric subset were compared with those in younger adult group. Results A total of 206 patients met our inclusion criteria (n = 110, <65 years; n = 96, >/=65 years). Etiology was most commonly iatrogenic (59.2%), and computed tomography led to diagnosis for 62.3% of patients for whom it was obtained. The Voice Handicap Index improved on average by 31.3 points after treatment (P < .001), with equal improvement between the patient subsets (P = .71). Swallowing, as objectively assessed by the National Outcomes Measurement System for modified barium swallow, showed a statistically significant improvement in the patient population as a whole (-0.9, P = .02) but was not significantly different within the subgroups (younger, P = .07; geriatric, P = .25). Conclusion Geriatric patients have similar voice and swallowing outcomes as younger adults and should be treated equally aggressive.
PubMed-ID: 29533712
http://dx.doi.org/10.1177/0194599818756310

An assessment of (18) F-FDG PET/CT for thoracic screening and risk stratification of pulmonary nodules in multiple endocrine neoplasia type 1.
Clin Endocrinol (Oxf), 88(5):683-91.
A. So, O. Pointon, R. Hodgson and J. Burgess. 2018.
CONTEXT: Bronchopulmonary neuroendocrine tumours (bpNETs) and thymic carcinoid (ThC) are features of multiple endocrine neoplasia type 1 (MEN 1), and surveillance guidelines recommend periodic thoracic imaging. The optimal thoracic imaging modality and screening frequency remain uncertain as does the prognosis of small lung nodules when identified. OBJECTIVES: To evaluate fluorodeoxyglucose positron emission tomography/computed tomography ((18) F-FDG PET/CT) for identification and prognostic assessment of thoracic lesions in MEN 1. DESIGN: Retrospective observational study. SETTING AND PARTICIPANTS: Fifty consecutive MEN 1 patients undergoing screening with (18) F-FDG PET/CT at a tertiary referral hospital between July 2011 and December 2016. INTERVENTIONS: (18) F-FDG PET/CT. OUTCOME MEASURES: Pulmonary and thymic lesion prevalence, size, functional characteristics and behaviour. RESULTS: Thirteen patients (26.0%) exhibited pulmonary nodules with multiple nodules identified in nine (18.0%). An asymptomatic 31 mm FDG-avid ThC was identified in one patient (2%). Of the 13 patients with pulmonary nodules, four (8.0%) exhibited 13 FDG-avid nodules (mean size 10.1 +/- 9.1 mm), and nine (18.0%) demonstrated 26 FDG nonavid nodules (mean size 6.9 +/- 5.8 mm). All FDG-avid lesions increased in size vs 11 (42.3%) FDG nonavid lesions (P = .0004). For FDG-avid and nonavid nodules, the median doubling time was 24.2 months (IQR 11.4-40.7) and 48.6 months (IQR 37.0-72.2), respectively. Nodule resection was undertaken in two patients, typical bronchial carcinoid diagnosed in one (FDG nonavid) and metastatic renal cell carcinoma in the second (FDG avid). CONCLUSION: Thoracic imaging with (18) F-FDG PET/CT effectively identifies pulmonary nodules and ThC. FDG-avid pulmonary lesions are significantly more likely to progress than nonavid lesions.
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http://dx.doi.org/10.1111/cen.13573

Ο ΒΙΟΣ ΤΗ ΧΕΙΡΟΥΡΓΙΚΗ ΑΝΑΦΥΕΤΑΙ *[sic]*
World J Surg, 42(2):317-20.
D. Linos. 2018.
PubMed-ID: 29116371
http://dx.doi.org/10.1007/s00268-017-4326-7